Primaquine for reducing *Plasmodium falciparum* transmission (Review)

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This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2012, Issue 9

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[Intervention Review]

Primaquine for reducing *Plasmodium falciparum* transmission

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Editorial group: Cochrane Infectious Diseases Group.
Publication status and date: New, published in Issue 9, 2012.
Review content assessed as up-to-date: 5 July 2012.

Citation: Graves PM, Gelband H, Garner P. Primaquine for reducing *Plasmodium falciparum* transmission. *Cochrane Database of Systematic Reviews* 2012, Issue 9. Art. No.: CD008152. DOI: 10.1002/14651858.CD008152.pub2.

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ABSTRACT

Background

Mosquitoes become infected with malaria when they ingest gametocyte stages of the parasite from the blood of a human host. *Plasmodium falciparum* gametocytes are sensitive to the drug primaquine (PQ). The World Health Organization (WHO) recommends giving a single dose or short course of PQ alongside primary treatment for people ill with *P. falciparum* infection to reduce malaria transmission. Gametocytes themselves cause no symptoms, so this intervention does not directly benefit individuals. PQ causes haemolysis in some people with glucose-6-phosphate dehydrogenase (G6PD) deficiency so may not be safe.

Objectives

To assess whether a single dose or short course of PQ added to treatments for malaria caused by *P. falciparum* infection reduces malaria transmission and is safe.

Search methods

We searched the following databases up to 10 April 2012 for studies: the Cochrane Infectious Diseases Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library*; MEDLINE; EMBASE; LILACS; *meta*Register of Controlled Trials (*m*RCT) and the WHO trials search portal using 'malaria*', 'falciparum', and 'primaquine' as search terms. In addition, we searched conference proceedings and reference lists of included studies, and we contacted likely researchers and organizations for relevant trials.

Selection criteria

Trials of mass treatment of whole populations (or actively detected fever or malaria cases within such populations) with antimalarial drugs, compared to treatment with the same drug plus PQ; or patients with clinical malaria being treated for malaria at health facilities randomized to short course/single dose PQ versus no PQ.

Data collection and analysis

Two authors (PMG and HG) independently screened all abstracts, applied inclusion criteria, and abstracted data. We sought data on the effect of PQ on malaria transmission intensity, participant infectiousness, the number of participants with gametocytes, and gametocyte density over time. We stratified results by primary treatment drug as this may modify any PQ effect. We calculated the area under the curve (AUC) for gametocyte density over time for comparisons for which data were available, and also sought data on

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haematologic and other adverse effects. We used GRADE guidelines to assess evidence quality, and this is reflected in the wording of the results: high quality ("PQ reduces ...."); moderate quality ("PQ probably reduces ..."); low quality ("PQ may reduce...."); and very low quality ("we don't know if PQ reduces....").

Main results

We included 11 individually randomized trials, with a total of 1776 individuals. The 11 trials included 20 comparisons with partner drugs, which included chloroquine (CQ), sulfadoxine-pyrimethamine (SP), mefloquine (MQ), quinine (QN), artesunate (AS), and a variety of artemisinin combination therapies (ACTs). For G6PD deficiency, studies either did not test (one study), tested and included all (one study), included only G6PD deficient (one study), excluded G6PD deficient (two studies), or made no comment (six studies).

None of the trials we included assessed effects on malaria transmission (incidence, prevalence, or entomological inoculation rate (EIR)) in the trial area.

With non-artemisinin drug regimens, PQ may reduce the infectiousness to mosquitoes of individuals treated, based on one small study with large effects (Risk Ratio (RR) 0.06 on day 8 after treatment, 95% confidence interval (CI) 0 to 0.89; low quality evidence). Participants who received PQ had fewer circulating gametocytes up to day 43 (log(10) AUC relative decrease from 24.3 to 27.1%, one study (two comparisons), moderate quality evidence); and there were 38% fewer people with gametocytes on day 8 (RR 0.62, 95% CI 0.51 to 0.76, four studies (five comparisons), moderate quality evidence). We did not identify any study that looked for effects of the drug on haemolytic anaemia.

With artemisinin-based drug regimens, we do not know if PQ influences infectiousness to mosquitoes, as no study has examined this directly. PQ probably reduces infectiousness, based on reduction in log(10) AUC (relative decrease range from 26.1% to 87.5%, two studies (six comparisons), moderate quality evidence); and reduces by 88% the number of participants with gametocytes on day 8 (RR 0.12, 95% CI 0.08 to 0.20, four studies (eight comparisons), moderate quality evidence).

When used with artemisinin-based regimens, we do not know if PQ results in haemolytic anaemia; one trial reported percent change in mean haemoglobin against baseline, and for the PQ group this indicated a significantly greater drop at day 8 in those given PQ (very low quality evidence). Overall, the safety of PQ used in single dose or short course was poorly evaluated.

Authors' conclusions

We do not know whether PQ added to treatment regimens for patients with *P. falciparum* infection reduces transmission of malaria. In individual patients, it reduces gametocyte prevalence and density. In practical terms, even if PQ results in large reductions in gametocytes in people being treated for malaria, there is no reliable evidence that this will reduce transmission in a malaria-endemic community, where many people are infected but have no symptoms and are unlikely to be treated. Since PQ is acting as a monotherapy against gametocytes, there is a risk of the parasite developing resistance to the drug. In terms of harms, there is insufficient evidence from trials to know whether the drug can be used safely in this way in populations where G6PD deficiency occurs.

In light of these doubts about safety, and lack of evidence of any benefit in reducing transmission, countries should question whether to continue to use PQ routinely in primary treatment of malaria. Further synthesis of observational data on safety and new trials may help elucidate a role for PQ in malaria elimination, or in situations where most infected individuals are symptomatic and receive treatment.

PLAIN LANGUAGE SUMMARY

Should people treated for malaria caused by *P. falciparum* infection take a single dose of primaquine along with primary treatment?

Drugs that cure malaria caused by *P. falciparum* infection do not necessarily directly affect the gametocyte, which is the stage of the parasite that infects mosquitoes to complete the transmission cycle. Primaquine (PQ), a drug with antimalarial properties, does not cure *P. falciparum* infection but does kill *P. falciparum* gametocytes. Because of this property, this drug has long been recommended as a single dose or short course add-on to *P. falciparum* infection treatment regimens. It is now recommended by the World Health Organization (WHO) and several national malaria control programs, with the intention of reducing community level malaria transmission. However, this drug also has potentially serious side effects in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency, a common genetic variant. When they take this drug it may cause haemolysis (disintegration of red blood cells) which can be serious. This review examines the evidence of benefits and harms of PQ from trials where it has been used as an additional treatment intended to prevent malaria transmission.

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We found no studies testing whether the drug influences transmission intensity of malaria, and just one small study suggesting it reduces the infectiousness of the parasite present in infected people to the mosquito. PQ probably reduces the potential infectiousness of the parasite in people, as measured by the numbers of gametocytes circulating in the blood for up to six weeks after treatment. Regarding safety, one study reported that there was a greater reduction in haemoglobin values in the PQ group at day 8, so the safety of the drug remains uncertain if given to populations where G6PD occurs. Evidence of benefit and of safety is insufficient to recommend routine use of PQ as an add-on for people being treated for malaria.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Primaquine for preventing infectiousness with ACT treatments

Patient or population: patients with symptomatic malaria
Settings: endemic malarial areas
Intervention: primaquine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk Primaquine				
Malaria incidence, prevalence or EIR - not measured				0 studies		
People infectious to mosquitoes - not measured				0 studies		
Gametocytaemia Log(10) area under curve of density over time. Scale from: 0 to 100. Follow-up: 43 days			Relative decrease ranged from 26.1 to 87.5%	907 (2 studies[1])	⊕⊕⊕◯ **moderate**[2]	
Participants with gametocytes Microscopy Follow-up: 8 days	**242 per 1000**	**36 per 1000** (22 to 58)	**RR 0.15** (0.09 to 0.24)	1006 (4 studies[3])	⊕⊕⊕◯ **moderate**[4,5]	
Mean percent change in haemoglobin[6] Follow-up: 28 days	The mean percent change in haemoglobin in the control groups was **0.03 % change**	The mean percent change in haemoglobin in the intervention groups was **0.06 lower**		101 (1 study)	⊕◯◯◯ **very low**[7,8]	

		(0.11 to 0.02 lower)		

*The basis for the **assumed risk** (eg the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Includes two trials with six comparisons. We excluded one trial as high risk of bias (Vasquez 2009) due to small sample size and large difference in baseline gametocyte count in the two groups

[2] Downgraded by 1 for imprecision: wide range of estimates in two trials (six comparisons)

[3] Includes four trials, with eight comparisons: one trial included five separate comparisons with AS-AQ, DHAP, AS-MQ, and AL (Smithuis 2010)

[4] No serious risk of bias: two studies did not conceal allocation but these trials report smaller effect sizes.

[5] Downgraded by 1 for indirectness: the reduction in gametocytes has only been demonstrated in Myanmar. In the three other studies gametocyte carriage was low in both groups on day 8, and no differences were detected.

[6] Shekalaghe 2007 reported relative decrease in haemoglobin against baseline in both groups at day 8, 15, 29 and 43 in all participants irrespective of G6PD status. The comparison between those receiving primaquine and those not was significant at day 8 and these results are presented in the SOF. It was not significantly different at the other time points.

[7] Downgraded by 2 for indirectness:the percentage of people with large drops in haemoglobin, not the mean change in the population, is the important safety outcome..

[8] Downgraded by 1 for imprecision: only one study in 101 people to detect an adverse effect that, if present, is likely to be relatively uncommon.

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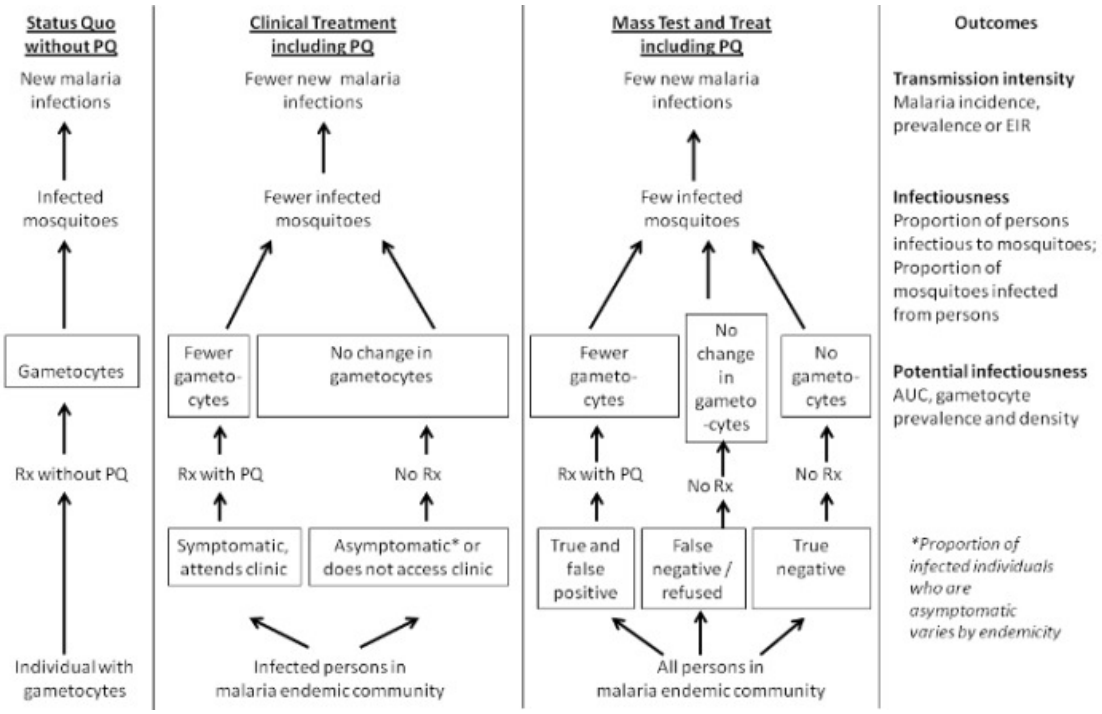
BACKGROUND

Gametocytes are the sexual stage of the *Plasmodium* parasite and are present in the bloodstream of an infected person. Mosquitoes become infected with the parasite when they ingest these stages. Drugs for treating *P. falciparum* infection do not directly target the gametocyte stage ('Status quo without PQ' in Figure 1). However, primaquine (PQ) is a drug that has a direct impact on gametocytes, and for this reason several national malaria control programmes have for many years recommended PQ as a single dose or short course add-on to *P. falciparum* treatment regimens to give to people when they are sick with malaria with the goal of reducing transmission at the community level. This is now the World Health Organization (WHO) current policy ('Clinical treatment with PQ' in Figure 1) (WHO 2010). However, this drug may cause haemolysis (disintegration of blood cells) in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency, a common genetic variant. PQ is also used to treat *P. vivax* infection, but this is the subject of another review (Galappaththy 2007).

Figure 1.



Description of the condition

Malaria is caused by protozoan parasites of the genus *Plasmodium* and these parasites are transmitted by female *Anopheles* mosquitoes. In infections with three *Plasmodium* species, *P. vivax*, *P. ovale*, and *P. malariae,* gametocytes (haploid sexual stages) form early during the infection of the human host (before and during clinical illness). The fourth species, *P. falciparum*, takes about 10 days for gametocytes to develop and they are usually found in the later stages of the clinical infection. Whether they are present at the time of treatment depends upon when treatment is sought. This means that some patients are gametocytaemic at treatment, and some only up to 10 days later, if at all. If the primary drug used to treat the infection is successful at clearing the blood-stage parasites, no new gametocytes can develop. However, if the treatment is unsuccessful (eg if the parasites are resistant to the drug used, which may be the case if chloroquine (CQ) or another failing drug is used), gametocytaemia will be prolonged.

Within the mosquito host, gametocytes form gametes which recombine to begin the next generation. Gametocytes in human blood are not a cause of clinical malaria symptoms, but without this stage no further parasite transmission via mosquito hosts is possible. The mean circulation time of mature *P. falciparum* game-

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tocytes in humans has been estimated by microscopy or polymerase chain reaction (PCR) to be between 3.4 to 6.5 days (Smalley 1977; Eichner 2001; Bousema 2010). However, different cohorts circulate together and non-immune individuals can remain gametocytaemic for months if left untreated.

Not all gametocytes are infectious to mosquitoes and the mere presence of gametocytes in blood does not equate to infectivity. Infectivity can be measured by directly feeding mosquitoes on individuals or their blood via membrane feeders (reviewed by Killeen 2006 and Bousema 2011) or by indirect estimates from infection rates in wild-caught mosquitoes (Graves 1990; Lines 1991). The number of gametocytes required for transmission from an infected person to a mosquito to occur was estimated to be in the range of 100 to 300 gametocytes per μL blood (Carter 1988). Gametocyte densities are estimated by light microscopy to be usually in the range of 5 to 150 per μL blood in immune individuals carrying these stages. However, PCR studies have shown that the proportion of gametocyte carriers (predominantly those with low density) in the population seems to be routinely underestimated in endemic areas (Okell 2008), and most gametocytaemias are probably in people who are asymptomatic.

Overall in the population, the percentage of bites on humans that result in infection in the mosquito has been estimated to range between 0.3% to 46%, although most estimates are in the range of 1% to 10% (Killeen 2006). Most studies assessed infectiousness to mosquitoes in people known to be gametocyte carriers (Graves 1988; Killeen 2006) but some studies have shown that asymptomatic people are frequently infectious (Bousema 2011).

After uptake of a *P. falciparum* infected bloodmeal by the mosquito, gametocytes mature into male and female gametes. When fertilized, diploid oocysts develop on the mosquito's stomach wall and subsequently mature into sporozoites that migrate to the salivary glands, ready to be released into the next host to be bitten. The median number of oocysts formed in wild caught infected mosquitoes is two to three (Rosenberg 2008). Each oocyst develops thousands of sporozoites, but only about 20% are thought to reach the mosquito salivary glands, and fewer than 25 sporozoites on average are ejected during mosquito bloodfeeding (Rosenberg 1990; Rosenberg 2008).

Description of the intervention

In this review we assessed the effects of PQ given in a single dose or as a short course added to a partner drug as standard treatment for malaria, with the intention of reducing parasite transmission from the infected person to mosquitoes and hence reducing the number of subsequent malaria cases.

The pharmacokinetic mode of action of PQ, an 8-amino-quinoline, is not well understood, but it is known to be rapidly metabolized, with a half-life of six hours (White 1992). PQ kills late-stage *P. falciparum* gametocytes (Burgess 1961; Pukrittayakamee 2004; Chotivanich 2006) but does not directly affect the asexual stages of *P. falciparum* (Arnold 1955; Pukrittayakamee 2004). It does not appear to affect the early or maturing gametocytes (Bhasin 1984; White 2008) although it does have some activity against the asexual stages of *P. vivax* (Pukrittayakamee 1994) as well as killing liver stage hypnozoites of *P. vivax* and *P. ovale.*

Because artemisinin drugs also kill some immature gametocytes (Chotivanich 2006), the effect of PQ may be different if given with non-artemisinin treatments compared with adding it to artemisinin treatments, and for this reason the analysis is stratified in this review. Some non-artemisinin drugs may even increase the number of gametocytes that would otherwise develop (Drakeley 2006; Barnes 2008).

How the intervention might work

The theory behind PQ use is that by administering PQ to *P. falciparum* infected patients, they have a reduced number of gametocytes in their bloodstreams and transmission of the parasite is reduced.

When given as an adjunct to clinical treatment, the only groups that receive PQ are those that are symptomatic and attend a clinic. Thus the effect on transmission presumes that PQ not only effectively reduces gametocytes in the sick patients, but in the overall community. However, within any community it is likely that there will be carriers of *P. falciparum* gametocytes who have not been treated ('clinical treatment' in Figure 1). This point highlights the importance of seeking community studies that have measured the impact on transmission in humans.

On an individual basis, a decrease in potential infectiousness can be detected from a decrease in the proportion of people with gametocytes, a reduction in the number of gametocytes per person, a reduction in the duration of gametocytaemia, or by a combination of these parameters in an area under the curve (AUC) measure (Mendez 2006); see Figure 1. More directly, a reduction in infectiousness can also be measured by comparing the proportion of treated and untreated people who are infectious to mosquitoes, or by comparing the proportion of mosquitoes infected or intensity of infections produced in mosquitoes (ie number of oocysts per infected mosquito), or both. Finally, an impact on malaria transmission intensity, either through the number of infected mosquitoes biting people in a given time period (entomological inoculation rate (EIR)) or measures of malaria infection in humans (malaria incidence or prevalence) are important outcomes to ascertain Figure 1).

More recently, with the move toward a target of elimination, some policy makers are considering mass treatment strategies (von Seidlein 2003) such as mass drug administration or 'mass test and treat', where all people in a community are tested and, if positive, treated for malaria as a way to reduce transmission or contain outbreaks once transmission is reduced to low levels. In this instance, it seems more likely that a higher proportion of the population with gametocytes will be detected and treated, and that this could

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be effective in reducing or interrupting transmission. This policy is relatively new, and being considered in countries with lower intensity transmission, on islands or at the northern and southern fringes of malaria distribution or both (GMAP 2008; Mendis 2009). Effective antimalarial drugs are likely to play a large role in this new strategy. One of the questions in this effort is whether there is a role for PQ, given in addition to curative antimalarial drugs (including artemisinin combination therapies (ACTS)), for the treatment of *P. falciparum* malaria, to further reduce the transmissibility of the infections (White 2008).

Why it is important to do this review

PQ could be a tool in malaria elimination if it has the intended effect of reducing *P. falciparum* transmission. Use of PQ has also been suggested to prevent the spread of artemisinin resistance in Southeast Asia. This review contributes to an evaluation of the evidence that exists and exposes gaps that should be examined in the near future, and shows the evidence base to define the conditions under which it is beneficial to use PQ.

Single-dose or short-course PQ in addition to a partner drug is now recommended standard treatment for malaria caused by *P. falciparum* infection in a number of countries, mainly in Asia and South America. WHO malaria treatment guidelines (WHO 2010) recommend "addition of a single dose of PQ (0.75 mg/kg) to artemisinin combination treatment (ACT) for uncomplicated falciparum malaria as an antigametocyte medicine, particularly as a component of pre-elimination or an elimination programme". The guidelines state that this recommendation is supported by high quality evidence, while acknowledging that studies on the impact of this strategy are very limited. The guidelines cite just one study (Shekalaghe 2007) which is included in this review. In our attempt to comprehensively clarify the evidence behind the WHO guidelines, we have included both single dose and short-course PQ for primary treatment of *P. falciparum* infection in this review.

The primary antimalarial drug to which PQ is added may also influence any added impact of PQ. The situation has changed since ACTs were introduced, as artemisinin-based drugs kill immature (but not mature) gametocytes and may have some transmission reducing effects (Price 1996). Artemisinin-based drugs appear to be more effective at reducing gametocyte densities and transmission than older drugs (Okell 2008), possibly modifying any additional effect of PQ. However, it is hard to distinguish the effects of drugs acting directly on the gametocytes from the indirect effect of just reducing the numbers of asexual parasites that could develop into gametocytes. Therefore, evidence should be developed that takes account of any artemisinin-based drug (or other partner) effect, if possible.

It is known from experimental challenge studies that PQ kills mature gametocytes and reduces infectiousness of *P. falciparum* parasites to mosquitoes (Rieckmann 1968; Rieckmann 1969). In these trials, PQ given at one to two week intervals (usually without partner drug) markedly reduced infectiousness of both Malayan CAMP and Uganda I strains of *P. falciparum* in small numbers of semi-immune volunteers. There was suggestion of dose dependence, with doses of 15 mg being less consistently effective, and effects of 30 mg being perhaps less rapid than 45 mg. However Bunnag 1980 did not observe any difference in gametocyte outcomes between regimens using 15 mg PQ (five days) or single doses of 30 mg or 45 mg PQ in adults.

