Intermittent Treatment of Infants for the Prevention of Malaria: A Systematic Review

2008

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ABSTRACT

Background

Malaria is responsible for morbidity and mortality in infants living in affected areas. The use of drugs at regular intervals during the first one to two years of life is being considered as a method of reducing the impact of malaria within this group.

Objectives

To evaluate the use of intermittent treatment with antimalarial drugs as a method of malaria prevention in infants living in affected areas and to present the findings in accordance with the requirements for a Cochrane Collaboration systematic review.

Search strategy

The Cochrane Library of Systematic Reviews, Medline, Science Direct, Scirus and Scopus were searched for studies relevant to this systematic review.

Selection criteria

Randomised, controlled trials evaluating antimalarial drugs given intermittently to infants compared to a placebo or no drug in infants aged between one month and two years living in areas endemic for malaria.

Data collection and analysis

Data was independently extracted and assessed for methodological quality. Relative risk (RR) with 95% confidence intervals (CI) were used for meta-analysis.

Main results

Nine trials (10,226 participants) met the inclusion criteria.

Authors' conclusions

Intermittent treatment of infants is effective at reducing the incidence of clinical malaria.

PLAIN LANGUAGE SUMMARY

Infants given antimalarial drugs intermittently are less likely to suffer from malaria but more studies are needed to ensure that the treatment is safe and sustainable.

Malaria is a serious disease, particularly for infants that have not had the opportunity to develop immunity against it. Over a million children under the age of five die of malaria each year. Those infants that survive early infections and live within endemic areas do develop immunity that can provide some degree of protection against severe malaria. The review of trials found that infants that were given intermittent preventative treatment for the disease were less likely to suffer from clinical malaria and severe anaemia. Those treated also had fewer hospital admissions, although there was no effect on the number of deaths between those treated and those not treated. There was also no extra risk of clinical malaria, severe anaemia, death or hospital admission for those given intermittent treatment once treatment had ended and no evidence that treatment affected vaccinations for measles, tetanus, polio or hepatitis B if given at the same time. Further studies are needed to ensure that the treatment is safe and that it does not lead to, or suffer from, the development of drug resistant parasites.

BACKGROUND

Malaria

Malaria is a disease caused by protozoan parasites of the genus Plasmodium. Infection is transmitted to humans via the bite of infected female anopheline mosquitoes, which act as both the vector and definitive host of the parasite. Malaria is common throughout the tropics and subtropics, including much of Africa, Asia and South America, and may occur perennially or seasonally depending upon local conditions and vector species (White, 2003).

Four strains of Plasmodium affect humans; these are *P. falciparum* (malignant tertian malaria), *P. vivax* (benign tertian malaria), *P. ovale* (ovale tertian malaria) and *P. malariae* (quartan malaria). The most clinically significant of these strains is *P. falciparum* and it is responsible for the vast majority malaria-associated deaths.

Pathogenesis

Malaria occurs when sporozoites are injected into a human host by an infected anopheline mosquito. These sporozoites then travel to the liver where they enter hepatocytes, multiply and develop into schizonts which burst and release merozoites into the blood. *P. vivax* and *P. ovale* are able to remain within hepatocytes as hypnozoites for extended periods of time before releasing merozoites into the blood.

Each merozoite finds and penetrates an individual erythrocyte where it will develop into a trophozoite and then either produce more merozoites or gametocytes. Merozoites go on to infect more erythrocytes, causing an amplification effect through each generation. Gametocytes, the sexual stage of the parasites lifecycle, cause no pathology and require being taken up by an appropriate mosquito during a blood meal to continue their development.

Infection with *P. vivax*, *P. ovale* or *P. malariae* tends to be less severe than *P. falciparum*, although mixed infections occur where parasite populations overlap (Bruce *et al*., 2008). Infection may be asymptomatic with those infected being unaware of their status. Alternatively, the disease may cause symptoms such as intermittent fever, headache and lethargy at levels ranging from mild (uncomplicated)

to life-threatening (severe) with complications such as severe anaemia and cerebral involvement occurring with falciparum malaria.

P. falciparum is particularly strongly associated with mortality amongst all age groups and the disease is responsible for the deaths of over a million children in Africa alone each year (Grobusch *et al*., 2007). Major causes of mortality include anaemia and cerebral malarial, with the latter often being associated with persistent neurological deficit in some of those who survive (Roca-Feltrer *et al*., 2008). Anaemia is caused by merozoites breaking out of infected erythrocytes to colonise fresh cells and destroying the old cells in the process. When this occurs on a large scale the number of erythrocytes available to carry oxygen may drop substantially and severe anaemia may result. Malarial anaemia is of particular concern for individuals who may already be anaemic due to low levels of dietary iron. In these circumstances malarial anaemia may compound existing anaemia and increase the likelihood of morbidity and mortality. Cerebral malaria occurs when *P. falciparum* parasites cause infected erythrocytes to sequester themselves in cerebral capillaries and adhere to the vessel walls and other infected and non-infected erythrocytes (rosetting). These clumps of cells inhibit the flow of blood to affected portions of the brain, causing tissue damage and often death. Sequestration may also occur in capillary beds of other organs and be responsible for multi-organ damage or failure (White, 2003).

Treatment and Prevention

Individuals living in areas endemic for malaria develop partial immunity to the disease over time. In order for this immunity to be maintained, the immune system must be constantly challenged by sustained parasitaemia (Kitua *et al*., 1997) or by repeated reinfection (Menendez *et al*, 2007). For this reason those subjected to periodic or epidemic malaria may be unable to maintain their immune status (Sama *et al*., 2000). A similar situation occurs when immune individuals leave an endemic area for a period of time and then return only to find themselves susceptible again.

Neonates gain some degree of immunity from maternal antibodies but this protection is fleeting (Haghdoost *et al*., 2007). As a result, infants living in endemic regions, who have lost passive maternal protection but have not yet developed any degree of

active immune response for themselves, may be particularly at risk. As there is no vaccine currently available for malaria (Sharma & Pathak, 2008), the only way for an infant to gain immunity is through the acquisition of an infection, which may in itself prove fatal.

There are various chemotherapeutic options for the treatment of clinical malaria, the choice of which to use being governed by factors such as cost, availability and local parasite sensitivity (White, 2003). For many years chloroquine (CQ), a 4-Aminoquinoline drug, formed the basis for the treatment of malaria. CQ has many advantages over other treatments, being inexpensive, widely available and well tolerated. However, years of overuse and under-dosing have applied a considerable selection pressure on plasmodium parasites and this has hastened the development of CQ resistance. This resistance is now widespread and has forced the adoption of more costly first-line drugs, such as sulfadoxine-pyrimethamine (SP), in order to reliably treat the disease (Winstanley & Ward, 2006). Resistance has also appeared to SP and this too is spreading (Ekland & Fidock, 2008). As a result, health providers have been forced to look at other, even more expensive options, such as artemisinin combination therapy. It is often the poorest countries, such as many in sub-Saharan Africa, which are most affected and least able to afford the premium required for newer drugs.

Prevention measures exist that reduce the likelihood of infection but all come with disadvantages. Bed nets, either insecticide impregnated or not, are highly effective at reducing the incidence of malaria where the mosquito vector is ecologically associated with humans and their domestic environment. However, nets need to be used correctly, be maintained in a good state of repair and, if impregnated, re-treated periodically if they are to remain effective (Wiseman *et al*., 2006). Residual indoor insecticide spraying, typically with dichlorodiphenyltrichloroethane (DDT), is also effective with endophilic vectors, but this efficacy is reduced as DDT resistance spreads (Santolamazza *et al*., 2008). Chemoprophylaxis, such as adopted by travellers, is effective where the parasite is drug-sensitive but the use of life-long prophylaxis has implications for financial sustainability, health and the development of parasite resistance (Schlagenhauf & Petersen, 2008).

Intermittent Preventative Treatment

An alternative chemotherapeutic approach exists which seeks to strike a balance between efficacy, cost and drug resistance. It is called intermittent preventative (or presumptive) treatment or IPT and involves the periodic (but not prophylactic) use of a full therapeutic course of anti-malarial treatment regardless of infection status (Schellenberg *et al*., 2006). As drug use is periodic, associated costs – both material and logistic – are lower than for chemoprophylaxis. The selection pressure applied to the parasites is also reduced, although it is likely to be greater than simply treating clinical cases as they arise. Finally, IPT may allow the development/maintenance of acquired resistance due to the gaps between treatments during which infection can occur (Meremikwu *et al*., 2008).

Concerns exist regarding the use of IPT and include its 'non-therapeutic' use as risk factor for the acceleration of drug resistance and of rebound malaria. Rebound refers to the fear that IPT, while protecting against clinical malaria, may prevent the development of acquired immunity by not allowing a significant immune response to develop between treatments. As IPT is generally considered to be a short-term strategy for at-risk individuals, this lack of immunity could cause significant vulnerability once treatment was ended (Dicko *et al*., 2008).

Although any effective antimalarial may be considered for use in IPT, SP has been the most common choice in recent trials (Meremikwu *et al*., 2008). Its advantages include that treatment is by a single dose, that the drug is inexpensive (although it is more expensive than CQ) and that it persists within the blood for a longer period of time than other drugs (Gatton *et al*., 2004). The residual nature of SP means that may provide longer-term protection against plasmodium infection.

The use of IPT in pregnancy (IPTp) has been demonstrated to have significant benefits for both the mother and baby and is recommended by the WHO (2003). Work on other high-risk groups is ongoing and published work includes a systematic review by Meremikwu *et al*. (2008) on IPT in children. However, to date no review has been published on the efficacy of IPT specifically with infants (IPTi) where it may be possible to efficiently include the intervention as part of other routine health interventions. Focusing IPTi around childhood vaccination programmes, for example,

may confer both cost and logistic advantages (Chandramohan *et al*., 2007). However, little is know regarding what, if any, interactions may occur between vaccinations and antimalarial drugs if given at the same time (Macete *et al*., 2006).

There are further concerns with regard to the use of IPT, which have so far helped to limit their widespread adoption. Cost is naturally an important factor, in as much as the countries most affected by malaria are usually amongst the poorest, with limited funds to direct towards preventative medicine. There is also the fear that the extended and prolonged use of an antimalarial, particularly a long-acting drug like SP (Mayor *et al.*, 2008) might apply an intense selection pressure on the plasmodium parasite, causing the rapid development and expansion of drug resistance (O'Meara *et al*., 2006; Alexander *et al*., 2007). This is of particular concern as multi-drug resistant *P. falciparum* continues to spread (Plowe, 2005) and as it does so more pressure will be placed on other more costly drugs (Shanks, 2006).

