Primaquine or other 8-aminoquinoline for reducing Plasmodium falciparum transmission (Review)

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Primaquine or other 8-aminoquinoline for reducing *Plasmodium falciparum* transmission

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**Abstract**

**Background**

Mosquitoes become infected with *Plasmodium* when they ingest gametocyte-stage parasites from an infected person's blood. *Plasmodium falciparum* gametocytes are sensitive to 8-aminoquinolines (8AQ), and consequently these drugs could prevent parasite transmission from infected people to mosquitoes and reduce the incidence of malaria. However, when used in this way, these drugs will not directly benefit the individual.

In 2010, the World Health Organization (WHO) recommended a single dose of primaquine (PQ) at 0.75 mg/kg alongside treatment for *P. falciparum* malaria to reduce transmission in areas approaching malaria elimination. In 2013, the WHO revised this to 0.25 mg/kg to reduce risk of harms in people with G6PD deficiency.

**Objectives**

To assess the effects of PQ (or an alternative 8AQ) given alongside treatment for *P. falciparum* malaria on malaria transmission and on the occurrence of adverse events.

**Search methods**

We searched the following databases up to 5 January 2015: the Cochrane Infectious Diseases Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (Issue 1, 2015); MEDLINE (1966 to 5 January 2015); EMBASE (1980 to 5 January 2015); LILACS (1982 to 5 January 2015); metaRegister of Controlled Trials (mRCT); and the WHO trials search portal using 'malaria*', 'falciparum', 'primquine', 8-aminoquinoline and eight individual 8AQ drug names as search terms. In addition, we searched conference proceedings and reference lists of included studies, and contacted researchers and organizations.

**Selection criteria**

Randomized controlled trials (RCTs) or quasi-RCTs in children or adults, comparing PQ (or alternative 8AQ) as a single dose or short course alongside treatment for *P. falciparum* malaria, with the same malaria treatment given without PQ/8AQ.
Data collection and analysis

Two review authors independently screened all abstracts, applied inclusion criteria and extracted data. We sought evidence of an impact on transmission (community incidence), infectiousness (mosquitoes infected from humans) and potential infectiousness (gametocyte measures). We calculated the area under the curve (AUC) for gametocyte density over time for comparisons for which data were available. We sought data on haematological and other adverse effects, asexual parasite clearance time and recrudescence. We stratified the analysis by artemisinin and non-artemisinin treatments; and by PQ dose (low < 0.4 mg/kg; medium ≥ 0.4 to < 0.6 mg/kg; high ≥ 0.6 mg/kg). We used the GRADE approach to assess evidence quality.

Main results

We included 17 RCTs and one quasi-RCT. Eight trials tested for G6PD status: six then excluded participants with G6PD deficiency, one included only those with G6PD deficiency, and one included all irrespective of status. The remaining 10 trials either did not report on whether they tested (eight trials), or reported that they did not test (two trials).

Nine trials included study arms with artemisinin-based treatments and eleven included study arms with non-artemisinin-based treatments.

Only one trial evaluated PQ given as a single dose of less than 0.4 mg/kg.

**PQ with artemisinin-based treatments:** No trials evaluated effects on malaria transmission directly (incidence, prevalence or entomological inoculation rate) and none evaluated infectiousness to mosquitoes. For potential infectiousness, the proportion of people with detectable gametocytes on day eight was reduced by around two-thirds with the high dose PQ category (RR 0.29, 95% confidence interval (CI) 0.22 to 0.37; seven trials, 1380 participants, *high quality evidence*) and the medium dose PQ category (RR 0.30, 95% CI 0.16 to 0.56; one trial, 219 participants, *moderate quality evidence*). For the low dose category, the effect size was smaller and the 95% CIs include the possibility of no effect (dose: 0.1 mg/kg: RR 0.67, 95% CI 0.44 to 1.02; one trial, 223 participants, *low quality evidence*). Reductions in log(10)AUC estimates for gametocyte density on days 1 to 43 with medium and high doses ranged from 24.3% to 87.5%. For haemolysis, one trial reported percent change in mean haemoglobin against baseline and did not detect a difference between the two arms (*very low quality evidence*).

**PQ with non-artemisinin treatments:** No trials assessed effects on malaria transmission directly. Two small trials from the same laboratory in China evaluated infectiousness to mosquitoes, and reported that infectivity was eliminated on day 8 in 15/15 patients receiving high dose PQ compared to 1/15 in the control group (*low quality evidence*). For potential infectiousness, the proportion of people with detectable gametocyte infection on day 8 was reduced by three-fifths with high dose PQ category (RR 0.39, 95% CI 0.25 to 0.62; four trials, 186 participants, *high quality evidence*), and by around two-fifths with medium dose category (RR 0.60, 95% CI 0.49 to 0.75; one trial, 216 participants, *high quality evidence*), with no trial in the low dose PQ category reporting this outcome. Reduction in log(10)AUC for gametocyte density days 1 to 43 were 24.3% and 27.1% for two arms in one trial giving medium dose PQ. No trials systematically sought evidence of haemolysis.

Two trials evaluated the 8AQ bulaquine, and suggest the effects may be greater than PQ, but the small number of participants (N = 112) preclude a definite conclusion.

**Authors’ conclusions**

In individual patients, PQ added to malaria treatments reduces gametocyte prevalence, but this is based on trials using doses of more than 0.4 mg/kg. Whether this translates into preventing people transmitting malaria to mosquitoes has rarely been tested in controlled trials, but there appeared to be a strong reduction in infectiousness in the two small studies that evaluated this. No included trials evaluated whether this policy has an impact on community malaria transmission.

For the currently recommended low dose regimen, there is currently little direct evidence to be confident that the effect of reduction in gametocyte prevalence is preserved, or that it is safe in people with G6PD deficiency.

**Plain language summary**

A single dose of primaquine added to malaria treatment to prevent malaria transmission

We conducted a review of the effects of adding a single dose (or short course) of primaquine to malaria treatment with the aim of reducing the transmission of malaria. We searched the literature up to 05 January 2015 and included 17 randomized controlled trials (RCTs) and one quasi-RCT.
What is primaquine and how might it reduce transmission

Primaquine is an antimalarial drug which does not cure malaria illness, but is known to kill the gametocyte stage of the malaria parasite which infects mosquitoes when they bite humans. Primaquine is also known to have potentially serious side effects in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency, an enzyme deficiency common in many malaria endemic settings. In these people, high doses of primaquine given over several days damages red blood cells and causes anaemia, and sometimes these events may be life-threatening.

The World Health Organization (WHO) recommends adding a single dose of primaquine to falciparum malaria treatment with the intention of reducing malaria transmission and to contribute to malaria elimination. In 2013, the WHO amended their guideline, reducing the PQ dose from 0.75 mg/kg to 0.25 mg/kg to reduce the risk of haemolysis, combined with indirect evidence suggesting this was as effective as the higher dose.

What the research says

We found no eligible studies that tested whether primaquine added to malaria treatment reduces community transmission of malaria.

When added to currently recommended treatments for malaria (artemisinin-based combination therapy), we found no studies evaluating the effects of primaquine on the number of mosquitoes infected. However, primaquine does reduce the duration of infectiousness of the human host to mosquitoes (defined as the period that gametocytes are detected circulating in the blood) when given at doses greater than 0.6 mg/kg (high quality evidence) and at doses between 0.4 and 0.6 mg/kg (moderate quality evidence). We only found one study using 0.1 mg/kg with an estimate consistent with a smaller reduction in gametocytes, but the analysis was underpowered and did not reach statistical significance (low quality evidence).

In older studies when used with treatments not currently recommended, two studies showed that primaquine at doses of 0.75 mg/kg reduced the number of mosquitoes infected after biting humans (low quality evidence). Doses above 0.4 mg/kg reduced the duration of detectable gametocytes (high quality evidence). No studies examined primaquine using the low dose currently recommended.

Some studies excluded patients with G6PD deficiency, some included them and some did not comment. Overall the safety of PQ given as a single dose was poorly evaluated across all studies, so these data do not demonstrate whether the drug is safe or potentially harmful at dosing levels currently recommended.
### Summary of Findings for the Main Comparison

| Outcomes | Illustrative comparative risks* (95% CI) | Relative effect (95% CI) | Number of participants (trials) | Quality of the evidence (GRADE) |
|----------|-----------------------------------------|--------------------------|---------------------------------|---------------------------------|
|          | Assumed risk                            | Corresponding risk        |                                 |                                 |
|          | Control                                 | PQ                       |                                 |                                 |
| Malaria incidence, prevalence or EIR | -                                      | -                        |                                 | -                               |
| People infectious to mosquitoes    | -                                      | -                        |                                 | -                               |
| Participants with gametocytes on microscopy or PCR  
  (day 8) | Dose <0.4 mg/kg                          | RR 0.67 (0.44 to 1.02)   | 223 (1 trial)                   | ⊕⊕⊕ 2.3.4 low                   |
|                                      | 34 per 100                               | 23 per 100 (15 to 35)    |                                 |                                 |
|                                      | Dose 0.4 to 0.6 mg/kg                    | RR 0.30 (0.16 to 0.56)   | 219 (1 trial)                   | ⊕⊕⊕⊕ 2.4.5.6 moderate           |
|                                      | 35 per 100                               | 11 per 100 (6 to 20)     |                                 |                                 |
|                                      | Dose > 0.6 mg/kg                         | RR 0.29 (0.22 to 0.37)   | 1380 (7 trials)                 | ⊕⊕⊕⊕⊕ high 7.8.9               |
|                                      | 30 per 100                               | 9 per 100 (7 to 11)      |                                 |                                 |

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**PQ for reducing *P. falciparum* transmission with artemisinin-based treatments**

**Patient or population:** People with symptomatic malaria  
**Settings:** Malaria-endemic areas  
**Intervention:** Single dose or short course PQ plus malaria treatment including an artemisinin derivative  
**Control:** Malaria treatment including an artemisinin derivative, without PQ
The mean percent drop in Hb from baseline in the control group was 15%.

The mean percent drop in Hb from baseline in the intervention groups was 3% lower (from 10% lower to 4% higher).

*The basis for the assumed risk (for example, 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).

PQ: Primaquine; CI: Confidence interval; RR: Risk ratio; AUC: area under curve; G6PD: glucose-6-phosphate dehydrogenase; AS: artesunate; AQ: amodiaquine; DHAP: dihydroxyartemisinin-piperaquine; MQ: mefloquine; AL: artemether-lumefantrine.

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.

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1. AUC estimates (log(10)AUC for day 1 to 43) are included as footnotes for each dosing strata.
2. No serious risk of bias: includes one trial with no risk of bias detected.
3. Downgraded by 2 for very serious imprecision: one small trial with CIs that include 50% reduction and no effect.
4. There was no log(10)AUC day 1 to 43 % reduction data for this dose.
5. Downgraded by 1 for serious imprecision. A single trial with few events.
6. Not downgraded for serious indirectness: however this is a single trial from a single setting.
7. Includes seven trials, with 11 comparisons: one trial included five separate comparisons with AS-AQ, DHAP, AS-MQ, and AL (Smithuis 2010).
8. No serious inconsistency: whilst there is marked quantitative heterogeneity, the studies with no demonstrable effect had few events. Not downgraded.
9. Log(10)AUC day 1 to 43 % reduction: range from 21.1% to 87.5%. We included four trials with 12 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.
10. 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 PQ and those not did not demonstrate a difference at any time point. We presented day 43 in this table.
11. Downgraded by 2 for very serious indirectness: the percentage of people with large drops in haemoglobin, not the mean change in the population, is the important safety outcome; and the estimates are averages in a small population (N = 99) that includes people with normal G6PD function so unlikely to detect effects in a small subgroup with a relatively uncommon adverse event.
BACKGROUND

Malaria is a febrile illness due to infection with the Plasmodium parasite, and is transmitted between humans via mosquitoes. Of the five Plasmodium species known to cause illness in humans, Plasmodium falciparum is the most common, especially in sub-Saharan Africa, and causes the majority of severe illnesses and deaths. The clinical illness develops due to the presence of asexual stage parasites (sporozoites) in the person’s bloodstream, but transmission to mosquitoes is via the sexual stage parasites (gametocytes), which develop from sporozoites at some point after infection.

Artemisinin-based combination therapies (ACTs) are currently recommended worldwide as the primary treatment for symptomatic P. falciparum malaria (WHO 2010). The artemisinin derivatives treat the clinical illness by rapidly reducing the number of circulating schizonts and merozoites, which also reduces the potential for these stages to develop into gametocytes for onward transmission. The artemisinin derivatives have been shown to kill early developing gametocytes, but they have no direct effects on mature gametocytes (Price 1996; Chotivanich 2006; Okell 2008a; Okell 2008b). The partner drugs in ACTs (mefloquine, amodiaquine, piperaquine, lumezantrine and sulfadoxine-pyrimethamine) are schizonticides with variable effects on gametocytes, and none adequately targets mature gametocytes (Drakeley 2006; Barnes 2008). In untreated infection, gametocytes can remain present for months as successive new generations are produced, and even following treatment they may persist for several weeks (Smalley 1977; Eichner 2001; Bousema 2010).

The mean circulation time of a mature P. falciparum gametocyte 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). The infectivity of a person depends on the density of gametocytes in the bloodstream (Carter 1988; Bousema 2012). The percentage of bites on people that result in mosquito infection ranges between 0.3% and 46%, although most estimates are in the range of 1% to 10% (Graves 1988; Killeen 2006; Churcher 2013).

After uptake of a P. falciparum-infected blood-meal 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 when biting the next host. 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 blood-feeding (Rosenberg 1990; Rosenberg 2008).

Primaquine (PQ) is the only drug in common use that is known to kill mature P. falciparum gametocytes (Burgess 1961; Pukrittayakamee 2004; Chotivanich 2006), and with the recent emphasis on malaria elimination, there has been a renewed interest and emerging literature on PQ’s potential value in reducing malaria transmission (Eziefula 2012; White 2012; WHO 2012b; White 2013). PQ is an 8-aminoquinoline (8AQ) whose pharmacokinetic mode of action is not well understood, but it is known to be rapidly metabolized, with a half-life of six hours (White 1992). PQ does not directly affect P. falciparum asexual stages which cause the clinical illness (Arnold 1955; Pukrittayakamee 2004) and does not appear to affect the early or maturing gametocytes (Bhasin 1984; White 2008). Consequently, a combination of PQ and an artemisinin-derivative (as part of ACT) would target all gametocyte stages and have the greatest potential for reducing onward transmission to mosquitoes (WHO 2012b; White 2013).

One of the constraints to widespread use of PQ is that the drug is known to be a haemolytic trigger in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency. The deficiency is X-linked and expressed in a wide variety of variants and levels of G6PD deficit (Howes 2013). PQ can occasionally cause serious haemolytic anaemia, haemoglobinuria and renal failure. The effect depends on the degree of enzyme deficiency, the dose of PQ and the pattern of the exposure. These occasional, but clearly serious, adverse effects have led to a reputation of being “unsafe” although little is known about haemolysis at low doses of PQ (Ashley 2014).

The WHO 2010 Guidelines for the Treatment of Malaria recommended adding a single dose of PQ at 0.75 mg/kg to treatment for uncomplicated P. falciparum malaria in people who are not G6PD-deficient with the goal of reducing transmission at the community level (WHO 2010). However, since testing for G6PD deficiency was rarely done and due to the concerns about the safety of this single dose, the WHO convened a special expert review group in 2012 to reconsider this recommendation (WHO 2012a). The expert group concluded that 1) G6PD testing should be done more widely; 2) countries already implementing single dose PQ should reduce the dose to 0.25 mg/kg in G6PD-deficient patients; and 3) countries not currently implementing single dose PQ but which are targeting malaria elimination, or are threatened by artemisinin resistance, should add 0.25 mg/kg PQ to treatment for uncomplicated P. falciparum malaria (White 2012). This was then incorporated into a revised WHO recommendation (WHO 2012b).