During the course of a natural infection, it is not known when PQ should be given for maximum effect. The most important unknown is whether the reduction in gametocyte numbers then results in a meaningful reduction in infectiousness and hence transmission of the disease, with lower incidence of new infections in the local community.

OBJECTIVES

1. To assess whether giving PQ when treating *P. falciparum* infection reduces:

- malaria transmission intensity;
- infectiousness of infected people to mosquitoes;
- potential infectiousness (gametocyte prevalence and density over time).

2. To estimate the frequency of severe or haematological adverse events associated with single dose or short course PQ when it has been used for this purpose.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) where the unit of randomization is an individual or a cluster (such as a village or community). Cluster-RCTs must have at least two clusters per arm.

Trials that evaluate giving PQ accompanying treatment of symptomatic patients; and trials evaluating mass treatment strategies (either mass treatment without diagnosis or of people treated after detection as infected through mass test-and-treat programmes).

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Types of participants

Adults or children with *P. falciparum* infection or a mixed infection of *P. falciparum* and other *Plasmodium* species. For individual RCTs, eligible studies must diagnose patients by blood slide, rapid diagnostic test, or other valid molecular method; for cluster-RCTs, diagnosis could be by clinical judgment if that was standard in the trial area at the time of the trial.

Types of interventions

Intervention

A single dose or short course (up to seven days) of PQ administered with partner drug(s).

Control

Identical treatment for malaria not including PQ (or substituting placebo for PQ).

Types of outcome measures

Primary outcomes

a) Malaria transmission intensity (in cluster-RCTs)
- Prevalence
- Incidence
- EIR

b) Infectiousness
- Individuals infectious to mosquitoes
- Mosquitoes infected by direct feeding

c) Potential infectiousness
- AUC of gametocyte density (y-axis) over time (x-axis)
- Gametocyte prevalence (estimated by microscopy or PCR)
- Gametocyte density (estimated by microscopy or PCR)
- Gametocyte clearance time (duration of gametocyte carriage)

Secondary outcomes

- Presence of asexual stage parasites (may be reported as treatment failure rate)
- Asexual parasite clearance time (duration of asexual carriage)

Adverse events

- Serious adverse events leading to hospital admission or death
- Haematologic effects
  - Haemolysis (higher prevalence)
  - Haemoglobin concentration (decline)
  - Packed cell volume (decline)

Search methods for identification of studies

We attempted to identify all relevant trials, regardless of language or publication status (published, unpublished, in press, and in progress).
The search strategy is shown in Appendix 1.

Electronic searches

Databases

We searched the following databases using the search terms and strategy described in Appendix 1: the Cochrane Infectious Diseases Group Specialized Register (accessed 10 April 2012); the Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (issue 3 2012); MEDLINE (1966 to 10 April 2012); EMBASE (1980 to 10 April 2012) ; and LILACS (1982 to 10 April 2012). We also searched the *meta*Register of Controlled Trials (*m*RCT) and the WHO trials search portal (both accessed 10 April 2012) using 'malaria*', 'falciparum', and 'Primaquine ' as search terms.

Conference proceedings

We searched the following conference proceedings for relevant abstracts: the MIM Pan-African Malaria Conferences and the American Society of Tropical Medicine and Hygiene (ASTMH) to December 2009.

Searching other resources

Researchers and organizations

We contacted researchers at LSHTM who are authors of some of the included and in-progress trials, and other experts in the field of malaria chemotherapy, including those at WHO.

Reference lists

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

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Data collection and analysis

Selection of studies

Two authors (PMG and HG) independently screened all citations and abstracts identified by the search strategy, including ongoing studies, to identify potentially eligible studies. We independently assessed full reports of potentially eligible studies for inclusion in the review. Notably, we did not contact any of the trial authors for clarification regarding inclusion (although some were contacted later about details of their studies) because it was clear whether trials were or were not eligible for inclusion. We used translations of two papers published in Chinese to assess eligibility. We resolved differences of opinion by discussion with PG. We documented one instance of duplicate reports of the same study (in different languages).

Data extraction and management

Two authors (PMG and HG) independently extracted the following information for each trial using a data extraction form designed by the authors for this review.

Characteristics of trial

- Design (randomized or quasi-randomized, type of randomization)
- Dates and duration of trial

Characteristics of participants

- Number of participants
- Age and sex of participants
- Proportion with G6PD deficiency
- Inclusion criteria
- Exclusion criteria

Characteristics of interventions

- Type of drug, dose, and schedule

Presented outcomes

- Description of outcomes presented in the papers

Other

- Location of trial, setting, and source of funding

Outcomes data

For each trial, two authors (PMG and HG) extracted data on the trial outcomes eligible for inclusion in this review, for the PQ and non-PQ groups. We extracted the number of participants randomized and the numbers analysed in each treatment group for each outcome. For dichotomous data outcomes (proportion of participants with gametocytes or asexual stages, proportion of participants infectious to mosquitoes, and proportion of mosquitoes infected), we extracted the number of participants experiencing the event of interest and the total number of patients or mosquitoes in each treatment arm of each study. For continuous outcomes (AUC for gametocyte numbers over time), we extracted arithmetic or geometric means and standard deviations for each treatment group by day of assessment, together with the numbers of patients in each group. We noted details on the method of determining parasite presence and density, for example light microscopy (if so, the method of staining and number of fields examined), PCR, or other methods.

For G6PD deficiency, we noted the sex of the carrier (if available) and the method used to determine G6PD deficiency, ie either phenotypically (by enzyme function) or PCR (by genotype). We adopted the definition of 'deficient' used in the trials that assessed this outcome. We extracted adverse event data for each individual type of event wherever possible. Where adverse events were reported separately for more than one dose (for short-course regimens), we attempted to record the average number of people reporting each adverse event for each dose. If trials reported the occurrence of adverse events at more than one time point following a single dose, but did not record the total number of people reporting each event, we attempted to record the events occurring in the first time period.

In cases of disagreement, we double checked the data and we came to a consensus through discussion between all three authors.

Assessment of risk of bias in included studies

PMG and HG independently assessed the risk of bias of the included trials using a pro forma. We assessed the risk of bias in studies as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For each trial included, we assigned a score of low, unclear or high risk of bias for the following components: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other biases.

For sequence generation and allocation concealment, we described the methods used, if given. For blinding, we described who was blinded and the blinding method. For incomplete outcome data we reported the percentage and proportion of loss to follow-up (the number of patients for whom outcomes are not measured/the number randomized), if given. For selective outcome reporting, we stated any discrepancies between the methods and the results

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in terms of the outcomes measured and the outcomes reported; we also stated if we knew that an outcome was measured but was not reported in the publication. For other biases we described any other trial features that we believe could have affected the trial's results (eg whether a trial was stopped early or if no sample size calculation was included). We resolved disagreements between authors by discussion.

We reported the results of the risk of bias assessment in a 'Risk of bias' table and displayed them in a 'Risk of bias' summary and 'Risk of bias' graph (Figure 2; Figure 3).

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Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

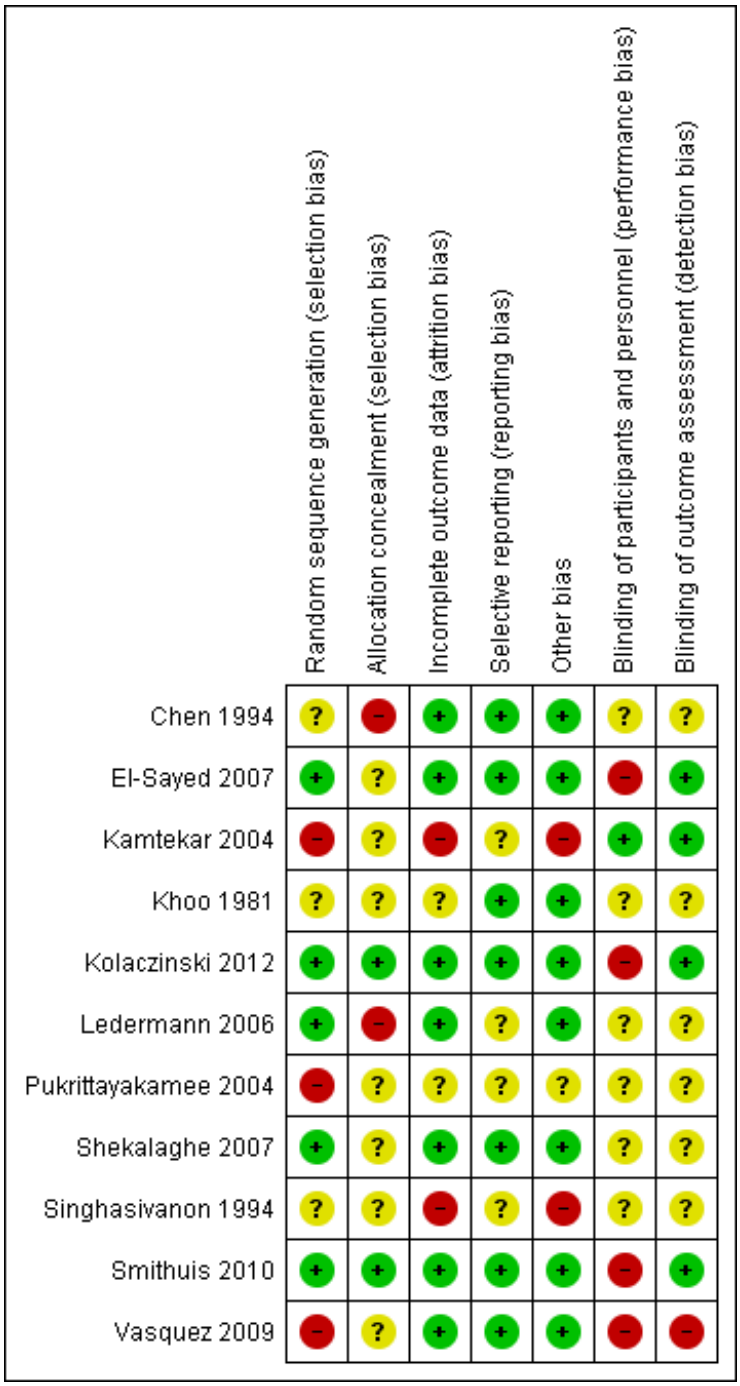

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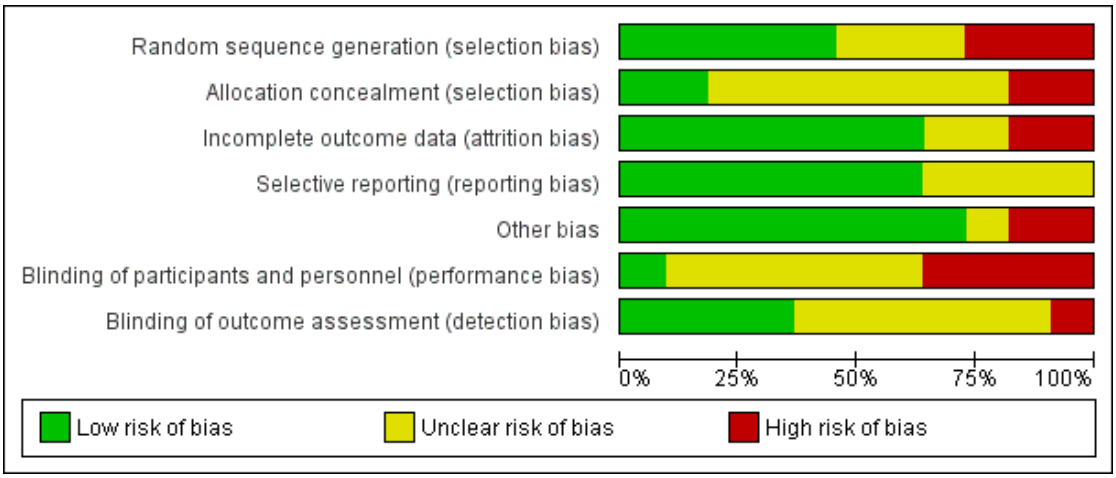
Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Measures of treatment effect

We analysed the data using Review Manager (RevMan) 5.1. For dichotomous data, we estimated the Risk Ratio (RR) and used the Mantel-Haenszel method with fixed-effect, or with random-effects if there was heterogeneity. For continuous data, we estimated the mean difference (MD). All results are presented with 95% confidence intervals (CIs). We reported results only for days after the first day of PQ treatment, which, in some trials, was later than the beginning of primary treatment.

We estimated AUC for trials that reported gametocyte numbers (either as summary measure by group in the paper, or calculated from individual patient data supplied by the authors) for trials that reported gametocyte outcomes for days 1, 8, 15, 29, and 43. Since few patients had gametocytes up to day 43, we also estimated AUC only up to day 29 for the same trials. The AUC is a weighted sum of gametocyte densities, with weights proportional to the difference in time between adjacent sampling points as described by Dunyo 2006 and Mendez 2006 in trials assessing gametocytaemia after sulfadoxine-pyrimethamine (SP) treatment. However, Mendez 2006 used follow-up days 4 to 22 (reported as days 3 to 21 in trial), which do not encompass the early days of highest gametocytaemia nor the participants who still had gametocytes after day 21.

The formulas used were:

AUC (days 1 to 29) = ((8-1)*(G1+G8)/2)+((15-8)*(G15+G8)/2)+((29-15)*(G29+G15)/2)/28 for days 1 through 29

AUC (days 1 to 43) = ((8-1)*(G1+G8)/2)+((15-8)*(G15+G8)/2)+((29-15)*(G29+G15)/2)+((43-29)*(G43+G29)/2)/42 for days 1 through 43

where Gx = mean gametocyte density on day X (estimated using data from all participants still enrolled on day X). Log(10) AUC values were estimated using geometric mean gametocyte density.

Unit of analysis issues

All trials we included were individually randomized and analysed. We did not find any cluster-RCTs.

Dealing with missing data

Where data were missing from the trials or if details were unclear, we attempted to contact the authors and were successful in four cases. We used complete case analysis for trials with missing data.

Assessment of heterogeneity

We assessed heterogeneity between the trials by examining the forest plot to check for overlapping confidence intervals, using the Chi^2 test for heterogeneity with a 10% level of significance, and the I^2 statistic using a value of 50% to represent moderate levels of heterogeneity.

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Assessment of reporting biases

There were insufficient trials within each comparison to assess the likelihood of small study effects, such as publication bias, by examining a funnel plot for asymmetry.

Data synthesis

We stratified the analyses by partner drug, as we anticipated heterogeneity in estimates of PQ efficacy due to the different effects of the partner drugs on the asexual and sexual stages of *P. falciparum.*
We combined partner drug groups for some comparisons, either because trials did not distinguish partner drug groups (eg CQ or CQ plus SP) or to group trials of related drugs (mefloquine (MQ), MQ+SP).
We also grouped all trials that included an artemisinin compound (comparison 5) with and without PQ, for two reasons. Firstly, artemisinins may kill early-stage gametocytes and secondly, ACTs are the currently recommended first-line treatment for *P. falciparum*. Comparisons 1 to 5 were stratified by timepoint after treatment. In comparison 6, we assessed only on day 8 the outcome of percentage of people with gametocytes and combined all trials (both artemisinin-based and non-artemisinin-based) that started PQ any time up to day 7.
Throughout this review, we designated the first day of treatment as day 1 rather than day 0 as reported in some trials. Where not stated as mg/kg, the PQ dose is reported as the adult dose; trials stated that the dose was adjusted for children.
When no statistically significant heterogeneity between trials was detected, we applied the fixed-effect meta-analysis model. When statistically significant heterogeneity was observed within groups that could not be explained by subgroup or sensitivity analyses, we used a random-effects meta-analysis model to synthesize the data.
When substantial heterogeneity was determined from the assessments of heterogeneity (ie high I^2 value, low Chi^2 statistic P value, or when a pooled meta-analysis result is considered to be meaningless because of clinical heterogeneity) we did not carry out meta-analysis but instead present a forest plot with the pooled effect suppressed.

Subgroup analysis and investigation of heterogeneity

In our protocol, we had stated we would investigate heterogeneity in relation to drug resistance pattern, the parasite density before treatment and the local endemicity of malaria. However, were too few trials for this analysis.

Sensitivity analysis

There were insufficient trials to conduct a sensitivity analysis to investigate the robustness of the results to the quality (risk of bias) components.

RESULTS

Description of studies

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

Results of the search

The search identified 46 potentially relevant publications, of which 15 were excluded at abstract stage (Figure 4). In one case, two publications (in different languages) described the same trial (Chen 1994). Of the 31 remaining trials, 20 were excluded on reading of the full paper, leaving 11 trials that were included. Five of the trials included more than one comparison (different drugs, doses, or schedules); overall there were 20 distinct comparisons and 1776 individuals.

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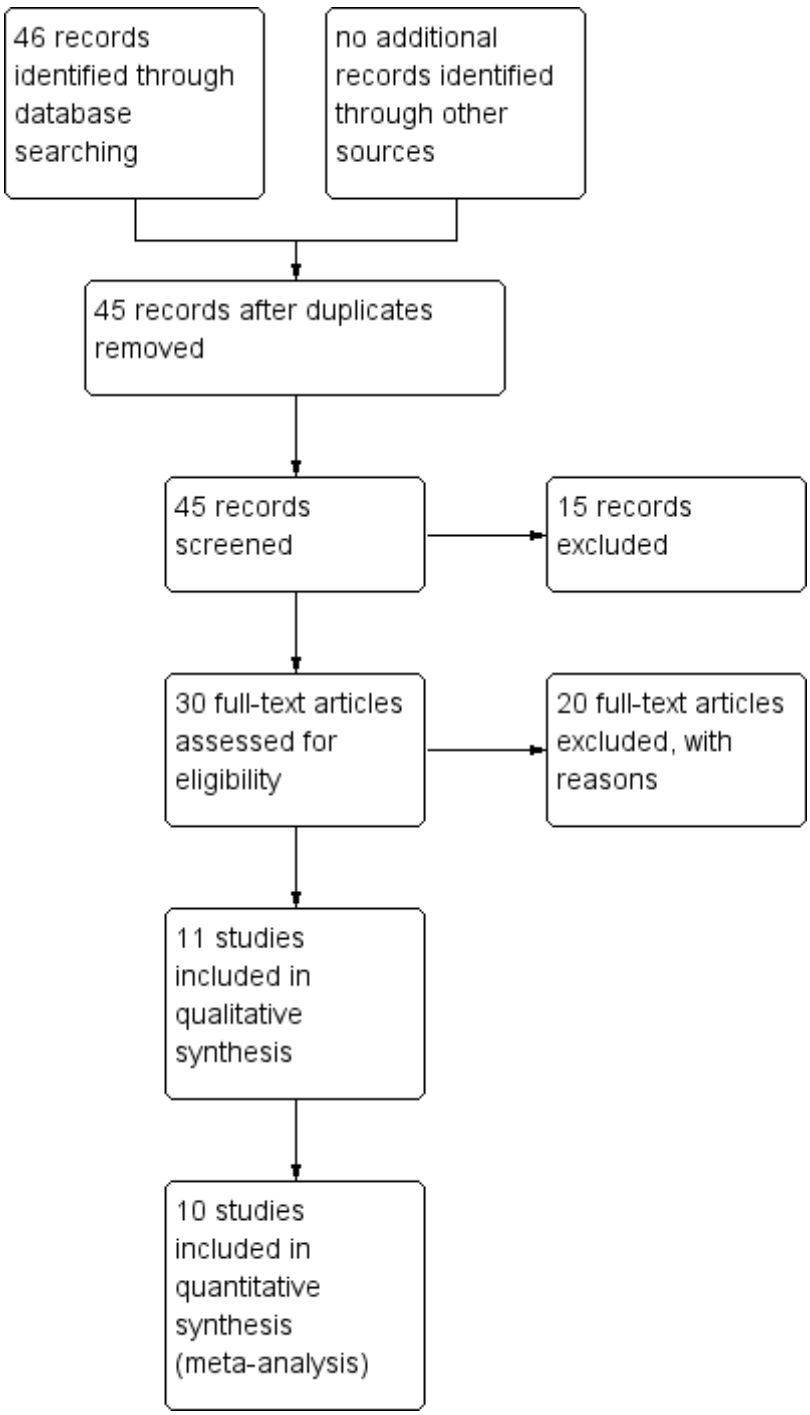
Figure 4. Study flow diagram.



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Included studies

We did not identify any community trials examining malaria transmission intensity (measuring incidence of malaria, prevalence, or EIR). For direct measures of infectiousness, one small trial (Chen 1994) in China compared the infectiousness to mosquitoes of people treated with MQ only to those treated with MQ plus PQ.
The remaining 10 trials examined the impact of PQ on various measures of gametocytes in trial subjects after treatment. One trial (Shekalaghe 2007) reported on AUC as a summary combined measure of gametocyte prevalence and density.

Participants

For G6PD deficiency, two studies did not screen (Kamtekar 2004; Smithuis 2010), one study screened and included all (Shekalaghe 2007), one study only included deficient participants (Khoo 1981), two studies included only non-deficient participants (Pukrittayakamee 2004; Ledermann 2006), and the remaining five studies made no comment (Chen 1994; El-Sayed 2007; Kolaczinski 2012; Singhasivanon 1994; Vasquez 2009).