Another issue, perhaps of more immediate concern to the individual, is the possible effect of IPTi on the retardation of a competent immune response to plasmodium in children from endemic settings. The intermittent use of antimalarials may be protective but unless the immune systems of children are regularly exposed to parasite antigens, they may not acquire immunity against malaria (Kitua *et al*., 1997). If this exposure occurs only following the cessation of IPT then the incidence of clinical malaria within the treatment group may rise significantly at that point (Greenwood *et al*., 1995). This rebound effect may be associated with surges of morbidity and mortality within age groups normally resistant to the more severe effects of malaria due to earlier and repeated exposure.

IPTi may have the potential to reduce both morbidity and mortality levels in young children, although there are potential risks associated with its use. Although individual studies have considered particular types of IPTi in a range of settings, a comprehensive overview of both the effectiveness and risks of the intervention is required to enable its comprehensive evaluation as a public health option.

OBJECTIVES

The objective of this study was to evaluate the literature pertaining to the use of intermittent preventative treatment of malaria in infants less than two years of age in order to evaluate all current evidence.

CRITERIA FOR CONSIDERING STUDIES FOR REVIEW

Types of studies

Randomised, controlled trials.

Types of participants

Infants aged between one month and two years living within an area endemic for malaria.

Types of intervention

Intervention

A full treatment course of antimalarial chemotherapy given intermittently, irrespective of dose or drug used.

Control

Placebo or no drug.

Types of outcome measures

Primary

Clinical malaria

Severe anaemia (as defined by the trial)

Secondary

Death (all causes)

Hospital admissions

Parasitaemia

Effect on immune response to vaccination

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

An attempt was made to identify all published trials.

Databases

The following databases were interrogated using the search terms described in Table 01.

- The Cochrane Database of Systematic Reviews (1988 to May 2008)
- Medline (1980 to May 2008)
- EMBASE (1980 to May 2008)
- LILACS (1982 to May 2008)
- ScienceDirect (1980 to May 2008)

Reference lists

The reference lists from all the studies identified by the initial searches were also checked.

METHODS OF THE REVIEW

Trial selection

The literature was independently searched for candidate studies and full reprints were obtained for each trial. Eligibility for inclusion in the review was assessed through described inclusion criteria.

Assessment of the methodological quality

The methodological quality of each study was assessed by the reviewer. All studies used double-blinded allocation concealment whereby neither the patient nor the caregiver/assessor was aware of which treatment was being given. The inclusion of randomised participants in each study was considered adequate if at least 90% of those randomised were used and remained within their original groups up to analysis.

Data extraction

Data was independently extracted from each trial according to the outcome measures.

Data analysis

Review Manager 5[1] was used to analyse the data and risk ratio (RR) with 95% confidence intervals (CI) were calculated as the basis for meta-analysis. Intention-to-treat analysis was used where all randomised participants were accounted for.

Heterogeneity was evaluated through visual examination of forest plots and through the use of a chi-squared test for heterogeneity. Sensitivity analyses were conducted for clinical malaria and severe anaemia as these were the primary outcomes of the review. Funnel plots were produced to evaluate symmetry in case of bias but no clear pattern was observed.

DESCRIPTION OF STUDIES

Interrogation of the literature identified 23 potentially relevant studies and nine of these met the inclusion criteria (see 'Characteristics of included studies'). Of those excluded, one used a study population including children over two years of age, three contained data that was not extractable for meta-analysis, one looked at growth and

[1] software used for preparing and maintaining Cochrane reviews

nutritional status only and nine were not randomised, controlled trials. The nine studies that met the inclusion criteria form the systematic review and meta-analysis.

Location

All the studies selected (10,226 participants) were conducted in Africa; Ghana (3), Senegal (1), Gabon (1), Mozambique (1) and Tanzania (3). Two of the Tanzanian studies were conducted on the same population (Schellenberg *et al*., 2001; Schellenberg *et al*., 2005). Schellenberg *et al.* (2005) was an extended study to follow up the same population as Schellenberg *et al*. (2001) eighteen months after ending treatment.

Malaria endemicity

The pattern of malarial transmission varied between the studies. Transmission was perennial in studies from Tanzania (2), Gabon (1) and Mozambique (1), perennial with seasonal variation in studies from Ghana (2) and Tanzania (1) and seasonal in studies from Ghana (1) and Senegal (1). Six studies described malaria transmission in the area as holoendemic.

Trial design

Eight of the trials used randomised individuals and one used randomised household units (cluster randomised). Length of follow-up ranged from thirteen weeks to two years, with a mean follow-up time of seventeen months.

Intervention

SP was the most commonly used antimalarial and was used in seven of the studies (Chandramohan *et al*., 2005; Grobusch *et al*., 2007; Kobbe *et al*., 2007a; Macete *et al*., 2006; Mockenhaupt *et al*., 2007; Schellenberg *et al*., 2001; Schellenberg *et al*., 2005). One trial used SP plus artesunate (AS) (Cissé *et al*., 2006) and one trial used amodiaquine (AQ) (Massaga *et al*., 2003).

Seven of the interventions were given alongside Expanded Program on Immunization (EPI) vaccinations. Three studies treated at the ages of 3, 9 and 15 months of age (Grobusch *et al*., 2007; Kobbe *et al*., 2007a; Mockenhaupt *et al*., 2007). Two studies treated at 2, 3 and 9 months of age (Schellenberg *et al*., 2001;

Schellenberg *et al*., 2005) and one study treated at 3, 4 and 9 months of age (Macete *et al.,* 2006). Chandramohan *et al*. (2005) treated four times during the first year of life, each approximately 3 months apart. These were given at attendance for DPT-2 (diphtheria, polio and tetanus vaccination), at DPT-3, at measles vaccination and at 12 months of age.

Two studies did not use vaccination schedules to time the application of antimalarial treatment. Massaga *et al.* (2003) treated infants aged between 12 and 16 weeks every sixty days over a six month period. Cissé *et al.* (2006) gave intermittent treatment once a month for three months to children aged from 2 to 59 months, although data for children over 24 months was excluded from this review.

Schellenberg *et al*. (2005) was a follow-up study of Schellenberg *et al*. (2001) and evaluated outcomes eighteen months following the cessation of treatment.

Co-interventions

Three of the studies provided iron supplementation to all participants (Chandramohan *et al*., 2005; Schellenberg *et al*., 2001; Schellenberg *et al*., 2005). Massaga *et al*. (2003) gave iron supplementation to some participants and a placebo to others in order to assess the role of iron in treatment efficacy. The remainder of the studies did not provide iron supplements but did not prohibit their use.

All the studies reported the use of bed nets within the study population (either insecticide treated or untreated) but no study used nets as an intervention. Chandramohan *et al*. (2005) identified a similar number of bed net users within both treatment (19%) and control (17%) groups, as did Cissé *et al.* (2006) and Macete *et al*. (2006), all reporting a similar prevalence. The studies by Grobusch *et al*. (2007) and Schellenberg *et al*. (2001) described far higher levels of bed net use, ranging from around 68% (Schellenberg *et al*., 2001) to 80% (Grobusch *et al*., 2007). Kobbe *et al*. (2007a) reported slightly lower bed net usage at 39% (treatment) and 38% (control), with Massaga *et al*. (2003) reporting similar figures. The population

studied by Mockenhaupt *et al*. (2007), however, demonstrated very low bed net usage in comparison to the other studies at only 3%.

Outcomes

All of the studies reported on the number of infants who developed malaria and seven provided data on first or single episodes; six of these during the intervention period and one during extended follow-up. Five studies reported on severe anaemia, although different definitions were used for this outcome; packed cell volume (PCV) less than 25% (two studies), PCV less than 24% (two studies) and haemoglobin level (Hb) less than 5.0 g/dL (one study).

Other relevant outcomes were death from any cause (eight studies), hospital admissions (six studies), parasitaemia (≥ 5000 parasites per µl) (three studies) and the effect on immune response to vaccination (three studies).

METHODOLOGICAL QUALITY

Generation of allocation sequence

All studies used appropriate methods to generate the allocation sequence.

Eight of the studies describe using computer-based randomisation to generate their allocation sequence. One study used generated blocks of clusters (cluster randomization), three used individual randomisation and four used block randomisation. One study (Kobbe *et al*., 2007a) did not describe the method of allocation, other than to state that it was randomised.

Allocation concealment

All studies used placebos identical in appearance to treatment drugs and provided in similar packaging (bottles, sealed envelopes or blister packs). Similarity of taste was described by Massaga *et al*. (2003) but slight differences were reported by Cissé *et al.* (2006). Taste similarity was unclear in the remaining studies.

Blinding

All studies reported using double-blinding.

Inclusion of all randomised participants in the analysis

Three studies included more than 90% of randomised participants in the analysis. The remaining studies reported an attrition rate of between 12% (Chandramohan *et al.*, 2005) and 49% (Grobusch *et al*., 2007). The loss to follow-up figure stated by Grobusch *et al*. (2007) was due largely to a high migration rate within the study population; 514 of the original study population of 1189 participants migrated out of the study area during the trial.

RESULTS

Part one describes the effects of intermittent treatment on infants during the intervention period and part two examines the effects once the intervention was stopped.

1) During intervention

Clinical malaria

Six studies (5518 participants) were used to construct the meta-analysis for the number of episodes of clinical malaria. There was a substantial range of effect sizes between studies, from RR 0.18 (95% CI 0.13 to 0.24, 1088 participants) demonstrated by Cissé *et al.* (2006) to RR 0.90 (95% CI 0.80 to 1.00, 1070 participants) described by Kobbe *et al*. (2007a). Overall, the intermittent use of antimalarials was significantly better at preventing clinical malaria, at a 5% significance level, than placebo controls (RR 0.55, 95% CI 0.36 to 0.84; *see* analysis 01.01).

Despite being in broad agreement on outcome, heterogeneity between the studies remained strongly significant even when analysed separately according to seasonality of malaria transmission (*see* analysis 02.01) and by the antimalarial drug used (*see* analysis 03.01). However, heterogeneity was partially reduced when studies were stratified according to the use of iron supplementation. Although not significantly better or worse at preventing clinical malaria, the two studies that utilised iron supplementation (Massaga *et al.,* 2003; Schellenberg *et al.,* 2001) shared demonstrably similar results (*see* analysis 04.01). Heterogeneity remained significant for studies that did not use iron supplementation, although it disappeared when the outlying results reported by Cissé *et al.* (2006) were excluded from the meta-analysis.