How the intervention might work

A single dose of PQ could contribute to reducing malaria transmission through its effects on mature gametocytes, and it is reasonable to assume that reducing the density and duration of gametocytes in the blood of infected people will reduce the duration of potential infectiousness to mosquitoes at the level of the individual (see Figure 1). However, any subsequent effects on the number of
mosquitoes infected from infected people (infectiousness), or the number of new malaria infections in the community (transmission) cannot be assumed and requires estimation of these effects using reliable methods.

**Figure 1.** Review logic framework: The potential points in the Plasmodium parasite life cycle that could be impacted by PQ and the outcomes used to measure impact.

Infectiousness to mosquitoes can be measured directly by allowing mosquitoes to feed on infected individuals who have been treated with and without PQ (Killeen 2006; Bousema 2012), or estimated indirectly by measuring the infection rates of wild-caught mosquitoes (Graves 1990; Lines 1991). Community-level transmission can be measured through large cluster-randomized trials, or less reliably through controlled before-and-after studies. Within any community there are people who are carriers of *P. falciparum* gametocytes but who do not seek treatment (Bousema 2011). This is most apparent in areas of high endemicity, where much of the adult population has acquired immunity, so low level parasitemias do not produce symptoms. This reservoir of gametocytes in untreated adults will continue to facilitate community level transmission and may dilute any possible effect of PQ in moderate to high level transmission settings. Indeed, these dilutional effects may even be important in low transmission settings.

Recently, with the move toward a target of elimination, some policy makers are considering mass treatment strategies (von Seidlein 2003; Sturrock 2013) 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 or treated, or both, and that this could be effective in reducing or interrupting transmission. This policy is being considered in countries with lower intensity transmission, or 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 question in this effort is whether there is a role for PQ given in addition to curative antimalarial drugs, including ACTs, to further reduce the infection transmissibility (White 2008).

The transmission blocking potential of PQ has also been suggested as a strategy to reduce the spread of artemisinin-resistant parasites in Southeast Asia (Breman 2012).

**Why it is important to do this review**

PQ could play a role in *P. falciparum* malaria control, particularly malaria elimination and possibly eradication. Defining the strategies in which PQ will be most effective depends on getting the details right on dose, timing and the situations in which it is used. Effectiveness may vary considerably, but adverse effects - particularly the haemolytic effects of PQ - occur independently of effectiveness. That is, even if used in situations when it is largely ineffective, the rate of adverse reactions will be constant. Since it is the haemolytic effects that are often foremost in the minds of government health staff, building a case for the use of the drug depends on convincing evidence of its value in malaria control, including in implementation of WHO recommendations. This Cochrane Review makes use of existing data to clarify what is and is not known, and to identify which missing pieces are critical to defining effective uses of PQ.
OBJECTIVES

1. To assess whether giving PQ or other 8AQ in addition to standard treatment for *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) or quasi-RCTs including individual- or cluster-RCTs. Cluster-RCTs must have had at least two clusters per arm.

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 have diagnosed patients by blood slide, rapid diagnostic test or other valid molecular method; for cluster-RCTs, diagnosis could have been 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 or other 8AQ added to malaria treatment(s).

Control
Identical treatment for malaria not including PQ/8AQ (or substituting placebo for PQ/8AQ); or using a different 8AQ with same malaria treatment, or using different dose of PQ/8AQ with same malaria treatment(s).

Types of outcome measures

Primary outcomes

Figure 1 provides an outline of transmission of malaria that helps clarify these terms.

a) Transmission
   - Entomological inoculation rate;
   - Malaria incidence;
   - Malaria prevalence.

b) Infectiousness
   - People who infect mosquitoes;
   - Mosquitoes infected by direct feeding.

c) Potential infectiousness
   - Area under the curve (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).

Adverse events

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

Secondary outcomes

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

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).
Electronic searches

Databases
We searched the following databases up to 5 January 2015 using the search terms and strategy described in Appendix 1: the Cochrane Infectious Diseases Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL), published in The Cochrane Library (Issue 1, 2015); MEDLINE (1966 to 5 January 2015); EMBASE (1980 to 5 January 2015); and LILACS (1982 to 5 January 2015). Also, we checked the metaRegister of Controlled Trials (mRCT) and the WHO trials search portal (both accessed 5 January 2015) using ‘malaria*’, ‘falciparum’, ‘primaquine’, ‘8-aminoquinoline’ and eight other individual 8AQ names 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 the London School of Hygiene and Tropical Medicine who were authors of some of the included and in-progress trials, other trial authors and other experts in the field of malaria chemotherapy, including those based at the WHO.

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

Data collection and analysis

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

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

Characteristics of trial
- Design (RCT or quasi-RCT; type of randomization);
- Dates and duration of trial.

Characteristics of participants
- Number of participants;
- Age and sex of participants;
- Proportion with G6PD deficiency;
- Proportion with gametocytes at onset of trial;
- 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;
- Local endemicity of malaria.

Outcomes data
For each trial, 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 infected 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 trial. 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 number 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 stated) and the method used to determine G6PD deficiency, 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 reached consensus through discussion between all three review authors.

Assessment of risk of bias in included studies

PMG and HG independently assessed the risk of bias of the included trials as recommended in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). For each included trial, 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 of the number randomized), if given. For selective outcome reporting, we stated any discrepancies between the methods and the results 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 could have affected the trial’s results (for example, whether a trial was stopped early or if no sample size calculation was included). We resolved any disagreements through 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).
Figure 2. Risk of bias summary: review authors’ judgements about each risk of bias item for each included trial.
Figure 3. Risk of bias graph: review authors’ judgements about each risk of bias item presented as percentages across all included trials.

Measures of treatment effect

We analysed the data using Review Manager (RevMan). 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. If trials reported gametocyte outcomes for days 1, 8, 15, 29, and 43, we estimated AUC using either the summary gametocyte measures reported by group in the paper or by calculation from individual patient data supplied by the authors. Since few patients had gametocytes up to day 43, we also estimated AUC only up to day 15 and 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 Méndez 2006 in trials assessing gametocytaemia after sulfadoxine-pyrimethamine (SP) treatment. However, Méndez 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. We used the following formulas:

$$\text{AUC (days 1 to 15)} = \frac{((8-1)\cdot(G1+G8)/2)+((15-8)\cdot(G15+G8)/2)}{14}$$ for days 1 through 15

$$\text{AUC (days 1 to 29)} = \frac{((8-1)\cdot(G1+G8)/2)+((15-8)\cdot(G15+G8)/2)+((29-15)\cdot(G29+G15)/2)}{28}$$ for days 1 through 29

$$\text{AUC (days 1 to 43)} = \frac{((8-1)\cdot(G1+G8)/2)+((15-8)\cdot(G15+G8)/2)+((29-15)\cdot(G29+G15)/2)+((43-29)\cdot(G43+G29)/2)}{42}$$ for days 1 through 43

where Gx = mean gametocyte density on day X (estimated using data from all participants still enrolled on day X). We estimated log(10)AUC values using geometric mean gametocyte density. When one trial contained more than one comparison with the same placebo group and there was an analysis total or subtotal, we divided the placebo group participants between the comparisons to avoid underestimating the CI.

Unit of analysis issues

All the included trials were individually randomized and analysed. No cluster-RCTs met the inclusion criteria for the review.

Dealing with missing data

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

Assessment of heterogeneity
We assessed heterogeneity between the trials by examining the forest plots to check for overlapping CIs, using the Chi² test for heterogeneity with a 10% level of significance and the I² statistic with a value of 50% to represent moderate levels of heterogeneity.

Assessment of reporting biases

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

Data synthesis

We stratified trials by non-artemisinin or artemisinin based malaria treatment regimens and described which antimalarial drug was used for each comparison in the footnote. Also we stratified by PQ dose category: low (< 0.4 mg/kg), medium (≥ 0.4 to < 0.6 mg/kg) and high (≥ 0.6 mg/kg dose); by schedule (single dose day 1 or 2, single dose day 3 or 4, and multiple dose days 1 to 7) and grouped the 8AQ drugs as PQ and other. 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, we reported the PQ dose as the adult dose with the equivalent dose reported as mg/kg; most trials stated that the dose was adjusted for children and we made this assumption if not. When there was no statistically significant heterogeneity between trials, we applied the fixed-effect meta-analysis model. When we observed statistically significant heterogeneity within groups that could not be explained by subgroup or sensitivity analyses, we used a random-effects meta-analysis model. When we determined substantial heterogeneity from the assessments of heterogeneity (such as high I² value, low Chi² statistic P value) or when a pooled meta-analysis result was considered meaningless because of clinical heterogeneity, we did not undertake meta-analysis but instead presented a forest plot with the pooled effect suppressed.

Subgroup analysis and investigation of heterogeneity

In our protocol, we stated we would investigate heterogeneity in relation to drug resistance pattern, the parasite density before treatment and the local endemicity of malaria. However, we identified 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

Results of the search

In the first version of this review (Graves 2012), we identified 45 potentially relevant publications from literature searches. Two publications (in different languages) described the same trial (Chen 1994), leaving 44 distinct trials. We excluded 13 at abstract stage, excluded 20 after reading the full text article and included 11 trials in the review.

For the 2014 update, we repeated the searches since we had expanded the scope of the review to include other 8AQ and comparisons of different doses of PQ and other 8AQ. We identified 65 more potential studies in addition to the 45 previously identified, which we rescreened due to revised inclusion criteria. We identified an additional 41 papers from reference lists, personal knowledge of new papers, or people consulted. A further search was done in January 2015 which identified one further abstract for screening. Of the 152 abstracts we screened, we selected 73 for full text review. Five papers were duplicates, we could not locate three articles and we included a total of 18 trials (Figure 4). These 18 trials included a total of 30 distinct comparisons of different malaria treatment drugs, doses or schedules.
Figure 4. Study flow diagram.

111 records identified through database searching
41 additional records identified through other sources

152 records after duplicates removed

152 records screened
79 records excluded

55 full-text articles excluded
47 did not meet the inclusion criteria;
3 awaiting assessment (not located as full text);
5 were duplicates of same article, cited differently.

73 full-text articles assessed for eligibility

18 studies included
Included studies

All 18 included trials were RCTs or quasi-RCTs. Two trials compared PQ and balaquine (BQ), while 16 trials compared PQ versus no PQ. One trial of PQ (Khoo 1981) did not distinguish between short or long course of PQ and therefore no outcomes are included in this review. One trial did not include any gametocyte outcomes (Wang 2006).

Sixteen trials examined the impact of PQ or 8AQ on various measures of potential infectiousness, such as gametocyte prevalence over time or density in participants after treatment, gametocyte clearance time or gametocyte circulation time. Most trials assessed gametocyte prevalence by microscopy but two trials reported both microscopy and PCR (Shekalaghe 2007; Eziefula 2013) and one reported only PCR detection (El-Sayed 2007).

Two trials (Shekalaghe 2007; Eziefula 2013) reported log(10)AUC as a summary combined measure of gametocyte prevalence and density over time, using PCR estimates of density. For gametocytes detected by microscopy, we calculated the outcomes of AUC and log(10)AUC for four additional studies that provided appropriate information, either in the publications or from the authors (Vasquez 2009; Smithuis 2010; Kolaczinski 2012; Sutanto 2013).

For direct measures of infectiousness, two small trials in China (Chen 1993a; Chen 1994) evaluated the infectiousness to mosquitoes of people treated with mefloquine (MQ) compared to MQ+PQ.

Only five trials reported adverse effects quantitatively: three for anaemia outcomes (El-Sayed 2007; Shekalaghe 2007; Eziefula 2013) and two for other outcomes (Wang 2006; Sutanto 2013).

No community trials examining malaria transmission intensity (measuring incidence of malaria, prevalence or EIR) met the inclusion criteria.

Participants

Participants were people attending health clinics for treatment. Four trials did not state the participants’ ages (Chen 1993a; Chen 1994; Khoo 1981; El-Sayed 2007) and three trials included children only: Singhchasivanon 1994 (five to 12 years); Shekalaghe 2007 (three to 15 years); and Eziefula 2013 (one to 10 years). Six trials used a wide age range of children and adults: Wang 2006 (six to 60 years); Vasquez 2009 (≥ one year); Smithuis 2010 (> six months); Arango 2012 (one to 75 years); Kolaczinski 2012 (three to 70 years); and Sutanto 2013 (≥ five years). The remaining five trials included teenagers and adults only: Gogtay 2004 (> 18 years); Kamtekar 2004 (> 16 years); Pukrittayakamee 2004 (15 to 62 years); Gogtay 2006 (> 16 years); and Ledermann 2006 (≥ 15 years). See the Characteristics of included studies section. For G6PD deficiency, two trials did not screen participants (Kamtekar 2004; Smithuis 2010), one trial screened and included all participants (Shekalaghe 2007), one trial included only G6PD-deficient participants (Khoo 1981), six trials included only non-deficient participants (Gogtay 2004; Pukrittayakamee 2004; Gogtay 2006; Ledermann 2006; Eziefula 2013; Sutanto 2013) and the remaining eight studies made no comment (Chen 1993a; Chen 1994; Singhchasivanon 1994; Wang 2006; El-Sayed 2007; Vasquez 2009; Arango 2012; Kolaczinski 2012); see Table 1.

Interventions

Non-artemisinin-based regimens

Eleven trials (15 treatment arms) evaluated PQ or BQ, given alongside non-artemisinin-based treatments.

Nine trials (13 treatment arms) evaluated PQ given alongside the following: chloroquine alone (CQ) (three trials, four arms), CQ alone or CQ+SP (one trial, one arm), SP (one trial, one arm), mefloquine (MQ) (two trials, two arms), MQ+SP (one trial, one arm), quinine (QN) (two trials, three arms), and amodiaquine (AQ)+SP (one trial, one arm).

The analysis enumerating trials by partner drugs gives a total of 20, not 18, because there were two trials that tested two types of non-artemisinin based treatments.

Two trials (two treatment arms) evaluated PQ given alongside the following: QN (one trial, one arm) and QN plus doxycycline (one trial, one arm).

Artemisinin-based regimens

Nine trials (13 treatment arms) evaluated PQ given alongside artemisinin-based treatments: artesunate (AS) (two trials, two arms), AS+SP (two trials, two arms), AS+MQ (three trials, four arms), AS+AQ (one trial, one arm), artemether-lumefantrine (AL) (two trials, four arms) and dihydroxyartemisinin-piperazine (DHAP) (two trials, two arms).

Again, the analysis above enumerating trials by partner drug gives 12, not 9, because one trial tested four different types of artemisinin based treatment.

Dose

Most trials used a target dose equivalent to 0.75 mg/kg PQ per day (adult dose 45 mg/day), see Table 1. The exceptions were:

- Khoo 1981: adult dose of 25 mg or approximately 0.42 mg/kg/day;
- Kolaczinski 2012: (two comparisons) 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);
• Wang 2006: adult dose of 22.5 mg or approximately 0.38 mg/kg per day;
• Eziefula 2013: evaluated 0.1, 0.4 and 0.75 mg/kg and placebo.