Interventions

Non-artemisinin-based regimens

CQ or CQ combinations: CQ was the partner drug in one comparison of a multi-arm study (Kolaczinski 2012, Pakistan) and in the trial of Khoo 1981 (Malaysia). However, Khoo 1981 did not distinguish *P. falciparum* and *P. vivax* cases and hence the number of days of PQ given. CQ combined with SP was the partner drug in two comparisons of a multi-arm study in Indonesia (Ledermann 2006). CQ or CQ + SP were used in one comparison of a multi-arm study in India (Kamtekar 2004). The results across the two partner treatments were combined.
SP: SP was the partner drug in one comparison of a multi-arm study in Pakistan (Kolaczinski 2012).
MQ or MQ combinations: MQ was the partner drug in one trial in China (Chen 1994). MQ + SP (fixed combination, also known as MSP) was the partner drug in one trial in Thailand (Singhasivanon 1994).
Quinine (**QN):** QN was studied in three comparisons, in two multi-arm studies: Kamtekar 2004 (India) (one comparison) and Pukrittayakamee 2004 (Thailand) (two comparisons).

Artemisinin-based regimens

Artesunate (AS) monotherapy was the partner drug in one comparison of a multi-arm study in Thailand (Pukrittayakamee 2004). AS + SP was the partner drug in two trials: El-Sayed 2007 (Sudan) and Shekalaghe 2007 (Tanzania). AS + amodiaquine (AQ) was the partner drug in one comparison of a multi-arm study: Smithuis 2010 (Myanmar). Artemether-lumefantrine (AL) was the partner drug in one comparison of a multi-arm study in Myanmar (Smithuis 2010). AS + MQ was studied in Colombia (Vasquez 2009) and two comparisons of a multi-arm study in Myanmar (Smithuis 2010). Dihydroxyartemisinin-piperaquine (DHAP) was the partner drug in one comparison of a multi-arm study in Myanmar (Smithuis 2010).

Dose

Most trials used the equivalent of 0.75 mg/kg PQ per day (adult dose 45 mg/day). The exceptions were:

- Khoo 1981: adult dose of 25 mg or approximately 0.42 mg/kg/day;
- Kolaczinski 2012: 0.5 mg/kg or adult dose 30 mg/day;
- Pukrittayakamee 2004: the trial with QN had two arms, one with 0.25 mg/kg and the other 0.5 mg/kg per day (adult dose 15 mg or 30 mg per day respectively); the comparison with AS used 0.5 mg/kg per day (adult dose 30 mg per day).

Schedule

Most trials used a single dose of PQ given on the following days:
Day 1: Chen 1994, Kolaczinski 2012 (one of two comparisons), Ledermann 2006 (one of two comparisons), Singhasivanon 1994, Smithuis 2010 (five comparisons);
Day 3: Kolaczinski 2012 (one of two comparisons), Ledermann 2006 (one of two comparisons), Vasquez 2009;
Day 4: Kamtekar 2004 (one of two comparisons), El-Sayed 2007, Shekalaghe 2007;
Day 8: Kamtekar 2004 (one of two comparisons).
Two trials used a longer course of PQ:
3 days: Khoo 1981;
7 days: Pukrittayakamee 2004 (three comparisons).
Details of the trial locations, partner drugs, PQ doses and schedules are shown in Table 1.

Excluded studies

Reasons for exclusion of 20 trials are shown in the Characteristics of excluded studies. Among the trials considered, four were conducted in populations attempting to estimate the effect of PQ on transmission (Hii 1987; Doi 1989; Kaneko 1989; Shekalaghe 2011). None of these could be included because they either were not randomized, had insufficient clusters per arm, or had no appropriate comparison or control group of partner drug without PQ.

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Risk of bias in included studies

Out of the 11 studies, those that demonstrated low risk of bias were in the minority for sequence generation (five studies), allocation concealment (two studies), blinding of participants (one study), and blinding of outcomes assessment (four studies); see Figure 2 and Figure 3. We did not identify concerns with incomplete outcome data or selective reporting.

The exclusion of G6PD-deficient people from the PQ group in Pukrittayakamee 2004 is a post-randomization exclusion. We had no reason to suppose it biased the primary outcomes but it could have affected assessment of adverse effects.

Note that when one study contained more than one comparison with the same placebo group, we did not divide the placebo group participants between the comparisons (due to small numbers in most trials). This may have resulted in overestimation of the precision of some results.

Effects of interventions

See: **Summary of findings for the main comparison** Primaquine for preventing infectiousness with ACT treatments; **Summary of findings 2** Primaquine for preventing infectiousness with non-ACT malaria treatment

For malaria transmission intensity (prevalence, incidence, or EIR) we found no community cluster-RCTs measuring these outcomes.

Regarding infectiousness, we found one trial (Chen 1994) that measured this in 18 patients for non-artemisinin drugs (see comparison 3 below).

All other trials reported potential infectiousness, ie effects of PQ on gametocyte prevalence, density or clearance time, or both. Only one trial (Shekalaghe 2007) reported a summary measure of potential infectiousness (AUC); we calculated this for other trials with available data.

Non-artemisinin-based partner regimens

CQ or CQ combination partner treatments (comparison 1)

For the outcome of participants with gametocytes at various timepoints after treatment, we found three trials (Kamtekar 2004; Ledermann 2006 (two comparisons) Kolaczinski 2012) with reduction in the groups given PQ that was significant in the combined analysis on day 8, 12, 15, 22 and 29 (Analysis 1.1). One arm of Ledermann 2006 received PQ on day 1 and the other on day 3. There was no apparent difference in the outcome between these two arms (Analysis 1.1).

One trial also assessed the proportion with 'viable gametocytes' as determined by presence of exflagellating microgametocytes on stained blood slides (Kamtekar 2004). This is relatively subjective, but the results were similar to the proportion with gametocytes.

Data from one other trial in this comparison (Khoo 1981) could not be used because it did not distinguish between patients with *P. falciparum* and *P. vivax* and their respective treatment with either 3-day or 14-day PQ. There was a much higher risk of adverse haemolytic events in those who received PQ in the Khoo 1981 trial (OR of 22.27 for both haemolysis and need for blood transfusion), but the results could not be included in this systematic review because the groups combined participants receiving a short course (3 days) of PQ with those receiving a 14-day regimen. The most unusual aspect of the study, however, is that only individuals with G6PD deficiency were included.

There was no effect of PQ added to CQ on prevalence of asexual parasites at day 29 (parasitological treatment failure, whether or not the results were adjusted for new infections detected by PCR) in Kolaczinski 2012 (Analysis 1.2).

SP partner treatments (comparison 2)

Using SP as the partner drug with measurements at different time points from days 1 to 43, one trial showed an effect of PQ on people with gametocytes, which was significant from day 15 to day 36 (Kolaczinski 2012; Analysis 2.1).

There was no effect of PQ added to SP on prevalence of asexual parasites at day 29 (parasitological treatment failure) in Kolaczinski 2012 (Analysis 2.2).

MQ or MQ-SP combination partner treatments (comparison 3)

One small trial in China (Chen 1994) with only nine participants per group tested directly the impact of PQ on infectiousness to mosquitoes. The results showed that while on day 1 all patients in the trial were infectious to *Anopheles dirus* mosquitoes, after a dose of PQ on day 1 the proportion of people infectious was reduced to 0 when measured on day 5 and day 8 (Analysis 3.1). By day 15 and day 22 the difference was attenuated as infectiousness in the control group declined.

Chen 1994 also examined the number of mosquitoes infected after feeding on trial participants (Analysis 3.2). None of the mosquitoes feeding on people receiving PQ were infected, with over 64% infected at day 5 after feeding on the group not receiving PQ (RR 0.01, 95% CI 0.0 to 0.14), with the effect still evident up to day 22, although the proportion infected in the control group declined over time.

The Chen 1994 trial also included an artemisinin (ART) arm, but there was no comparison of ART with and without PQ. However, on indirect comparison, ART appeared at least as effective at reducing infectiousness as MQ+PQ (compared to MQ alone).

Gametocyte clearance time (in days) was estimated in a trial of MQ+SP with and without PQ (Singhasivanon 1994). Clearance time was significantly reduced in the PQ group with a mean difference of -14.90 days (95% CI -18.18 to -11.62). (Analysis 3.3).

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In Singhasivanon 1994 there was no significant effect of PQ on asexual clearance time (Analysis 3.4).

None of these trials reported on haemolysis, other haematological measures, or severe adverse events. Singhasivanon 1994 reported the following adverse effects: nausea (3/11 MQ+SP versus 1/7 MQ+SP+PQ), vomiting (2/11 versus 2/7), dizziness (1/11 versus 1/7) and all children with an adverse event (3/11 versus 2/7). These counts represented no significant differences between groups.

QN partner treatments (comparison 4)

Two trials with different schedules tested this comparison. One (Kamtekar 2004) gave single-dose PQ on day 8, after the 7-day course of QN was finished. The other trial (Pukrittayakamee 2004) had two arms ('low' 0.25 mg/kg and 'high' 0.50 mg/kg doses of PQ) but in both comparisons, the PQ was given for 7 days along with the QN. Both of these doses were low compared to the standard 0.75 mg/kg per day used in most of the other trials, but in Pukrittayakamee 2004 the PQ course was unusually long (ie total PQ dose 1.75 or 3.5 mg/kg over 7 days).

There was no difference between the QN+PQ and QN groups (either dose) regarding the proportion of people with gametocytes on day 8 in Pukrittayakamee 2004 (Analysis 4.1). Only the Kamtekar 2004 trial continued follow-up after day 8, and there was no difference in the proportion of people with gametocytes at day 15, after which no one in either arm had gametocytes (Analysis 4.1).

The median gametocyte clearance time was reduced in Pukrittayakamee 2004 from 216 hours to 48 hours with 0.5 mg/kg PQ, or 87 hours with 0.25 mg/kg PQ, although results were not presented in a form that could be shown graphically. The mean asexual parasite clearance time of 78 to 80 hours was no different between groups (Analysis 4.2).

Artemisinin-based partner regimens

AS or ACT partner treatments (comparison 5)

Microscopy analysis revealed that PQ clearly reduced the number of people infected with gametocytes (Analysis 5.1), on day 8 (RR 0.15, 95% CI 0.09 to 0.24, four trials, eight comparisons), day 15 (RR 0.10, 95% CI 0.04 to 0.22, three trials, seven comparisons), day 22 (RR 0.06, 95% CI 0.01 to 0.24, two trials, six comparisons, three with estimable results) and day 29 (RR 0.15, 95% CI 0.05 to 0.51, three trials, seven comparisons, three with estimable results). In Smithuis 2010, new gametocytaemia (by microscopy) on day 7 was also reduced by PQ (one of 272 versus 10 of 268; RR 0.1, 95% CI 0.01 to 0.76, P = 0.006).

Two trials examined gametocytes by PCR rather than microscopy. In one trial (Shekalaghe 2007), a reduction in gametocyte prevalence was observed on day 8 and day 15 (Analysis 5.2). However, in the other trial (El-Sayed 2007), giving PQ did not lead to a detectable difference between the two groups on these two follow-up days, although there were very few participants with gametocytes in the control group. Given the clear statistical and clinical heterogeneity between the two estimates (related to different numbers of participants with gametocytes in the comparator arm in these two studies) we did not combine them in meta-analysis Analysis 5.2. In Shekalaghe 2007, with additional follow-up day 29, reduction in gametocyte prevalence was significant (RR 0.23, 95% CI 0.08 to 0.62), and on day 43, it was not (Analysis 5.2).

Gametocyte density over time was assessed by microscopy in the trials of Shekalaghe 2007, Smithuis 2010 (five comparisons) and Vasquez 2009, and is analysed further below using the AUC measure estimated from data provided by the authors. For PCR detected gametocyte density, Shekalaghe 2007 provided geometric mean and inter-quartile range (IQR) on days 1, 4, 8, 15, 29 and 43, and mean density was consistently lower in the PQ than the non-group, for days when gametocytes were detected (with PQ: 5.8, IQR 0.8 to 55.1; without PQ: 15.8, IQR 4.1 to 85.8).

Gametocyte clearance time is presented in Shekalaghe 2007 and was significantly lower in the PQ group (6.3 days, 95% CI 4.7 to 8.5) than in the non-PQ group (28.6 days, 95% CI 17.0 to 48.0, P < 0.001). Smithuis 2010 also reported significantly lower gametocyte clearance time in the PQ groups, reported as person gametocytaemia weeks standardized per 1000 person-weeks of follow-up. This was 5.5 weeks in the ACT+PQ groups versus 65.5 weeks in the non-PQ groups (RR 11.9, 95% CI 7.4 to 20.5, P < 0.001) and the difference was very large for each individual partner drug. Although the duration of gametocyte carriage (without PQ) was significantly longer for AS+AQ, AL and DHAP than for AS+MQ, there was no significant difference in length of gametocyte carriage between the ACT groups when PQ was added (Smithuis 2010).

Shekalaghe 2007 was the only trial to present a comparison of AUC of gametocyte density (by PCR) over time, with a 95% CI derived from generalized estimation equations. Shekalaghe 2007 derived AUC from gametocyte densities estimated on days 1, 4, 8, 15, 29 and 43 (reported in trial as days 0, 3, 7, 14, 28 and 42). There was a significant reduction in AUC in the PQ groups over 43 days after treatment, reported as mean of 1.5 (IQR 0.3 to 8.8) in the PQ group versus 11.1 (IQR 2.2 to 53.8) in the non-PQ group (P < 0.001). We used trial raw data to estimate geometric mean and SD for this variable (Analysis 5.3) and observed a significant reduction in AUC (expressed as log(10)) with a mean difference of -0.88 [-1.32, -0.43].

There was no difference between PQ and non-PQ groups in proportion of participants with asexual parasites (Analysis 5.4) or asexual parasite clearance time (Analysis 5.5). No difference in asexual recrudescence rates was noted in Smithuis 2010.

For haematologic adverse events, Smithuis 2010 stated that there were no cases of severe anaemia (<5g/dL) or blackwater fever in any group. El-Sayed 2007 showed that there was no difference in packed cell volume between groups at day 7 (34.2% (15 to 44%) versus 36.2% (26 to 42%)) or day 14 (35.2% versus 35.4%). The difference was not significant at either day 7 (0.78, (-0.75 to 0.23)

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P = 0.32) or day 14 (0.86, (-0.31 to +2.0) P = 0.15). In Shekalaghe 2007, although there was also no reduction in mean haemoglobin by group (Analysis 5.6), there was a significantly greater change (decrease) in haemoglobin status in the PQ group on day 8; haemoglobin decreased by 5% in the PQ group compared to 1% in the non-PQ group (Analysis 5.7). These findings suggest that rather than look at population mean of haemoglobin, it would be more meaningful to examine the proportion of individuals who had serious adverse events: Shekalaghe 2007 state that 8 of 52 children in the PQ group had 20% reduction in haemoglobin by day 8, compared to 0 of 53 children in the control group. However, it is also stated that no child developed clinical symptoms related to anaemia or a haemoglobin below 5 g/dL. The effect on haemoglobin in the PQ group was transient and was no longer significant by day 15.

El-Sayed 2007 assessed he minor adverse effects of vomiting, insomnia and itching and found no difference between groups. Smithuis 2010 found a higher percentage of patients in the PQ groups had abdominal pain (16%; N = 397 versus 11%; N = 411, P = 0.05); frequencies of dizziness, nausea, anorexia, diarrhoea, palpitations, sleeplessness, headache and vomiting were not increased in the PQ groups.

Summary stratified by non-artemisinin and artemisinin regimens

A summary across all drugs, stratified into two groups (partner drug including or not including an artemisinin-based drug) was conducted.

Outcome 1. Gametocytes on day 8 (comparison 6)

A single outcome, percent of participants with microscopy-detected gametocytes on day 8, is displayed for this comparison, as a representative outcome across the trials. The QN comparison of Kamtekar 2004 was excluded, because PQ was not given until day 8, but all others are included. The day on which PQ was given varies and is shown for each trial in footnotes in Analysis 6.1. The data have been subgrouped by whether or not the partner drug was an artemisinin-based treatment. This comparison shows that, overall, PQ reduced the prevalence of gametocytaemia on day 8 following treatment (RR 0.36, 95% CI 0.30 to 0.43) Analysis 6.1. The individual trials nearly all trended in the direction of a reduction, and this is true of non-artemisinin-based (RR 0.62, 95% CI 0.51 to 0.76) as well as artemisinin-based partner drugs (RR 0.12, 95% CI 0.08 to 0.20) (Analysis 6.1).

Outcome 2. AUC

The AUC was estimated here for microscopy-determined densities for Shekalaghe 2007, Smithuis 2010 (five comparisons), Vasquez 2009 and Kolaczinski 2012 (two comparisons), using the mean (or geometric mean) gametocyte density by group at each day of measurement. . Since trials were not consistent in the days on which they estimated gametocyte density, the days on which measurements were available for all trials were used (days 1, 8, 15, 29 and 43; see Methods section). AUC was estimated up to day 29 (Table 2) and day 43 (Table 3). Results are presented separately by non-artemisinin-based and artemisinin-based partner drugs below and given for log(10) AUC in the summary of findings tables for days 1-43.

Table 2 and Table 3 show that all trials except Vasquez 2009 demonstrated reduction in the AUC after PQ. The reduction ranged from -50.8% to 91.7% up to day 29 and from -41.3% to 82.6% up to day 43. Using the log(10) AUC, the reduction ranged from -7.0% to 27.3% up to day 29 and -15.8% to 87.5% up to day 43.

The Vasquez 2009 trial was an exception suggesting increase in AUC after PQ, possibly due to the small sample size and differing mean gametocyte counts by group at baseline in this trial. Excluding Vasquez 2009, reductions in AUC varied from 37.9% to 91.7% for days 1 to 29, and 42.1% to 82.6% for days 1 to 43 using the mean gametocyte density. Using the log(10) AUC, the reduction ranged from 8.3% to 27.3% for days 1 to 29 and 24.3% to 87.5% for days 1 to 43.

Considering non-artemisinin and artemisinin-based partner drugs separately (excluding Vasquez 2009), the reductions for day 1-43 for non-artemisinin partner drugs were 74.6% and 80.8% (one trial, two comparisons); and for artemisinin partner drugs ranged from 42.1% to 82.6%; two trials, six comparisons; (Table 3), using simple arithmetic calculation of the AUC. Reductions for day 1-29 were similar (Table 2).

Calculating using the log(10) AUC, for non-artemisinin partner drugs for day 1-43 the estimates were 24.3% and 27.1% (one trial, two comparisons); and for artemisinin partner drugs the range was 26.1% to 87.5% (two trials, six comparisons; Table 3). Reductions for day 1-29 were similar (Table 2).

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ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Primaquine for preventing infectiousness with non-ACT malaria treatment

Patient or population: patients with symptomatic malaria
Settings: endemic malarial areas
Intervention: primaquine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Primaquine				
Malaria incidence, prevalence or EIR - not measured				-		
People infectious to mosquitoes (day 8) Follow-up: 22 days	**100 per 100**	**5 per 100** (0 to 80)	**RR 0.05** (0 to 0.8)	18 (1 study)	⊕⊕◯◯ **low**[1,2]	
Gametocytaemia Log(10) area under curve of density over time. Scale from: 0 to 100. Follow-up: 43 days			Relative decrease ranged from 24.3 to 27.1%	219 (1 study)	⊕⊕⊕◯ **moderate**[3]	
Participants with gametocytes Microscopy Follow-up: 8 days	**Study population**		**RR 0.62** (0.51 to 0.76)	446 (4 studies)	⊕⊕⊕◯ **moderate**[4]	
	619 per 1000	**384 per 1000** (315 to 470)				
Evidence of haemolysis				0 studies		

*The basis for the **assumed risk** (eg the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded by 1 for risk of bias: this study did not conceal allocation, and no method of allocation is described
[2] Downgraded by 1 for imprecision: this single study is underpowered which limits the confidence in the results
[3] Downgraded by 1 for indirectness: one study, with two comparisons, and thus only two estimates of AUC (24.3% and 27.1% reduction)
[4] Downgraded by 1 for risk of bias: one study with two comparisons is good quality, but all the other three studies have methodological deficiencies

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DISCUSSION

Summary of main results

PQ used in clinical treatment

With artemisinin-based drug regimens

See Summary of findings for the main comparison

Malaria transmission intensity and infectiousness: we do not know if PQ has an effect with artemisinin-based regimens, as no study has examined this.

Potential infectiousness: PQ probably reduces potential infectiousness, based on log(10) AUC to day 43 (relative decrease range from -26.1 to 87.5%, two studies (six comparisons), moderate quality evidence); and on participants with gametocytes on day 8 (RR 0.15, 95% CI 0.09 to 0.24, four studies (eight comparisons), moderate quality evidence).

Haemolytic anaemia: we do not know if PQ results in haemolytic anaemia. One study examined % change in mean haemoglobin against baseline and found that overall the haemoglobin had declined more in those treated with PQ at day 8 (but not at day 15, 29 and 43) (very low quality evidence).

With non-artemisinin-based drug regimens

See Summary of findings 2

Malaria transmission intensity: we do not know if PQ has an effect, as no study has examined this.

Infectiousness: PQ may reduce infectiousness, based on one small study with large effects from China (RR 0.05, 95% CI 0 to 0.79, one study; low quality evidence).

Potential infectiousness: PQ probably reduces potential infectiousness, based on: log(10) AUC (to day 43, relative decrease was 24.3 and 27.1%, one study (two comparisons), moderate quality evidence); and participants with gametocytes on day 8 (RR 0.62, 95% CI 0.51 to 0.76, four studies (five comparisons); moderate quality evidence).

Haemolytic anaemia: we do not know if PQ results in haemolytic anaemia as no study in this systematic review has examined this.

PQ in mass test and treat programmes

We found no trials that assessed this (Figure 1).