Three studies were not included in the meta-analysis. Two of these only reported counts of malaria episodes and not the numbers of children developing one or more cases of clinical malaria. The third study, by Schellenberg *et al.* (2005), related only to a period of extended follow up and was not comparable to the other studies in this analysis, which evaluated the study population throughout the intervention period. The study by Massaga *et al.* (2003) consisted of three trials, evaluating an antimalarial (AQ), iron supplementation and an antimalarial plus iron supplementation, against placebo controls. As analysis 01.01 was primarily concerned with the effectiveness of antimalarials for the prevention of clinical malaria, the data from the antimalarial-only arm of the trial (145 participants) were included. However, where stratified by iron supplementation (*see* analysis 04.01), all applicable data from the trial were included within the appropriate strata.

Severe anaemia

Six studies (7104 participants) provided data for severe anaemia. All the studies considered total events alone, except for Kobbe *et al*. (2007a), which considered first or single events and total events separately. For first or single events, Kobbe *et al*. (2007a) found no significant effect of antimalarial treatment on severe anaemia (RR 1.00, 95% CI 0.48 to 2.08, 1070 participants; *see* analysis 01.02).

For total events the studies did not display significant heterogeneity and so a fixed model was used. Study results varied from RR 0.34 (95% CI 0.17 to 0.68; 145 participants) reported by Massaga *et al.* (2006) to RR 1.21 (95% CI 0.60 to 2.44; 1070 participants) stated by Kobbe *et al*. (2007a). Overall, the meta-analysis found a significant difference between treatment and control for the prevention of severe anaemia at a 5% significance level (RR 0.75, 95% CI 0.67 to 0.85; *see* analysis 01.02).

Two studies could not be used for this meta-analysis as they did not provide data on anaemia. A third study by Grobusch *et al*. (2007) provided data for moderate anaemia only and so was excluded from this analysis.

As with clinical malaria, trials were also stratified according to whether or not iron supplementation was provided to participants. Three studies reported using iron supplementation (3330 participants) for this outcome and four did not (3918), including the trial by Massaga *et al.* (2006), which provided data for both with and without supplementation. There was significant heterogeneity within both strata, but the studies that provided iron supplementation were associated with a lower incidence of severe anaemia (RR 0.53, 95% CI 0.32 to 0.90) than those that did not (RR 0.91, 95% CI 0.80 to 1.02; *see* analysis 04.02). No significant differences were observed by stratifying the trials according to seasonality or the drug used.

Death from any cause

Eight studies provided data for death from any cause during the intervention period (9204 participants). No significant differences between treatment and control groups were detected in any of the studies that provided data for this outcome and there was an overall risk ratio of 1.04 (95% CI 0.84 to 1.29; *see* analysis 01.03). Point estimates provided by Cissé *et al.* (2006) and Grobusch *et al*. (2007) suggested a positive effect for antimalarials but their confidence intervals were wide due to the low number of events.

One study (Chandramohan *et al*., 2005) described nine more deaths in the treatment group than in the control group (44 versus 35) but sensitivity analysis did not show this as being significant (RR 1.26, 95% CI 0.81 to 1.94, 2485 participants).

Hospital admission for any cause

Overall, hospital admissions were significantly lower in the treatment groups than in the control groups where this outcome was described (RR 0.83, 95% CI 0.74 to 0.84, 7105 participants; *see* analysis 01.04). Massaga *et al.* (2003) demonstrated a particularly strong protective effect (RR 0.42, 95% CI 0.24 to 0.74, 146 participants), although this effect was weaker in other studies and insignificant in Kobbe *et al.* (2007a) (RR 0.99, 95% CI 0.80 to 1.23, 1070 participants).

Parasitaemia

Three studies (4755) provided data for parasitaemia (≥5000 parasites per µl of blood). There was no significant heterogeneity and analysis generated a risk ratio of 0.80 (95% CI 0.76 to 0.84) in favour of antimalarial treatment, *see* analysis 01.05.

Protective antibody titres

Two studies gave data on the effect of antimalarials on protective antibody titres (3628 participants). Macete *et al*. (2006) reported on tetanus, diphtheria, polio, hepatitis B and measles and Schellenberg *et al.* (2001) on tetanus, diphtheria and measles. No significant differences were found between treatment and control for any of these titres (RR 0.98, 95% CI 0.97 to 1.00; *see* analysis 01.06), although the point estimate for measles derived from Schellenberg *et al.* (2001) suggested a slightly reduced (although not significant) serological response to the measles vaccine within the treatment group (RR.0.87, 95% CI 0.76 to 1.00).

2) Impact after stopping intervention

Clinical malaria

Four trials (5164 participants) reported on clinical malaria during follow-up once intervention had ceased. Although significant heterogeneity was detected between these studies, all were in broad agreement for the outcome. No significant differences were detected by any of the studies or by meta-analysis (RR 1.01, 95% CI 0.93 to 1.10; *see* analysis 05.01). Chandramohan *et al*. (2005), Kobbe *et al.* (2007a) and Mockenhaupt et al. (2007) all used a similar follow-up period of eight months, from one month post-intervention. Schellenberg *et al.* (2005) followed up participants for approximately 14 months, also beginning one month following the cessation of treatment.

Severe anaemia

The same four trials that reported on the post-intervention incidence of clinical malaria reported for this outcome (Chandramohan *et al.*, 2005; Kobbe *et al.*, 2007a; Mockenhaupt et al., 2007; Schellenberg *et al.*, 2005). All studies provided data based on total events, except for Kobbe *et al.* (2007a) where data for both single and total events were given. Heterogeneity was not significant at 5% and no significant

differences were detected between the treatment and control groups for either single (RR 1.25, 95% CI 0.34 to 4.63, 1070 participants) or total events (RR 0.97, 95% CI 0.84 to 1.11, 5164 participants; *see* analysis 05.02).

Death from any cause

Three studies provided data for this outcome (4609 participants). Chandramohan *et al*. (2005) reported 33 deaths in the treatment group (1243 participants) and 26 deaths in the control group (1242 participants) while the point estimates derived from Kobbe *et al.* (2007a) and Mockenhaupt et al. (2007) both slightly favoured treatment over control. However, overall no significant differences were identified by either independent analysis of the study data or by meta-analysis (RR 0.98, 95% CI 0.66 to 1.47; *see* analysis 05.03).

Hospital admission for any cause

Two studies reported on the number of hospital admissions during the post-intervention period (3555 participants) but no significant differences between treatment and control were evident (RR 1.02, 95% CI 0.84 to 1.25; *see* analysis 05.04).

Parasitaemia

Two studies provided data on the incidence of parasitaemia during the post-intervention period. A significant difference between treatment and control was identified for this outcome (RR 1.12, 95% CI 1.02 to 1.23, 3555 participants; *see* analysis 05.05), suggesting a greater risk of parasitaemia in the treatment group. This was primarily due to the findings reported by Chandramohan *et al*. (2005) as the trial described by Kobbe *et al*. (2007a) demonstrated no significant differences.

Protective measles antibody titres

Only Schellenberg *et al.* (2005) provided data on post-intervention protective antibody titres (measles) and no significant differences were detected between treatment and control in this study (RR 0.94, 95% CI 0.87 to 1.02; *see* analysis 05.06).

DISCUSSION

All of the studies included in the review were based in Africa, where *P. falciparum* is the major cause of malaria, itself a significant cause of morbidity and mortality (Snow *et al*., 2005). Transmission patterns were provided by each of the nine studies included within the review. Care was taken to avoid double-counting of participants as some published studies were based on the same population as earlier studies. Where this occurred, the most appropriate and inclusive studies were used and further reports on the same population, unless additive (such as that by Schellenberg *et al*., 2005), were excluded. All studies appeared adequately powered, although Massaga *et al.* (2003) initially assumed a smaller loss to follow-up than actually achieved. Loss to follow-up figures varied between the trials from as low as 6% up to 49%, which was a concern as large losses may affect study validity (Fewtrell *et al*., 2008). However, opinions vary with regard to the level at which loss to follow-up becomes important, with some authors suggesting a loss to follow-up of up 80% being acceptable for epidemiological studies (Kristman *et al*., 2004).

Although the studies included in the review used differing methods of sequence allocation, all demonstrated adequate randomisation, concealment and blinding. Any study failing to meet adequate standards for these components could be subject to a number of forms of bias and so provide unreliable or misleading results (Moher *et al*., 1999). As a consequence of this risk, studies which failed to meet these standards of rigor (or failed to describe their methods in sufficient detail) were excluded from the review.

Significant heterogeneity was observed for clinical malaria, both during and following the intervention period. Heterogeneity was also detected for hospital admissions for any cause during the intervention period. Heterogeneity was not significant for other outcomes. Patterns of heterogeneity were examined further for the primary outcome of clinical malaria by subgroup analysis according to drug type and seasonality. Visual examination of stratified forest plots suggested better IPTi outcomes for clinical malaria in areas of seasonal transmission and where artesunate was utilised in conjunction with SP. However, as only one trial took place in an area of seasonal transmission and this was the same study that used artesunate, the applicability of its results to other settings and drug regimens may be limited.

Overall, intermittent treatment reduced the incidence of clinical malaria in infants, regardless of the seasonality of transmission or the drug regimen used. The intervention also reduced the incidence of severe anaemia, hospital admissions and parasitaemia. Where trials were stratified according to iron supplementation, there was no difference between those studies that included iron and those that did not on the incidence of clinical malaria. The provision of supplemental iron was, however, associated with a reduced incidence of severe anaemia while trials without an iron supplement had no significant effect on this outcome.

The review did not provide evidence that intermittent treatment of infants had any effect on death rate. This may have been due to the low number of reported deaths and the trials being insufficiently powered to detect this outcome; death was not declared as a primary outcome for any of the included studies.

A key concern with the use of intermittent treatment for the prevention of malaria in infants is that it may prevent the development of natural immunity, putting the child at risk of rebound (an increase in malaria-associated morbidity and/or mortality) once treatment ends. Four of the included studies used extended periods of follow-up in an attempt to detect rebound but no significant increase in clinical malaria, severe anaemia, deaths or hospital admissions were observed. A small but significant increase in parasitaemia was detected in the treatment group, suggesting that the risk of developing ≥5000 parasites per µl of blood was greater after the intervention period for those who had received IPT. However, this was the only evidence of potential rebound identified by the review.