The Pukrittayakamee 2004 trial assessed gametocyte prevalence both before and shortly after treatment, presumably on day 1. The average prevalence after treatment was 33.5%, and when combined with the “on admission” rates, the overall gametocyte prevalence was 55.7%, ranging from 37.0% to 72% by group. The details of the trial locations, malaria treatments, gametocyte prevalence, PQ doses and schedules are in Table 1.

Schedule
Most trials used a single dose of PQ given on the following days and we regarded the first day of any treatment as day 1:
• Day 1: Chen 1993a; Chen 1994; Singhasivanon 1994; Ledermann 2006 (one of two comparisons); Smithuis 2010 (five comparisons); and Kolaczinski 2012 (one of two comparisons);
• Day 2: Arango 2012 (two comparisons);
• Day 3: Ledermann 2006 (one of two comparisons);
• Vasquez 2009; Kolaczinski 2012 (one of two comparisons); Eziefula 2013; and Sutanto 2013;
• Day 4: Gogtay 2004; Kamtekar 2004 (one of two comparisons); Gogtay 2006; El-Sayed 2007; and Shekalaghe 2007;
• Day 8: Kamtekar 2004 (one of two comparisons).

Three trials used a longer course of PQ:
• Three days: Khoo 1981;
• Five days: Wang 2006;
• Seven days: Pukrittayakamee 2004 (three comparisons).

Prevalence of gametocytes at start of trial
Five trials included only people with gametocytes at onset (as detected by microscopy) (Chen 1993a; Chen 1994; Gogtay 2004; Kamtekar 2004 (both comparisons); Gogtay 2006). However Kamtekar 2004 reported this variable as “within 3 days” rather than on day 1. Four trials did not report this statistic (Khoo 1981; Singhasivanon 1994; Ledermann 2006 (both comparisons); Wang 2006).

In the remaining trials, one had low gametocyte prevalence at onset (El-Sayed 2007, prevalence by microscopy 3.8%, by PCR 11.8%). Trials with initial prevalence between 17.1% and 27.1% were: Pukrittayakamee 2004 (all three comparisons); Vasquez 2009; Arango 2012; Kolaczinski 2012 (both comparisons); Eziefula 2013; and Sutanto 2013. Shekalaghe 2007 reported gametocyte prevalence by microscopy of 22.6% but by PCR of 87.7%. Eziefula 2013 observed a similar ratio between microscopy and PCR prevalence, with microscopy prevalence by arm of 20.4% to 24.3% and PCR prevalence of 78.4% to 86.7%. Excluding trials that included only gametocyte carriers, the five arms of the Smithuis 2010 trial showed the highest prevalences, with gametocyte prevalence (microscopy) between 29% and 38%.

Outcomes
For malaria transmission intensity (prevalence, incidence or EIR), we found no community cluster-RCTs measuring these outcomes. Regarding infectiousness, two trials (Chen 1993a; Chen 1994) measured this in 12 and 18 patients, respectively, for non-artemisinin drugs (in both cases MQ) with and without PQ. All other trials (except Wang 2006) reported potential infectiousness: the effects of PQ on gametocyte prevalence, density or clearance time, or all three outcomes. Only Shekalaghe 2007 and Eziefula 2013 reported a summary measure of potential infectiousness using AUC of gametocyte density over time; we calculated this for four other trials with available data. We estimated the AUC for microscopy-determined densities for trials of both non-artemisinin and artemisinin-based malaria treatments. In the former category we had only Kolaczinski 2012 (two comparisons). There were four trials with this information for artemisinin-based partners: Shekalaghe 2007, Smithuis 2010 (five comparisons), Sutanto 2013 and Vasquez 2009. The estimate used the mean (or geometric mean) gametocyte density by group at a sequence of reported days of measurement. Since trials were not consistent in the days on which they estimated gametocyte density, we used the days on which measurements were available for all trials (days 1, 8, 15, 29 and 43; see Methods section). We estimated AUC up to day 15 (Table 2), day 29 (Table 3) and day 43 (Table 4). Results are presented separately by non-artemisinin-based and artemisinin-based malaria treatments below and given for log(10)AUC in the ‘Summary of findings’ tables for days 1 to 43.

Wang 2006 reported only asexual stage outcomes and Khoo 1981 reported data that could not be used as the length of PQ course was not clear.

Excluded studies
We have listed the reasons for exclusion of 47 trials in the Characteristics of excluded studies section. Some additional details are given here.
Six community-based trials did not meet criteria for inclusion. Both Hii 1987 (mass drug administration (MDA) with SP+PQ (30 mg adult dose, 0.5 mg/kg) + insecticide treated net (ITN) versus ITN only in Sabah, Malaysia) and Shekalaghe 2011 (MDA with SP+AS+PQ (0.75 mg/kg) versus placebo) did not have appropriate comparison groups. Doi 1989 was a community-based observational trial of mass test and treat with SP+PQ (0.7 to 1 mg/
kg) in one intervention village, two schools in two other intervention villages and one control village (SP only) on the coast of north Sumatra, Indonesia. There was no 'before' data from these villages and in the control site it appears that some children received treatment with PQ. Kaneko 1989, also in north Sumatra, Indonesia, tested mass fever test and treat or mass test and treat, or both, in school children. The drugs used were SP+PQ in one intervention village and SP in one control village. Apart from there being only one cluster (village) per arm and non-randomized, the main reason for exclusion was that the intensity of effort on case detection appeared much greater in the intervention village, resulting in 75% of people in the intervention village being treated over a 29-day period versus 18% in the control village over a 14-day period. The Barber 1932 trial in Liberia was a trial of MDA that administered the 8AQ plasmoquine approximately twice weekly to ~135 people for periods ranging from nine to 28 days with follow-up for several weeks. Plasmoquine had a large (although short-lived) impact on transmission in this trial, as assessed by mosquito infections. However the main reasons for its exclusion were the lack of malaria treatment given together with plasmoquine, non-comparable control site and lack of parasite outcomes in the control group. In the MDA trial of Clyde 1962 in Tanzania, AQ+PQ was given every 1, 2 or 4 weeks to over 93% of the populations residing in three sites near Morogoro, Tanzania for periods ranging by site between 26 and 39 weeks. The dose of PQ was 30 mg (~0.5 mg/kg for an adult) given to everyone over six years of age, with half dose given to those aged between 0 and 5 years. Transmission was greatly reduced, especially in the sites receiving MDA every one or two weeks (although transmission was not interrupted). We excluded this trial because everyone received malaria treatment as well as PQ, so the additional impact of PQ cannot be assessed. We excluded several controlled or uncontrolled before-and-after studies, and non-randomized comparative case series or trials. They were generally studies of small numbers of people on whom mosquitoes were fed before and after they ingested PQ, with or without other malaria treatment. These studies, which include Barber 1929, Barber 1932, Jerace 1933, Mackerras 1949, Jeffery 1956, Young 1959, Gunders 1961, Jeffery 1963, Rieckmann 1968, Rieckmann 1969, Clyde 1970 and Clyde 1971, have been reviewed by White 2012 and White 2013 but did not meet our inclusion criteria. Abay 2013 also reviewed two of these before-and-after studies which had four patients in total (Rieckmann 1968; Clyde 1971). Two studies used varying doses of PQ (Jeffery 1956; Rieckmann 1969), as did Burgess 1961 and Bunnag 1980. However, Burgess 1961 gave doses according to participants’ age rather than testing different doses in comparable patients, and there was no other malaria treatment drug given. In Bunnag 1980 all received malaria treatment (SP) in addition to PQ. We sought publications for Chinese trials cited in White 2012, White 2013 and by personal communication from Professor Li Guo Qiao. We were unable to locate two (Chen 1993b; Li 2006); the others were translated where required. We excluded the following studies on the basis of no appropriate comparison (either all groups got PQ or there was no comparator group with same dose of malaria treatment drug but no PQ) (Che 1987; Yang 1989; Che 1990; Huang 1996; Lin 2004; Sun 2011) or lack of randomization (Cai 1985; Huang 1993). Three other trials of artemether with and without PQ in Africa (Huang 2001; Li 2007; Li 2010) were stated to be randomized, but we excluded them due to the late administration of PQ (after five to seven days of artemether) and lack of gametocyte outcomes.

**Risk of bias in included studies**

Of the 18 included studies, the risk of bias assessment for concealment of allocation was adequate in four trials; methods of random allocation were adequate in 10; and blinding of outcome assessment adequate in seven; see Figure 2 and Figure 3. Pukrittayakamee 2004 excluded G6PD-deficient people from the PQ group post-randomization. We had no reason to suppose it biased the primary outcomes but it could have affected assessment of adverse effects.

**Effects of interventions**

See: Summary of findings for the main comparison Summary of findings table 1; Summary of findings 2 Summary of findings table 2

**PQ as part of non-artemisinin-based treatment regimens (Comparison 1)**

Eleven trials contributed comparisons to this analysis, of which one trial tested both low dose and moderate dose PQ regimens over seven days (Pukrittayakamee 2004) and one trial (two comparisons) tested moderate dose PQ (Kolaczinski 2012) The remainder were high dose. One trial (Kho 1981) did not report results in a usable manner since it did not distinguish between short and long course PQ (for *P. vivax*) in participants.

**Gametocyte prevalence**

There were fewer people with gametocytes (detected by microscopy) in the PQ group at days 8, 15, 22, 29 and 36 (Analysis 1.1). The largest number of trials and comparisons was included at day 8 (RR 0.54, 95% CI 0.44 to 0.65; five trials, 402 participants, seven comparisons) and the effect appeared larger at day 15 (RR 0.31, 95% CI 0.22 to 0.43; four trials, 366 participants, seven comparisons). The trials included three with CQ or CQ combination partner treatment (Kamtekar 2004; Ledermann 2006 (two comparisons); Kolaczinski 2012); one with SP (Kolaczinski 2012); one with AQ+SP (Arango 2012 (one comparison); one with MQ (Chen 1993a); and two with quinine (Kamtekar 2004 (one comparison); Pukrittayakamee 2004 (two comparisons)).
Gametocyte clearance time or duration of gametocyte carriage (the average number of days each person has gametocytes)

The outcome of gametocyte clearance time is presented per person as the number of hours or days until gametocytes disappear, sometimes described as "duration of gametocyte carriage". Pukrittayakamee 2004 makes a distinction between these two parameters, with average gametocyte clearance time being the total hours to permanent disappearance of gametocytes, while gametocyte carriage adjusts for intermittent periods of time without gametocytes. This can obviously only be presented for participants that had gametocytes at onset of the trial, which in this trial included participants with gametocytes shortly after treatment (presumably on day 1) as well as those who had them on admission; PQ was given for seven days in this trial.

Gametocyte clearance time (in days) was significantly reduced in the PQ group in Singhasivanon 1994 (which had MQ+SP partner) with a mean difference of -14.90 days (95% CI -18.18 to -11.62; Analysis 1.2). The median gametocyte clearance time was also reduced in Pukrittayakamee 2004 (two comparisons; partner QN) from 216 (range six to 624) hours with quinine only to 87 (range five to 207 hours) hours with 0.5 mg/kg PQ and to 48 (range six to 324) hours with 0.25 mg/kg PQ: There was no significant difference between the median clearance time in the two PQ arms (P = 0.45).

AUC of gametocyte density over time

Gametocyte density over time up to day 43 was assessed by microscopy in Kolaczinski 2012 (two comparisons). We analysed the data further using the AUC and log(10)AUC measures for days one to 15, one to 29 and one to 43, estimated from data provided by the trial authors (Table 2; Table 3; Table 4). Reductions in AUC for non-artemisinin malaria treatment regimens were 84.5% and 88.6% up to day 15, 83.6% and 91.7% up to day 29, and 74.6% and 80.8% up to day 43 (one trial, two comparisons). Using the log(10)AUC, for non-artemisinin malaria treatment regimens the estimates were 21.4% and 26.0% up to day 15, 19.1% and 27.3% to day 29, and 24.3% and 27.1% to day 43 (one trial, two comparisons).

Infectiousness to mosquitoes

Two small trials in China (Chen 1993a; Chen 1994), with only six and nine participants per group respectively, directly tested the impact of PQ added to MQ on infectiousness to mosquitoes. On day 1 all patients in the trial were infectious to Anopheles dirus mosquitoes, but after a dose of PQ on day 1 the proportion of people infectious was reduced to 0 when measured on days 2, 5 and 8 (Analysis 1.3). By day 15 and day 22 the difference was attenuated as infectiousness in the control group declined. Chen 1994 also reported the number of mosquitoes infected after feeding on trial participants (Analysis 1.4; note the CIs are not corrected for repeated observations in the same patients). 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, with the effect still evident up to day 22, although the proportion infected in the control group declined over time.

Asexual parasites at day 29 (recrudescence or reinfection)

In Kolaczinski 2012 there was no effect of PQ (added to either CQ or SP) on prevalence of asexual parasites at day 29 (parasitological treatment failure), whether or not the results were adjusted for new infections detected by PCR (Analysis 1.5).

Asexual parasite clearance

There was no effect of PQ on asexual clearance time in Singhasivanon 1994 (added to MQ+SP) or Pukrittayakamee 2004 (two comparisons, added to QN) (Analysis 1.6).

Adverse effects

Patients with G6PD deficiency were excluded (two trials), the only patients included (one trial), not screened for (two trials), or not reported or commented on (six trials). The trials with non-artemisinin regimens did not report adverse effects well or consistently. None of these trials reported on haemolysis, other haematological measures or severe adverse events. Singhasivanon 1994 found no difference in frequency of reported adverse effects (nausea, vomiting or dizziness) over 28 days follow-up (Analysis 1.7).

We could not use data from one trial with non-artemisinin partner, CQ, because it did not distinguish between patients with P. falciparum and P. vivax and their respective treatments (Khoo 1981). 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 we could not include the results because the groups combined participants receiving a short course (three days) of PQ with those receiving a 14-day regimen. The most unusual aspect of the trial, however, is that it only included individuals with G6PD deficiency.

Dose and schedule

Dose of PQ

We stratified trials into low, medium and high dose category PQ. Kolaczinski 2012 used the 0.5 mg/kg medium dose in two comparisons (with CQ or SP). Three trials used the high dose category 0.75 mg/kg of PQ: Arango 2012 in one comparison with AQ + SP; Ledermann 2006 in two comparisons, both with CQ+SP; and Kamtekar 2004 in one comparison with CQ or (CQ+SP). No
trials for the outcome of gametocyte prevalence at day 8 used the low dose category. Both the medium and high dose reduced the prevalence of gametocytes at day 8: RR 0.60, 95% CI 0.49 to 0.75 for medium dose, two comparisons; and RR 0.39, 95% CI 0.25 to 0.62 for high dose, five comparisons (Analysis 1.8).

Schedule of PQ

We stratified this comparison into two groups: single dose on day 1 or 2, and single dose day 3 or 4. The comparison is indirect, although the schedule giving PQ on day 3 or 4 seemed to have a greater effect. 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 1.9).

PQ as part of artemisinin-based treatment regimens (Comparison 2)

Nine trials contributed comparisons to this analysis, including ACTs (seven trials) and artemisinin monotherapy (two trials) for malaria treatment. Only one trial tested a low dose PQ regimen with 0.1 mg/kg total dose.