Overall completeness and applicability of evidence

Effectiveness

The trials included in this systematic review are all the ones we identified that provide reliable evidence bearing on the main question: whether, and under what circumstances, does PQ reduce infectiousness sufficiently to reduce overall transmission in an area? None of the trials that fulfilled the inclusion criteria addressed this question directly, so we cannot draw direct conclusions to answer the question. We can infer from the evidence that PQ does reduce gametocyte prevalence and density in treated individuals - including those treated with artemisinin-based drugs - and that PQ probably would reduce transmission in a population, used at an appropriate stage of malaria control. That stage cannot be predicted with the information available but we believe that it could be determined with specific trials, modelling studies, or both.

Four studies not included in this review (Doi 1989, Hii 1987, Kaneko 1989, Shekalaghe 2011) did attempt to measure the effect of PQ on transmission but were excluded because they did not provide reliable evidence (even though they are frequently cited as evidence for PQ reducing transmission). They were excluded because of concurrent interventions that might have contributed to the results reported; or because they did not compare treatment with and without PQ; or were too small (including only one cluster per treatment). The table of Characteristics of excluded studies specifies the reasons each was excluded.

Only one small trial included in this review (Chen 1994) (nine participants per arm) measured infectiousness of participants to mosquitoes directly, and reported marked effects. All other trials used proxy measures such as gametocyte prevalence and density, duration of gametocyte carriage, or the combined measure of AUC. While there is a relationship between measures of gametocyte prevalence/density and infectiousness, this is not well defined and the proxy measures do not give a quantitative estimate of the absolute infectiousness of individuals. An analysis using a modelled relationship between gametocyte density and infectiousness, such as that done by Barnes 2005 and Barnes 2008, is required to adequately estimate a reduction in infectiousness from the effect on individuals.

The trials have answered the question of whether PQ added to partner drugs reduces the prevalence and density of gametocytes, which it does with most of the drug treatment regimens with which it has been tested. The level of reduction in microscopy-detected gametocyte prevalence by PQ was 85 to 90% when measured at single time points on days 8 and 15 in the comparison with artemisinin-based drugs.

There is a need for a summary measure of potential infectiousness after drug treatment, such as is provided by the AUC. However, standardization in the days used to estimate AUC and the formula (arithmetic or geometric mean) are needed. Only one trial (Shekalaghe 2007) formally compared AUC between study arms in a statistically valid manner. Where individual patient data were available from other trials, the AUC could be calculated. We compared the AUC over 29 and 43 days after treatment. By using

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this method the reduction in overall potential infectiousness by artemisinin-based drugs ranged from 42% to 83% (AUC) and 24% to 88% (log(10) AUC) over days 1 through 43, excluding the Vasquez 2009 trial. Thus estimates of reduction in potential infectiousness using AUC are generally lower than the reduction estimated using prevalence of gametocytes on single follow-up days. Both the AUC and prevalence estimates would be improved with gametocyte measurements on more days nearer treatment with PQ (eg days 2, 3, 4), since PQ is likely to have its greatest impact in the early period of infectiousness, when gametocytes are most prevalent and at highest density. Choosing to estimate effect on days 5, 8 or later may bias the estimate of effect, but is unlikely to change the main conclusions of the review.

PQ could be used in two ways to reduce malaria transmission: 1) given only to people who present for treatment because of clinical symptoms (after parasitologic confirmation of malaria) or 2) given to all infected people (symptomatic and asymptomatic) as part of a test-and-treat strategy. These alternatives are shown diagrammatically in Figure 1, but neither question is addressed by studies included in this review, which all involve treatment of symptomatic people and do not assess impact on transmission intensity in the area. The proportion of infected people who are asymptomatic will vary based on endemicity. It is possible that PQ may have a greater impact on transmission in low endemic areas or under test-and-treat strategies where a greater proportion of infected people receive it, but this has not been demonstrated.

An early study not included here (Clyde 1962) used a mass drug administration strategy in Tanzania in which amodiaquine (AQ) and PQ (adult dose 30 mg or 45 mg) were given every 1, 2 or 4 weeks to everyone in three fairly isolated sites of > 5000 people in an attempt to interrupt transmission of *P. falciparum.* No group was given AQ only, so the relative impact of PQ is not known. Weekly or biweekly AQ+PQ given to >93% of the population reduced prevalence and sporozoite rates to low levels, but did not interrupt transmission; however starting prevalence was high (ranging from 60 to 90% in children under 5 years, to 25 to 35% in adults) in the study areas.

Modelling studies have suggested that PQ be delayed to day 8 after primary treatment in order to maximise the effect, given the delay in gametocyte development in *P. falciparum* (Lawpoolsri 2009). However, this assumes prompt treatment seeking during the early asexual phase. Trials in this review had varying proportions of gametocyte carriers at time of treatment. If patients already have gametocytes at treatment, it does not seem advisable to wait for another 8 days before giving PQ, if the practice is adopted.

Safety

PQ brings with it a serious safety concern: haemolysis that could be severe, life-threatening, or even fatal, in those with G6PD deficiency phenotypes. G6PD is an enzyme that protects cells from oxidative damage, to which red blood cells are particularly vulnerable. PQ can cause erythrocytes to haemolyse (rupture) in the absence of G6PD. Though often referenced as a single condition, almost 400 variants of the G6PD gene have been identified (Carter 2011). The PQ sensitivity phenotype has been characterized for only three of the variants (Baird 2011). The two best known and most widespread types are A-, most common in Africa and those of African descent, and B-, which occurs most frequently around the Mediterranean, in Asia, and parts of the Pacific.

Of the studies included in this review, Ledermann 2006 excluded people with G6PD deficiency; in Pukrittayakamee 2004, people with G6PD deficiency were excluded from the PQ arm; and in Shekalaghe 2007, all patients were treated but screened first and results reported according to G6PD status. G6PD status was ignored in the remaining trials. If patients were routinely tested for G6PD deficiency before treatment, it might be possible to avoid haemolytic events, but screening for G6PD deficiency is rarely undertaken, and even biochemical phenotype testing requires specialized equipment, laboratory skills, and refrigeration (Baird 2011).

Very few studies appeared to record adverse events, and surprisingly, haematological outcomes were rarely systematically sought. Most minor adverse effects such as nausea, vomiting, dizziness, insomnia, or itching were not significantly different between PQ and control groups, although abdominal pain was greater with PQ in one trial (Smithuis 2010). No severe or life threatening adverse effects were mentioned, except in Khoo 1981 where all participants were G6PD deficient and it was not clear whether the seven participants (out of 23 enrolled) experiencing haemolysis and needing blood transfusion had received 3-day or 14-day PQ. El-Sayed 2007 did not detect a reduction in packed cell volume in Sudan, a low endemic area of Africa; G6PD status of participants was not stated. Shekalaghe 2007 did not detect a difference in mean haemoglobin in Tanzania. However, when the results were presented as relative haemoglobin concentration in the publication, there was a statistically significant decrease in haemoglobin on day 7, most pronounced in children with G6PD deficiency of the A- variant, although no clinical symptoms of anaemia or other adverse effects or haemoglobin less than 5 g/dL were observed. By one month post-treatment, levels had recovered.

G6PD deficiency affects an estimated 400 million people worldwide (Carter 2011). The distribution is roughly analogous to the distribution of malaria transmission now or in the recent past, leading to the suggestion that the G6PD deficiency offers some advantage against malaria. Other evidence corroborates this finding, but is not considered further here.

As with other drugs that were developed decades ago (in the 1940s, in this case), PQ has not undergone the intense evaluation that would be required of new drugs today. This, along with a selective history of use, has led to the situation faced now: the drug is recommended for widespread use even though relatively little is known about the effect of PQ in individuals with G6PD deficiency from a wide range of phenotypes and genotypes. Baird and Surjadjaja recount this history in detail in their 2011 paper (Baird 2011). They make the point that the apparent comfort with recommend-

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ing PQ for gametocytocidal use in people with *P. falciparum* has its roots in the experience of using PQ to prevent relapses in US servicemen who had been infected with *P. vivax* in the Korean War. Many of these were African Americans who carried the A- variant which results in only mild haemolysis after full treatment for *P. vivax*. They experience a transient drop in haematocrit that recovers after a couple of months (Reeve 1992). In the A- variant, only older erythrocytes are haemolyzed on exposure to PQ, and the red blood cell population recovers and stabilizes, even with continued use. In the B- variant, all erythrocytes, including young ones, are haemolyzed. Continued dosing with PQ (as would be used for radical cure of *P. vivax*) seems ill advised, since even a single 45 mg dose can cause severe effects (Clyde 1981).

Even if screening were done, it has been suggested that haemolysis ranging from mild to severe may occur after a single dose of PQ even in people with normal G6PD status, when PQ is added to AS+SP (Shekalaghe 2010). However, patients treated for malaria may haemolyse even without PQ. This study classified G6PD deficiency by genotype and it is possible that deficient phenotypes of unknown genotypes were misclassified as normal.

Nevertheless, according to Baird 2011: "The free application of 45 mg PQ to patients with falciparum malaria lacks supporting assessments of safety across the range of G6PD variants exposed to risk of potentially serious harm".

Drug resistance

PQ is an important drug to maintain in the malaria pharmacopeia. It is the only widely available therapy for eliminating parasites from hepatocytes in *P. vivax* and *P. ovale* infections (Wells 2010). Some evidence of resistant *P. vivax* has emerged, though the extent of resistance is not well reported. Even without such evidence, however, the history of antimalarials and resistance is quite clear: the parasite will develop resistance and drugs will be lost, sooner or later. Since resistance to CQ became widespread, WHO has revised guidelines to prohibit treatment of uncomplicated malaria with a single antimalarial, based on evidence that multiple drugs, with different modes of action, will make it much less likely that resistant parasites will emerge. Although that guidance is applied largely to drugs used to treat asexual stages of falciparum malaria, the principle applies to PQ as well. And even though PQ is given along with other antimalarials when it is used to reduce transmission, it is basically monotherapy for the gametocytes, which are not affected by the other drugs. To our knowledge, no attempt has been made to create resistant gametocytes in the laboratory, a type of study commonly undertaken for drugs used for primary malaria treatment - in those cases, inducing resistance in blood-stage parasites.

The trials in this review do not mention PQ resistance as a potential threat, nor is it discussed by WHO. PQ should certainly be used where it is of clinical importance (in *P. vivax* and *P. ovale* infections), but its effectiveness against *P. falciparum* gametocytes could be reduced by use. Use should therefore be limited to situations in which it is likely to have a meaningful anti-transmission effect.

Quality of the evidence

The quality of the evidence for an effect of PQ on gametocytes in individuals seems reasonable, with moderate quality evidence in non-artemisinin-based and artemisinin-based regimens.

However, the quality of the evidence on the substantive outcomes is poor, and there is little evidence from these trials in relation to the serious adverse events known to be associated with this drug.

Potential biases in the review process

None known.

Agreements and disagreements with other studies or reviews

The findings of this review provide very little support for current WHO treatment guidelines (WHO 2010). While there is good evidence that PQ reduces gametocyte prevalence, density and AUC, there is no evidence that it is effective in reducing transmission. If PQ is given only to the fraction of infected people attending for treatment, it may not be covering enough of the infectious population to make any difference to the overall human infectious reservoir.

We found insufficient reliable evidence to recommend PQ in primary treatment for reducing transmission in a community.

As with all antimalarial drugs, there is a global responsibility to maintain the effectiveness of PQ for as long as possible without withholding it when needed. In this case, that translates into using it to reduce transmission only if there is reasonable evidence that it actually has that effect. Otherwise, it will be used to little or no effect, but its value for radical cure may be diminished by the development of resistant parasites.

We agree with the ethical issues raised by Baird 2011 and their conclusion that PQ should not be used without first screening for G6PD deficiency.

AUTHORS' CONCLUSIONS

Implications for practice

Single dose or short course PQ should not be added to routine treatment of *P. falciparum* with ACTs until: 1) it has been demonstrated that reducing infectivity of treated people in a variety of endemic situations reduces transmission on a community basis; 2) further research is done on safety and the adverse hematological

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effects for both G6PD and non-G6PD carriers; 3) we understand more about the proportion of gametocyte carriers who present to receive treatment in a given population and time period and 4) the cost of the policy balanced against the potential benefit is explored. In any case, patients should be screened for G6PD deficiency and those with variants predisposing to haemolysis should not be given PQ.

Implications for research

PQ may well have a strategic role in malaria control and elimination, but it has not yet been defined, and research to support this definition is needed. As a first step, studies summarizing measures of infectiousness to mosquitoes over an extended period including the days immediately following treatment, as well as defining the proportion of asymptomatic people treated, are needed. Stratification of studies into participants with and without gametocytes at initial treatment is recommended.

The dynamics of gametocytes after treatment need to be understood for the currently most used drugs in primary treatment. That information can then be fed into models used to predict transmission effects and eventually, community-based trials should be conducted to measure directly the effects of PQ on transmission (incidence) in defined endemicities. The question of effectiveness of PQ when used in mass treatment or mass test-and-treat strategies for elimination is a separate issue that can also be approached in modelling as well as experimental studies.

A variety of research studies are required:

1. Dose optimization studies with ACTs as partner drugs, varying the total amount of PQ needed and the schedule for administration, to maximize the effect on gametocytes and minimize adverse effects.

2. Studies of the effects of PQ on individuals with common G6PD-deficiency variants, to be conducted before PQ is used in communities.

3. Studies on induction of PQ-resistant gametocytes to help define likelihood of resistance development and identify possible mechanisms of resistance.

4. Research and development of rapid field-usable tests for G6PD deficiency.

For studies of the effect of PQ on transmission, G6PD screening should always be conducted on participants, results reported according to G6PD phenotype, and hematologic endpoints should be reported. For detecting gametocytes, PCR can be used if available but microscopy probably identifies the majority of the people with highest potential infectiousness. We also recommend that gametocytaemia be reported as AUC, or that both density and prevalence at different times be reported so that AUC can be calculated, and that AUC measurements should include the first few days of treatment. Statistical methods for comparing AUC in different treatment groups should be developed and applied.

ACKNOWLEDGEMENTS

We thank authors of Shekalaghe 2007, Vasquez 2009, Smithuis 2010, and Kolaczinski 2012 for providing unpublished data for this review. Isabela Ribeiro assisted with assessing trials in Portuguese for inclusion. David Sinclair assisted with the Summary of Findings tables. We are grateful to our affiliated Institutions and Organizations, and thank the referees and editors for their very important comments and encouragement. The editorial base for the Cochrane Infectious Disease Group is funded by the Department for International Development (DFID), UK, for the benefit of developing countries.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Chen 1994

Methods	Possibly individually randomized controlled trial (stated to be randomized but no information given) Dates of study not reported.
Participants	27 patients with slide positive *P. falciparum* including both asexual stages and gametocytes. No information given on age or sex. All dosages appear to be adult dosages Site: malaria endemic Hainan Island, China. Exclusion criteria: history of antimalarial treatment for present attack
Interventions	1. Artemisinin: 1200 mg per day for 5 days (not included in review) 2. MQ: 750 mg single dose day 1 (reported as day 0). 3. MQ + PQ:750 mg single dose + 45 mg single dose day 1 (reported as day 0)
Outcomes	1. Gametocyte density: days 5, 8, 15, 22, 29 (reported in paper as days 4, 7, 14, 21, 28 since first day was day 0). Given as percent of initial density on chart only 2. Percentage of participants infectious to *An. dirus:* days 5, 8, 15, 22 (reported as days 4, 7, 14, 21). 3. Percentage of mosquitoes infected: days 5, 8, 15, 22 (reported as days 4, 7, 14, 21)
Notes	For gametocyte density, graph only of percentages; no raw numbers given except range of asexuals and gametocyte numbers reported for each group on day 1 (reported as day 0)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on sequence generation. Describes process as participants "divided into groups A, B, and C". Equal number in each group and lack of detail suggests randomization not done adequately
Allocation concealment (selection bias)	High risk	No data to suggest any measures to conceal allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing participants in intervention groups 2 and 3.
Selective reporting (reporting bias)	Low risk	No obvious selective reporting.
Other bias	Low risk	No indication of other bias.

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Chen 1994 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.

El-Sayed 2007

Methods	Individually randomized controlled trial. Dates of study: Randomization June 2004; trial done 17 Aug 2004 to 3 Sep 2004
Participants	104 persons with asymptomatic *P. falciparum* positive by slide and positive for gametocytes by PCR. No information given on age and sex Site: Two villages in East Sudan where there is seasonal malaria, mainly *P. falciparum,* during Oct to Dec. Exclusion criteria: pregnancy, history of sulfa allergy, fever or other symptoms, *Plasmodium* spp other than *P. falciparum* present.
Interventions	1. AS: Children < 50 kg: 4 mg/kg; All > 50 kg: 200 mg (2 100-mg tabs) days 1, 2, 3 (reported as days 0, 1, 2) SP: Children < 50 kg: 25 mg/kg S + 1.25 mg/kg P; All > 50 kg: 3 tablets of 500 mg S+25 mg P 2. As for 1 above plus PQ 0.75 mg/kg day 4 (reported as day 3)
Outcomes	1. Proportion of persons with *P. falciparum* parasites by PCR days 4, 8 and 15 (reported as days 3, 7 and 14) 2. Proportion of persons with gametocytes by RT-PCR days 8 and 15 (reported as days 7 and 14) 3. Adverse events days 2, 3, 4, 8 and 15 (reported as days 1, 2, 3, 7 and 14) 4. Packed cell volume days 1, 8 and 15 (reported as days 0, 7 and 14)
Notes	The trial was conducted about 2 months after the initial screening for positives (asymptomatic carriers)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The list of carriers was sorted according to village and age to ensure that the treatment groups were balanced with respect to these two variables. The random allocation of this ordered list into the treatment arms was then created using restricted randomization with a block size of 12 in STATA v7..."

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El-Sayed 2007 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No information given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 3 out of 104 participants did not complete the follow up
Selective reporting (reporting bias)	Low risk	No obvious selective reporting.
Other bias	Low risk	No indication of other bias.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients and health staff were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Lab staff doing PCR were blinded.

Kamtekar 2004

Methods	Individually randomized controlled trial, comprising two distinct comparisons a: (CQ or [CQ+SP]) with and without PQ and b: QN with and without PQ Dates of study: not given.
Participants	57 persons age >/= 16 years with symptomatic uncomplicated and 46 with severe (WHO criteria) *P. falciparum* malaria, diagnosed by thick and thin blood slides. Gametocytaemic within first 72 hrs with > 55 *P. falciparum* gametocytes/μL Site: urban areas of Mumbai, India. Exclusion criteria: Pregnant or lactating, treatment for malaria within last two weeks, co-infection with *P.vivax*, history of PQ allergy.
Interventions	Comparison a: for uncomplicated malaria 1. CQ or (CQ+SP) CQ 10 mg/kg on days 1 and 2; 5 mg/kg on day 3; SP 1500 mg S, 75 mg P on day 1; Placebo for PQ on day 4. 2. [CQ or (CQ+SP)] + PQ As above in 1, substituting PQ 45 mg for placebo on day 4 Comparison b: (for severe malaria) 3. QN QN 10 mg/kg every 8 hrs for 24-48 hrs and orally for total of 7 days Placebo for PQ on day 8. 4. QN +PQ As above in 3, substituting PQ 45 mg for placebo on day 8.
Outcomes	1. Proportion of persons with gametocytes, days 1, 4, 8, 15, 22, 29 2. Proportion of persons with viable gametocytes (exflagellation), days 1, 4, 8, 15, 22, 29 3. Gametocyte density (given as range) days 1, 4, 8, 15, 22, 29

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Kamtekar 2004 (*Continued*)

Notes	No screening for G6PD deficiency. It is not stated how many got SP in addition to CQ or why

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	'simple computer generated randomization code'. Not all patients had gametocytes on day 1. Inclusion criteria were that the person had to have gametocytes in the first 72 hours (from day 1?). This suggests some post randomization inclusions or exclusions
Allocation concealment (selection bias)	Unclear risk	No information.
Incomplete outcome data (attrition bias) All outcomes	High risk	Originally there were 57 persons included in uncomplicated comparison (a), of whom 2 were lost to follow up and 9 were not evaluated as they showed CQ resistance There were 46 in severe comparison (b), of whom 3 were lost to follow up The final numbers evaluated in each group were (a) 22 and 24 (b) 22 and 21
Selective reporting (reporting bias)	Unclear risk	No obvious selective reporting.
Other bias	High risk	It was not clear why some patients got SP and others did not, and the numbers in each group are not given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study used a placebo for PQ. Patients and health workers were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Slide readers were blinded.

Khoo 1981

Methods	Individually randomized controlled trial. Dates of study: between June 1976 and March 1978.
Participants	69 persons (adults and children of both sexes, no ages specified) with G6PD deficiency (full or partial by Brewer's methaemoglobin reduction test) who were slide positive for malaria (*P. falciparum*, *P. vivax* or mixed).

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Khoo 1981 (*Continued*)

	Site: Sabah, Malaysia. Exclusion criteria:other associated clinical conditions.
Interventions	1. CQ 1.5 g CQ over 3 days for *P. falciparum*, *P. vivax* or mixed, less for children 2. CQ + PQ CQ as above plus 75 mg PQ over 3 days for *P. falciparum*; 201 mg PQ over 14 days for *P. vivax* and mixed infections; less for children 3. SP (not included in this review) 1.5 g S and 75 mg P, single dose
Outcomes	1. Hemolysis 2. Proportion cleared parasites by 72 hours 3. Need for blood transfusion 4. Renal failure
Notes	The participants are not divided by *P. falciparum*, *P. vivax* or mixed, so it is not possible to use the data.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"those found G6PD deficient were randomly assigned."
Allocation concealment (selection bias)	Unclear risk	No information given.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information given.
Selective reporting (reporting bias)	Low risk	No apparent selective reporting.
Other bias	Low risk	No indication of other bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.