Although one benefit of IPTi is that it may be given at the same time as routine childhood vaccinations, there exists uncertainty as to whether the use of antimalarials might negatively affect the development of post-vaccination immunity if the two treatments are given concurrently (O'Meara *et al*., 2005). Although limited data was available for review there was no evidence to suggest that the SP had any effect on subsequent antibody titres for measles, tetanus, diphtheria, polio or hepatitis B, although data for other antimalarials were not available.

This systematic review has demonstrated that evidence from randomised, controlled trials supports the use of intermittent preventative treatment of infants to reduce the incidence of clinical malaria, severe anaemia (in conjunction with supplemental iron) and hospital admissions. However, the review has not found any evidence that the use of IPT reduces mortality in infants and this will remain an unanswered question until further data becomes available from studies adequately powered to detect this outcome. It is also hoped that future studies will evaluate issues such as the effect of IPTi on parasite resistance, the efficacy and practicality of drugs other than SP and the long-term safety of the intervention. In order to be of practical value, there would also need to be an economic evaluation of the intervention to evaluate its cost-effectiveness, not least because of the seeming lack of effectiveness of IPTi at reducing infant mortality.

Implications for practice

While there is no evidence to suggest that the use of IPTi reduces mortality, there is strong evidence that its use reduces the incidence of clinical malaria and therefore of morbidity amongst infants. The use of IPTi appears safe based on current data and no evidence of anticipated rebound was identified in this review. The clinical effectiveness and safety of the intervention mean that its use in conjunction with routine infant vaccinations may have the potential to provide important public health benefits.

As no evidence was found in this review that the use of an antimalarial without iron supplementation protects against severe anaemia, iron should be provided where anaemia is a concern. However, as iron supplementation made no demonstrable difference to the incidence of clinical malaria, there was no evidence from this review to suggest that its inclusion in treatment would be beneficial in settings where clinical malaria was the principal outcome of interest.

Although IPTi appears promising, there remain many uncertainties regarding its use. Whether or not it would actually reduce infant mortality, speed up drug resistance or interfere with immune response to vaccinations are still unclear. Until further studies have evaluated these factors, for a range of antimalarials, it may not be appropriate to adopt the intervention on a large scale.

Implications for research

Much further work is needed in the evaluation of IPTi as an effective public health intervention. All included studies, other than Massaga *et al*. (2006), used SP either alone or in combination with artesunate (Cissé *et al.*, 2006). SP works well for IPT as it is long-lasting and provides an extended period of protection in comparison to other drugs, such as artesunate (Shanks, 2006). Also, unlike alternatives such as AQ, SP can be given in a single dose rather than over several days (Nsimba *et al*., 2008), making it ideal for single visit directly observed use. However, resistance to SP is quick to develop and is spreading across Africa (Ekland & Fidock, 2008), which may mean that the remaining effective lifespan of the drug could be very limited. More work may be necessary to evaluate the use of drugs other than SP for IPTi as the drug may be of little value once local resistance is established.

More data are also required to properly evaluate whether there would be any affect of using antimalarials at vaccination on the subsequent development of antibodies. Only two studies used in this review reported on response to IPT of post-vaccination antibody titres and only Macete *et al*. (2006) provided data for a range of different vaccinations. Although there does not appear to be a negative interaction based on current data, there is still much uncertainty which requires resolution.

Most of the evidence identified by this review was related to the use of IPTi in settings where malaria transmission is perennial. The only trial to consider IPTi in an area of seasonal transmission was Cissé *et al.* (2006) and this study used the highly effective drug combination of artesunate and SP. Munday (2007) states that the burden of malaria tends to shift towards older children in areas of seasonal transmission. In addition, the other trials used either SP or AQ alone and for these reasons the studies are difficult to compare. Additional trials within areas of seasonal malaria transmission and using a range of antimalarials could help to provide the data necessary to address this issue.

It may also be of value to consider the potential interactions of innate parasite resistance within certain host populations. For example, there is evidence that communities with a high prevalence of thalassaemia demonstrate improved

resistance to severe malaria caused by *P. falciparum* (Mockenhaupt et al., 2001), although this effect may only be significant in older children and adults (Enevold *et al*., 2008).

CONCLUSIONS

The use of intermittent preventative treatment of infants for the prevention of malaria shows much promise. This review finds evidence that its use reduces the incidence of clinical malaria without interfering with immune response to vaccinations or increasing the risk of malaria once treatment has ended. However, the term IPTi is rather broad in that it includes a range of settings, transmission profiles, antimalarial drugs and concurrent interventions, such as the provision of iron supplementation. This review has attempted to tease out some of these factors by stratifying data according to seasonality, drug type and the use of supplemental iron. A clearer picture has emerged as a result but so has the realisation that there is a very real shortage of appropriate studies to inform public health decision makers. To make the situation even more complex, the continual development and spread of drug resistance may mean that once sufficient evidence becomes available, the situation on the ground may have changed and drugs that had previously been effective no longer are. Although the use of SP may be convenient from a cost and management perspective, it cannot be relied upon to always be so. If other drugs then become relied upon for intermittent treatment, health planners need to know if this use risks impacting on the susceptibility of *P. falciparum* to first line, curative treatments.

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TABLES

Table 01. Characteristics of included studies

Study	**Chandramohan *et al*. (2005)**
Methods	Cluster randomised controlled trial Length of follow up: 21 months
Participants	Number enrolled: 2485 infants Inclusion criteria: Infants living permanently in the study area and aged 3 months
Interventions	Intermittent treatment when receiving DPT-2, DPT-3 or measles vaccinations and at 12 months of age (1) Sulfadoxine-pyrimethamine: one tablet; 1243 infants (2) Placebo: 1242 infants (3) Iron: 2.5 ml (15mg elemental iron) twice weekly for four weeks; 2485 infants
Outcomes	(1) Clinical episodes of malaria (2) Severe anaemia (3) Hospital admissions
Notes	Location: Kassena-Nankana district, Ghana Malaria transmission: Seasonal
Allocation concealment	Double-blinded

Study	**Cissé *et al*. (2006)**
Methods	Randomised controlled trial Length of follow up: 13 weeks
Participants	Number enrolled: 1136 children Inclusion criteria: Children living permanently in the study area and aged between 2 and 59 months Exclusion criteria: Severe malaria or other severe conditions
Interventions	Intermittent treatment once a month for three months (1) Sulfadoxine-pyrimethamine: (25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine); plus artesunate: 4mg/kg ; 542 children (2) Placebo: 546 children
Outcomes	(1) Clinical episodes of malaria
Notes	Location: Niakhar district, Senegal Malaria transmission: Seasonal

Allocation concealment	Double-blinded

Study	**Grobusch *et al*. (2007)**
Methods	Randomised controlled trial Length of follow up: 18 months
Participants	Number enrolled: 1189 infants Inclusion criteria: Infants living permanently in the study area, aged 3 months, not reporting allergies to sulfa drugs and with no history of severe hepatic or renal dysfunction
Interventions	Intermittent treatment at 3, 9 and 15 months of age (1) Sulfadoxine-pyrimethamine: Half a tablet (250 mg sulfadoxine and 12.5 mg pyrimethamine); 594 infants (2) Placebo: 595 infants
Outcomes	(1) Clinical episodes of malaria (2) Severe anaemia
Notes	Location: Lambaréné, Moyen Ogooné province, Gabon Malaria transmission: Perennial
Allocation concealment	Double-blinded

Study	**Kobbe *et al*. (2007a)**
Methods	Randomised controlled trial Length of follow up: 21 months
Participants	Number enrolled: 1070 infants Inclusion criteria: Infants living permanently in the study area and aged 3 months
Interventions	Intermittent treatment at 3, 9 and 15 months of age (1) Sulfadoxine-pyrimethamine: 250 mg sulfadoxine and 12.5 mg pyrimethamine; 535 infants (2) Placebo: 535 infants
Outcomes	(1) Clinical episodes of malaria (2) Severe anaemia (3) Hospitalisation (4) Death
Notes	Location: Afigya Sekyere district, Ashanti region, Ghana Malaria transmission: Holoendemic. Perennial with seasonal peaks
Allocation concealment	Double-blinded

Study	**Macete *et al*. (2006)**
Methods	Randomised controlled trial Length of follow up: 1 year
Participants	Number enrolled: 1503 infants Inclusion criteria: Infants living permanently in the study area, aged 3 months, not reporting allergies to sulfa drugs and not requiring hospital admission
Interventions	Intermittent treatment at 3, 4 and 9 months of age (1) Sulfadoxine-pyrimethamine: >5kg, one quarter tablet; 5-10kg, one half-tablet; >10kg, one tablet; 748 infants (2) Placebo: 755 infants
Outcomes	(1) Clinical episodes of malaria (2) Severe anaemia (3) Hospital admissions
Notes	Location: Manhiça district, Maputo Province, Mozambique Malaria transmission: Perennial
Allocation concealment	Double-blinded

Study	**Massaga *et al*. (2003)**
Methods	Randomised controlled trial Length of follow up: 300 days
Participants	Number enrolled: 291 infants Inclusion criteria: Infants living permanently in the study area and aged 12 to 16 weeks attending clinic for growth monitoring or to receive their third pertussis-tetanus-poliovirus vaccination
Interventions	Intermittent treatment every sixty days with iron supplementation provided daily (1) Amodiaquine: Given over three days in doses of 10 mg/kg, 10 mg/kg and 5 mg/kg; 74 infants (2) Amodiaquine plus iron: Amodiaquine over three days in doses of 10 mg/kg, 10 mg/kg and 5 mg/kg, and iron as 2.5 mL ferric ammonium citrate (3 mg elemental iron/mL); 72 infants (3) Iron: 2.5 mL ferric ammonium citrate (3 mg elemental iron/mL) daily; 73 infants (4) Placebo: 72 infants

Outcomes	(1) Clinical episodes of malaria (2) Severe anaemia (3) Hospital admissions
Notes	Location: Muheza district, Tanzania Malaria transmission: Perennial/holoendemic with seasonal peaks
Allocation concealment	Double-blinded