Gametocyte prevalence

Microscopy analysis revealed that PQ clearly reduced the number of people with gametocytes on day 8 (RR 0.21, 95% CI 0.08 to 0.54; five trials, 1071 participants, nine comparisons), day 15 (RR 0.09, 95% CI 0.04 to 0.19; four trials, 995 participants, eight comparisons), day 22 (RR 0.10, 95% CI 0.03 to 0.32; three trials, 858 participants, seven comparisons, four with estimable results) and day 29 (RR 0.17, 95% CI 0.04 to 0.72; four trials, 945 participants, eight comparisons, four with estimable results) (Analysis 2.1). We used the random-effects model due to heterogeneity. In Smithuis 2010, new gametocytinaemia (by microscopy) on day 8 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). Three trials examined gametocytes by PCR rather than (or in addition) to microscopy. In Shkalaghe 2007 and Eziefula 2013, a reduction in gametocyte prevalence was observed on day 8 and day 15 (Analysis 2.2). However, in El-Sayed 2007, giving PQ did not lead to detectably lower numbers of people with gametocytes 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 trial estimates (related to different numbers of participants with gametocytes in the comparator arm in these two studies), we used the random-effects model to combine the trials in meta-analysis (Analysis 2.2). In Shkalaghe 2007 which had additional follow-up on day 29, reduction in gametocyte prevalence was significant (RR 0.23, 95% CI 0.08 to 0.62; one trial, 90 participants), and on day 43, it was not (one trial, 79 participants, Analysis 2.2). Note that the trial of Eziefula 2013 was reported as a non-inferiority analysis comparing lower dose groups with the previously recommended 0.75 mg/kg. In this review, in order to combine trials for analysis, results in each arm have been compared with the single placebo group, and where meta-analysis is done, numbers in the placebo group have been divided into three to avoid biasing the CIs.

Gametocyte clearance time or duration of gametocyte carriage (the length of time each person has gametocytes)

Several trial authors presented gametocyte clearance time (the number of hours or days until gametocytes disappear, sometimes described as “duration of gametocyte carriage”. As noted above, Pukrittayakamee 2004 makes a distinction between these two parameters, with gametocyte carriage adjusting for intermittent periods of time without gametocytes. Gametocyte clearance time in days was presented in Shkalaghe 2007 and was significantly lower (by PCR) 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). In Eziefula 2013, also by PCR, the gametocyte clearance time was not significantly longer in the 0.1 mg/kg group (8.0 days, 95% CI 6.6 to 9.4) or the 0.4 mg/kg group (6.3 days, 95% CI 5.1 to 7.5) than the 0.75 mg/kg group (6.6 days, 95% CI 5.3 to 7.8); however the 0.75 mg/kg group had significantly shorter gametocyte clearance time than the placebo group (12.4 days, 95% CI 9.9 to 15.0). Smithuis 2010, using microscopy, 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 malaria treatment regimen. 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). Pukrittayakamee 2004 reported reduction in median gametocyte clearance time from 138 (range 12-264) hours with artesunate alone to 73 (range 6 to 145) hours with artesunate and 7 days of PQ (0.5 mg/kg).

Gametocyte circulation time

Another outcome related to gametocytes estimated by PCR in Eziefula 2013 and Shkalaghe 2007 was the mean life (circulation time) of gametocytes (this is reported per gametocyte rather than per person as for gametocyte clearance time above). In Eziefula 2013 the circulation time per gametocyte was significantly longer in the 0.1 mg/kg group (1.47 days, 95% CI 1.22 to 1.73) than in the other two groups (0.95 and 0.98 days in the 0.4 and 0.75 mg/kg groups respectively), and was similar to the placebo group.
(1.97 days, 95% CI 1.64 to 2.31). In Shekalaghe 2007, the mean gametocyte circulation time was reduced from 4.6 days (95% CI 2.9 to 7.3) after AS+SP alone to 0.5 days (95% CI 0.2 to 1.2) after AS+SP plus PQ (P < 0.001).

**AUC of gametocyte density over time**

Gametocyte density over time was assessed by microscopy in the artemisinin-based regimen trials of Shekalaghe 2007, Smithuis 2010 (five comparisons), Sutanto 2013 and Vasquez 2009, and we analysed this further using data provided by the authors (Table 2; Table 3; Table 4). All trials except Vasquez 2009 demonstrated reduction in the AUC after PQ. The reduction ranged from -63.7% to 67.3% up to day 15, -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 -8.6% to 18.4% up to day 15, from -7.0% to 27.3% up to day 29 and -15.8% to 87.5% up to day 43. Vasquez 2009 was an exception suggesting an 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 19.2% to 67.3% for days 1 to 15, 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 3.9% to 18.4% for days 1 to 15, 8.3% to 27.3% for days 1 to 29 and 24.3% to 87.5% for days 1 to 43.

Eziefula 2013 used a duration of 14 days to estimate AUC using PCR, but the results were not reported separately by group and day so cannot be shown in Table 2. However the log(10)AUC in each the intervention group was not significantly different from placebo. It was 3.8 (95% CI 1.7 to 8.2) gametocytes per µL per day in the placebo group, 3.8 (1.8 to 7.8) in the 0.1 mg/kg group, 2.1 (1.0 to 4.5) in the 0.4 mg/kg group, and 2.0 (0.9 to 4.3) in the 0.75 mg/kg group.

Using PCR-detected gametocyte density estimates, Shekalaghe 2007 provided geometric mean and interquartile range (IQR) values on days 1, 4, 8, 15, 29 and 43. Mean density was consistently lower in the PQ than the non-PQ group, for days when gametoctyes were detected (with PQ: 5.8, IQR 0.8 to 55.1; without PQ: 15.8, IQR 4.1 to 85.8). Shekalaghe 2007 also presented a statistical comparison of AUC of gametocyte density (by PCR) over a 43-day period, with a 95% CI derived from generalized estimation equations. 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).

**Asexual parasite prevalence**

Analysis 2.3 shows the participants who had asexual parasites at several time points after treatment. This analysis suggests a lower proportion of asexual parasites at day 29 in the PQ group reflecting possible recrudescence, late treatment failure or reinfection. However, Wang 2006 did not adjust for reinfections by PCR. In the other trials and time periods, there was no difference between PQ and non-PQ groups in the low proportion of people with asexual parasites.

**Asexual parasite clearance**

Pukrittayakamee 2004 noted no difference in parasite clearance time (Analysis 2.4).

**Adverse effects**

For haematologic adverse events, Smithuis 2010 stated that there were no cases of severe anaemia (< 5 g/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), P = 0.32) or day 14 (0.86, (-0.31 to 2.0), P = 0.15). Sutanto 2013 observed no significant difference in mean haemoglobin between groups at days 1, 8 and 43.

In Shekalaghe 2007, although there was also no reduction in mean haemoglobin by group (Analysis 2.5), 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 2.6). These findings suggest that rather than looking at population mean of haemoglobin, it would be more meaningful to examine the proportion of individuals who had serious adverse events: Shekalaghe 2007 stated that eight of 52 children in the PQ group had a 20% reduction in haemoglobin by day 8, compared to 0 of 53 children in the control group. However, Shekalaghe 2007 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.

Eziefula 2013 used the outcome ‘mean max decrease in haemoglobin’ from enrolment to day 29 and this was not significantly different between the intervention groups or with placebo. Other haematological outcomes were ‘day of haemoglobin nadir’ - day 3 in all groups; maximum % decrease in haemoglobin (significantly lower in the 0.75 mg/kg group than placebo, P = 0.023) and % of patients with haemoglobin < 50 g/L (no differences between groups). No children needed blood transfusion or had black urine or any other severe adverse events.

El-Sayed 2007 assessed the 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. Sutanto 2013 and Wang 2006 observed no differences between groups regarding other adverse effects (Analysis 2.7).

### Dose and schedule

#### Dose of PQ

We stratified trials into low, medium and high dose PQ category and assessed the prevalence of gametocytes at day 8 by either microscopy or PCR (Analysis 2.8). Only Eziefula 2013 used a low dose category for this outcome - in this case 0.1 mg/kg. There were fewer patients with gametocytes in the PQ group, but the analysis for comparisons with placebo was underpowered (Analysis 2.8). One trial used a medium dose category, with clear effect in Eziefula 2013 with 0.4 mg/kg single dose (Analysis 2.8), and an overall effect estimate in this dose category of RR 0.30 (95% CI 0.16 to 0.56; one trial, 219 participants). The high dose category of ≥ 0.6 mg/kg reduced the prevalence of gametocytes at day 8: RR 0.29, 95% CI 0.22 to 0.37; seven trials, 1380 participants, 11 comparisons; Analysis 2.8.

#### Schedule of PQ

We stratified this comparison into two groups: single dose on day 1 or 2, and single dose day 3 or 4 (Analysis 2.9). This indirect comparison suggested a greater effect of single dose on days 1 to 2 than on days 3 to 4.

### Summary analysis of gametocytes on day 8 (Comparison 3)

We have shown a single outcome, percent of participants with microscopy or PCR-detected gametocytes on day 8, for this comparison as a representative outcome across the trials. We subgrouped the data by whether or not the malaria treatment was artemisinin-based. We included only PCR data from the one trial that reported both microscopy and PCR outcomes, to avoid duplicate reporting of the same patients (Shekalaghe 2007).

We excluded the QN comparison of Kamtekar 2004 because PQ was not given until day 8, but included all other trials with gametocyte outcomes at day 8 (all trials except Khoo 1981, Pukrittayakamee 2004 and Wang 2006).

The day on which PQ was given and the gametocyte detection method varied and are presented for each trial in the footnotes in Analysis 3.1. This comparison shows that, overall, PQ reduced the prevalence of gametocythaemia on day 8 following treatment (RR 0.38, 95% CI 0.27 to 0.52, 11 trials 1994 participants, 20 comparisons). The individual trials nearly all trended in the direction of a reduction, but an indirect comparison suggested a smaller effect for non-artemisinin-based (RR 0.54, 95% CI 0.38 to 0.77; five trials, 402 participants) than for artemisinin-based malaria treatments (RR 0.32, 95% CI 0.20 to 0.51; seven trials, 1392 participants, Analysis 3.1).

### Comparison of different 8AQ (Comparison 4)

Two small trials compared the effect of bulaquine and PQ on gametocyte prevalence at day 8 (Gogtay 2004; Gogtay 2006). Both trials suggested a greater reduction of gametocytes by bulaquine (RR 0.41, 95% CI 0.26 to 0.66; two trials, 112 participants, Analysis 4.1). Neither trial concealed allocation.
### PQ for reducing *P. falciparum* transmission with non-artemisinin-based treatments

**Patient or population:** People with symptomatic malaria  
**Settings:** Malaria-endemic areas  
**Intervention:** Single dose or short course PQ plus malaria treatment which does not include an artemisinin derivative  
**Control:** Malaria treatment not including an artemisinin derivative, without PQ

| Outcomes | Illustrative comparative risks* (95% CI) | Relative effect (95% CI) | Number of participants (trials) | Quality of the evidence (GRADE) |
|----------|------------------------------------------|--------------------------|---------------------------------|-------------------------------|
|          | Assumed risk                             | Corresponding risk        |                                 |                               |
|          | Control                                  | PQ                        |                                 |                               |
| Malaria incidence, prevalence or EIR | -                                       | -                        | -                               | -                             |
| People infectious to mosquitoes (day 8) | 93 per 100 (1 to 39)                    | 7 per 100                 | RR 0.07 (0.01 to 0.45)          | 30 (2 trials)                 |
|                                                    |                                         |                          |                                 |⊕⊕⊕⊕ low2,3                     |
| Participants with gametocytes on microscopy (day 8) | Dose <0.4 mg/kg                        | -                        | -                               | (0 trials)                    |
|                                                    | Dose 0.4 to 0.6 mg/kg                   | RR 0.60 (0.49 to 0.75)    | 216 (1 trial)                  |⊕⊕⊕⊕ high4,5                   |
|                                                    | 70 per 100 (35 to 53)                   | 43 per 100                |                                 |                               |
|                                                    | Dose > 0.6 mg/kg                        | RR 0.39 (0.25 to 0.62)    | 186 (4 trials)                 |⊕⊕⊕⊕ high6,7                  |
|                                                    | 35 per 100 (9 to 22)                    | 14 per 100                |                                 |                               |
### Evidence of haemolysis

|   |   |   |   |   |
|---|---|---|---|---|
|   |   |   |   | 0 trials 6, 7 |

*The basis for the **assumed risk** (for example, 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).

**PQ**: Primaquine; **CI**: Confidence interval; **RR**: Risk ratio; **EIR**: entomological inoculation rate; **G6PD**: glucose-6-phosphate dehydrogenase.

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**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.

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1. High category dose PQ used in both studies > 0.6 mg/kg.
2. Downgraded by 1 for serious risk of bias: allocation was not concealed; both experiments were performed by the same author team and the methods were unclear.
3. Downgraded by 1 for serious imprecision: the sample size is small (N = 30; downgraded by 2) but the effect is large (upgraded by 1).
   - In the control group, infectivity wanes by day 15.
4. No serious imprecision: although the sample size is limited, the effect is large.
5. **Log(10)AUC day 1 to 43 % reduction relative decrease**: 2 estimates from one trial of 24.3% to 27.1% (N = 219), assessed as moderate quality evidence.
6. We could not use data from Khoo 1981 because it did not distinguish between patients with *P. falciparum* and *P. vivax* and their respective treatments. There was a much higher risk of adverse haemolytic events in those who received PQ (OR of 22.27 for both haemolysis and need for blood transfusion), but the participants included those receiving a short course (three days) of PQ with those receiving a 14-day regimen.
7. For the 10 included trials, the G6PD status of participants varied: two trials excluded patients with G6PD deficiency trials), one trial included only those with G6PD deficiency, two trials did not screen for G6PD deficiency, and five trials did not report or comment on screening for G6PD status. No trials systematically reported on adverse effects.
**Discussion**

**Summary of main results**

**PQ with artemisinin-based regimens**

See Summary of findings for the main comparison. When added to current artemisinin-based therapy, a single dose of PQ above 0.4 mg/kg reduces the proportion of people with detectable gametocytaemia on day eight by about two thirds (high quality evidence), and can reduce the log10AUC estimates for gametocytaemia by up to 87.5%. However, only a single trial evaluated lower doses (0.1 mg/kg), and the effect size was smaller with a 95% CI which included no effect (low quality evidence). No trials evaluated effects on infectiousness to mosquitoes, or on malaria transmission directly (incidence, prevalence, or entomological inoculation rate).

**PQ with non-artemisinin-based regimens**

See **Summary of findings 2**. When added to non-artemisinin-based treatment regimens, a single dose of PQ above 0.4 mg/kg reduces the proportion of people with detectable gametocytaemia on day 8 by around a third (low quality evidence), and may reduce infectiousness to mosquitoes (low quality evidence). No trials assessed effects on malaria transmission directly.

**Overall completeness and applicability of evidence**

**What is known**

Adding PQ to treatment doses of artemisinin-based combination therapies appears to be an effective strategy to reduce the duration of potential infectiousness to mosquitoes (gametocytaemia). Large effects have been seen across trials from different epidemiological settings (Tanzania, Uganda, Myanmar and Sumatra) and with different artemisinin-based treatments (AS+SP, AL, AS+AQ, AS+MQ, AS and DHAP). Further studies evaluating this at single doses above 0.4 mg/kg are therefore probably unnecessary.

**What is unknown**

While reducing the duration of gametocytaemia can be assumed to reduce infectiousness at the level of the individual, it remains unclear whether it will impact on community level transmission as reliable trials have never evaluated this. We excluded the older trials, which are often cited as proof of an effect on community transmission, from this review because either: i) they lacked an adequate control group (Clyde 1962); ii) they did not apply the interventions equally in intervention and control groups or had no ‘before’ data (Doi 1989; Kaneko 1989); iii) administered PQ alongside vector control co-interventions which may equally be responsible for any effect seen (Hii 1987; Kaneko 2000); or iv) administered PQ or 8AQ alone and not alongside treatment regimens (which is the policy currently being considered) (Barber 1932).