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Kolaczinski 2012

Methods	Individually randomized controlled trial. Dates of study: between July and January, from 2000 to 2003.
Participants	237 individuals aged from 3 to 70 years, in 5 villages for Afghan refugees in Pakistan Inclusion: > 2 years of age, *P. falciparum* mono-infection, confirmed by slide, will be resident during entire follow-up period Exclusions: pregnancy, signs of severe malaria, report of antimalarial drug in past 21 days, other serious disease
Interventions	1. CQ 3 days 25 mg/kg. 2. CQ+PQ CQ as in 1; PQ on day 3 (0.5 mg/kg). 3. SP 25:1.25 mg/kg in single dose. 4. SP+PQ SP as in 3; PQ on same day (0.5 mg/kg).
Outcomes	1. Clinical treatment failure (PCR non-adjusted and adjusted) 2. Gametocytes on day 8. 3. Gametocyte density on days 1 to 8 of follow-up. 4. Genotyping of resistant strains for CQ and SP-specific mutations
Notes	Also included CQ + AS and SP + AS arms, compared with CQ +/- PQ and SP +/- PQ arms, respectively

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients numbered sequentially at enrolment. Random numbers with treatment assignment from Excel-generated lists, then paired with patient numbers
Allocation concealment (selection bias)	Low risk	Patient number concealed until after enrolment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	209 of 237 randomized completed treatment and at least one follow-up test. 47 (13%) of those randomized did not contribute data. Variable numbers tested during follow-up (see analyses)
Selective reporting (reporting bias)	Low risk	None detected.
Other bias	Low risk	None noted.

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Kolaczinski 2012 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Identified in report as 'single-blind'. Manager (gave Rx) not blinded; patients, microscopists and health workers 'partially blinded' due to different drug appearance and times of follow-up. No placebos used, but vitamin given to those in non-PQ arms
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Implied only.

Ledermann 2006

Methods	Individually randomized controlled trial. Date of study July-Oct 2001.
Participants	117 malaria cases with *P. falciparum* >/= 400 asexual stages/μL (thick film) recruited by mass blood survey and passive case detection. Symptoms not required Age: >/=15 years Site: Central Java, Indonesia, an area with high CQ resistance and resurgent malaria approximately equal *P. falciparum* and *P. vivax*. Exclusion criteria: Pregnancy, breast feeding, body weight < 40kg, G6PD deficiency, history of antimalarial or antibiotic in last 7 days, severe or complicated malaria, history or allergy or adverse reaction to study medications, Pv or mixed infection
Interventions	1. CQ only (not included in this review). 2. CQ+SP. CQ 150 mg base, 10, 10 and 5 mg/kg on days 1, 2, 3 (reported as days 0, 1, 2) SP 500 mg S 25 mg P on day 1 (reported as day 0). 3. CQ+SP as for group 2 above plus PQ 45 mg on day 1 (reported as day 0) 4. CQ+SP as for group 2 above plus PQ 45 mg on day 3 (reported as day 2)
Outcomes	1. Parasite clearance time assessed at days 1, 3, 8, 15, 22, 29 or day of recurrent parasitaemia (reported as days 0, 2, 7, 14, 21, 28) 2. Fever clearance time at days 2, 3, 4, 5, 8, 12, 15, 19, 22, 29 3. Proportion of persons with gametocytes (from chart) days 1 to 29 4. Adverse events.
Notes	Some comparisons in the results reported include the CQ only group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Study subject codes were assigned to treatment arms by a random process (not specified)

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Ledermann 2006 (*Continued*)

Allocation concealment (selection bias)	High risk	Eligibles were assigned a sequential participant number by the screening physician. Pre-packaged treatment but not stated whether allocation was concealed
Incomplete outcome data (attrition bias) All outcomes	Low risk	7% of participants withdrew before day 28.
Selective reporting (reporting bias)	Unclear risk	Abstract states that drugs were well tolerated and safe but no evidence is given in report
Other bias	Low risk	No indication of other bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding was implied only.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding was implied only.

Pukrittayakamee 2004

Methods	Individually randomized controlled trial. Time of study not stated.
Participants	176 patients with acute uncomplicated *P. falciparum*. After exclusion of QN+tetracycline group: 146. Age 14 to 62. All male. Site: Hospital for Tropical Diseases, Bangkok, Thailand. Exclusion criteria: Severe malaria, mixed malaria infection, history of drug hypersensitivity, any antimalarial within last 48 hrs, urine positive for sulfonamide or 4-aminoquinoline Persons with G6PD deficient phenotype were excluded from receiving PQ
Interventions	1. QN QN sulfate (300 mg salt/tab) at 10 mg salt/kg, 3x per day for 7 days 2. QN+tetracycline (excluded from this review). 3. QN+PQ low dose QN as above in 1 plus PQ 15 mg base/tab, 0.25 mg/kg base (adult dose 15 mg base) daily for 7 days 4. QN+PQ high dose QN as above in 1 plus PQ 0.50 mg/kg base (adult dose 30 mg base) daily for 7 days 5. AS AS 50 mg salt/tab 3.3 mg/kg (adult dose 200 mg) on day 1 and 1.65 mg/kg (adult dose 100 mg) daily on days 2 to 7

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	6. AS+PQ (high dose) AS as above plus PQ 0.5 mg/kg base daily on days 1 to 7.
Outcomes	1. Parasite clearance time: measured at 12 hrs until clearance 2. Gametocyte clearance time: median, 12 hrs until clearance 3. Fever clearance time (measured every 4 hr at first and then every 6-12 hrs until resolution of fever 4. Parasite reduction ration at 48 hrs. 5. Reappearance of infection *P. falciparum*/*P. vivax* up to 28 days. 6. Prevalence of gametocytes on admission/after treatment/total 7. Gametocyte carriage: total number of hours for which gametocytes were detectable
Notes	Patients with recrudescence of *P. falciparum* or relapse of *P. vivax* were re-treated with 7 day QN+tetracycline or 'standard doses' of CQ+PQ respectively; not clear if they were excluded from further study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Method not stated. Patients with G6PD deficiency were excluded from getting PQ which suggests randomization was biased
Allocation concealment (selection bias)	Unclear risk	No information given.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	122/142 of the original participants in the 5 groups studied here completed follow up. Patients with recrudescences of *P. falciparum* or relapse of *P. vivax* were re-treated with QN+tetracycline or CQ+PQ respectively; not clear if they were excluded from further study
Selective reporting (reporting bias)	Unclear risk	Not detected.
Other bias	Unclear risk	Those who were unable to stay in hospital until clearance of both fever and parasites were excluded from study of fever clearance time
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.

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Shekalaghe 2007

Methods	Individually randomized controlled trial. Time of study Jun to Sept 2006.
Participants	108 children with fever > 37.5 °C or history of fever in last 48 hours and *P. falciparum* mono-infection 500 - 100,000/μL. Age 3 to 15 years. Both sexes. Site: Mynuzi health center, NE Tanzania, a hyperendemic area with rainy seasons in Mar-June and Oct-Dec Exclusion criteria: Hb < 8, inability to take drugs orally, known hypersensitivity to meds, reported anti-malarial treatment in last 2 weeks, evidence of chronic disease or acute infection other than malaria, domicile outside study area, signs of severe malaria, eligible for other malaria studies
Interventions	1. AS+SP AS: 4 mg/kg once daily for 3 days SP: S 25 mg/kg and P: 1.125 mg/kg 2. AS+SP+PQ As above for AS and SP plus PQ base 0.75 mg/kg on the third day
Outcomes	1. Proportion of persons with gametocytes (by microscopy) days 1, 4, 8, 15, 29, 43 (reported as 0, 3, 7, 14, 28, 42) 2. Proportion with gametocytes (by PCR), same time points. 3. Gametocyte density by PCR. 4. AUC for gametocyte presence. 5. Adverse events. 6. Adequate clinical and parasitological response. 7. Haemoglobin.
Notes	Hb outcome assessed with respect to G6PD variant.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Generated in STATA 8.0 using restricted randomization with block size of 20
Allocation concealment (selection bias)	Unclear risk	Pre-prepared envelopes (but person who opened envelope administered treatment)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 2 out of 108 failed to complete follow-up.
Selective reporting (reporting bias)	Low risk	Why no day 22 results?
Other bias	Low risk	No indication of other bias.

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Shekalaghe 2007 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study physician evaluated patients, opened envelopes, and administered treatment. Other staff were blinded. Not clear of participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.

Singhasivanon 1994

Methods	Study design: Individually randomized controlled trial. Time of study: not stated.
Participants	23 persons with uncomplicated *P. falciparum* malaria, parasitaemia between 1-5 per 1000 rbc. Age 5 to 12 years, sex not stated. Exclusion criteria: antimalarial drugs, urine with quinoline and sulfonamide drugs, other diseases, hematocrit </=20%, inability to take oral medication
Interventions	1. MSP MQ 20 mg/kg; S 40 mg base/kg; P 2 mg/kg; single dose. 2. MSP + PQ As above plus PQ 0.75 mg/kg single dose. MSP+PQ crushed and mixed with 30 ml syrup (83% dextrose).
Outcomes	1. Gametocyte clearance time (days) (assessed twice daily until negative, then once daily, by blood slide) 2. Adverse drug reactions, assessed once daily in first week then once a week 3. Parasite clearance time (hrs). 4. Fever clearance time (hrs). 5. Cure rate.
Notes	Those who vomited within 3 hr of Rx were excluded - this is a post randomization exclusion

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information given.
Allocation concealment (selection bias)	Unclear risk	No information given.
Incomplete outcome data (attrition bias) All outcomes	High risk	Outcomes only reported for 18 of the 23 participants.

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Singhasivanon 1994 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	No information given.
Other bias	High risk	Those who vomited within 3 hr of Rx were excluded- this is a post randomization exclusion
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.

Smithuis 2010

Methods	Study design: Individually randomized controlled trial (5 comparisons - 10 arms) Follow up: Patients were asked to return weekly for 9 weeks for assessment and at any other time they were unwell Dates: Dec 2008 to March 2009.
Participants	Number: 808 persons attending clinics in Myanmar. Inclusion criteria: Age > 6 months, weight > 5kg, *P. falciparum* mono-infection 500 to 200,000 parasites/µL or co-infection with *P. vivax*, informed consent. Exclusion criteria: Pregnancy, signs of severe malaria, severe malnutrition, history of hypersensitivity to any of the study drugs, severe malnutrition, concomitant febrile illness, history of psychiatric disorder, a full course of MQ in the previous 9 weeks or any other antimalarial in the previous 48 hrs
Interventions	Each of the five study arms was divided into two where one half also received a one-off dose of 0.75 mg/kg PQ on day 1 Groups: 1+2. AS plus amodiaquine, fixed dose combination: 25 mg/67.5 mg or 50 mg/135 mg or 100 mg/270 mg tablets • AS 4 mg/kg once daily for 3 days • AQ 10.8 mg base/kg once daily for 3 days 3+4. Artemether-lumefantrine, fixed dose combination: 20 mg/120 mg tablets • A 3.3 mg/kg in two divided doses each day for 3 days • L 19.8 mg/kg in two divided doses each day for 3 days • Advised to consume fatty food or breast feed before each dose 5+6. ASplus MQ, fixed dose combination: 25 mg/55 mg or 100 mg/220 mg tablets (artesunate: Guilin, Lariam: Hoffman-La Roche) • AS 4 mg/kg once daily for 3 days • MQ 8.8 mg/kg once daily for 3 days 7+8. Artesunate plus MQ, loose combination (artesunate: Guilin, Lariam: Hoffman-La Roche) • AS 4 mg/kg once daily for 3 days • MQ 25 mg base/kg as a single dose on day 1 (reported as day 0)

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	9+10. Dihydroartemisinin-piperaquine, fixed-dose combination: 40 mg/320 mg or 20 mg/160 mg tablets (Artekin: Holleykin) • DHA 2.5 mg/kg once daily for 3 days • P 20 mg/kg once daily for 3 days First dose supervised, all others unsupervised.
Outcomes	1. Recurrent parasitaemia at day 15, 29, 43 and 64 (reported as days 14, 28, 42 and 63). 2. Treatment failure due to *P. falciparum.* 3. Gametocytaemia prevalence. 4. Person-gametocyte weeks. 5. Haemoglobin on days 1 and 64. 6. Adverse events (monitoring not described).
Notes	Funding: Médecins sans Frontières (Holland).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'After patients were screened and enrolled in the study, they were stratified prospectively into three age groups (1-4 years, 5-14 years and older than 14 years). Patients were randomly assigned in equal numbers to receive one of the five different treatments. They were then randomly assigned either a single dose of PQ ... or not.'
Allocation concealment (selection bias)	Low risk	'Treatment allocations were put in sealed envelopes in blocks of 50 for each age group, and random assignment was achieved by patients drawing an envelope from a box after enrollment. When the box was empty, another 50 envelopes were added.'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition is low in absolute numbers and unlikely to have introduced significant bias
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No indication of other bias.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label trial for patients and medical staff.

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Smithuis 2010 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Microscopists were blinded.

Vasquez 2009

Methods	Individually randomized controlled trial. Time of study: Apr 2007 to Feb 2008.
Participants	50 persons with uncomplicated *P. falciparum* diagnosis by thick blood slide, 150-50,000 parasites per μL Age 1 yr and over, both sexes. Exclusion criteria: pregnant, mixed infection, danger signs and complications, allergy to antimalarials, serious illness at time or presentation, antimalaria treatment in last 72 hrs, MQ in last 4 weeks
Interventions	1. AS+MQ Age 1-6: AS 50 mg on days 1, 2, 3 (reported as 0, 1, 2); MQ 250 mg on day 2 Age 7-13: AS 100 mg on days 1, 2, 3, MQ 250 mg on days 1, 2, 3 Age > 13: AS 200 mg on days 1, 2, 3, MQ 500 mg on days 1, 2, 3 2. AS+MQ+PQ As above plus PQ: Age 1-6: 0.3-0.6 mg/kg day 3 (reported as day 2). Age 7-13: 22.5 mg/kg day 3. Age > 13: 45 mg day 3.
Outcomes	Assessed on days 2, 3, 4, 8, 15, 22, 29, 36, 43. 1. Clinical recurrence. 2. Parasitemia prevalence. 3. Parasite density. 4. Fever resolution. 5. Prevalence of gametocytes. 6. Density of gametocytes. 7. Adverse effects.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Seems to be alternate allocation following order of arrival ("segun el orden de llegada")
Allocation concealment (selection bias)	Unclear risk	Not clear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts noted.

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Selective reporting (reporting bias)	Low risk	No evidence of bias.
Other bias	Low risk	No suggestion of other bias.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Seems not be blinded ("con determination no *ciega* del efecto en grupos iguales").
Blinding of outcome assessment (detection bias) All outcomes	High risk	

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

Study	Reason for exclusion
Arango 2012	Not randomized.
Baird 2002	Outcome is cure of asexual infection. No gametocyte outcomes
Bunnag 1980	Comparison of SP plus either 5 day PQ 15 mg, single dose PQ 30 mg or single dose PQ 45 mg in patients with and without gametocytes at presentation. No regimen without PQ. Authors state they will do further studies, including transmission. No difference in gametocyte outcomes between regimens and gametocytes persisted for up to 21 days
Che 1987	No mention of randomization. No valid comparison group (pyronaridine phosphate plus sulfadoxine plus PQ versus pyronaridine phosphate only)
Clyde 1971	Prophylactic efficacy trial of drug regimens, some including PQ, against sporozoite challenge. Gametocytocidal effect of single dose 45 mg PQ tested in 7 *P. falciparum* gametocyte carriers but no comparison group. Gametocytes cleared in 4 to 9 days in these persons. Inhibition of oocyst development despite presence of gametocytes after PQ treatment also demonstrated in 2 persons but with no controls
da Silva 1984	Trial of treatment regimens, some including PQ, for *P. vivax* and *P. falciparum.*
Doi 1989	Non-randomized community observational study.
Giao 2004	No gametocyte outcomes.
Gogtay 1999	Compares QN+PQ against QN+bulaquine. Not a relevant comparison
Gogtay 2004	Compares QN+Doxycyline+PQ against QN+doxycycline+bulaquine. Not a relevant comparison
Gogtay 2006	No appropriate control group. Seems to be part of a CQ+PQ versus CoArtem trial but only reports results from one arm

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(*Continued*)

Hii 1987	Controlled before and after study comparing SP+PQ+ITN versus SP+PQ only. Only one cluster per arm and no group without PQ
Huang 2001	No gametocyte outcomes.
Kaneko 1989	Non-randomized community trial comparing SP+PQ in one village with SP only in another. Only one cluster per arm
Karbwang 1992	Pharmacokinetic study; no gametocyte outcomes or control group
Santana 2007	Study of 14 day regimen of 15 mg PQ. Some *P. falciparum* cases were included but study did not distinguish between the patients with *P. falciparum* and *P. vivax* . Study was a comparison of association between methaemoglobinaemia after 14 day PQ in persons with and without G6PD deficiency
Shekalaghe 2010	Randomized comparison of anaemia after SP+AS+PQ versus placebo. Children with haemoglobin < 8g were excluded from receiving PQ
Shekalaghe 2011	Trial was a comparison of SP+AS+PQ versus placebo. No comparison of groups with and without PQ
Suputtamongkol 2003	Comparison of MQ+AS versus MQ+PQ. No appropriate control group
Tangpukdee 2008	Comparison of Artequick (contains PQ) with MQ+AS. No appropriate control group and no gametocyte outcomes

Characteristics of studies awaiting assessment *[ordered by study ID]*

Ishii 2009

Methods	Unclear
Participants	Residents of trial villages in Solomon Islands (number not given)
Interventions	Testing of clinical malaria patients for G6PD and addition of single dose PQ to a partner drug if appropriate
Outcomes	Village prevalence of malaria
Notes	

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

Eziefula ongoing

Trial name or title	Evaluation of the efficacy and safety of PQ in uncomplicated falciparum malaria in Uganda
Methods	Individually randomized trial
Participants	Inclusion criteria: >/= 1 yr-10 years; both genders; 38 ° C (tympanic) or history of fever in last 24 hours; *P. falciparum* parasitaemia < 500,000/µL; normal G6PD enzyme function Exclusion criteria: enrolled in another study; evidence of severe illness/danger signs; known allergy to medications; haemoglobin < 8 g/dL; started menstruation; pregnant or breastfeeding; PQ taken in last 4 weeks; blood transfusion in last 90 days; Non-falciparum malaria co-infection
Interventions	PQ
Outcomes	Primary: 1. Fall in Hb from enrollment to day 28. 2. Mean days to gametocyte clearance. Secondary: 1. Follow-up day of Hb nadir. 2. GI symptoms. 3. Serious adverse events. 4. AUC of gametocyte density during 14 days of follow-up. 5. Need for blood transfusion.
Starting date	December 2011
Contact information	Alice Eziefula; chi.eziefula@gmail.com
Notes	

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DATA AND ANALYSES

Comparison 1. GIVEN WITH CQ, OR CQ+SP

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with gametocytes	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Day 4	1	139	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.69, 1.42]
1.2 Day 8	3	303	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.34, 0.60]
1.3 Day 12	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.01, 0.49]
1.4 Day 15	3	270	Risk Ratio (M-H, Fixed, 95% CI)	0.12 [0.05, 0.26]
1.5 Day 22	3	227	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.03, 0.31]
1.6 Day 29	3	201	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.10, 0.86]
1.7 Day 36	1	19	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.13, 2.82]
1.8 Day 43	1	12	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.06, 8.90]
2 Participants with asexual parasites (treatment failure day 29)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Not PCR adjusted	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.75, 1.09]
2.2 PCR adjusted	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.65, 1.16]

Comparison 2. GIVEN WITH SP

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with gametocytes	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Day 2	1	84	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.32, 1.16]
1.2 Day 3	1	83	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.45, 1.27]
1.3 Day 4	1	82	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.35, 1.04]
1.4 Day 8	1	79	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.60, 1.01]
1.5 Day 15	1	73	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.48, 0.95]
1.6 Day 22	1	73	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.34, 0.78]
1.7 Day 29	1	66	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.19, 0.72]
1.8 Day 36	1	62	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.09, 0.97]
1.9 Day 43	1	61	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.47]
2 Participants with asexual parasites (treatment failure day 29)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Not PCR adjusted	1	74	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [0.45, 5.33]
2.2 PCR adjusted	1	74	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [0.45, 5.33]

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Comparison 3. GIVEN WITH MQ, OR MQ+SP

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants infectious	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Day 5	1	18	Risk Ratio (M-H, Fixed, 95% CI)	0.05 [0.00, 0.79]
1.2 Day 8	1	18	Risk Ratio (M-H, Fixed, 95% CI)	0.06 [0.00, 0.89]
1.3 Day 15	1	18	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 1.80]
1.4 Day 22	1	18	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 7.24]
2 Mosquitoes infected	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Day 5	1	161	Risk Ratio (M-H, Fixed, 95% CI)	0.01 [5.49, 0.14]
2.2 Day 8	1	152	Risk Ratio (M-H, Fixed, 95% CI)	0.01 [9.17, 0.23]
2.3 Day 15	1	168	Risk Ratio (M-H, Fixed, 95% CI)	0.04 [0.00, 0.71]
2.4 Day 22	1	152	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.00, 1.18]
3 Gametocyte clearance time (days)	1	18	Mean Difference (IV, Fixed, 95% CI)	-14.90 [-18.18, -11.62]
4 Asexual parasite clearance time (hrs)	1	18	Mean Difference (IV, Fixed, 95% CI)	-4.0 [-30.07, 22.07]