Study	**Mockenhaupt *et al.* (2007)**
Methods	Randomised controlled trial Length of follow up: 2 years
Participants	Number enrolled: 1200 infants Inclusion criteria: Infants living permanently in the study area and aged 3 months
Interventions	Intermittent treatment at 3, 9 and 15 months of age (1) Sulfadoxine-pyrimethamine: Half a tablet (125 mg sulfadoxine and 6.25 mg pyrimethamine); 600 infants (2) Placebo: 600 infants
Outcomes	(1) Clinical episodes of malaria (2) Severe anaemia
Notes	Location: Tamale, Ghana Malaria transmission: Hyperendemic/perennial with modest seasonal variation
Allocation concealment	Double-blinded

Study	**Schellenberg *et al*. (2001)**
Methods	Randomised controlled trial Length of follow up: 18 months
Participants	Number enrolled: 701 infants aged 2, 3 and 9 months attending immunization clinics for a second dose of diphtheria-pertussis-tetanus vaccine Inclusion criteria: Infants living permanently in the study area and having just received second dose of diphtheria-pertussis-tetanus vaccine and oral poliovirus vaccine. Exclusion criteria: Infants with illness requiring hospital admission
Interventions	Intermittent treatment at 2, 3 and 9 months of age

	(1) Sulfadoxine-pyrimethamine: 25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine; infants >5kg, one quarter tablet; infants 5-10kg, one half-tablet; infants >10kg, one tablet; 350 infants (2) Placebo: 351 infants (3) Iron (ferrous sulphate): 0.5 ml/day (125g/L); 701 infants
Outcomes	(1) Clinical episodes of malaria (2) Severe anaemia (3) Hospital admissions
Notes	Location: Ifakara, Tanzania Malaria transmission: Holoendemic/Perennial
Allocation concealment	Double-blinded

Study	**Schellenberg *et al*. (2005)**
Methods	Randomised controlled trial Length of follow up: 2 years
Participants	Number enrolled: 555 infants aged 2 years at assessment and 2, 3 and 9 months at treatment during immunization with diphtheria-pertussis-tetanus and measles vaccine Inclusion and exclusion criteria: As for Schellenberg *et al*., 2001
Interventions	Intermittent treatment at 2, 3 and 9 months of age (1) Sulfadoxine-pyrimethamine: 25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine; infants >5kg, one quarter tablet; infants 5-10kg, one half-tablet; infants >10kg, one tablet; 277 infants (2) Placebo: 278 infants (3) Iron (ferrous sulphate): 0.5 ml/day (125g/L); 701 infants
Outcomes	(1) Clinical episodes of malaria (2) Severe anaemia Assessed at 24 months of age
Notes	Location: Ifakara, Tanzania Malaria transmission: Perrenial/holoendemic The trial population was the same as Schellenberg *et al*. (2001) and this study represents an extended period of follow up.
Allocation concealment	Double-blinded

Table 02. Characteristics of excluded studies

Study	Reason for exclusion
Cairns *et al*., 2008	Reported on protective efficacy only. Data not extractable
Desai *et al*., 2003	Evaluated children up to 3 years of age
Egan *et al*., 2005	Not a randomised, controlled trial (editorial)
Gosling et al., 2008	Not a randomised, controlled trial (review article)
Greenwood, 2006	Not a randomised, controlled trial (review article)
Kobbe *et al*., 2007b	Evaluated spatial-temporal relationships. Data not extractable
Menendez *et al*., 2007	Comparative analysis of two included trials.
Meremikwu *et al*., 2008	Not a randomised, controlled trial (systematic review)
Munday, 2007	Not a randomised, controlled trial (review article)
Ntab *et al*., 2007	The effect of IPT on growth and nutritional status
O'Meara *et al*., 2005	Not a randomised, controlled trial (review article)
Pool *et al*., 2006	Reported on community attitudes to intervention.
Rosen and Breman, 2004	Not a randomised, controlled trial (review article)
Schreiber *et al*., 2007	Reported on immune response only. Data not extractable.
Verhoef *et al*., 2002	Evaluated children with a mean age of approximately 2 years

Table 03. Detailed search strategies

Search set	CDSR*	MEDLINE	EMBASE	LILACS	ScienceDirect
1	malaria	malaria	malaria	malaria	malaria
2	infants	infants	infants	infants	infants
3	intermittent treatment	intermittent treatment	intermittent treatment	intermittent treatment	intermittent treatment
4	IPT	preventative treatment	preventative treatment	preventative treatment	preventative treatment
5	IPTi	presumptive treatment	presumptive treatment	presumptive treatment	presumptive treatment
6		3 or 4 or 5	3 or 4 or 5	3 or 4 or 5	3 or 4 or 5
7		1 and 2 and 6	1 and 2 and 6	1 and 2 and 6	1 and 2 and 6

*Cochrane Database of Systematic Reviews

Table 04. Types of intervention

Trial	No. arms	Intervention	Iron supplementation	ITNs*
Chandramohan *et al.* (2005)	1	Sulfadoxine-pyrimethamine	Yes	No**
	2	Placebo	Yes	No**
Cissé *et al.* (2006)	1	Sulfadoxine-pyrimethamine plus artesunate	No	No
	2	Placebo	No	No
Grobusch *et al.* (2007)	1	Sulfadoxine-pyrimethamine	No	No
	2	Placebo	No	No
Kobbe *et al.* (2007a)	1	Sulfadoxine-pyrimethamine	No	No
	2	Placebo	No	No
Macete *et al.* (2006)	1	Sulfadoxine-pyrimethamine	No	No
	2	Placebo	No	No
Massaga *et al.* (2003)	1	Amodiaquine	Yes	No
	2	Amodiaquine	No	No
	3	Placebo	Yes	No
	4	Placebo	No	No
Mockenhaupt *et al.* (2007)	1	Sulfadoxine-pyrimethamine	No	No
	2	Placebo	No	No
Schellenberg *et al.* (2001)	1	Sulfadoxine-pyrimethamine	Yes	No
	2	Placebo	Yes	No
Schellenberg *et al.* (2005)	1	Sulfadoxine-pyrimethamine	Yes	No
	2	Placebo	Yes	No

* ITNs: Insecticide-treated bed nets provided

** ITNs not provided by the study but where used showed a positive combined effect

Table 05. Methodological quality of included trials

Trial	Sequence	Concealment	Blinding	Primary outcome(s)	No. at follow up	% loss
Chandramohan *et al.* (2005)	Adequate (cluster)	Adequate (identical drugs and placebo)	Double	Clinical malaria , severe anaemia (2485 participants)	2191	12% (inadequate)
Cissé *et al.* (2006)	Adequate (individual)	Adequate (slight taste differences reported)	Double	Clinical malaria (1136 participants)	872	23% (inadequate)
Grobusch *et al.* (2007)	Adequate (block)	Adequate (identical drugs and placebo)	Double	Clinical malaria , severe anaemia (1189 participants)	602	49% (inadequate)
Kobbe *et al.* (2007a)	Adequate (individual)	Adequate (identical drugs and placebo)	Double	Clinical malaria (1070 participants)	887	17% (inadequate)
Macete *et al.* (2006)	Adequate (individual)	Adequate (identical drugs and placebo)	Double	Clinical malaria , severe anaemia (1503 participants)	1375	9% (adequate)
Massaga *et al.* (2003)	Adequate (block)	Adequate (identical drugs and placebo)	Double	Clinical malaria , severe anaemia (291 participants)	216	26% (inadequate)
Mockenhaupt *et al.* (2007)	Adequate (block)	Adequate (identical drugs and placebo)	Double	Clinical malaria , severe anaemia (1200 participants)	1047	13% (inadequate)
Schellenberg *et al.* (2001)	Adequate (block)	Adequate (identical drugs and placebo)	Double	Clinical malaria , severe anaemia (701 participants)	661	6% (adequate)
Schellenberg *et al.* (2005)	Adequate (block)	Adequate (identical drugs and placebo)	Double	Clinical malaria , severe anaemia (555 participants)	555	N/A

ANALYSES

Table 06. Comparison 01: Intermittent treatment versus placebo: Main analysis

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Clinical malaria	6	5518	Risk Ratio (Random) 95% CI	0.55 (0.36 to 0.84)
02 Severe anaemia*	6	7104	Risk Ratio (Fixed) 95% CI	0.75 (0.67 to 0.85)
03 Death from any cause	8	9202	Risk Ratio (Fixed) 95% CI	0.99 (0.78 to 1.26)
04 Hospital admission for any cause	6	7105	Risk Ratio (Random) 95% CI	0.83 (0.74 to 0.92)
05 Parasitaemia*	3	4755	Risk Ratio (Fixed) 95% CI	0.80 (0.76 to 0.84)
06 Protective antibody titres	2	3628	Risk Ratio (Fixed) 95% CI	0.98 (0.97 to 1.00)

Table 07. Comparison 02: Intermittent treatment versus placebo: By seasonality

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Clinical malaria	6	5518	Risk Ratio (Random) 95% CI	0.55 (0.36 to 0.84)
02 Severe anaemia*	6	7104	Risk Ratio (Fixed) 95% CI	0.75 (0.67 to 0.85)

Table 08. Comparison 03: Intermittent treatment versus placebo: By drug

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Clinical malaria	6	5518	Risk Ratio (Random) 95% CI	0.55 (0.36 to 0.84)
02 Severe anaemia*	6	7104	Risk Ratio (Fixed) 95% CI	0.75 (0.67 to 0.85)

Table 09. Comparison 04: Intermittent treatment versus placebo: By iron supplementation

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Clinical malaria	7	5662	Risk Ratio (Random) 95% CI	0.55 (0.38 to 0.80)
02 Severe anaemia*	7	7248	Risk Ratio (Random) 95% CI	0.71 (0.57 to 0.88)

Table 10. Comparison 05: Intermittent treatment versus placebo: Impact after stopping intervention

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Clinical malaria	4	5164	Risk Ratio (Random) 95% CI	1.01 (0.93 to 1.10)
02 Severe anaemia*	4	5164	Risk Ratio (Fixed) 95% CI	0.97 (0.84 to 1.11)
03 Death from any cause	3	4609	Risk Ratio (Fixed) 95% CI	0.98 (0.66 to 1.47)
04 Hospital admission for any cause	2	3555	Risk Ratio (Fixed) 95% CI	1.02 (0.84 to 1.25)
05 Parasitaemia*	2	3555	Risk Ratio (Fixed) 95% CI	1.12 (1.02 to 1.23)
06 Protective measles antibody titres**	1	317	Risk Ratio (Fixed) 95% CI	0.94 (0.87 to 1.02)