In moderate and high transmission settings, a policy of adding PQ to malaria treatment regimens is highly unlikely to impact community transmission as most adults have a level of acquired immunity that reduces the probability that parasitaemia will cause clinical symptoms, and consequently they never seek care. These asymptomatic people are thought to represent the major source of gametocytes, and so will continue to facilitate transmission unless they are also treated with gametocytocidal drugs. Low transmission settings, especially those approaching elimination, are therefore more suited to the current policy as most people will develop symptoms following infection. However, Johnston 2014 recently modelled the effect of treatment, and concluded that the most important factor predicting success is the percentage of infected individuals treated with an ACT, and that adding PQ is of negligible benefit. They estimated that “it would require switching 180 people from ACTs to ACTs plus PQ to achieve the same transmission reduction as switching a single individual from untreated to treated with ACTs”.

Mass treatment programmes (where everyone in the community is treated at specified intervals until transmission is stopped) are a potential strategy to overcome the problem of asymptomatic gametocyte carriers (von Seidlein 2003; GMAP 2008; Mendis 2009; Sturrock 2013). However, in theory, mass treatment consisting only of primary treatment (an ACT alone) could interrupt transmission, and the effects of additional PQ (interrupting transmission more quickly, or at a lower coverage levels) are unknown (Poizot 2013).

Perhaps even more importantly, it also remains unknown whether the current WHO-recommended dose of 0.25 mg/kg PQ has the effects seen on gametocytes with higher doses. Whilst there is some indirect evidence in narrative summaries and analyses that have proposed widespread programmatic implementation of PQ (for example, Bunnag 1980, with no difference in gametocyte outcomes between 15 mg PQ for five days and single doses of 30 mg or 45 mg PQ in adults), there are only two controlled studies which have evaluated doses below 0.4 mg/kg. Puakrittayakamee 2004 showed reduced duraton of gametocyte carriage but used a seven-day course of 0.25 mg/kg PQ per day; Eziefula 2013 tested 0.1 mg/kg PQ but the result was imprecise with a 95% CI including important effects and no effect. The WHO revised recommendation therefore appears to be based more on concerns about safety than on proven efficacy of single dose of 0.25 mg/kg PQ.

In terms of safety, it is highly likely that adverse effects in people with G6PD deficiency will be less common with lower doses...
of PQ. However, the evidence to reliably demonstrate this with doses of 0.25 mg/kg does not currently exist. Most of the trials included in this review excluded individuals with G6PD deficiency, but in the few trials that included them no severe haematological effects were reported. However, there are hundreds of variants of G6PD deficiency (albeit only a few that are common) and an adequate picture of how PQ affects even the common ones is lacking. Without this evidence, national malaria control programmes may remain reluctant to introduce a drug for use in population-based programmes which has the potential to harm individuals. Health professionals and programme managers around the world are aware of the association between haemolysis, G6PD deficiency and PQ and will be wary of expanded use without evidence of relative safety.

The trials included in this review do not mention PQ resistance as a potential threat. PQ clearly should be used where it is of clinical importance, especially for P. vivax and P. ovale. Its effectiveness against those parasites could be compromised by resistance if used at low doses in populations where P. falciparum, P. vivax and P. ovale coexist. As for 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 Plasmodium parasites.

**Potential biases in the review process**
None known.

**Agreements and disagreements with other studies or reviews**
In a Cochrane Review of MDA (Poirot 2013), the authors found no studies directly comparing MDA regimens that included 8AQs with regimens that did not. In a secondary analysis, the authors then subgrouped the included non-RCTs by regimens with and without 8AQs. In high endemicity areas, two studies included PQ, and one study did not. During multiple MDA rounds, there were substantial drops in parasitaemia regardless of whether PQ was included. At one to three months, the studies without PQ showed larger impact than the one study that did, but this single observation from a non-randomized comparison cannot be relied upon. In a second similar subgroup analysis of four before-and-after studies, the stratified analysis was uninformative. In an opinion piece in the *Lancet*, the possibility that doses lower than 0.5 to 0.75 mg/kg might still be very effective in blocking transmission is raised (White 2013). Based on the current review, however, there is insufficient information to know whether the effect is preserved with doses of less than 0.4 mg/kg.

A review in the *Malaria Journal* provides an analysis of published and unpublished data on 158 subjects with different drug exposures spanning 80 years (White 2012). The methods and sources of data are not clearly specified, but the authors argue this provides evidence that PQ decreases infectivity much faster than the effect on gametocytes would suggest. Our review identified very limited data from controlled studies testing the effect of PQ on infectiousness to mosquitoes (two trials, with 30 participants, in people given non-artemisinin treatments), so was unable to confirm or refute this early effect on gamocyte viability.

In a more recent article in the *Malaria Journal*, White and colleagues criticise the second edition of this review (Graves 2014). The authors point out that the GRADE analysis, which suggests uncertainty around the effects of PQ in low doses on gametocytaemia, should take into account a dose response relationship that White and his colleagues observed (White 2014). Our stratification in the tables suggest that the effects are less with lower doses, but overall the amount of data in low dose groups is limited. The overall conclusion of White 2014 endorses the conclusions of this and all earlier editions of this Cochrane Review: there is a need for mosquito-feeding studies for “the assessment of transmission-blocking, dose-response relationships”; and these assessments are required before “indirect measures can be used confidently to make dosage recommendations” (White 2014).

A paper whose title implies it was a systematic review of the impact of artemisinin derivatives and PQ on infectiousness (Abay 2013) included only two before-and-after trials using PQ with small numbers of patients. Neither of these studies met our inclusion criteria (Rieckmann 1968; Clyde 1971). A historical review of patients treated at clinics in India with either AS+SP+PQ (single dose 0.75 mg/kg on the third treatment day, nine sites) or AS+SP alone (12 sites) observed that PQ reduced the gametocyte clearance time by 45% and the AUC of gametocyte density over time (up to 28 days) by about the same proportion (Shah 2013). They expressed the reduction as a hazard ratio with PQ increasing the rate of gametocyte clearance by 1.9 (95% CI 1.1 to 1.3). These results are consistent with our findings.

In relation to current WHO guidelines, no direct evidence was available to include in this systematic review to support the currently recommended 0.25 mg/kg dose as effective in reducing transmission either from individuals or in communities (WHO 2012b). Ongoing studies may help inform this current gap.

**Authors’ conclusions**

**Implications for practice**
Current policy recommendations that 0.25 mg/kg PQ should be added as a single dose to primary treatment for *P. falciparum* malaria in areas that are targeting elimination or are fac-
Given the high frequency of asymptomatic infections, information on individual patients should be combined with modelling or community-based trials of treatment regimens with and without PQ to determine the malaria and population characteristics under which PQ is likely to be an important additional contributor to malaria elimination programmes (including mass treatment and ‘test and treat’).

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REFERENCES

References to studies included in this review

Arango 2012 [published data only]
Arango EA, Upegui UA, Carmona-Fonseca J. Efficacy of different primaquine-based antimalarial regimens against Plasmodium falciparum gametocytemia. Acta Tropica 2012;122(2):177–82.

Chen 1993a [published data only]
Chen PQ, Li GQ, Guo XB, Fu YX, He KR, Fu LC, et al. A double blind study on the infectivity of gametocytes of P. falciparum in patients treated with mefloquine and Fansimef. Journal of Guangzhou College of Traditional Chinese Medicine 1993;10(1):1–5.

Chen 1994 [published data only]
Chen PQ, Li GQ, Guo XB. The infectivity of gametocytes of Plasmodium falciparum from patients treated with artemisinin [Chinese]. Zhonghua Yi Xue Za Zhi 1994;74(4):209–10, 253–4.

El-Sayed 2007 [published data only]
El-Sayed B, El-Zaki SE, Babiker H, Gadalla N, Ageep T, Mansour F, et al. A randomized open-label trial of artesunate-sulfadoxine-pyrimethamine with or without primaquine for elimination of sub-microscopic P. falciparum parasitaemia and gametocyte carriage in eastern Sudan. PLoS One 2007;2(12):e1311.

Eziefula 2013 [published data only]
* Eziefula AC, Bousema T, Yeung S, Kamya M, Owuraganise A, Gabagaya G, et al. Single dose primaquine for clearance of Plasmodium falciparum gametocytes in children with uncomplicated malaria in Uganda: a randomised, controlled, double-blind, dose-ranging trial. Lancet Infectious Diseases 2013;14(2):130–9.

Gogtay 2004 [published data only]
Gogtay NJ, Kamtekar KD, Dalvi SS, Chogle AR, Aigal U, Kshirsagar N. Preliminary report of the evaluation of the...
Primaquine or other 8-aminoquinoline for reducing Plasmodium falciparum transmission (Review)

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Burgess 1961 [published and unpublished data]
Burgess RW, Bray RS. The effect of a single dose of primaquine upon the gametocytes, gametogony and sporogony of Laverania (= Plasmodium falciparum). WHO/MAL/27/11. http://apps.who.int/iris/bitstream/10665/64747/1/WHO_Mal_27-1.pdf?ua=1 1960:1–10.

* Burgess RW, Bray RS. The effect of a single dose of primaquine upon the gametocytes, gametogony and sporogony of Laverania falciparum. Bulletin of the World Health Organization 1961;24:451–6.

Cai 1985 [published data only]
Cai XZ, Yang XP, He XZ, Zhan WC, Zhan X, Ye BS. The combined use of artemether, sulfadoxine, pyrimethamine and primaquine in the treatment of chloroquine-resistant falciparum malaria [Chinese]. Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi (Chinese Journal of Parasitology and Parasitic Diseases) 1985;3(2):81–4.

Carter 2011 [published data only]
Carter N, Pamba A, Duparc S, Wainbumbi JN. Frequency of glucose-6-phosphate dehydrogenase deficiency in malaria patients from six African countries enrolled in two randomized anti-malarial clinical trials. Malaria Journal 2011;10:241.

Che 1987 [published data only]
Che LG, Huang KG, Yang HL, Yu L, Lin ZL, Huang R. Combined use of pyronaridine, sulfadoxine and primaquine in areas with chloroquine-resistant falciparum malaria. Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi (Chinese Journal of Parasitology and Parasitic Diseases) 1987;5(3):194–6.

Che 1990 [published data only]
Che L, Huang K, Dong Y, Yang H, Yang P. Efficacy of two combined therapies for treatment of chloroquine-resistant P. falciparum [Chinese]. Chinese Journal of Parasitic Disease Control 1990;3(1):24–6.

Chevalley 2010 [published data only]
Chevalley S, Coste A, Lopez A, Pipi B, Valentin A. Flow cytometry for the evaluation of anti-plasmodial activity of drugs on Plasmodium falciparum gametocytes. Malaria Journal 2010;9:49.

Clyde 1962 [published data only]
Clyde DF. Mass administration of an antimalarial drug containing 4-aminoquinoline and 8-aminoquinoline in Tanganyika. Bulletin of the World Health Organization 1962;27:203–12.

Clyde 1970 [published data only]
Clyde DF, DuPont HL, Miller RM, McCarthy VC. Prophylactic and sporontocidal treatment of chloroquine resistant Plasmodium falciparum from Malaya. Transactions of the Royal Society of Tropical Medicine and Hygiene 1970;64(6):834–8.

Clyde 1971 [published data only]
Clyde DF, Miller RM, Music SI, McCarthy VC. Prophylactic and sporontocidal treatment of chloroquine-resistant Plasmodium falciparum from Vietnam. American Journal of Tropical Medicine and Hygiene 1971;20(1):1–5.

da Silva 1984 [published data only]
da Silva AR, Carneiro EW, dos Santos HJ. Response of human Plasmodium to antimalarials on the Island of Saint Louis, State of Maranhão, Brazil [Portuguese]. Resenha do Instituto de Medicina Tropical de São Paulo 1984;20(3):139–46.

Degowin 1966 [published data only]
Degowin RL, Eppes RB, Powell RD, Carson PE. The haemolytic effects of diaphenylsulfone (DDS) in normal subjects and in those with glucose-6-phosphate-dehydrogenase deficiency. Bulletin of the World Health Organization 1966;35(2):105–79.

Doi 1989 [published data only]
Doi H, Kaneko A, Panjaitan W, Ishii A. Chemotherapeutic malaria control operation by single dose of Fansidar plus primaquine in North Sumatra, Indonesia. Southeast Asian Journal of Tropical Medicine and Public Health 1989;20(3):341–9.

Giao 2004 [published data only]
Giao PT, de Vries PJ, Hung le Q, Binh TQ, Nam NV, Kager PA, CV8, a new combination of dihydroartemisinin, piperaquine, trimethoprim and primaquine, compared with atovaquone-proguanil against falciparum malaria in Vietnam. Tropical Medicine and International Health 2004;9(2):209–16.

Gogtay 1999 [published data only]
Gogtay NJ, Chogle AR, Soraljee JS, Marathe SN, Kehirsagar NA. Poor gametocytocidal activity of 45 mg primaquine in chloroquine-treated patients with acute, uncomplicated, Plasmodium falciparum malaria in Mumbai (Bombay): an issue of public-health importance. Annals of Tropical Medicine and Parasitology 1999;93(8):813–6.

Gundersen 1961 [published data only]
Gundersen AE. The effect of a single dose of pyrimethamine and primaquine in combination upon gametocytes and sporogony of Laverania falciparum: Plasmodium falciparum in Liberia. Bulletin of the World Health Organization 1961;24:650–3.

Hii 1987 [published data only]
Hii JL, Vun YS, Chin KF, Chua R, Tambakau S, Binisol ES, et al. The influence of permethrin-impregnated bednets and mass drug administration on the incidence of Plasmodium falciparum malaria in children in Sabah, Malaysia. Medical and Veterinary Entomology 1987;1(4):397–407.

Huang 1993 [published data only]
Huang ZS, Fu SG, Cai XZh. Combined use of pyronaridine/SP with primaquine for P. falciparum treatment [Chinese]. Journal of Hainan Medicine 1993;4(1):10–2.

Huang 1996 [published data only]
Huang ZN, Meng F, Fu S. Comparative studies on the treatment of drug-resistant P. falciparum with pyronaridine/SP and primaquine [Chinese]. Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi Chinese Journal Parasitology and Parasitic Diseases 1996;14(4):314–7.
Primaequine or other 8-aminoquinoline for reducing Plasmodium falciparum transmission (Review)

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Huang 2001 (published data only)
Huang JR, Gao YQ, Elie N. A study of artesether combined with primaquine in the treatment of falciparum malaria [Chinese]. (Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi) Chinese Journal of Parasitology and Parasitic Diseases 2001;19(5):308–9.

Jeffery 1956 (published data only)
Jeffery GM, Young MD, Eyles DE. The treatment of Plasmodium falciparum infection with chloroquine, with a note on infectivity to mosquitoes of primaquine- and pyrimethamine- treated cases. American Journal of Hygiene 1956;64(1):1–11.

Jeffery 1963 (published data only)
Jeffery GM, Collins WE, Skinner JC. Antimalarial drug trials on a multiresistant strain of Plasmodium falciparum. American Journal of Tropical Medicine and Hygiene 1963;12:844–50.

Jerace 1933 (published data only)
Jerace F, Giovannaia A. The sterilizing action of plasmochina on gametocytes of malaria parasites and its prophylactic importance [L’azione sterilizzante della plasmochina sui gametociti di parasiti malarieni e sua importanza profilatica]. Rivista di Malariologia 1933;12:475.