Comparison 4. GIVEN WITH QN

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with gametocytes	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Day 8	1	126	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.49, 2.78]
1.2 Day 15	1	43	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.07, 1.28]
1.3 Day 22	1	43	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 Day 29	1	43	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Asexual parasite clearance time (hours)	1	126	Mean Difference (IV, Fixed, 95% CI)	-1.44 [-9.76, 6.88]

Comparison 5. GIVEN WITH AS, OR WITH ACTs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with gametocytes (microscopy)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Day 4	1	49	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.10, 2.38]
1.2 Day 8	4	1006	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.09, 0.24]
1.3 Day 15	3	923	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.04, 0.22]
1.4 Day 22	2	776	Risk Ratio (M-H, Fixed, 95% CI)	0.06 [0.01, 0.24]
1.5 Day 29	3	873	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.05, 0.51]
1.6 Day 36	2	766	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.32]

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1.7 Day 43	3	847	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.04, 3.85]
2 Participants with gametocytes (PCR)	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Day 8	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Day 15	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Day 29	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Day 43	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Log(10) AUC of gametocyte density over time d1-43	1	106	Mean Difference (IV, Fixed, 95% CI)	-0.88 [-1.32, -0.43]
4 Participants with asexual parasites (PCR)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Day 8	1	94	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.30, 5.40]
4.2 Day 15	2	198	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.23, 4.15]
4.3 Day 29	1	106	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.35, 1.63]
4.4 Day 43	1	106	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.63, 2.03]
5 Asexual parasite clearance time	1	50	Mean Difference (IV, Fixed, 95% CI)	-6.0 [-16.31, 4.31]
6 Haemoglobin concentration	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Day 8	1	105	Mean Difference (IV, Fixed, 95% CI)	-0.39 [1.00, 0.22]
6.2 Day 15	1	106	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.53, 0.44]
6.3 Day 29	1	105	Mean Difference (IV, Fixed, 95% CI)	0.26 [-0.25, 0.77]
6.4 Day 43	1	103	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.61, 0.52]
7 % change in haemoglobin concentration	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Day 8	1	101	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.11, -0.02]
7.2 Day 15	1	102	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.08, 0.02]
7.3 Day 29	1	101	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.06, 0.07]
7.4 Day 43	1	99	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.10, 0.04]

Comparison 6. ALL TREATMENTS COMBINED

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with gametocytes at day 8 (microscopy)	7	1322	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.30, 0.43]
1.1 Non-artemisinin-based partner drug	4	446	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.51, 0.76]
1.2 Artemisinin-based partner drug	4	876	Risk Ratio (M-H, Fixed, 95% CI)	0.12 [0.08, 0.20]

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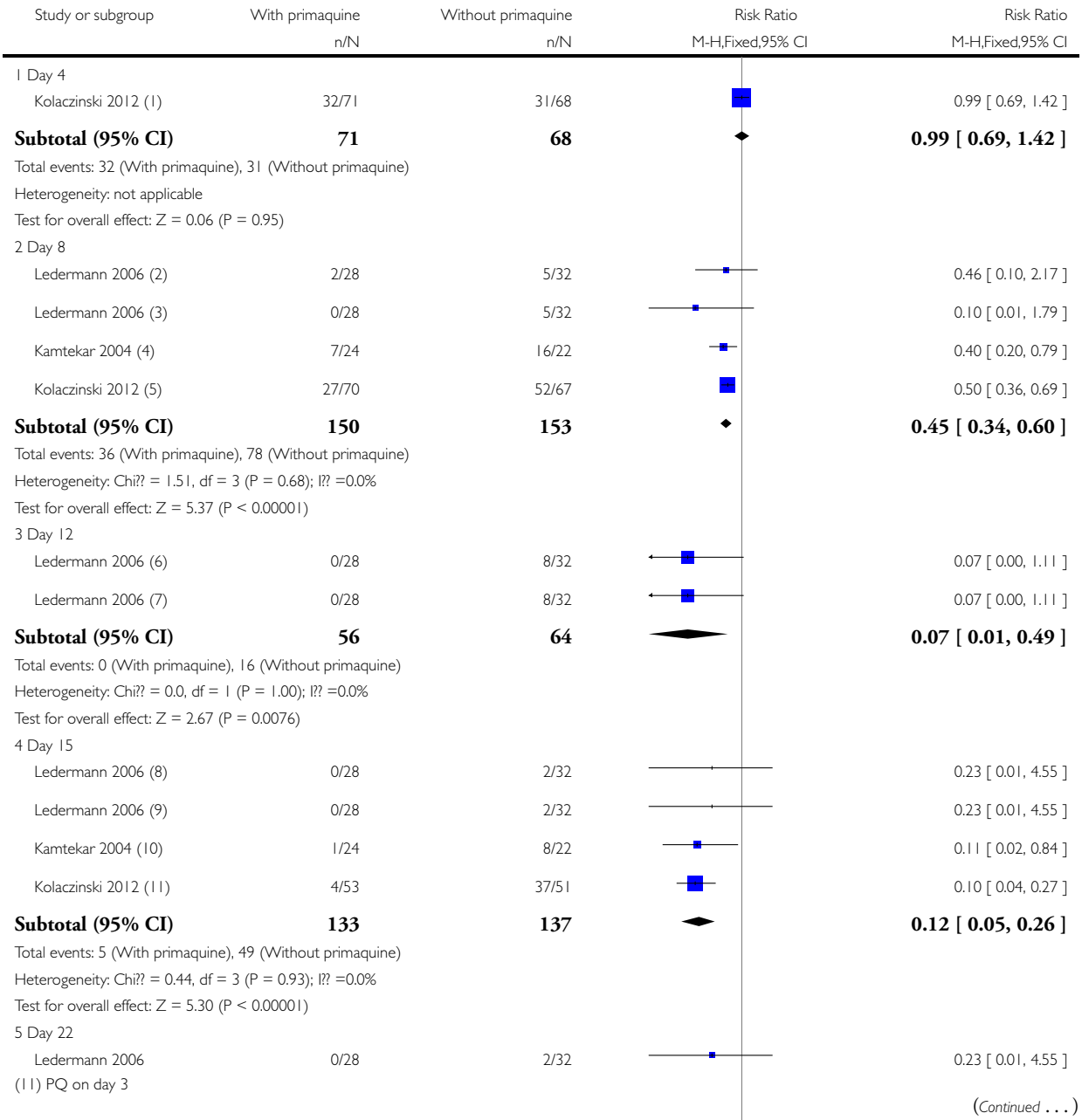
Analysis 1.1. Comparison 1 GIVEN WITH CQ, OR CQ+SP, Outcome 1 Participants with gametocytes.

Review: Primaquine for reducing *Plasmodium falciparum* transmission

Comparison: 1 GIVEN WITH CQ, OR CQ+SP

Outcome: 1 Participants with gametocytes



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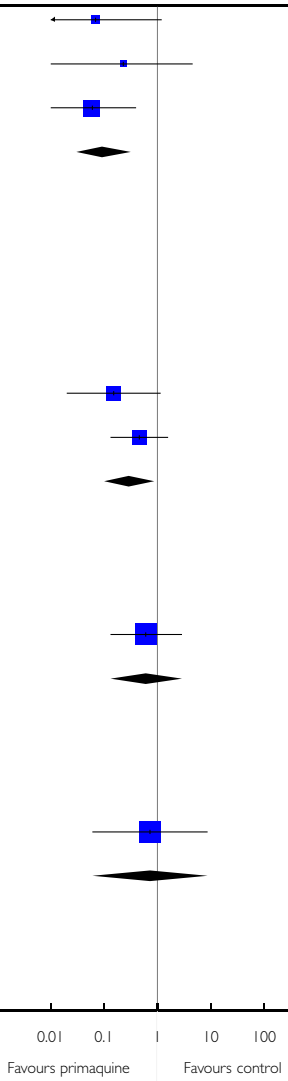
(. . . *Continued*)

Study or subgroup	With primaquine n/N	Without primaquine n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Kamtekar 2004	0/24	6/22		0.07 [0.00, 1.19]
Ledermann 2006	0/28	2/32		0.23 [0.01, 4.55]
Kolaczinski 2012	1/33	15/28		0.06 [0.01, 0.40]
Subtotal (95% CI)	**113**	**114**		**0.09 [0.03, 0.31]**
Total events: 1 (With primaquine), 25 (Without primaquine)				
Heterogeneity: Chi?? = 0.99, df = 3 (P = 0.80); I?? =0.0%				
Test for overall effect: Z = 3.81 (P = 0.00014)				
6 Day 29				
Ledermann 2006	0/28	0/32		0.0 [0.0, 0.0]
Ledermann 2006	0/28	0/32		0.0 [0.0, 0.0]
Kamtekar 2004	1/24	6/22		0.15 [0.02, 1.17]
Kolaczinski 2012	3/20	5/15		0.45 [0.13, 1.59]
Subtotal (95% CI)	**100**	**101**		**0.29 [0.10, 0.86]**
Total events: 4 (With primaquine), 11 (Without primaquine)				
Heterogeneity: Chi?? = 0.83, df = 1 (P = 0.36); I?? =0.0%				
Test for overall effect: Z = 2.24 (P = 0.025)				
7 Day 36				
Kolaczinski 2012	2/10	3/9		0.60 [0.13, 2.82]
Subtotal (95% CI)	**10**	**9**		**0.60 [0.13, 2.82]**
Total events: 2 (With primaquine), 3 (Without primaquine)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.65 (P = 0.52)				
8 Day 43				
Kolaczinski 2012	1/7	1/5		0.71 [0.06, 8.90]
Subtotal (95% CI)	**7**	**5**		**0.71 [0.06, 8.90]**
Total events: 1 (With primaquine), 1 (Without primaquine)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.26 (P = 0.79)				



(1) PQ on day 3
(2) PQ on day 1
(3) PQ on day 3
(4) PQ on day 4
(5) PQ on day 3
(6) PQ on day 1
(7) PQ on day 3
(8) PQ on day 1
(9) PQ on day 3
(10) PQ on day 4
(11) PQ on day 3

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Analysis 1.2. Comparison 1 GIVEN WITH CQ, OR CQ+SP, Outcome 2 Participants with asexual parasites (treatment failure day 29).

Review: Primaquine for reducing *Plasmodium falciparum* transmission

Comparison: 1 GIVEN WITH CQ, OR CQ+SP

Outcome: 2 Participants with asexual parasites (treatment failure day 29)

Study or subgroup	With primaquine n/N	Without primaquine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Not PCR adjusted					
Kolaczinski 2012	49/67	55/68		100.0 %	0.90 [0.75, 1.09]
Subtotal (95% CI)	**67**	**68**		**100.0 %**	**0.90 [0.75, 1.09]**
Total events: 49 (With primaquine), 55 (Without primaquine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.06 (P = 0.29)					
2 PCR adjusted					
Kolaczinski 2012	36/67	42/68		100.0 %	0.87 [0.65, 1.16]
Subtotal (95% CI)	**67**	**68**		**100.0 %**	**0.87 [0.65, 1.16]**
Total events: 36 (With primaquine), 42 (Without primaquine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.94 (P = 0.35)					
Test for subgroup differences: Chi?? = 0.05, df = 1 (P = 0.83), I?? =0.0%					

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Analysis 2.1. Comparison 2 GIVEN WITH SP, Outcome 1 Participants with gametocytes.

Review: Primaquine for reducing *Plasmodium falciparum* transmission

Comparison: 2 GIVEN WITH SP

Outcome: 1 Participants with gametocytes

Study or subgroup	With primaquine n/N	Without primaquine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Day 2					
Kolaczinski 2012	10/40	18/44		100.0 %	0.61 [0.32, 1.16]
Subtotal (95% CI)	**40**	**44**		**100.0 %**	**0.61 [0.32, 1.16]**
Total events: 10 (With primaquine), 18 (Without primaquine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.50 (P = 0.13)					
2 Day 3					
Kolaczinski 2012	14/39	21/44		100.0 %	0.75 [0.45, 1.27]
Subtotal (95% CI)	**39**	**44**		**100.0 %**	**0.75 [0.45, 1.27]**
Total events: 14 (With primaquine), 21 (Without primaquine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.07 (P = 0.28)					
3 Day 4					
Kolaczinski 2012	12/38	23/44		100.0 %	0.60 [0.35, 1.04]
Subtotal (95% CI)	**38**	**44**		**100.0 %**	**0.60 [0.35, 1.04]**
Total events: 12 (With primaquine), 23 (Without primaquine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.81 (P = 0.071)					
4 Day 8					
Kolaczinski 2012	24/36	37/43		100.0 %	0.77 [0.60, 1.01]
Subtotal (95% CI)	**36**	**43**		**100.0 %**	**0.77 [0.60, 1.01]**
Total events: 24 (With primaquine), 37 (Without primaquine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.92 (P = 0.055)					
5 Day 15					
Kolaczinski 2012	18/32	34/41		100.0 %	0.68 [0.48, 0.95]
Subtotal (95% CI)	**32**	**41**		**100.0 %**	**0.68 [0.48, 0.95]**
Total events: 18 (With primaquine), 34 (Without primaquine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.27 (P = 0.023)					
6 Day 22					
Kolaczinski 2012	14/33	33/40		100.0 %	0.51 [0.34, 0.78]
Subtotal (95% CI)	**33**	**40**		**100.0 %**	**0.51 [0.34, 0.78]**

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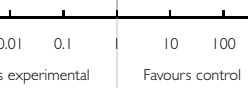
Study or subgroup	With primaquine n/N	Without primaquine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 14 (With primaquine), 33 (Without primaquine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.09 (P = 0.0020)					
7 Day 29					
Kolaczinski 2012	7/28	26/38		100.0 %	0.37 [0.19, 0.72]
Subtotal (95% CI)	**28**	**38**		**100.0 %**	**0.37 [0.19, 0.72]**
Total events: 7 (With primaquine), 26 (Without primaquine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.92 (P = 0.0036)					
8 Day 36					
Kolaczinski 2012	3/28	12/34		100.0 %	0.30 [0.09, 0.97]
Subtotal (95% CI)	**28**	**34**		**100.0 %**	**0.30 [0.09, 0.97]**
Total events: 3 (With primaquine), 12 (Without primaquine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.01 (P = 0.044)					
9 Day 43					
Kolaczinski 2012	0/27	4/34		100.0 %	0.14 [0.01, 2.47]
Subtotal (95% CI)	**27**	**34**		**100.0 %**	**0.14 [0.01, 2.47]**
Total events: 0 (With primaquine), 4 (Without primaquine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.34 (P = 0.18)					



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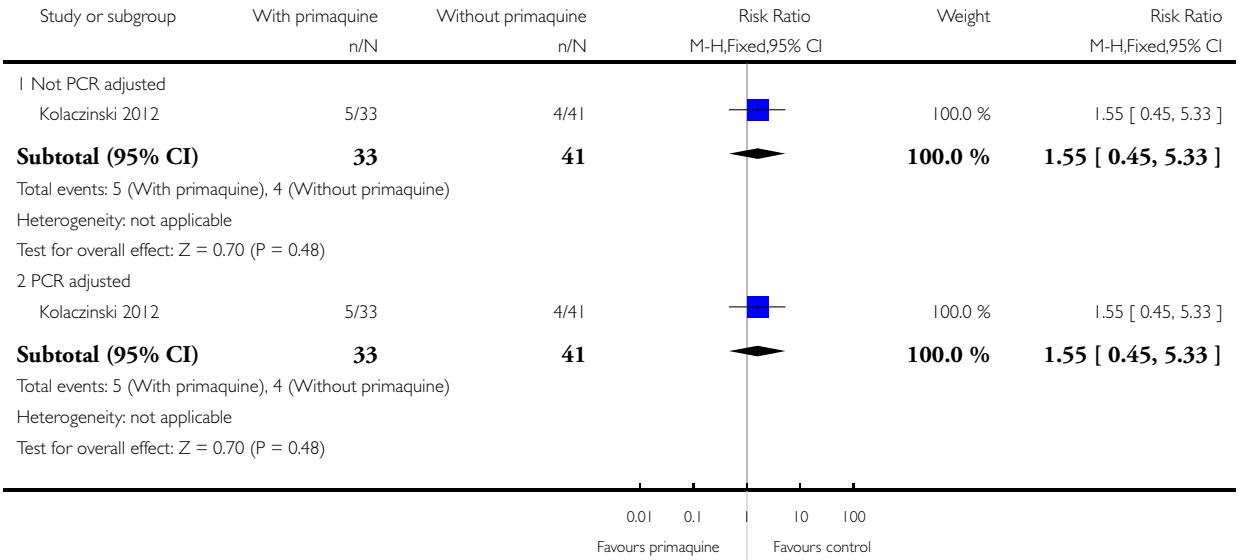
Analysis 2.2. Comparison 2 GIVEN WITH SP, Outcome 2 Participants with asexual parasites (treatment failure day 29).

Review: Primaquine for reducing *Plasmodium falciparum* transmission

Comparison: 2 GIVEN WITH SP

Outcome: 2 Participants with asexual parasites (treatment failure day 29)



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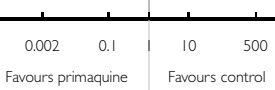
Analysis 3.1. Comparison 3 GIVEN WITH MQ, OR MQ+SP, Outcome 1 Participants infectious.

Review: Primaquine for reducing *Plasmodium falciparum* transmission

Comparison: 3 GIVEN WITH MQ, OR MQ+SP

Outcome: 1 Participants infectious

Study or subgroup	WIth primaquine n/N	Without primaquine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Day 5					
Chen 1994	0/9	9/9		100.0 %	0.05 [0.00, 0.79]
Subtotal (95% CI)	**9**	**9**		**100.0 %**	**0.05 [0.00, 0.79]**
Total events: 0 (WIth primaquine), 9 (Without primaquine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.13 (P = 0.033)					
2 Day 8					
Chen 1994	0/9	8/9		100.0 %	0.06 [0.00, 0.89]
Subtotal (95% CI)	**9**	**9**		**100.0 %**	**0.06 [0.00, 0.89]**
Total events: 0 (WIth primaquine), 8 (Without primaquine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.05 (P = 0.041)					
3 Day 15					
Chen 1994	0/9	4/9		100.0 %	0.11 [0.01, 1.80]
Subtotal (95% CI)	**9**	**9**		**100.0 %**	**0.11 [0.01, 1.80]**
Total events: 0 (WIth primaquine), 4 (Without primaquine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.55 (P = 0.12)					
4 Day 22					
Chen 1994	0/9	1/9		100.0 %	0.33 [0.02, 7.24]
Subtotal (95% CI)	**9**	**9**		**100.0 %**	**0.33 [0.02, 7.24]**
Total events: 0 (WIth primaquine), 1 (Without primaquine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.70 (P = 0.48)					



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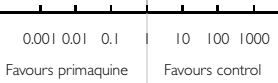
Analysis 3.2. Comparison 3 GIVEN WITH MQ, OR MQ+SP, Outcome 2 Mosquitoes infected.

Review: Primaquine for reducing *Plasmodium falciparum* transmission

Comparison: 3 GIVEN WITH MQ, OR MQ+SP

Outcome: 2 Mosquitoes infected

Study or subgroup	WIth primaquine n/N	Without primaquine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Day 5					
Chen 1994	0/88	47/73		100.0 %	0.01 [0.00, 0.14]
Subtotal (95% CI)	**88**	**73**		**100.0 %**	**0.01 [0.00, 0.14]**
Total events: 0 (WIth primaquine), 47 (Without primaquine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.35 (P = 0.00080)					
2 Day 8					
Chen 1994	0/62	49/90		100.0 %	0.01 [0.00, 0.23]
Subtotal (95% CI)	**62**	**90**		**100.0 %**	**0.01 [0.00, 0.23]**
Total events: 0 (WIth primaquine), 49 (Without primaquine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.99 (P = 0.0028)					
3 Day 15					
Chen 1994	0/81	12/87		100.0 %	0.04 [0.00, 0.71]
Subtotal (95% CI)	**81**	**87**		**100.0 %**	**0.04 [0.00, 0.71]**
Total events: 0 (WIth primaquine), 12 (Without primaquine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.20 (P = 0.028)					
4 Day 22					
Chen 1994	0/88	5/64		100.0 %	0.07 [0.00, 1.18]
Subtotal (95% CI)	**88**	**64**		**100.0 %**	**0.07 [0.00, 1.18]**
Total events: 0 (WIth primaquine), 5 (Without primaquine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.85 (P = 0.065)					



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Analysis 3.3. Comparison 3 GIVEN WITH MQ, OR MQ+SP, Outcome 3 Gametocyte clearance time (days).

Review: Primaquine for reducing *Plasmodium falciparum* transmission

Comparison: 3 GIVEN WITH MQ, OR MQ+SP

Outcome: 3 Gametocyte clearance time (days)

Study or subgroup	Wlth primaquine N	Mean(SD)	Without primaquine N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Singhasivanon 1994	7	7 (2.7)	11	21.9 (4.4)		100.0 %	-14.90 [-18.18, -11.62]
Total (95% CI)	**7**		**11**			**100.0 %**	**-14.90 [-18.18, -11.62]**

Heterogeneity: not applicable

Test for overall effect: Z = 8.90 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 3.4. Comparison 3 GIVEN WITH MQ, OR MQ+SP, Outcome 4 Asexual parasite clearance time (hrs).