*Total events

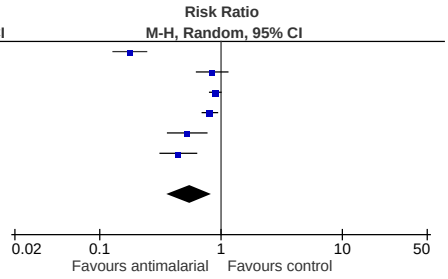
**Derived from a sample of the study population

GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01: Intermittent treatment versus placebo: Main analysis. Outcome 01 Clinical malaria

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Cisse et al., 2006	39	542	222	546	16.3%	0.18 [0.13, 0.24]
Grobusch et al., 2007	68	504	81	507	16.5%	0.84 [0.63, 1.14]
Kobbe et al., 2007	278	535	310	535	17.8%	0.90 [0.80, 1.00]
Macete et al., 2006	221	748	276	755	17.6%	0.81 [0.70, 0.93]
Massaga et al., 2003	24	73	45	72	15.8%	0.53 [0.36, 0.76]
Schellenberg et al., 2001	39	350	88	351	16.0%	0.44 [0.31, 0.63]
Total (95% CI)		**2752**		**2766**	**100.0%**	**0.55 [0.36, 0.84]**
Total events	669		1022			

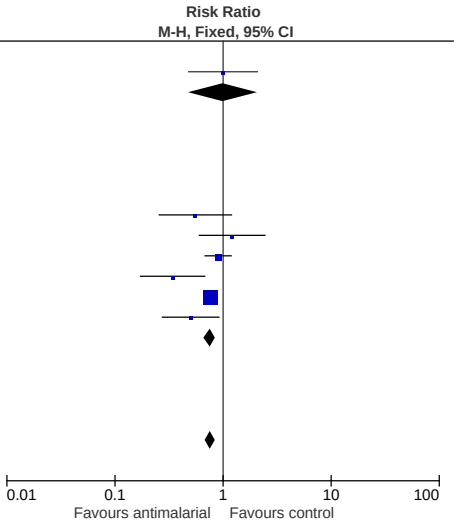
Heterogeneity: Tau² = 0.25; Chi² = 113.12, df = 5 (P < 0.00001); I² = 96%
Test for overall effect: Z = 2.80 (P = 0.005)



Analysis 01.02. Comparison 01: Intermittent treatment versus placebo: Main analysis. Outcome 02 Severe anaemia

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 First or single event						
Kobbe et al., 2007	14	535	14	535	2.9%	1.00 [0.48, 2.08]
Subtotal (95% CI)		**535**		**535**	**2.9%**	**1.00 [0.48, 2.08]**
Total events	14		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
1.2.2 Total events						
Chanramohan et al., 2005	10	1243	18	1242	3.8%	0.56 [0.26, 1.20]
Kobbe et al., 2007	17	535	14	535	2.9%	1.21 [0.60, 2.44]
Macete et al., 2006	83	748	93	755	19.4%	0.90 [0.68, 1.19]
Massaga et al., 2003	9	73	26	72	5.5%	0.34 [0.17, 0.68]
Mockenhaupt et al., 2007	215	600	283	600	59.2%	0.76 [0.66, 0.87]
Schellenberg et al., 2001	15	350	30	351	6.3%	0.50 [0.27, 0.92]
Subtotal (95% CI)		**3549**		**3555**	**97.1%**	**0.75 [0.67, 0.85]**
Total events	349		464			
Heterogeneity: Chi² = 10.90, df = 5 (P = 0.05); I² = 54%						
Test for overall effect: Z = 4.74 (P < 0.00001)						
Total (95% CI)		**4084**		**4090**	**100.0%**	**0.76 [0.68, 0.85]**
Total events	363		478			

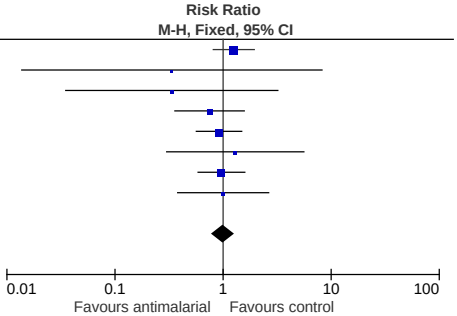
Heterogeneity: Chi² = 11.44, df = 6 (P = 0.08); I² = 48%
Test for overall effect: Z = 4.63 (P < 0.00001)



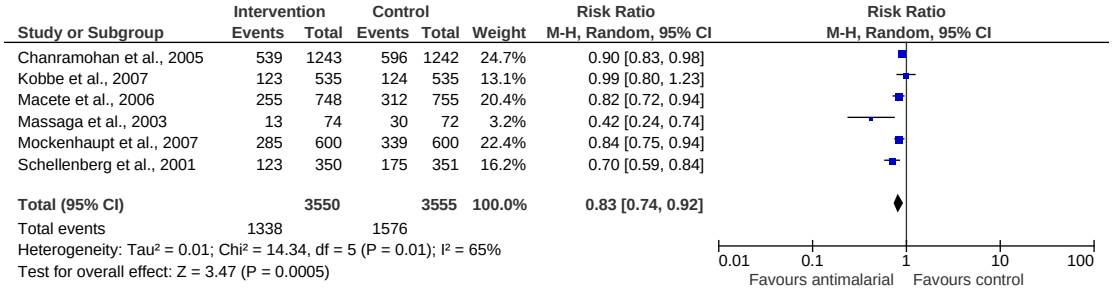
Analysis 01.03. Comparison 01: Intermittent treatment versus placebo: Main analysis. Outcome 03 Death from any cause

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chanramohan et al., 2005	44	1243	35	1242	27.1%	1.26 [0.81, 1.94]
Cisse et al., 2006	0	542	1	546	1.2%	0.34 [0.01, 8.22]
Grobusch et al., 2007	1	504	3	507	2.3%	0.34 [0.03, 3.21]
Kobbe et al., 2007	12	535	16	535	12.4%	0.75 [0.36, 1.57]
Macete et al., 2006	30	748	33	755	25.4%	0.92 [0.57, 1.49]
Massaga et al., 2003	4	74	3	72	2.4%	1.30 [0.30, 5.59]
Mockenhaupt et al., 2007	29	600	30	600	23.2%	0.97 [0.59, 1.59]
Schellenberg et al., 2001	8	350	8	351	6.2%	1.00 [0.38, 2.64]
Total (95% CI)		**4596**		**4608**	**100.0%**	**0.99 [0.78, 1.26]**
Total events	128		129			

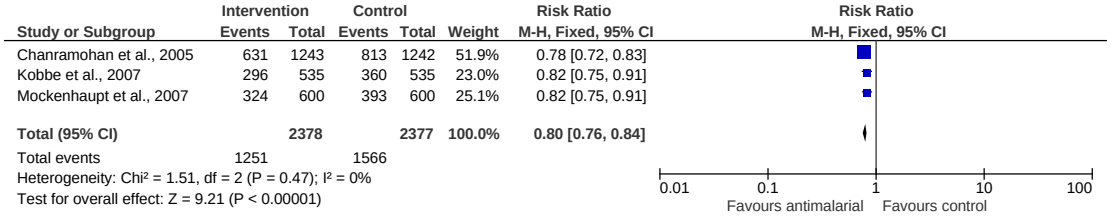
Heterogeneity: Chi² = 3.24, df = 7 (P = 0.86); I² = 0%
Test for overall effect: Z = 0.05 (P = 0.96)



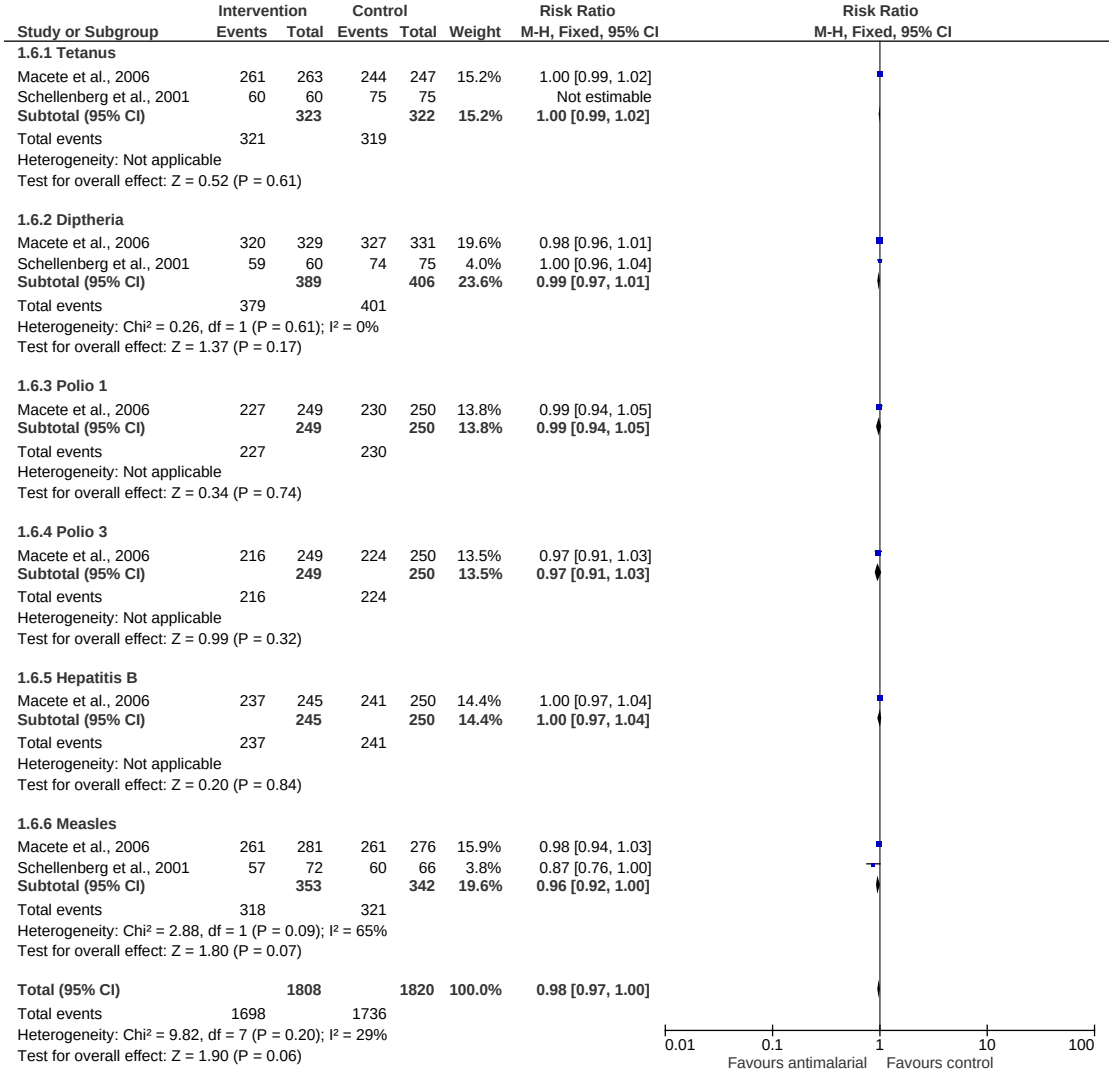
Analysis 01.04. Comparison 01: Intermittent treatment versus placebo: Main analysis. Outcome 04 Hospital admission for any cause