Kaneko 1989 (published data only)
Kaneko A, Kamei K, Suzuki T, Ishii A, Siajan R, Panjaitan W. Gametocytocidal effect of primaquine in a chemotherapeutic malaria control trial in North Sumatra, Indonesia. Southeast Asian Journal of Tropical Medicine and Public Health 1989;20(3):351–9.

Karbwang 1991 (published data only)
* Karbwang J, Molunto P, Bunnag D, Harinasuta T. Plasma quinine levels in patients with falciparum malaria when given alone or in combination with tetracycline with or without primaquine. Southeast Asian Journal of Tropical Medicine and Public Health 1991;22(1):72–6.

Karbwang 1992 (published data only)
Karbwang J, Na Bangchang K, Thanavibul A, Back DJ, Bunnag D. Pharmacokinetics of mefloquine in the presence of primaquine. European Journal of Clinical Pharmacology 1992;42(5):559–60.

Kyaw 1994 (published data only)
Kyaw P, Phone-Kyaw M, Aung-Naing Y, Aye-Lwin T. The use of primaquine in malaria infected patients with red cell glucose phosphate (G6PD) deficiency in Myanmar. Southeast Asian Journal of Tropical Medicine and Public Health 1994;25(4):710–3.

Li 2007 (published data only)
Li J, Xiao H, Wang W, Ma W, Rao B. Artemether combined with primaquine for P falciparum cases treatment [Chinese]. Clinical Medical Journal of China 2007;14(5):736–7.

Li 2010 (published data only)
Li WJ, Li XL. Observation of curative effect of falciparum malaria treatment with arteether/leumefantrine and primaquine [Chinese]. Journal of Modern Preventive Medicine 2010;37(5):973–5.

Lin 2004 (published data only)
Lin L, Wang D-L, Liu B, Hu G. Artesether combined with primaquine for treatment of malaria cases from UN peace force [Chinese]. Chinese Journal of Parasitic Disease Control 2004;17(5):5–6.

Mackerras 1949 (published data only)
Mackerras MJ, Ercole QN. Observations on the action of quinine, atebrin and plasmoquine on the gametocytes of Plasmodium falciparum. Transactions of the Royal Society of Tropical Medicine and Hygiene 1949;42(5):455–63.

Rieckmann 1968 (published data only)
Rieckmann KH, McNamara JV, Frischer H, Stockert TA, Carson PE, Powell RD. Gametocytocidal and sporontocidal effects of primaquine and of sulfadiazine with pyrimethamine in a chloroquine-resistant strain of Plasmodium falciparum. Bulletin of the World Health Organization 1968;38(4):625–32.

Rieckmann 1969 (published data only)
Rieckmann KH, McNamara JV, Kass L, Powell RD. Gametocytocidal and sporontocidal effects of primaquine upon two strains of Plasmodium falciparum. Military Medicine 1969;134(10):802–19.

Santana 2007 (published data only)
Santana MS, da Rocha MA, Arcanjo AR, Sardinha JF, Alecrim WD, Alecrim MD. Association of methemoglobinemia and glucose-6-phosphate dehydrogenase deficiency in malaria patients treated with primaquine [Associação de metemoglobinaemia e deficiência de glicose–6–fosfato desidrogenase em pacientes com malária tratados com primaquina]. Revista de Sociedade Brasileira de Medicina Tropical 2007;40(5):533–6.

Shah 2013 (published data only)
Shah NK, Schapira A, Juliano JJ, Srivastava A, MacDonald PD, Poole C, et al. Nonrandomized controlled trial of artesunate plus sulfadoxine-pyrimethamine with or without primaquine for preventing posttreatment circulation of Plasmodium falciparum gametocytes. Antimicrobial Agents and Chemotherapy 2013;57(7):2948–54.

Shekalaghe 2010 (published data only)
Shekalaghe SA, ter Braak R, Dauo M, Kavishe R, van den Bijlhaardt W, van den Bosch S, et al. In Tanzania, hemolysis after a single dose of primaquine coadministered with an artemisinin is not restricted to glucose-6-phosphate dehydrogenase-deficient (G6PD A-) individuals. Antimicrobial Agents and Chemotherapy 2010;54(5):1762–8.

Shekalaghe 2011 (published data only)
Shekalaghe SA, Drakeley C, van den Bosch S, ter Braak R, van den Bijlhaardt W, Mwanziva C, et al. A cluster-randomized trial of mass drug administration with a gametocytocidal drug combination to interrupt malaria transmission in a low endemic area in Tanzania. Malaria Journal 2011;10:247.

Sun 2011 (published data only)
Sun W-H, Traore A. Artesunate combined with primaquine in treatment study on delay or relapse of malaria [Chinese].
References to studies awaiting assessment

Chen 1993b (published data only)
Chen L. Efficacy of artemether/primaquine against drug resistant P. falciparum [Chinese]. Journal of Applied Medicine 1993;1(1):31–3.

Ishii 2009 (unpublished data only)
Ishii A, Ohta N, Owhashi M, Kawabata M, Chung D, Bobogare A, et al. Trials of transmission blocking of P. falciparum with single dose primaquine in villages of Solomon Islands. MIM conference October 2009 MIM 16723561.

Li 2006 (published data only)
Li J, et al. Arteether combined with primaquine for treatment of 50 PF cases [Chinese]. Journal of Applied Medicine 2006;22(19):2299–300.

References to ongoing studies

D’Alessandro (started 2013) (published data only)
Primaquine’s Gametocytocidal Efficacy in Malaria Asymptomatic Carriers Treated With Dihydroartemisinin-Piperaquine in The Gambia. Ongoing study August 2013; December 2014 (final data collection date for primary outcome measure).

Gosling (recruitment ended 2014) (published data only)
Phase 2a Dose Escalation Study of the Efficacy, Safety, and Pharmacokinetics of Low Dose Primaquine for Gametocytocidal Activity Against P. falciparum in Sub-Saharan Africa and South East Asia. Ongoing study September 2014 (final data collection date for primary outcome measure).

Indonesia (started 2013) (published and unpublished data)
Surveillance and Treatment With Dihydroartemisinin-piperaquine Plus Primaquine (MTC Belu) Sub-title: Impact of Mass Screening and Selective Treatment With Dihydroartemisinin-piperaquine Plus Primaquine on Malaria Transmission in High Endemic Area, Belu Regency, Nusa Tenggara Timur Province, Indonesia: a Randomized Cluster Trial. Ongoing study June 2013.

Mwiswelelo (started 2014) (published data only)
Efficacy and Safety of a Single Low-dose Primaquine Added to Standard Artemether-lumefantrine Treatment for the Clearance of Plasmodium Falciparum Gametocytes. Ongoing study Date of registration 16 March 2014 Date of first enrolment July 2014.

Sarr (started 2014) (published data only)
A trial of the safety of low dose primaquine in addition to ACTs commonly used in Senegal. Ongoing study Registered 10/11/2014; Date of first enrolment 15 November 2014.

Saunders (started 2012) (published data only)
Active Surveillance for P. falciparum Drug Resistance With Assessment of Transmission Blocking Activity of Single Dose Primaquine in Cambodia. Ongoing study December 2012; December 2014 (final data collection date for primary outcome measure).

Sawa DAPPI-1 (started 2014) (published data only)
A Double Blind Randomized Controlled Trial of Dihydroartemisinin-Piperaquine Alone and in Combination With Single Dose Primaquine to Reduce Post-treatment Malaria Transmission. Ongoing study Registration date 29 September 2014; first enrolment October 2014.

Shekalaqhe (started 2013) (published data only)
The Optimal Timing of Primaquine to Prevent Malaria Transmission After Artemisinin-Combination Therapy. Ongoing study May 2013; October 2013 (final data collection date for primary outcome measure).

Sirima SAFEPRIM (started 2014) (published data only)
Evaluation of the Safety of Primaquine in Combination With Arteether-lumefantrine in Glucose-6-phosphate Dehydrogenase Deficient Males With an Asymptomatic Malaria Infection in Burkina Faso (SAFEPRIM). Ongoing study Date of registration 11 June 2014. Date of first enrolment October 2014.

Spring (recruitment ended 2014) (published data only)
A trial of the safety of low dose primaquine in addition to ACTs commonly used in Senegal. Ongoing study Registered 10/11/2014; Date of first enrolment 15 November 2014.

References to ongoing studies

D’Alessandro (started 2013) (published data only)
Primaquine’s Gametocytocidal Efficacy in Malaria Asymptomatic Carriers Treated With Dihydroartemisinin-Piperaquine in The Gambia. Ongoing study August 2013; December 2014 (final data collection date for primary outcome measure).
Thailand (started 2012) (published and unpublished data)
Pharmacokinetic Study of Primaquine and Dihydroartemisinin-Piperaquine in Healthy Subjects. Ongoing study June 2012.

Tiono (started 2013) (unpublished data only)
Low Dose Primaquine for Clearance of Gametocytes: LOPRIM-1. Ongoing study September 2013.

Additional references

Abay 2013
Abay SM. Blocking malaria transmission to Anopheles mosquitoes using artemisinin derivatives and primaquine: a systematic review and meta-analysis. Parasites and Vectors 2013;6(1):278.

Arnold 1955
Arnold J, Alving AS, Hockwald RS, Clayman CB, Dern RJ, Beutler E, et al. The antimalarial action of primaquine against the blood and tissue stages of falciparum malaria (Panama, P-F-6 strain). Journal of Laboratory and Clinical Medicine 1955;46(3):391–7.

Ashley 2014
Ashley EA, Recht J, White NJ. Primaquine: the risks and the benefits. Malaria Journal 2014;13(1):418. [DOI: 10.1186/1475-2875-13-418]

Barnes 2008
Barnes KI, Little F, Mabuza A, Mgomezulu N, Govere J, Durheim D, et al. Increased gametocytemia after treatment: an early parasitological indicator of emerging sulfadoxine-pyrimethamine resistance in falciparum malaria. Journal of Infectious Diseases 2008;197(11):1605–13.

Bhasin 1984
Bhasin VK, Trager W. Chapter XI: Gametocytocidal effects in vitro of primaquine and related compounds on Plasmodium falciparum. In: Wernsdorfer WH, Trigg PI editor(s). Primaquine: pharmacokinetics, metabolism, toxicity and activity. UNDP/World Bank/WHO, 1984.

Boussera 2010
Boussera T, Okell L, Shekalaghe S, Griffin JT, Omar S, Sawa P, et al. Revisiting the circulation time of Plasmodium falciparum gametocytes: molecular detection methods to estimate the duration of gametocyte carriage and the effect of gametocytocidal drugs. Malaria Journal 2010;9:136.

Boussera 2011
Boussera T, Drakeley C. Epidemiology and infectivity of Plasmodium falciparum and Plasmodium vivax gametocytes in relation to malaria control and eradication. Clinical Microbiology Reviews 2011;24(2):377–410.

Boussera 2012
Boussera T, Dinglasan RR, Morlais I, Gouagna LC, van Warmen R, Awono-Ambene PH, et al. Mosquito feeding assays to determine the infectiousness of naturally infected Plasmodium falciparum gametocyte carriers. PLoS One 2012;7(8):e42821.

Breman 2012
Breman JG. Resistance to artemisinin-based combination therapy. Lancet Infectious Disease 2012;12(11):820–2.

Carter 1988
Carter R, Graves PM. Gametocytes. In: Wernsdorfer, MacGregor editor(s). Malaria: principles and practice of malariology. Edinburgh: Churchill Livingstone, 1988.

Chotivanich 2006
Chotivanich K, Sattabongkot J, Udomsangpetch U, Loosresuwan S, Day NP, Coleman RE, et al. Transmission-blocking activities of quinine, primaquine, and artesunate. Antimicrobial Agents and Chemotherapy 2006;50(6):1927–30.

Churcher 2013
Churcher TS, Bousema T, Walker M, Drakeley C, Schneider P, Ouédraogo AL, et al. Predicting mosquito infection from Plasmodium falciparum gametocyte density and estimating the reservoir of infection. eLife 2013;2:e00626.

Cockcroft 1976
Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31–41.

Drakeley 2006
Drakeley C, Sutherland C, Bousema JT, Sauerwein RW, Targett GA. The epidemiology of Plasmodium falciparum gametocytes: weapons of mass dispersion. Trends in Parasitology 2006;22(9):424–30.

Dunyo 2006
Dunyo S, Milligan P, Edwards T, Sutherland C, Targett G, Pinder M. Gametocytaemia after drug treatment of asymptomatic Plasmodium falciparum. PLoS Clinical Trials 2006;1(4):e20.

Eichner 2001
Eichner M, Diebner HH, Molineaux L, Collins WE, Jeffery GM, Dietz K. Genesis, sequestration and survival of Plasmodium falciparum gametocytes: parameter estimates from fitting a model to malaria therapy data. Transactions of the Royal Society of Tropical Medicine and Hygiene 2001;95 (5):497–501.

Eziefula 2012
Eziefula A, Gosling R, Hwang J, Hsiang M, Bousema T, von Seidlein L, et al. Rationale for short course primaquine in Africa to interrupt malaria transmission. Malaria Journal 2012;11:360.

GMAP 2008
Roll Back Malaria Partnership. Global Malaria Action Plan. Geneva: RBM/WHO, 2008.

Graves 1988
Graves PM, Burkot TR, Carter R, Cattani JA, Lagog M, Parker J, et al. Measurement of malarial infectivity of human populations to mosquitoes in the Madang area, Papua New Guinea. Parasitology 1988;96(Pt 2):251–63.

Graves 1990
Graves PM, Burkot TR, Saul AJ, Hayes RJ, Carter R. Estimation of anopheline survival rate, vectorial capacity and mosquito infection probability from malaria infection rates in villages near Madang, Papua New Guinea. Journal of Applied Ecology 1990;27:134–47.
Primaquine or other 8-aminoquinoline for reducing Plasmodium falciparum transmission (Review)

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WHO 2012a
World Health Organization. *WHO Evidence Review Group: The safety and effectiveness of single dose primaquine as a *P. falciparum* gametocytocide. Meeting Report. Geneva: World Health Organization, 2012.

WHO 2012b
World Health Organization. *Single dose primaquine as a gametocytocide in Plasmodium falciparum malaria. Updated WHO Policy Recommendation.* Geneva: Global Malaria Programme. World Health Organization, October 2012.