Review: Primaquine for reducing *Plasmodium falciparum* transmission

Comparison: 3 GIVEN WITH MQ, OR MQ+SP

Outcome: 4 Asexual parasite clearance time (hrs)

Study or subgroup	Wlth primaquine N	Mean(SD)	Without primaquine N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Singhasivanon 1994	7	93 (15)	11	97 (39.9)		100.0 %	-4.00 [-30.07, 22.07]
Total (95% CI)	**7**		**11**			**100.0 %**	**-4.00 [-30.07, 22.07]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.30 (P = 0.76)

Test for subgroup differences: Not applicable

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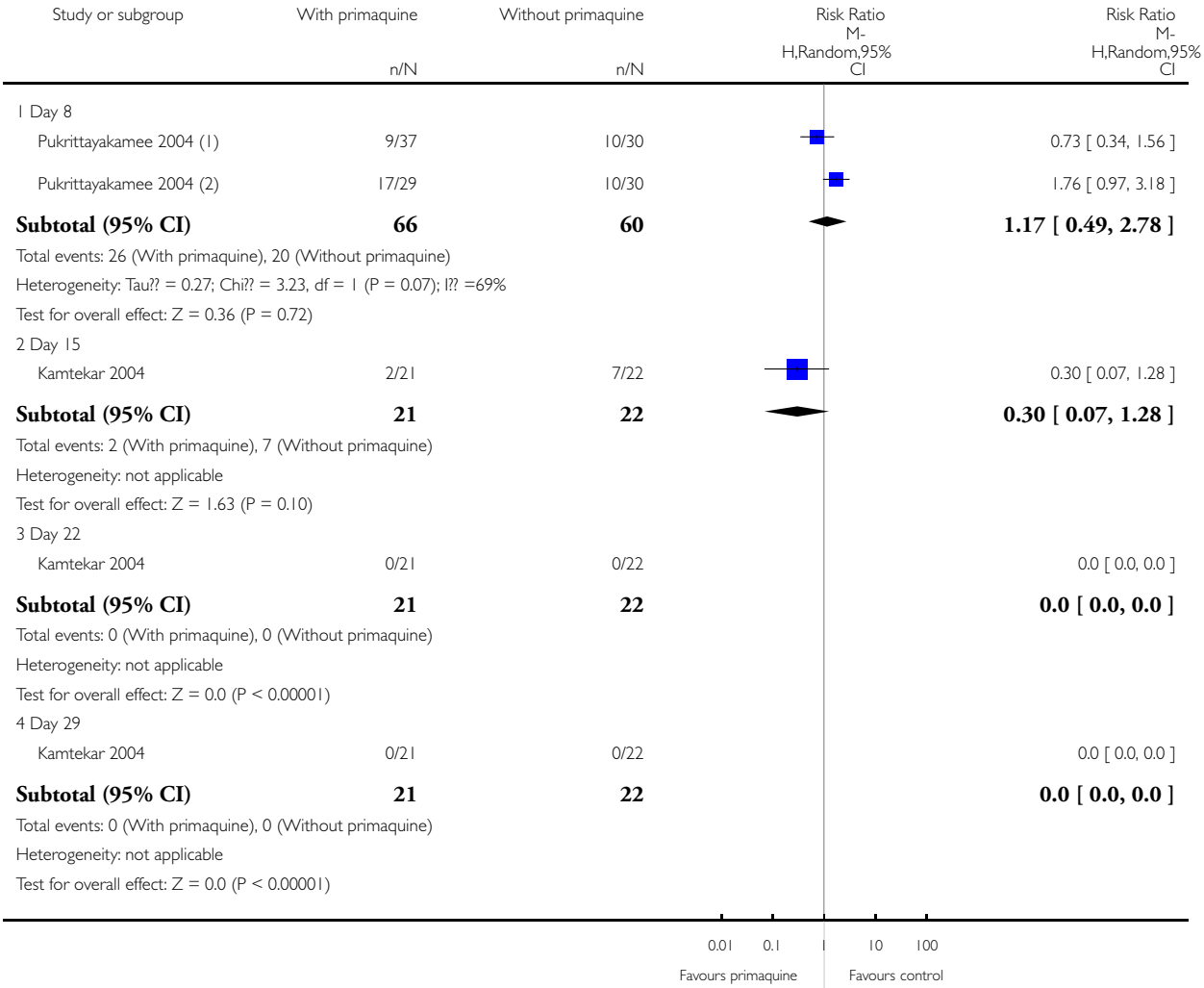
Analysis 4.1. Comparison 4 GIVEN WITH QN, Outcome 1 Participants with gametocytes.

Review: Primaquine for reducing *Plasmodium falciparum* transmission

Comparison: 4 GIVEN WITH QN

Outcome: 1 Participants with gametocytes



(1) PQ 0.5 mg/kg per day on days 1-7

(2) PQ 0.25 mg/kg per day on days 1-7

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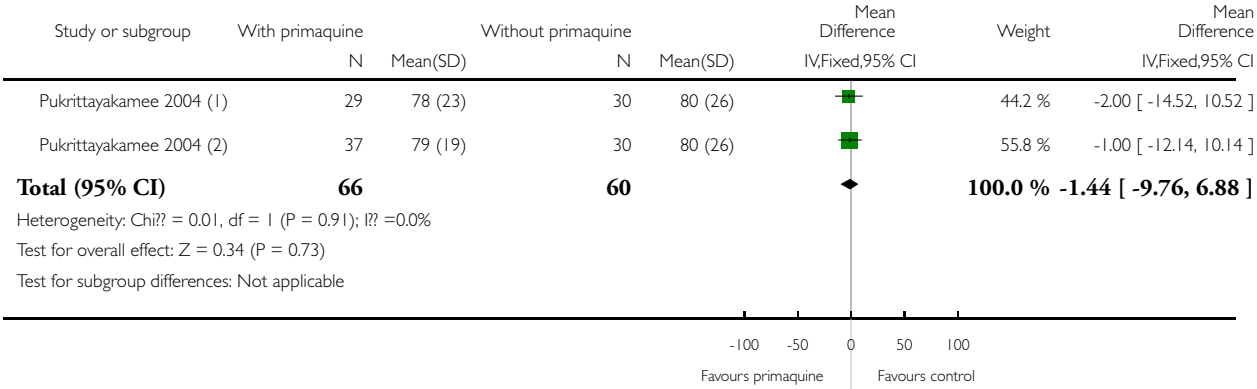
Analysis 4.2. Comparison 4 GIVEN WITH QN, Outcome 2 Asexual parasite clearance time (hours).

Review: Primaquine for reducing *Plasmodium falciparum* transmission

Comparison: 4 GIVEN WITH QN

Outcome: 2 Asexual parasite clearance time (hours)



(1) PQ 0.50 mg/kg per day on days 1-7

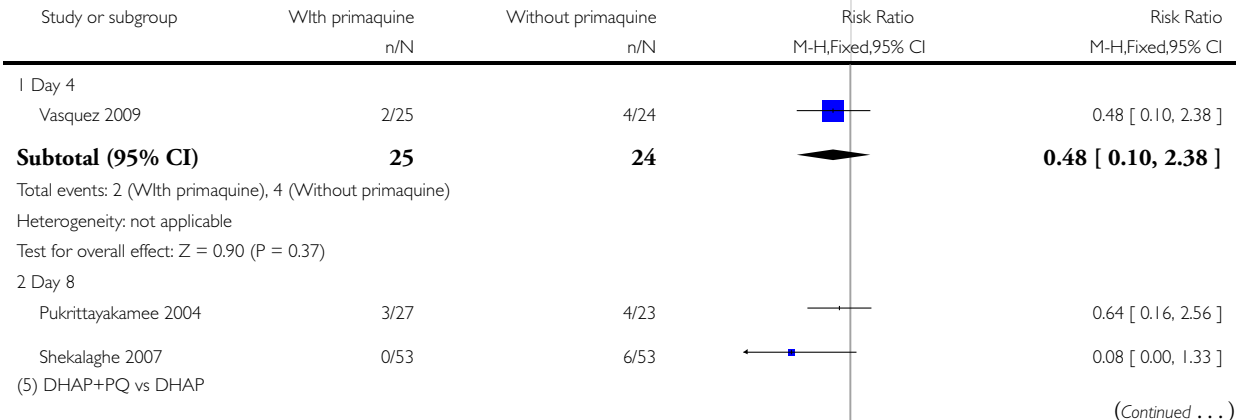
(2) PQ 0.25 mg/kg per day on days 1-7

Analysis 5.1. Comparison 5 GIVEN WITH AS, OR WITH ACTs, Outcome 1 Participants with gametocytes (microscopy).

Review: Primaquine for reducing *Plasmodium falciparum* transmission

Comparison: 5 GIVEN WITH AS, OR WITH ACTs

Outcome: 1 Participants with gametocytes (microscopy)



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Study or subgroup	Wlth primaquine n/N	Without primaquine n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Smithuis 2010 (1)	3/71	24/84		0.15 [0.05, 0.47]
Smithuis 2010 (2)	1/78	28/84		0.04 [0.01, 0.28]
Smithuis 2010 (3)	3/84	17/83		0.17 [0.05, 0.57]
Smithuis 2010 (4)	3/77	18/80		0.17 [0.05, 0.56]
Smithuis 2010 (5)	3/83	24/77		0.12 [0.04, 0.37]
Vasquez 2009	2/25	2/24		0.96 [0.15, 6.28]
Subtotal (95% CI)	**498**	**508**		**0.15 [0.09, 0.24]**
Total events: 18 (Wlth primaquine), 123 (Without primaquine)				
Heterogeneity: Chi?? = 10.21, df = 7 (P = 0.18); I?? =31%				
Test for overall effect: Z = 7.73 (P < 0.00001)				
3 Day 15				
Shekalaghe 2007	0/52	2/52		0.20 [0.01, 4.07]
Smithuis 2010	1/67	18/83		0.07 [0.01, 0.50]
Smithuis 2010	1/73	8/81		0.14 [0.02, 1.08]
Smithuis 2010	0/81	4/80		0.11 [0.01, 2.01]
Smithuis 2010	0/73	4/77		0.12 [0.01, 2.14]
Smithuis 2010	2/80	24/76		0.08 [0.02, 0.32]
Vasquez 2009	0/25	2/23		0.18 [0.01, 3.65]
Subtotal (95% CI)	**451**	**472**		**0.10 [0.04, 0.22]**
Total events: 4 (Wlth primaquine), 62 (Without primaquine)				
Heterogeneity: Chi?? = 0.73, df = 6 (P = 0.99); I?? =0.0%				
Test for overall effect: Z = 5.51 (P < 0.00001)				
4 Day 22				
Smithuis 2010	0/58	15/74		0.04 [0.00, 0.67]
Smithuis 2010	1/69	5/79		0.23 [0.03, 1.91]
Smithuis 2010	0/84	0/79		0.0 [0.0, 0.0]
Smithuis 2010	0/70	0/72		0.0 [0.0, 0.0]
Smithuis 2010	0/78	15/66		0.03 [0.00, 0.45]
Vasquez 2009	0/25	0/22		0.0 [0.0, 0.0]
Subtotal (95% CI)	**384**	**392**		**0.06 [0.01, 0.24]**
Total events: 1 (Wlth primaquine), 35 (Without primaquine)				
Heterogeneity: Chi?? = 1.91, df = 2 (P = 0.38); I?? =0.0%				
Test for overall effect: Z = 3.97 (P = 0.000073)				
5 Day 29				
Shekalaghe 2007	2/51	3/52		0.68 [0.12, 3.90]
Smithuis 2010	0/54	8/75		0.08 [0.00, 1.38]
Smithuis 2010	0/69	0/78		0.0 [0.0, 0.0]
(5) DHAP+PQ vs DHAP				

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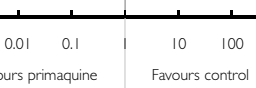
Study or subgroup	Wlth primaquine n/N	Without primaquine n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Smithuis 2010	0/82	0/76		0.0 [0.0, 0.0]
Smithuis 2010	0/67	0/70		0.0 [0.0, 0.0]
Smithuis 2010	0/75	10/77		0.05 [0.00, 0.82]
Vasquez 2009	0/25	0/22		0.0 [0.0, 0.0]
Subtotal (95% CI)	**423**	**450**		**0.15 [0.05, 0.51]**
Total events: 2 (Wlth primaquine), 21 (Without primaquine)				
Heterogeneity: Chi?? = 3.64, df = 2 (P = 0.16); I?? =45%				
Test for overall effect: Z = 3.05 (P = 0.0023)				
6 Day 36				
Smithuis 2010	0/55	0/76		0.0 [0.0, 0.0]
Smithuis 2010	0/70	0/74		0.0 [0.0, 0.0]
Smithuis 2010	0/80	0/79		0.0 [0.0, 0.0]
Smithuis 2010	0/69	0/70		0.0 [0.0, 0.0]
Smithuis 2010	0/71	2/75		0.21 [0.01, 4.32]
Vasquez 2009	0/25	0/22		0.0 [0.0, 0.0]
Subtotal (95% CI)	**370**	**396**		**0.21 [0.01, 4.32]**
Total events: 0 (Wlth primaquine), 2 (Without primaquine)				
Heterogeneity: Chi?? = 0.0, df = 0 (P = 1.00); I?? =0.0%				
Test for overall effect: Z = 1.01 (P = 0.31)				
7 Day 43				
Shekalaghe 2007	0/50	0/52		0.0 [0.0, 0.0]
Smithuis 2010	0/50	1/74		0.49 [0.02, 11.80]
Smithuis 2010	0/62	0/75		0.0 [0.0, 0.0]
Smithuis 2010	0/79	0/76		0.0 [0.0, 0.0]
Smithuis 2010	0/69	1/71		0.34 [0.01, 8.27]
Smithuis 2010	0/71	0/71		0.0 [0.0, 0.0]
Vasquez 2009	0/25	0/22		0.0 [0.0, 0.0]
Subtotal (95% CI)	**406**	**441**		**0.41 [0.04, 3.85]**
Total events: 0 (Wlth primaquine), 2 (Without primaquine)				
Heterogeneity: Chi?? = 0.02, df = 1 (P = 0.88); I?? =0.0%				
Test for overall effect: Z = 0.78 (P = 0.43)				



(1) ASAQ + PQ vs ASAQ

(2) AL+PQ vs AL

(3) AS+MQ (fixed dose) + PQ vs AS+MQ (fixed dose)

(4) AS+MQ (loose) + PQ vs AS+MQ (loose)

(5) DHAP+PQ vs DHAP

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Analysis 5.2. Comparison 5 GIVEN WITH AS, OR WITH ACTs, Outcome 2 Participants with gametocytes (PCR).

Review: Primaquine for reducing *Plasmodium falciparum* transmission

Comparison: 5 GIVEN WITH AS, OR WITH ACTs

Outcome: 2 Participants with gametocytes (PCR)

Study or subgroup	WIth primaquine n/N	Without primaquine n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Day 8				
El-Sayed 2007	4/48	3/46		1.28 [0.30, 5.40]
Shekalaghe 2007	8/51	36/51		0.22 [0.11, 0.43]
2 Day 15				
El-Sayed 2007	3/47	2/45		1.44 [0.25, 8.20]
Shekalaghe 2007	2/51	30/49		0.06 [0.02, 0.25]
3 Day 29				
Shekalaghe 2007	4/46	17/44		0.23 [0.08, 0.62]
4 Day 43				
Shekalaghe 2007	5/40	11/39		0.44 [0.17, 1.16]

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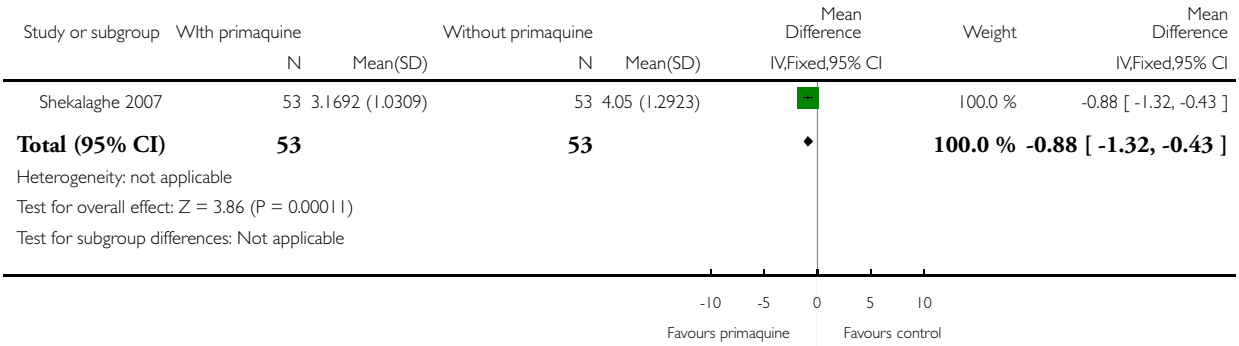
Analysis 5.3. Comparison 5 GIVEN WITH AS, OR WITH ACTs, Outcome 3 Log(10) AUC of gametocyte density over time d1-43.

Review: Primaquine for reducing *Plasmodium falciparum* transmission

Comparison: 5 GIVEN WITH AS, OR WITH ACTs

Outcome: 3 Log(10) AUC of gametocyte density over time d1-43

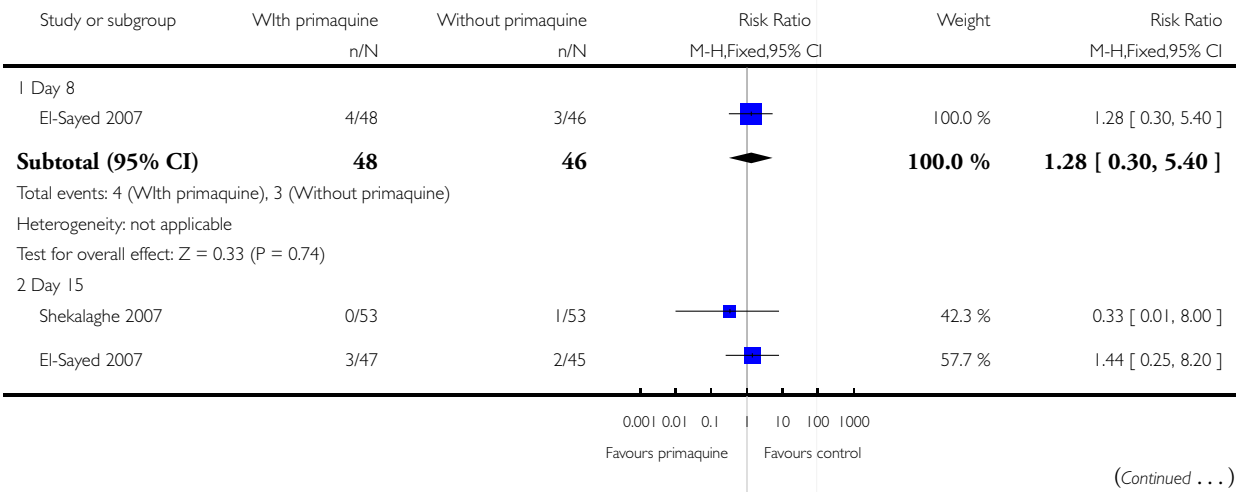


Analysis 5.4. Comparison 5 GIVEN WITH AS, OR WITH ACTs, Outcome 4 Participants with asexual parasites (PCR).

Review: Primaquine for reducing *Plasmodium falciparum* transmission

Comparison: 5 GIVEN WITH AS, OR WITH ACTs

Outcome: 4 Participants with asexual parasites (PCR)



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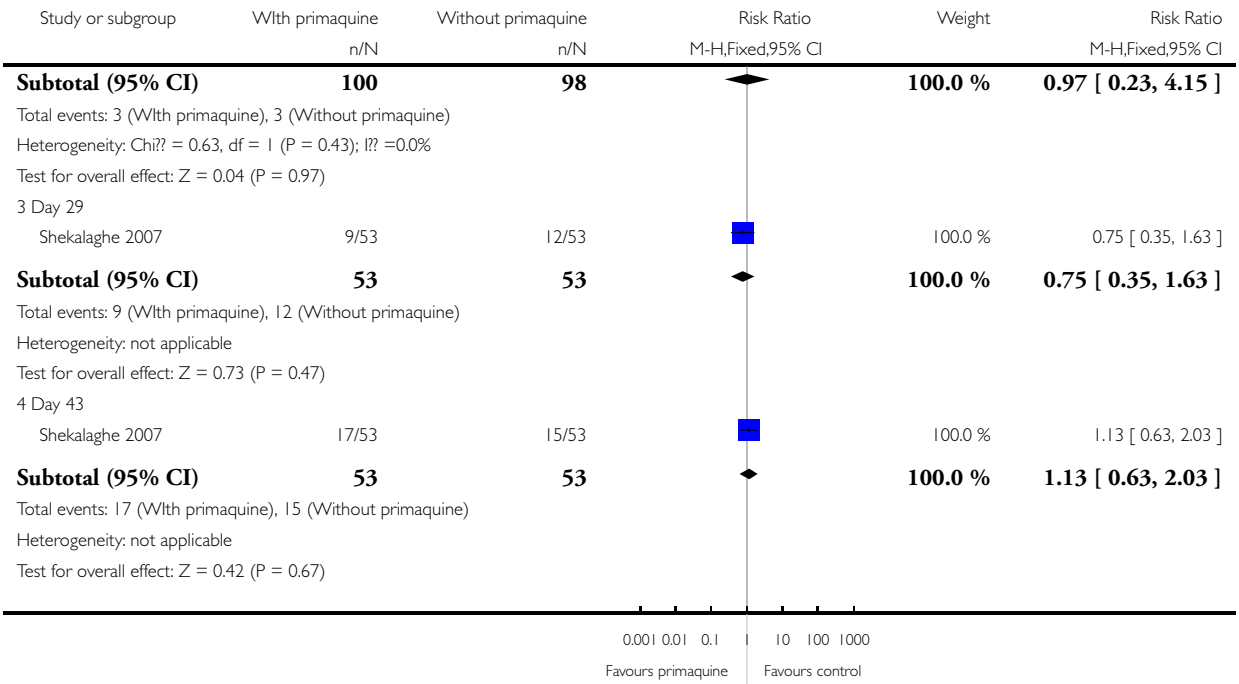
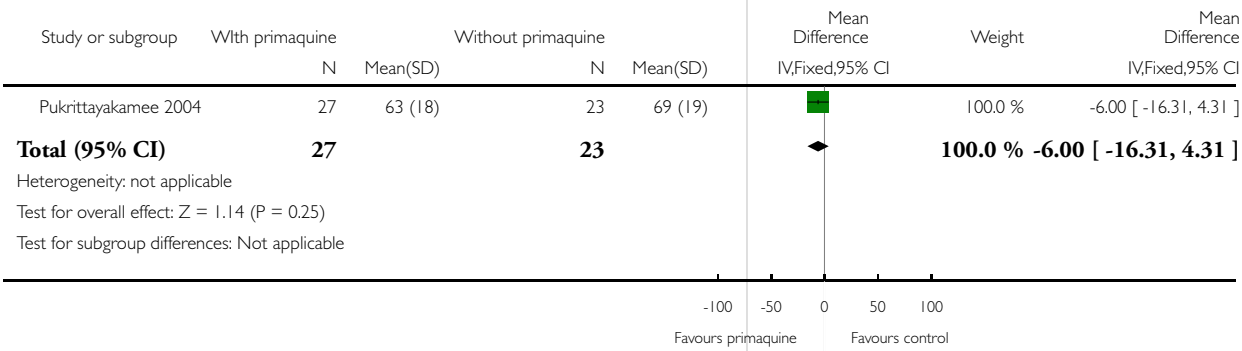


Analysis 5.5. Comparison 5 GIVEN WITH AS, OR WITH ACTs, Outcome 5 Asexual parasite clearance time.