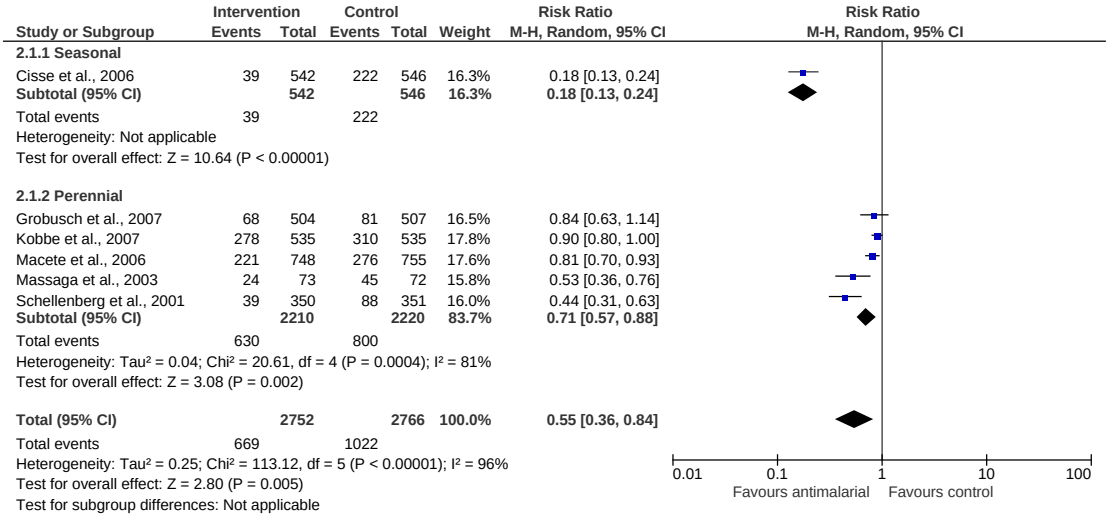
Analysis 01.05. Comparison 01: Intermittent treatment versus placebo: Main analysis. Outcome 05 Parasitaemia



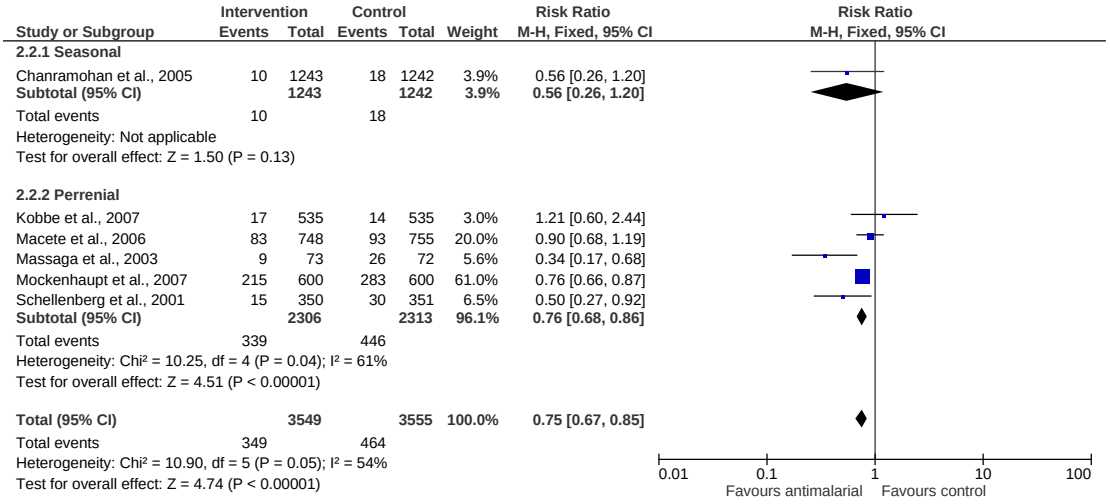
Analysis 01.06. Comparison 01: Intermittent treatment versus placebo: Main analysis. Outcome 05 Protective antibody titres



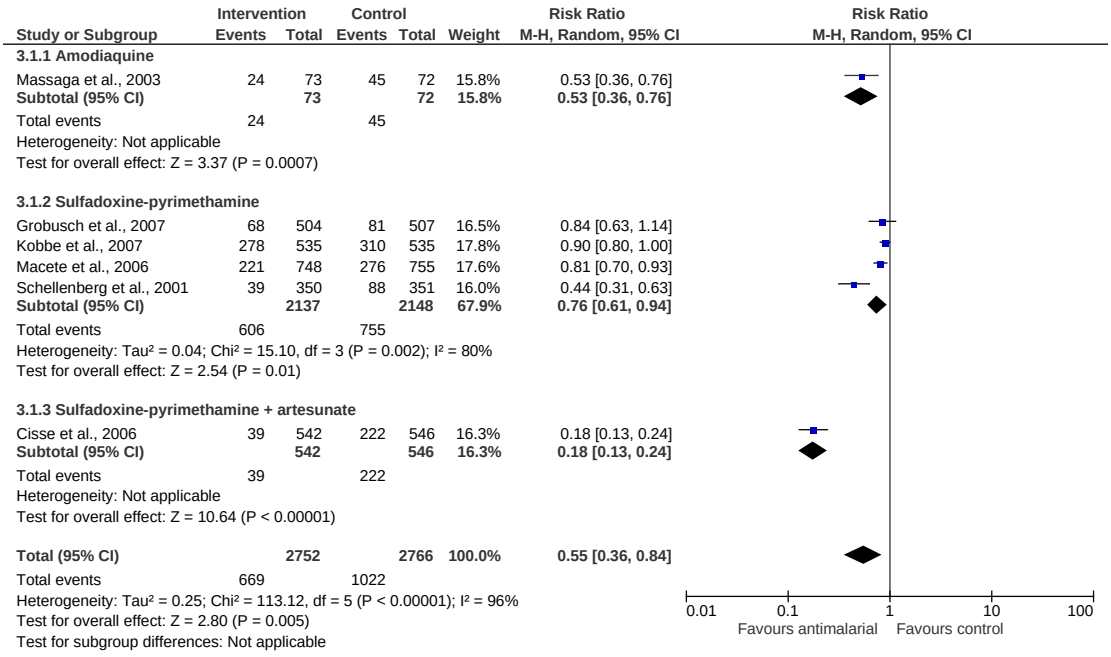
Analysis 02.01. Comparison 02: Intermittent treatment versus placebo: By seasonality. Outcome 01 Clinical malaria



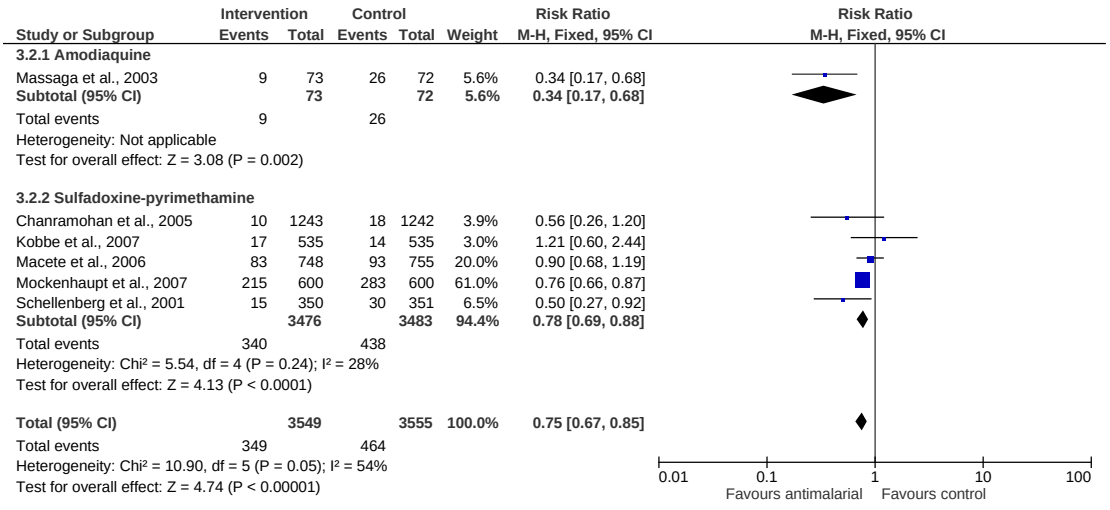
Analysis 02.02. Comparison 02: Intermittent treatment versus placebo: By seasonality. Outcome 02 Severe anaemia