References to other published versions of this review

Graves 2012
Graves PM, Gelband H, Garner P. Primaquine for reducing *Plasmodium falciparum* transmission. *Cochrane Database of Systematic Reviews* 2012, Issue 9. [DOI: 10.1002/14651858.CD008152.pub2]

Graves 2014
Graves PM, Gelband H, Garner P. Primaquine or other 8-aminoquinoline for reducing *P. falciparum* transmission. *Cochrane Database of Systematic Reviews* 2014, Issue 6. [DOI: 10.1002/14651858.CD008152.pub3]

* Indicates the major publication for the study
## Characteristics of included studies [ordered by study ID]

### Arango 2012

| Methods | Quasi-RCT: alternate allocation to AQ+SP and AQ+SP+PQ, then MQ+AS and MQ+AS+PQ |
|---------|--------------------------------------------------------------------------------|
| Participants | Inclusion criteria:  
1. Uncomplicated malaria  
2. Pf only  
3. Not pregnant  
4. Voluntary consent  
Colombia  
82 patients, aged one to 75 years (mean age ranged from 24 to 35 years in four groups)  
Gametocytes in 23/82 (28%) |
| Interventions | All loose combinations:  
1. AQ+SP  
2. AQ+SP+PQ  
3. MQ+AS  
4. MQ+AS+PQ  
AQ: 25 mg/kg total dose divided into 10 mg/kg on day 1 and 7.5 mg/kg on days 2 and 3  
SP: 25 mg/kg/1.25 mg/kg single dose on day 1  
MQ: 25 mg/kg total dose, divided into 8.3 mg/kg per day for 3 days  
AS: 4 mg/kg per day for 3 days  
PQ: 0.75 mg/kg, total single dose on day 2 |
| Outcomes | Day 1 (pretreatment with schizonticide), 4 and 8  
Asexual and gametocyte counts in thick smears  
Gametocyte prevalence  
Gametocyte density |
| Notes | No mention of G6PD status |

### Risk of bias

| Bias | Authors’ judgement | Support for judgement |
|------|--------------------|-----------------------|
| Random sequence generation (selection bias) | High risk | Alternate allocation. |
| Allocation concealment (selection bias) | Unclear risk | Not discussed. |
| Incomplete outcome data (attrition bias) | Low risk | No evidence of incomplete data. |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting. |
### Arango 2012 (Continued)

| Other bias                                           | Authors’ judgement | Support for judgement |
|------------------------------------------------------|--------------------|-----------------------|
| Blinding of participants and personnel (performance bias) | Unclear risk       | Not discussed.        |
| All outcomes                                         |                     |                       |
| Blinding of outcome assessment (detection bias)      | Unclear risk       | Not discussed.        |
| All outcomes                                         |                     |                       |

### Chen 1993a

| Methods                          | RCT               |
|----------------------------------|-------------------|
| Participants                     | 18 participants with *P. falciparum* |
| Interventions                    | A: MQ 750 mg  
B: MQ 750 mg + SP (1500 mg/75 mg)  
C: MQ 750 mg + PQ 45 mg  
All single doses  
Follow-up: 28 days for gametocytes and 21 days for infectiousness |
| Outcomes                         | Gametocyte prevalence at days 3, 8, 14 and 21  
Infectiousness to *An. dirus*  
Sporozoite infections in mosquitoes  
Infectivity of sporozoite-infected mosquitoes to subsequent patients |
| Notes                            | Only abstract available.  
Mosquitoes fed on the patients were allowed to develop sporozoites which were then fed on uninfected people. One of the MQ + PQ group passed the infection to a new person |

### Risk of bias

| Bias                                           | Authors’ judgement | Support for judgement |
|------------------------------------------------|--------------------|-----------------------|
| Random sequence generation (selection bias)    | Unclear risk       | Trial authors stated it was randomized in abstract. |
| Allocation concealment (selection bias)        | Unclear risk       | No information in abstract. |
| Incomplete outcome data (attrition bias)       | Low risk           | All patients were followed up. |
| All outcomes                                   |                     |                       |
| Selective reporting (reporting bias)           | Unclear risk       | No information in abstract. |
| Other bias                                     | Unclear risk       | None known.           |
### Chen 1993a (Continued)

| Blinding of participants and personnel (performance bias) | Low risk | Stated to be double blind in title. |
|---------------------------------------------------------|----------|-----------------------------------|
| Blinding of outcome assessment (detection bias)         | Unclear risk | No information in abstract. |
| All outcomes                                            |           |                                   |

### Chen 1994

| Methods | Possibly individually RCT (stated to be randomized but no information given) Dates of trial 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 750 mg single dose + PQ 45 mg single dose day 1 (reported as day 0) |
| Outcomes | 1. Gametocyte density: days 5, 8, 15, 22 and 29 (reported in paper as days 4, 7, 14, 21 and 28 since first day was day 0). Given as % of initial density on chart only 2. Percentage of participants infectious to *An. dirus*: days 5, 8, 15 and 22 (reported as days 4, 7, 14 and 21) 3. Percentage of mosquitoes infected: days 5, 8, 15 and 22 (reported as days 4, 7, 14 and 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. Trial authors described 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. |
El-Sayed 2007

Methods
Individually RCT
Dates of trial: Randomization June 2004; trial done 17 August 2004 to 3 September 2004

Participants
104 people 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 October to December.
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 (two 100 mg tabs) days 1, 2, and 3 (reported as days 0, 1, and 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 people with P. falciparum parasites by PCR days 4, 8 and 15 (reported as days 3, 7 and 14)
2. Proportion of people 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 two months after the initial screening for positives (asymptomatic carriers)

Risk of bias

| Bias | Authors’ judgement | Support for judgement |
|------|--------------------|-----------------------|

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. |
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. |

Chen 1994  (Continued)
### Random sequence generation (selection bias)

| Risk Level | Description |
|------------|-------------|
| Low        | "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." |

### Allocation concealment (selection bias)

| Risk Level | Description |
|------------|-------------|
| Unclear    | No information given. |

### Incomplete outcome data (attrition bias)

| Risk Level | Description |
|------------|-------------|
| Low        | Only three of 104 participants did not complete follow-up. |

### Selective reporting (reporting bias)

| Risk Level | Description |
|------------|-------------|
| Low        | No obvious selective reporting. |

### Other bias

| Risk Level | Description |
|------------|-------------|
| Low        | No indication of other bias. |

### Blinding of participants and personnel (performance bias)

| Risk Level | Description |
|------------|-------------|
| High       | Patients and health staff were not blinded. |

### Blinding of outcome assessment (detection bias)

| Risk Level | Description |
|------------|-------------|
| Low        | Lab staff doing PCR were blinded. |

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**Eziefula 2013**

**Methods**

Individually randomized placebo-controlled, double blind trial conducted December 2011 to March 2013

**Participants**

468 randomized, aged one to 10 years old, male and female

Inclusion criteria:
1. *P. falciparum* mono infection with parasite density lower than 500,000 parasites/µL
2. Normal G6PD enzyme function
3. Fever or history of fever in past 24 hours

Exclusion criteria:
1. Signs of severity
2. Haemoglobin concentration < 80 g/L
3. Known allergy to the trial drugs
4. Antimalarials taken within the past two days
5. PQ taken within the past four weeks
6. Blood transfusion within the past 90 days

**Interventions**

1. AL standard three day (twice per day) course + placebo (given with 5th AL dose, i.e., with 1st dose on 3rd day of treatment)
2. AL + 0.1 mg/kg PQ
3. AL + 0.4 mg/kg PQ
4. AL + 0.75 mg/kg PQ (reference)

| Outcomes | Primary efficacy: Mean duration of gametocyte carriage
|          | Secondary efficacy: Point prevalence of gametocytes on days 7, 10 and 14; gametocyte circulation time (days), AUC of gametocyte density
|          | Primary safety: Arithmetic mean maximum decrease in haemoglobin concentration from enrolment to day 28
|          | Secondary safety: Day of haemoglobin nadir, maximum percentage decrease in haemoglobin, percentage of participants with haemoglobin concentration lower than 50 g/L, requirement for blood transfusion, evidence of black urine, and frequency of severe adverse events

| Notes | G6PD enzyme function based on a fluorescence spot test (R&D Diagnostics, Aghia Paraskevi, Greece)

| Risk of bias |
|-------------|
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | Low risk | Computer-generated four-digit treatment assignment codes and allocated these to random dose groups in block sizes of 16 |
| Allocation concealment (selection bias) | Low risk | Only the pharmacist was aware of allocation. |
| Incomplete outcome data (attrition bias) | Low risk | Only 8% of patients were lost to follow-up. No group significantly different from others |
| Selective reporting (reporting bias) | Low risk | None detected or suspected. |
| Other bias | Low risk | None detected or suspected. |
| Blinding of participants and personnel (performance bias) | Low risk | “Masking syrup” added to all treatments to mask taste of drug |
| Blinding of outcome assessment (detection bias) | Low risk | Assessors were blinded. |
Methods

Allocated by "simple, computer-generated randomization code"

Participants

Twenty-two patients in Mumbai, India
Inclusion criteria:
1. > 18 years
2. Normal G6PD
3. > 55 P. falciparum gametocytes/µL on admission
Exclusion criteria:
1. Complicated malaria

Interventions

1. Quinine days 1 to 7: 30 mg/kg/day + PQ (45 mg)
2. Quinine days 1 to 7: 30 mg/kg/day + bulaquine (approximately 75 mg base)

Outcomes

Asexual and gametocyte counts on days 1, 4, 8, 15, 22 and 29
Adverse events

Notes

Risk of bias

| Bias                                             | Authors' judgement | Support for judgement                                               |
|--------------------------------------------------|--------------------|---------------------------------------------------------------------|
| Random sequence generation (selection bias)      | Low risk           | Computer-generated randomization.                                   |
| Allocation concealment (selection bias)          | Unclear risk       | Not reported.                                                       |
| Incomplete outcome data (attrition bias)         | Low risk           | No evidence of incomplete data.                                     |
| All outcomes                                     |                    |                                                                     |
| Selective reporting (reporting bias)             | Low risk           | No evidence of selective reporting.                                 |
| Other bias                                       | High risk          | Unbalanced allocation (9 versus 13) and small number of participants |
| Blinding of participants and personnel (performance bias) | Unclear risk | Not reported.                                                       |
| All outcomes                                     |                    |                                                                     |
| Blinding of outcome assessment (detection bias)  | Low risk           | Laboratory technician reading blood smears was blinded.             |
| All outcomes                                     |                    |                                                                     |
Methods

| Methods | Randomized (computer-generated) to PQ or bulaquine (1:2 ratio) after primary treatment with quinine + doxycycline |

Participants

| Participants | 93 participants in India |
|--------------|-------------------------|
| Inclusion criteria: | |
| 1. > 16 years | |
| 2. Male | |
| 3. Uncomplicated Pf only | |
| 4. > 55 P. falciparum gametocytes/µL on admission | |
| Exclusion criteria: | |
| 1. Antimalarial treatment in previous two weeks | |
| 2. Allergy to trial drug | |
| 3. G6PD deficient | |

Interventions

| Interventions | All patients: Quinine days 1 to 7: 30 mg/kg/day (10 mg/kg/day three times per day) + 100 mg doxycycline |
|---------------|------------------------------------------------------------------------------------------------------------------|
|               | Randomization and treatment on day 4 |
|               | 1. PQ |
|               | 2. Bulaquine |

Outcomes

| Outcomes | Gametocyte prevalence, density and viability on days 1, 4, 15, 22 and 29 |
|----------|------------------------------------------------------------------------|
|          | Adverse events |

Notes

| Notes | Gametocyte viability assessed by Shute's technique (exflagellation) |

Risk of bias

| Bias | Authors' judgement | Support for judgement |
|------|--------------------|-----------------------|
| Random sequence generation (selection bias) | Low risk | Computer-generated randomization. |
| Allocation concealment (selection bias) | Unclear risk | Not reported. |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | No evidence of incomplete data. Three participants (two bulaquine, one PQ) did not return for follow-up |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting. |
| Other bias | Low risk | None noted. |
| Blinding of participants and personnel (performance bias) All outcomes | Unclear risk | Not reported. |
Blinding of outcome assessment (detection bias)  
All outcomes  
Low risk  
Slide readers were blinded.

**Kamtekar 2004**

**Methods**  
Individually RCT, comprising two distinct comparisons a: (CQ or [CQ+SP]) with and without PQ and b: QN with and without PQ  
Dates of trial: Not given.

**Participants**  
57 people aged ≥ 16 years with symptomatic uncomplicated and 46 with severe (WHO criteria) *P. falciparum* malaria, diagnosed by thick and thin blood slides. Gametocyaemic 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  
All received CQ (some also got SP)  
Day 4: Randomized to PQ or placebo (45 mg)  
Comparison b: For severe malaria  
All received quinine  
Day 8: Randomized to PQ or placebo (dose 45 mg)  
Doses background drugs: CQ 10 mg/kg on days 1 and 2; 5 mg/kg on day 3; SP 1500 mg; quinine dose 10 mg/kg every 8 hrs for 24 to 48 hrs and orally for total of 7 days.

**Outcomes**  
1. Proportion of people with gametocytes, days 1, 4, 8, 15, 22 and 29  
2. Proportion of people with viable gametocytes (exflagellation), days 1, 4, 8, 15, 22 and 29  
3. Gametocyte density (given as range) days 1, 4, 8, 15, 22 and 29  

**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 people 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)

| Low risk | Trial used a placebo for PQ. Patients and health workers were blinded. |

Blinding of outcome assessment (detection bias)

| Low risk | Slide readers were blinded. |

Khoo 1981

Methods

| Individually RCT |
| Dates of trial: between June 1976 and March 1978. |

Participants

| 69 people (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). 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; 210 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. Haemolysis |
| 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. |
### Khoo 1981  (Continued)

| 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)          | Unclear risk       | No information given.                                                                  |
| All outcomes                                      |                    |                                                                                       |
| 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) | Unclear risk | Not reported.                                                                           |
| All outcomes                                      |                    |                                                                                       |
| Blinding of outcome assessment (detection bias)   | Unclear risk       | Not reported.                                                                           |
| All outcomes                                      |                    |                                                                                       |

### Kolaczinski 2012

| Methods                                           | Individually RCT   | Dates of trial: 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(S)/1.25(P) 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
### Kolaczinski 2012  (Continued)

| 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)         | 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.                                                                             |
| Blinding of participants and personnel (performance bias) | 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)  | Low risk           | Implied only.                                                                           |

### Ledermann 2006

| Methods                                          | Individually RCT   |
|--------------------------------------------------|--------------------|
| Date of trial                                   | July to 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 seven days, severe or complicated malaria, history or allergy or adverse reaction to trial 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) |

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### Ledermann 2006 (Continued)

| | 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 people 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 | Trial subject codes were assigned to treatment arms by a random process (not specified) |
| 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 RCT  
Dates of trial not stated. |
|---|---|
| Participants | 176 patients with acute uncomplicated *Plasmodium falciparum*. After exclusion of QN+tetracycline group: 146.  
Age 14 to 62. |
Pukrittayakamee 2004  (Continued)

| 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 4AQ. People with G6PD deficient phenotype were excluded from receiving PQ. |

**Interventions**

1. QN: QN sulfate (300 mg salt/tab) at 10 mg salt/kg, three times 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
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 to 12 hrs until resolution of fever)
4. Parasite reduction ratio 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 trial.