Review: Primaquine for reducing *Plasmodium falciparum* transmission

Comparison: 5 GIVEN WITH AS, OR WITH ACTs

Outcome: 5 Asexual parasite clearance time



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Analysis 5.6. Comparison 5 GIVEN WITH AS, OR WITH ACTs, Outcome 6 Haemoglobin concentration.

Review: Primaquine for reducing *Plasmodium falciparum* transmission

Comparison: 5 GIVEN WITH AS, OR WITH ACTs

Outcome: 6 Haemoglobin concentration

Study or subgroup	WIth primaquine N	Mean(SD)	Without primaquine N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Day 8							
Shekalaghe 2007	10.0965 (1.643201)	52	53	10.48 (1.544036)		100.0 %	-0.39 [-1.00, 0.22]
Subtotal (95% CI)	**52**		**53**			**100.0 %**	**-0.39 [-1.00, 0.22]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.24 (P = 0.22)							
2 Day 15							
Shekalaghe 2007	53	10.686 (1.16135)	53	10.73 (1.379669)		100.0 %	-0.04 [-0.53, 0.44]
Subtotal (95% CI)	**53**		**53**			**100.0 %**	**-0.04 [-0.53, 0.44]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.18 (P = 0.86)							
3 Day 29							
Shekalaghe 2007	53	11.448 (1.30371)	52	11.19 (1.3591)		100.0 %	0.26 [-0.25, 0.77]
Subtotal (95% CI)	**53**		**52**			**100.0 %**	**0.26 [-0.25, 0.77]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.99 (P = 0.32)							
4 Day 43							
Shekalaghe 2007	11.79718 (1.625543)	51	52	11.85 (1.273753)		100.0 %	-0.05 [-0.61, 0.52]
Subtotal (95% CI)	**51**		**52**			**100.0 %**	**-0.05 [-0.61, 0.52]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.17 (P = 0.87)							

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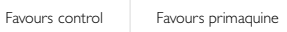
Analysis 5.7. Comparison 5 GIVEN WITH AS, OR WITH ACTs, Outcome 7 % change in haemoglobin concentration.

Review: Primaquine for reducing *Plasmodium falciparum* transmission

Comparison: 5 GIVEN WITH AS, OR WITH ACTs

Outcome: 7 % change in haemoglobin concentration

Study or subgroup	Wlth primaquine N	Mean(SD)	Without primaquine N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Day 8							
Shekalaghe 2007	-0.0513034 (0.1411953)	51	50	0.01 (0.0922952)		100.0 %	-0.06 [-0.11, -0.02]
Subtotal (95% CI)	**51**		**50**			**100.0 %**	**-0.06 [-0.11, -0.02]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.74 (P = 0.0061)							
2 Day 15							
Shekalaghe 2007	0.0148362 (0.134191)	52	50	0.04 (0.1272108)		100.0 %	-0.03 [-0.08, 0.02]
Subtotal (95% CI)	**52**		**50**			**100.0 %**	**-0.03 [-0.08, 0.02]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.06 (P = 0.29)							
3 Day 29							
Shekalaghe 2007	0.0930569 (0.1671262)	52	49	0.09 (0.1698335)		100.0 %	0.00 [-0.06, 0.07]
Subtotal (95% CI)	**52**		**49**			**100.0 %**	**0.00 [-0.06, 0.07]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.09 (P = 0.93)							
4 Day 43							
Shekalaghe 2007	0.1164377 (0.1546697)	50	49	0.15 (0.1973936)		100.0 %	-0.03 [-0.10, 0.04]
Subtotal (95% CI)	**50**		**49**			**100.0 %**	**-0.03 [-0.10, 0.04]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.92 (P = 0.36)							



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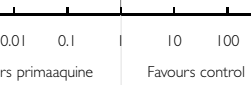
Analysis 6.1. Comparison 6 ALL TREATMENTS COMBINED, Outcome 1 Participants with gametocytes at day 8 (microscopy).

Review: Primaquine for reducing *Plasmodium falciparum* transmission

Comparison: 6 ALL TREATMENTS COMBINED

Outcome: 1 Participants with gametocytes at day 8 (microscopy)

Study or subgroup	with PQ n/N	without PQ n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Non-artemisinin-based partner drug					
Kolaczinski 2012 (1)	27/70	52/67		20.4 %	0.50 [0.36, 0.69]
Kolaczinski 2012 (2)	24/36	37/43		12.9 %	0.77 [0.60, 1.01]
Ledermann 2006 (3)	2/56	5/32		2.4 %	0.23 [0.05, 1.11]
Kamtekar 2004 (4)	7/24	16/22		6.4 %	0.40 [0.20, 0.79]
Pukrittayakamee 2004 (5)	26/66	10/30		5.3 %	1.18 [0.66, 2.13]
Subtotal (95% CI)	**252**	**194**		**47.5 %**	**0.62 [0.51, 0.76]**
Total events: 86 (with PQ), 120 (without PQ)					
Heterogeneity: Chi?? = 12.34, df = 4 (P = 0.02); I?? =68%					
Test for overall effect: Z = 4.80 (P < 0.00001)					
2 Artemisinin-based partner drug					
Pukrittayakamee 2004 (6)	3/27	4/23		1.7 %	0.64 [0.16, 2.56]
Smithuis 2010 (7)	3/68	24/60		9.8 %	0.11 [0.03, 0.35]
Smithuis 2010 (8)	1/71	28/56		12.0 %	0.03 [0.00, 0.20]
Smithuis 2010 (9)	3/81	17/66		7.2 %	0.14 [0.04, 0.47]
Smithuis 2010 (10)	3/74	18/62		7.5 %	0.14 [0.04, 0.45]
Smithuis 2010 (11)	3/80	24/53		11.1 %	0.08 [0.03, 0.26]
Shekalaghe 2007 (12)	0/53	6/53		2.5 %	0.08 [0.00, 1.33]
Vasquez 2009 (13)	2/25	2/24		0.8 %	0.96 [0.15, 6.28]
Subtotal (95% CI)	**479**	**397**		**52.5 %**	**0.12 [0.08, 0.20]**
Total events: 18 (with PQ), 123 (without PQ)					
Heterogeneity: Chi?? = 12.90, df = 7 (P = 0.07); I?? =46%					
Test for overall effect: Z = 8.81 (P < 0.00001)					
Total (95% CI)	**731**	**591**		**100.0 %**	**0.36 [0.30, 0.43]**
Total events: 104 (with PQ), 243 (without PQ)					
Heterogeneity: Chi?? = 77.83, df = 12 (P<0.00001); I?? =85%					
Test for overall effect: Z = 10.70 (P < 0.00001)					
Test for subgroup differences: Chi?? = 39.71, df = 1 (P = 0.00), I?? =97%					



(13) Partner drug AS+MQ; PQ on day 3

(*Continued* . . .)

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(. . . *Continued*)

Study or subgroup	with PQ n/N	without PQ n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
(1) Partner drug CQ: PQ on day 3					
(2) Partner drug SP: PQ on day 1					
(3) Partner drug CQ+SP; PQ on day 1 or 3					
(4) Partner drug CQ or (CQ+SP); PQ on day 4					
(5) Partner drug QN; PQ on days 1-7					
(6) Partner drug AS: PQ on days 1-7					
(7) Partner drug AS+AQ; PQ on day 1					
(8) Partner drug AL; PQ on day 1					
(9) Partner drug AS+MQ (fixed); PQ on day 1					
(10) Partner drug AS+MQ (loose); PQ on day 1					
(11) Partner drug DHAP; PQ on day 1					
(12) Partner drug AS+SP; PQ on day 4					
(13) Partner drug AS+MQ; PQ on day 3					

ADDITIONAL TABLES

Table 1. G6PD status, partner drugs, and PQ dose and treatment schedule

Comparator	Trial	Comparison	Place	G6PD status	Parasite species	Partner drug	PQ day(s) *	PQ dose per day
Non-artemisinin (CQ or CQ+SP)	Kamtekar 2004	a	India (Mumbai)	Not screened	Pf only	CQ days 1-3 or CQ days 1-3 + SP day 1	day 4	45 mg (~0.75 mg/kg)
	Khoo 1981		Malaysia (Sabah)	Only deficient (method: Brewer's methaemoglobin reduction test)	Pf, Pv or mixed	CQ days 1-3	days 1-3	25 mg (~0.42 mg/kg)
	Kolaczinski 2012	a	Pakistan	Not reported	Pf only	CQ days 1-3	day 3	0.5 mg/kg
	Ledermann 2006	a	Indonesia (Central Java)	Only non-deficient (method: semiquantitative glucose-6-phos-	Pf only	CQ days 1-3 + SP day 1	day 1	45 mg (~0.75 mg/kg)

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Table 1. G6PD status, partner drugs, and PQ dose and treatment schedule (*Continued*)

				phate dehydrogenase (G6PD) assay)				
	Ledermann 2006	b	Indonesia (Central Java)	Only non-deficient (method: semiquantitative glucose-6-phosphate dehydrogenase (G6PD) assay)	Pf only	CQ days 1-3 + SP day 1	day 3	45 mg (~0.75 mg/kg)
Non-artemisinin (SP)	Kolaczinski 2012	b	Pakistan	Not reported	Pf only	SP day 1	day 1	0.5 mg/kg
Non-artemisinin (MQ or MQ+SP)	Chen 1994		China (Hainan province)	Not reported	Pf only	MQ day 1	day 1	45 mg (~0.75 mg/kg)
	Singhasivanon 1994		Thailand (Bangkok)	Not reported	Pf only	MQ+SP fixed day 1	day 1	0.75 mg/kg
Non-artemisinin (QN)	Kamtekar 2004	b	India (Mumbai)	Not screened	Pf only	QN iv days 1-2 and orally days 1-7	day 8	45 mg (~0.75 mg/kg)
	Pukrittayakamee 2004	a	Thailand	Patients with G6PD deficiency were excluded from getting PQ (method not reported)	Pf only	QN days 1-7	days 1-7	0.25 mg base/kg
	Pukrittayakamee 2004	b	Thailand	Patients with G6PD deficiency were excluded from getting PQ	Pf only	QN days 1-7	days 1-7	0.5 mg base/kg

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Table 1. G6PD status, partner drugs, and PQ dose and treatment schedule (*Continued*)

				(method not reported)				
Artemisinin-based AS or ACT	El-Sayed 2007		Sudan (east)	Not reported	Pf only	AS+SP days 1-3	day 4	0.75 mg/kg
	Pukrit-tayakamee 2004	c	Thailand	Patients with G6PD deficiency were excluded from getting PQ (method not reported)	Pf only	AS days 1-7	days 1-7	0.5 mg base/kg
	Shekalaghe 2007		Tanzania (North east)	Screened and all included (method: detection of single nucleotide polymorphisms in the human G6PD gene (G202A, A376G) by a simple high throughput PCR using sequence specific oligonucleotide probes (SSOPs) and ELISA testing)	Pf only	AS+SP days 1-3	day 4	0.75 mg/kg
	Smithuis 2010	a	Myanmar (3 states)	Not screened	Pf or mixed	AS+AQ days 1-3	day 1	0.75 mg/kg
	Smithuis 2010	b	Myanmar (3 states)	Not screened	Pf or mixed	AL days 1-3	day 1	0.75 mg/kg

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Table 1. G6PD status, partner drugs, and PQ dose and treatment schedule (*Continued*)

	Smithuis 2010	c	Myanmar (3 states)	Not screened	Pf or mixed	AS+MQ fixed dose days 1-3	day 1	0.75 mg/kg
	Smithuis 2010	d	Myanmar (3 states)	Not screened	Pf or mixed	AS days 1-3 + MQ day 1 loose	day 1	0.75 mg/kg
	Smithuis 2010	e	Myanmar (3 states)	Not screened	Pf or mixed	DHAP days 1-3	day 1	0.75 mg/kg
	Vasquez 2009		Colombia (Antioquia)	Not reported	Pf only	AS+MQ days 1-3 (MQ only on day 2 for children < 6)	day 3	45 mg (~0.75 mg/kg)

* first day of any treatment = day 1
Pf = *P. falciparum;* Pv = *P. vivax*

Table 2. AUC of gametocyte density over time, days 1 to 29 after treatment

Partner drug type	Trial	Partner drug	AUC with PQ days 1-29	AUC without PQ days 1-29	**% reduction AUC days 1-29**	log(10) AUC with PQ days 1-29	log(10) AUC without PQ days 1-29	**% reduction log(10) AUC days 1-29**
Non-artemisinin based	Kolaczinski 2012	CQ	732.98	8777.24	**91.7**	2.87	3.94	**27.3**
	Kolaczinski 2012	SP	2111.55	12847.37	**83.6**	3.32	4.11	**19.1**
Artemisinin based	Shekalaghe 2007	AS+SP	40.30	87.69	**54.0**	1.61	1.94	**17.4**
	Smithuis 2010	AS+AQ	141.08	649.46	**78.3**	2.15	2.81	**23.6**
	Smithuis 2010	AL	197.57	318.23	**37.9**	2.3	2.5	**8.3**
	Smithuis 2010	AS+MQ fixed	240.79	535.40	**55.0**	2.38	2.73	**12.7**

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Table 2. AUC of gametocyte density over time, days 1 to 29 after treatment (*Continued*)

	Smithuis 2010	AS+MQ loose	183.51	321.96	**43.0**	2.26	2.51	**9.7**
	Smithuis 2010	DHAP	307.14	952.93	**67.8**	2.49	2.98	**16.5**
	Vasquez 2009	AS+MQ	526.40	349.04	**-50.8**	2.72	2.54	**-7.0**

Table 3. AUC of gametocyte density over time, days 1 to 43 after treatment

Partner drug type	Trial	Partner drug	AUC with PQ days 1-43	AUC without PQ days 1-43	**% reduction AUC days 1-43**	log(10) AUC with PQ days 1-43	log(10) AUC without PQ days 1-43	**% reduction log(10) AUC days 1-43**
Non-artemisinin based	Kolaczinski 2012	CQ	71.02	279.13	**74.6**	1.85	2.45	**24.3**
	Kolaczinski 2012	SP	85.47	445.65	**80.8**	1.93	2.65	**27.1**
Artemisinin based	Shekalaghe 2007	AS+SP	1.16	3.22	**64.1**	0.06	0.51	**87.5**
	Smithuis 2010	AS+AQ	3.36	19.29	**82.6**	0.53	1.29	**59.1**
	Smithuis 2010	AL	4.70	8.12	**42.1**	0.67	0.91	**26.1**
	Smithuis 2010	AS+MQ fixed	5.73	12.75	**55.0**	0.76	1.11	**31.4**
	Smithuis 2010	AS+MQ loose	4.37	7.74	**43.5**	0.64	0.89	**27.9**
	Smithuis 2010	DHAP	7.38	25.49	**71.1**	0.87	1.41	**38.3**
	Vasquez 2009	AS+MQ	12.53	8.87	**-41.3**	1.10	0.95	**-15.8**

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APPENDICES

Appendix 1. Search strategy

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]
1	malaria	MALARIA, FALCIPARUM/ DRUG THERAPY	MALARIA, FALCIPARUM/ DRUG THERAPY	MALARIA FALCIPARUM/ DRUG THERAPY	Malaria AND falciparum
2	Primaquine	Malaria AND falciparum ti, ab	Malaria AND falciparum ti, ab	Malaria AND falciparum ti, ab	Primaquine*
3	1 and 2	1 or 2	1 or 2	1 or 2	1 and 2
4	-	PRIMAQUINE/ ADMINISTRATION AND DOSAGE/ THERAPEUTIC USE	PRIMAQUINE/ ADMINISTRATION AND DOSAGE/ THERAPEUTIC USE	PRIMAQUINE	-
5	-	Primaquine ti, ab	Primaquine ti, ab	Primaquine ti, ab	-
6	-	4 and 5	4 and 5	4 and 5	-
7	-	3 and 6	3 and 6	3 and 6	-
8	-	-	Limit 7 to Humans	Limit 7 to Human	-

[a] Cochrane Infectious Diseases Group Specialized Register.
[b] Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Lefebvre 2011); upper case: MeSH or EMTREE heading; lower case: free text term.

HISTORY

Protocol first published: Issue 4, 2009

Review first published: Issue 9, 2012

CONTRIBUTIONS OF AUTHORS

Two authors (PMG and HG) independently screened all abstracts, applied inclusion criteria, and abstracted data. PG helped structure the review, and contributed to the logic framework of the SOF tables. All authors contributed to the writing of the review, the interpretation of the results, and the conclusions drawn.

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DECLARATIONS OF INTEREST

We certify that we have no affiliations with or involvement in any organization or entity with a direct financial interest in the subject matter of the review (eg employment, consultancy, stock ownership, honoraria, expert testimony).

This review and the salary of PG is supported by a DFID grant aimed at ensuring the best possible systematic reviews, particularly Cochrane Reviews, are completed on topics relevant to the poor in low- and middle-income countries. DFID does not participate in the selection of topics, in the conduct of the review, or in the interpretation of findings.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Department for International Development, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1) After reading the trials, several new outcomes were added and some outcomes were modified; two outcomes were deleted.

Changes to Primary outcomes:

- Proportion of participants with gametocytes (ADDED: by microscopy and PCR).
- ADDED: Proportion of participants infectious.
- ADDED: Gametocyte density (by microscopy and PCR).
- ADDED: Gametocyte clearance time (also called duration of gametocyte carriage).

The primary outcomes were ordered to capture the three categories: transmission intensity, infectiousness, and potential infectiousness.

Changes to Secondary outcomes:

- DELETED: AUC of asexual parasite density over time. No relevant data were identified.
- ADDED: Asexual clearance time.

Changes to Adverse events:

- DELETED: All adverse events (data reported was minimal and not in a form that was easily summarised. The main question is whether there are serious adverse events).

- Haemolysis or drop in haemoglobin or PCV (as assessed/defined in each trial). (MODIFIED BY deleting reference to G6PD since these outcomes occur in non-G6PD people too. MODIFIED by adding PCV since this was used in some trials as measure of anaemia).

2) We deleted the objective: "To compare the effects of different doses and schedules of PQ given to reduce infectiousness" and the definition of 'control' in comparisons was modified accordingly. Only controls without PQ were included. Comparison of different doses of PQ with identical partner drug was deleted since it does not answer the important question of whether adding PQ is effective.

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One trial with two arms using different doses of PQ with same partner drug was included as two separate arms within the same comparison.

3) We planned to use the following comparisons described in the protocol:

- CQ (with and without PQ, or with different doses of PQ)
- SP (with and without PQ, or with different doses of PQ)
- CQ plus sulfadoxine + pyrimethamine (with and without PQ, or with different doses of PQ)
- Artemisinin derivatives (with and without PQ, or with different doses of PQ)
- Other drugs (with and without PQ, or with different doses of PQ)

In the review, the groups changed, some were added, and some were combined for the following reasons:

a) some trials combined two types of partner drug, not distinguishing the patients who received each one (eg CQ or CQ plus SP).

b) there were many different artemisinin derivatives and combinations tested, with few trials of each, so these were grouped within the same comparison. Combinations of an artemisinin derivative with SP were also grouped here.

3) There were no cluster-RCTs so we deleted how we would manage them from the methods. If we include any cluster-randomized trials in future editions, we will check that trials have correctly adjusted for clustering and, if not, attempt to make this adjustment. When the analyses have not adjusted for clustering, we will make attempts to adjust the results for clustering by multiplying the standard errors of the estimates by the square root of the design effect, where the design effect is calculated as DEff=1+(m-1)*ICC. This assumes that the necessary information is reported, ie the average cluster size (m) and the intra-cluster correlation coefficient (ICC).

4) We intended a sensitivity analysis to investigate the robustness of the results to the quality (risk of bias) components, but were unable to do so as there were insufficient trials. If appropriate and necessary, we will conduct sensitivity analysis on cluster-randomized trials using a range of estimates for the ICC to see if clustering could influence the individual trial's result.

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