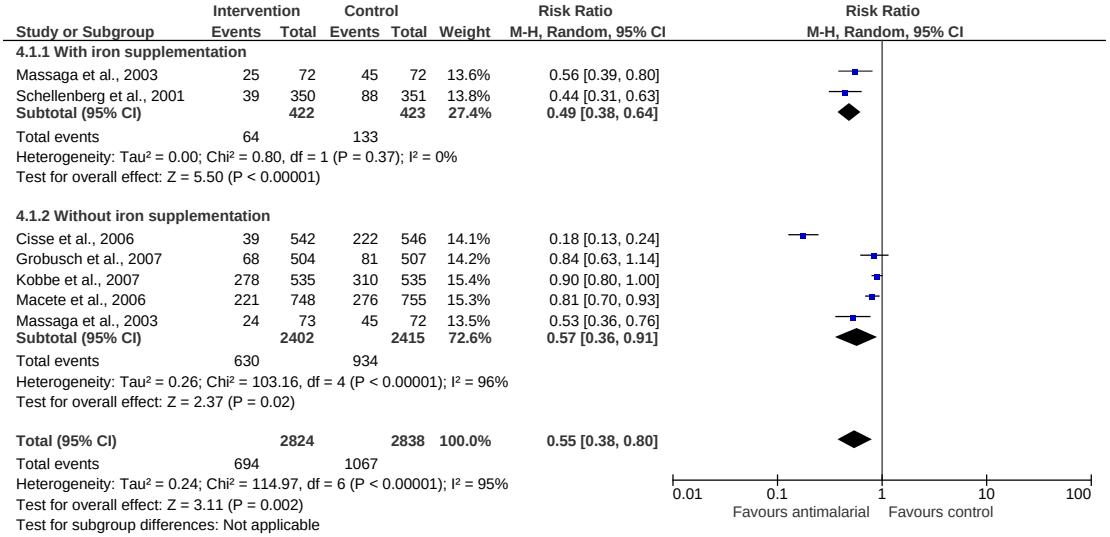
Analysis 03.01. Comparison 03: Intermittent treatment versus placebo: By drug. Outcome 01 Clinical malaria



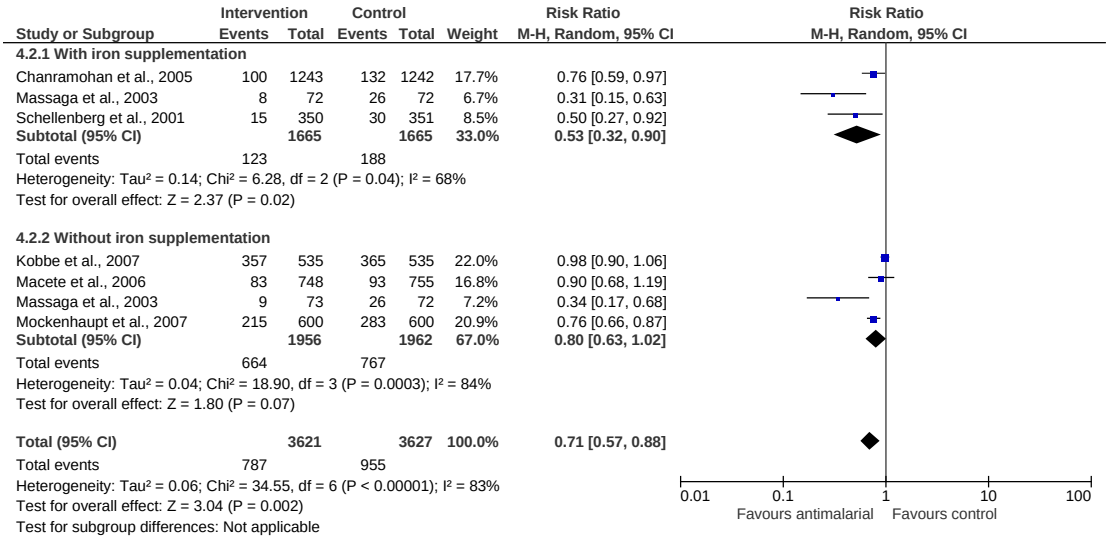
Analysis 03.02. Comparison 03: Intermittent treatment versus placebo: By drug. Outcome 02 Severe anaemia



Analysis 04.01. Comparison 04: Intermittent treatment versus placebo: Iron supplementation. Outcome 01 Clinical malaria

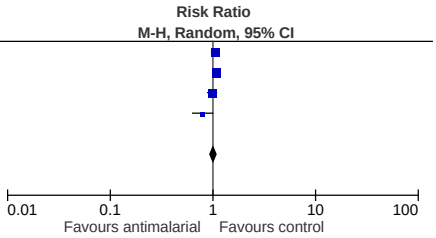


Analysis 04.02. Comparison 04: Intermittent treatment versus placebo: Iron supplementation. Outcome 02 Severe anaemia



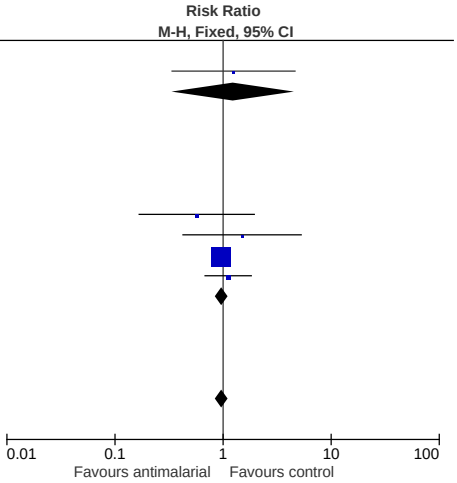
Analysis 05.01. Comparison 05: Intermittent treatment versus placebo: Impact after stopping intervention. Outcome 01 Clinical malaria

Study or Subgroup	Intervention Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Chanramohan et al., 2005	609	1243	579	1242	30.5%	1.05 [0.97, 1.14]
Kobbe et al., 2007	396	535	365	535	31.7%	1.08 [1.00, 1.17]
Mockenhaupt et al., 2007	311	525	319	529	27.0%	0.98 [0.89, 1.08]
Schellenberg et al., 2005	88	277	111	278	10.7%	0.80 [0.64, 1.00]
Total (95% CI)		**2580**		**2584**	**100.0%**	**1.01 [0.93, 1.10]**
Total events	1404		1374			
Heterogeneity: Tau² = 0.00; Chi² = 8.10, df = 3 (P = 0.04); I² = 63%						
Test for overall effect: Z = 0.27 (P = 0.79)						



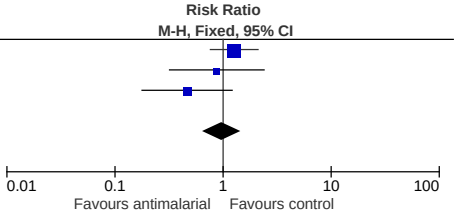
Analysis 05.02. Comparison 05: Intermittent treatment versus placebo: Impact after stopping intervention. Outcome 02 Severe anaemia

Study or Subgroup	Intervention Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.2.1 First or single event						
Kobbe et al., 2007	5	535	4	535	1.5%	1.25 [0.34, 4.63]
Subtotal (95% CI)		**535**		**535**	**1.5%**	**1.25 [0.34, 4.63]**
Total events	5		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						
5.2.2 Total events						
Chanramohan et al., 2005	4	1243	7	1242	2.7%	0.57 [0.17, 1.95]
Kobbe et al., 2007	6	535	4	535	1.5%	1.50 [0.43, 5.29]
Mockenhaupt et al., 2007	208	525	220	529	83.9%	0.95 [0.82, 1.10]
Schellenberg et al., 2005	30	277	27	278	10.3%	1.12 [0.68, 1.82]
Subtotal (95% CI)		**2580**		**2584**	**98.5%**	**0.97 [0.84, 1.11]**
Total events	248		258			
Heterogeneity: Chi² = 1.54, df = 3 (P = 0.67); I² = 0%						
Test for overall effect: Z = 0.46 (P = 0.65)						
Total (95% CI)		**3115**		**3119**	**100.0%**	**0.97 [0.85, 1.12]**
Total events	253		262			
Heterogeneity: Chi² = 1.69, df = 4 (P = 0.79); I² = 0%						
Test for overall effect: Z = 0.40 (P = 0.69)						

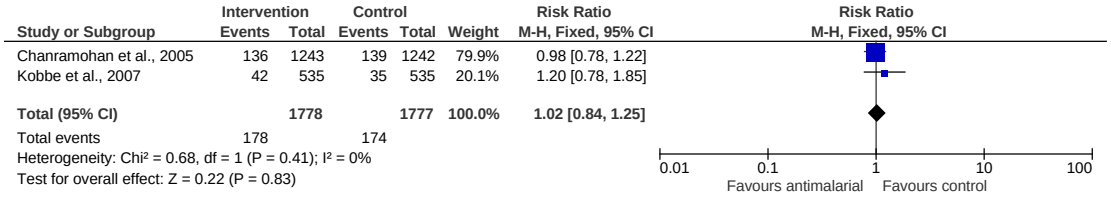


Analysis 05.03. Comparison 05: Intermittent treatment versus placebo: Impact after stopping intervention. Outcome 03 Death from any cause

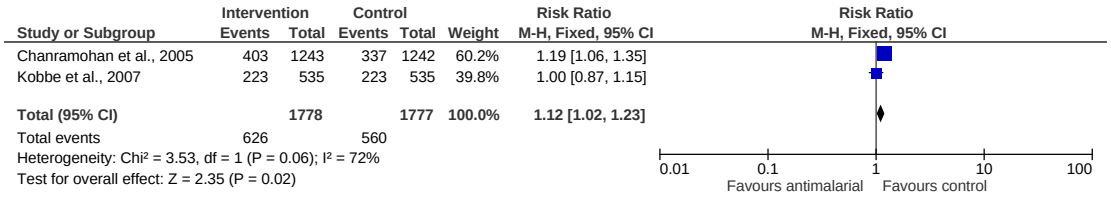
Study or Subgroup	Intervention Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chanramohan et al., 2005	33	1243	26	1242	55.4%	1.27 [0.76, 2.11]
Kobbe et al., 2007	7	535	8	535	17.0%	0.88 [0.32, 2.40]
Mockenhaupt et al., 2007	6	525	13	529	27.6%	0.47 [0.18, 1.21]
Total (95% CI)		**2303**		**2306**	**100.0%**	**0.98 [0.66, 1.47]**
Total events	46		47			
Heterogeneity: Chi² = 3.36, df = 2 (P = 0.19); I² = 40%						
Test for overall effect: Z = 0.10 (P = 0.92)						



Analysis 05.04. Comparison 05: Intermittent treatment versus placebo: Impact after stopping intervention. Outcome 04 Hospital admission for any cause



Analysis 05.05. Comparison 05: Intermittent treatment versus placebo: Impact after stopping intervention. Outcome 05 Parasitaemia



Analysis 05.06. Comparison 05: Intermittent treatment versus placebo: Impact after stopping intervention. Outcome 06 Protective measles antibody titres