**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 trial |
| Selective reporting (reporting bias) | Unclear risk | Not detected. |
### Pukrittayakamee 2004 (Continued)

| Other bias | Unclear risk | Those who were unable to stay in hospital until clearance of both fever and parasites were excluded from trial of fever clearance time |
|------------|--------------|------------------------------------------------------------------------------------------------------------------|

| Blinding of participants and personnel (performance bias) | Unclear risk | Not reported. |
|----------------------------------------------------------|--------------|---------------|
| All outcomes                                             |              |               |

| Blinding of outcome assessment (detection bias) | Unclear risk | Not reported. |
|-------------------------------------------------|--------------|---------------|
| All outcomes                                    |              |               |

### Shekalaghe 2007

| Methods | Individually RCT  
Dates of trial: June 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 to 100,000/µL.  
Age three to 15 years.  
Both sexes.  
Site: Mynuzi health centre, North-Eastern Tanzania, a hyperendemic area with rainy seasons in March to June and October to December  
Exclusion criteria: Hb < 8, inability to take drugs orally, known hypersensitivity to meds, reported anti-malarial treatment in last two weeks, evidence of chronic disease or acute infection other than malaria, domicile outside trial 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 people with gametocytes (by microscopy) days 1, 4, 8, 15, 29 and 43 (reported as 0, 3, 7, 14, 28 and 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 |
|------|--------------------|-----------------------|
|      |                    |                       |
### Shekalaghe 2007  (Continued)

| Risk of Bias | Low risk | Generated in STATA 8.0 using restricted randomization with block size of 20 |
|-------------|----------|--------------------------------------------------------------------------|
| 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 | No information given. |
| Other bias | Low risk | No indication of other bias. |
| Blinding of participants and personnel (performance bias) All outcomes | Unclear risk | Trial physician evaluated patients, opened envelopes, and administered treatment. Other staff were blinded. Not clear if participants were blinded |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | Not stated. |

### Singhasivanon 1994

| Methods | Individually RCT Dates of trial: not stated. |
|---------|---------------------------------------------|
| Participants | 23 people with uncomplicated *P. falciparum* malaria, parasitaemia between 1 to 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 three hours of Rx were excluded - this is a post randomization exclusion |

**Risk of bias**
### Singhasivanon 1994

#### 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. |
| Selective reporting (reporting bias)                                | Unclear risk       | No information given.  |
| Other bias                                                           | High risk          | Those who vomited within three hours 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

- Individually RCT (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: December 2008 to March 2009.

#### Participants

- Number: 808 people attending clinics in Myanmar.
- Inclusion criteria: Age > 6 months, weight > 5 kg, *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 trial drugs, severe malnutrition, concomitant febrile illness, history of psychiatric disorder, a full course of MQ in the previous nine weeks or any other antimalarial in the previous 48 hrs.

#### Interventions

- Each of the five trial 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. AL, fixed-dose combination: 20 mg/120 mg tablets.
  - A 3.3 mg/kg in two divided doses each day for 3 days
Smithuis 2010  (Continued)

| 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 to 4 years, 5 to 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 enrolment. When the box was empty, another 50 envelopes were added” |
| Incomplete outcome data (attrition bias) | Low risk | Attrition is low in absolute numbers and unlikely to have introduced significant bias |
### Selective reporting (reporting bias)

| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting. |
|--------------------------------------|----------|-------------------------------------|

### Other bias

| 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. |
|--------------|-----------|-----------------------------------------------|

### Blinding of outcome assessment (detection bias)

| All outcomes | Low risk | Microscopists were blinded. |
|--------------|----------|----------------------------|

### Sutanto 2013

**Methods**

- Two-arm open-label RCT
- Follow-up: Days 1, 2, 3, 7, 14, 21, 28, 35 and 42, and any other day in between if they felt ill. Thin and thick blood smears and dried blood spot for genotyping
- Dates of randomization: December 2008 to March 2010

**Participants**

- 188 (178 left on day 3) + 186 (171 day 3). Analysis based on those still present on day 3
- Setting: Hanura Primary Health Center, Padang Cermin district, Lampung province located at the southern end of Sumatra
- Endemicity: Low malaria endemicity with a malaria prevalence of 1.8% across all age groups. Seasonal transmission
- Inclusion criteria:
  1. Parasite density ≥ 1000 parasites/µL
  2. Age ≥ 5 years
  3. Normal glucose-6-phosphate dehydrogenase (G6PD) enzyme levels based on a qualitative test
  4. Haemoglobin level ≥ 8 g/dL
  5. Negative pregnancy test (assessed by human chorionic gonadotropin urine test) or not breastfeeding
  6. No signs of severe malnutrition
  7. No other chronic diseases
  8. No history of allergy to the trial drugs
  9. Ability to return for 42 days of follow-up

**Interventions**

- 1. Standard 3-day DHAP (fixed-dose tablets of 40 mg dihydroartemisinin and 320 mg piperaquine; D-ARTEPP, Guilin Pharmaceutical Co, Ltd)
  2. DHAP as in intervention 1; PQ: Day 3, single dose of 0.75 mg/kg, rounded to the nearest half tablet. Mean dose was 0.74 mg/kg (range, 0.5 to 0.94 mg/kg)

**Outcomes**

- 1. Gametocyte prevalence-days 7, 14, 21, 28, 35 and 42
- 2. Gametocyte clearance rates by day 42 in patients with gametocytes on day 3
- 3. Recurrence of asexual stages of *P. falciparum*, PCR adjusted and unadjusted for reinfections
- 4. Gametocyte development by day 42 in patients who were gametocyte free on day 3
5. Gametocyte densities between days 3 and 42 inclusive
6. Asexual infection recurrence by PCR
7. Hemoglobin on days 7, 42
8. Adverse events

### Vasquez 2009

#### Methods
- Individually RCT
- Dates of trial: April 2007 to Feb 2008.

#### Participants
- 50 people with uncomplicated *P. falciparum* diagnosis by thick blood slide, 150 to 50,000 parasites/µL
- Age one year and over, both sexes.
- Exclusion criteria: Pregnant, mixed infection, danger signs and complications, allergy to antimalarials, serious illness at time or presentation, antimalarial treatment in last 72 hrs, MQ in last four weeks.

#### Interventions
- 1. AS+MQ
  - Age 1 to 6: AS 50 mg on days 1, 2, 3 (reported as 0, 1, 2); MQ 250 mg on day 2
  - Age 7 to 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

---

**Sutanto 2013** *(Continued)*

| Bias                                      | Authors’ judgement | Support for judgement |
|-------------------------------------------|--------------------|-----------------------|
| Random sequence generation (selection bias) | Low risk           | Computer-generated sequences in blocks of four. |
| Allocation concealment (selection bias)   | Low risk           | Opaque envelopes used in order at the health centre. |
| Incomplete outcome data (attrition bias)  | Low risk           | No evidence of differential attrition. |
| Selective reporting (reporting bias)      | Low risk           | No evidence of selective reporting. |
| Other bias                                | Low risk           | None detected. |
| Blinding of participants and personnel (performance bias) | High risk         | No blinding, no PQ placebo. |
| Blinding of outcome assessment (detection bias) | Unclear risk   | No information. |
### Vasquez 2009 (Continued)

| Age Group | Primaquine Dose |
|-----------|-----------------|
| Age 1 to 6 | 0.3 to 0.6 mg/kg day 3 (reported as day 2) |
| Age 7 to 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, and 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) | Low risk | No dropouts noted. |
| 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) | High risk | Does not seem to be blinded (“con determinación no ciega del efecto en grupos iguales”) |
| Blinding of outcome assessment (detection bias) | High risk | |

**Wang 2006**

**Methods**
- Individually RCT

**Participants**
- Number of participants: 214 (no dropouts mentioned)
- Gabon International Tropical Medicine Institute
- Age range: 6 to 60
- All have *P. falciparum* malaria clinical symptoms and blood smear positive.
Wang 2006  (Continued)

1. Trial group: 108, male 50, female 58, age 16.4 ± 10.5
2. Control group: 106, male 52, female 54, age 18.2 ± 9.4
Exclusion criteria:
N/A

**Interventions**
1. Artesunate IM injection, daily for 5 days, 1.2 mg/kg each dose, first dose double.
PQ 3 tablets (base 7.5 mg/tablet, children use half) once a day, for 5 days
2. Only artesunate IM injection daily for 5 days, 1.2 mg/kg each dose, the first dose double total 5 days

**Outcomes**
1. Fever clearance time: (hrs) below 37°C continuously measured four times
2. Clinical cure rate at day 7
3. Adverse events (not specified)
4. Recrudescence rate: Symptoms appeared again after clinical cure; parasite appeared in blood smear by 28 days
Follow-up: 28 days

**Notes**

**Risk of bias**

| Bias                                                                 | Authors’ judgement | Support for judgement                                                                                     |
|---------------------------------------------------------------------|--------------------|----------------------------------------------------------------------------------------------------------|
| Random sequence generation (selection bias)                         | Low risk           | Stated to be randomized, and the fact that numbers per group are not equal supports this contention       |
| Allocation concealment (selection bias)                             | Unclear risk       | No information given.                                                                                   |
| Incomplete outcome data (attrition bias) All outcomes               | Unclear risk       | Not stated.                                                                                              |
| Selective reporting (reporting bias)                                | Unclear risk       | Not stated.                                                                                              |
| Other bias                                                          | Unclear risk       | Unknown.                                                                                                |
| Blinding of participants and personnel (performance bias) All outcomes| Unclear risk       | Not stated to be blinded.                                                                               |
| Blinding of outcome assessment (detection bias) All outcomes        | Unclear risk       | Not stated to be blinded.                                                                               |

AL = artemether-lumefantrine; AQ = amodiaquine; AS = artesunate; CQ = chloroquine; DHAP = dihydroartemisinin-piperaquine; G6PD = glucose-6-phosphate dehydrogenase; IM = intramuscular; MQ = mefloquine; PCR = polymerase chain reaction; Pf = Plasmodium falciparum; PQ = primaquine; QN = quinine; RCT = randomized controlled trial; SP = sulfadoxine-pyrimethamine.

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

| Study         | Reason for exclusion                                                                                                                                 |
|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| Baird 2002    | Outcome is cure of asexual infection. No gametocyte outcomes                                                                                           |
| Barber 1929   | Not a RCT or quasi-RCT. No controls.                                                                                                                  |
| Barber 1932   | MDA with PQ; no other drug.                                                                                                                               |
| Brueckner 1998| Participants were not infected. Safety only trial.                                                                                                        |
| Bunnag 1980   | Comparison of SP plus either five 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. Not a RCT or quasi-RCT. Authors state they will do further studies, including transmission. No difference in gametocyte outcomes between regimens, and gametocytes persisted for up to 21 days |
| Burgess 1961  | Comparison of 15 mg, 30 mg and 45 mg dose of PQ. Outcomes were gametocyte prevalence, density, percent of mosquitoes infected and mean oocysts per mosquito up to eight days. Not a RCT or quasi-RCT. No other drug. Although this trial used different doses by group (12 participants total), they were assigned to participants based on age or body size, and therefore it was not a valid comparison of different doses |
| Cai 1985      | Not a RCT.                                                                                                                                               |
| Carter 2011   | No 8AQ in trial.                                                                                                                                          |
| Che 1987      | No mention of randomization. No valid comparison group (pyronaridine phosphate plus sulfadoxine plus PQ versus pyronaridine phosphate only)          |
| Che 1990      | No appropriate control group.                                                                                                                               |
| Chevalley 2010| In vitro studies only. Not a RCT.                                                                                                                         |
| Clyde 1962    | All patients got PQ.                                                                                                                                          |
| Clyde 1970    | Individual before-and-after study, but small number of patients and not controlled                                                                      |
| Clyde 1971    | Individual before-and-after study, but small number of patients and not controlled                                                                      |
| da Silva 1984 | Trial of treatment regimens, some including PQ, for *P. vivax* and *P. falciparum*.                                                                      |
| Degowin 1966  | No 8AQ in trial.                                                                                                                                          |
| Doi 1989      | Community observational study. Except for a small pilot study, everyone in the intervention villages got PQ. There no 'before' data from these villages. In the control site, some children received treatment |
| Giao 2004     | No appropriate control group (trial of CV8 (contains PQ) versus atovaquone-proguanil)                                                                     |
| Reference       | Description                                                                                                                                 |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Gogtay 1999     | Compares QN+PQ against QN+bulaquine. Not a relevant comparison                                                                               |
| Gunders 1961    | Before-and-after studies of gametocytes and mosquito feeds on people with gametocytes given pyrimethamine and PQ in doses ranging from 10 mg to 40 mg base. No group without other drug |
| 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 1993      | Not a RCT. Unbalanced groups.                                                                                                               |
| Huang 1996      | PQ given to both intervention groups in same regimen. Malaria treatment regimen was varied (low and higher dose pyronardine/SP)                 |
| Huang 2001      | No gametocyte outcomes.                                                                                                                     |
| Jeffery 1956    | Non-randomized comparison of gametocytes and infectivity of artificially infected patients treated with CQ or CQ+PQ                          |
| Jeffery 1963    | Observational study of gametocytes and infectivity of two patients given PQ                                                               |
| Jerace 1933     | Case series studying gametocytes and infectivity of patients given PQ                                                                      |
| Kaneko 1989     | Non-randomized community trial comparing SP+PQ in one village with SP only in another. Only one cluster per arm. The trial was predominantly mass fever test and treat but 75% of people in the intervention village were treated versus 18% in the control village |
| Karbwang 1991   | Not randomized, no gametocyte outcomes.                                                                                                      |
| Karbwang 1992   | Pharmacokinetic study; no gametocyte outcomes or control group                                                                                 |
| Kyaw 1994       | No control group. All patients got PQ.                                                                                                       |
| Li 2007         | No gametocyte outcomes.                                                                                                                     |
| Li 2010         | No gametocyte outcomes.                                                                                                                     |
| Lin 2004        | All patients got PQ.                                                                                                                        |
| Mackerras 1949  | No other malaria treatment; one patient fed on before and after PQR                                                                       |
| Rieckmann 1968  | Two patients given 45 mg PQ only and fed on by mosquitoes before and after. No other malaria treatment or control group                         |
| Rieckmann 1969  | 18 patients given CQ alone (N = 2), CQ plus 45 mg PQ (N = 3), or PQ alone in doses ranging from 15 to 45 mg, at either single dose or at one to two week intervals, and fed on before and after one of the doses of PQ. Non-randomized or quasi-randomized |
**Characteristics of studies awaiting assessment** [ordered by study ID]

| Study ID   | Methods                                                                 | Participants                                                                 | Interventions                                                                 | Outcomes                                                                 | Notes                     |
|------------|--------------------------------------------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------|---------------------------|
| Chen 1993b | 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 people with and without G6PD deficiency. | -                                                                             |                                                                              |                                                                           | Study not yet located     |
| Shah 2013  | Review of 21 trials from national drug resistance monitoring system of India. Compares 9 sites where AS+SP+PQ was used with 12 sites where it was not. | -                                                                             |                                                                              |                                                                           |                           |
| Shekalaghe 2010 | Randomized comparison of anaemia after SP+AS+PQ versus placebo. Children with haemoglobin < 8 g 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 | -                                                                             |                                                                              |                                                                           |                           |
| Sun 2011   | Artesunate + PQ versus Quinimax only. No appropriate control group.       | -                                                                             |                                                                              |                                                                           |                           |
| 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. | -                                                                             |                                                                              |                                                                           |                           |
| Yang 1989  | All patients got PQ, though different doses of PQ and other malaria treatments. | -                                                                             |                                                                              |                                                                           |                           |
| Yeramian 2005 | PQ given only to *P. vivax* patients for 14 days. | -                                                                             |                                                                              |                                                                           |                           |
| Young 1959 | No other malaria treatment; case series of PQ given either daily, twice a week or weekly to Pf patients. | -                                                                             |                                                                              |                                                                           |                           |
### Ishii 2009

| Method          | 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 other malaria treatment if appropriate |
| Outcomes        | Village prevalence of malaria |

| Notes | Study not yet located |

### Li 2006

| Method          |                      |
|-----------------|----------------------|
| Participants    |                      |
| Interventions   |                      |
| Outcomes        |                      |

| Notes | Study not yet located |

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

#### D’Alessandro (started 2013)

| Trial name or title                                                                 | Primaquine’s Gametocytocidal Efficacy in Malaria Asymptomatic Carriers Treated With Dihydroartemisinin-Piperaquine in The Gambia |
|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
| Methods                                                                             | Randomized, open label                                                                                                   |
| Participants                                                                       | 1200 participants will be recruited                                                                                      |
| Inclusion criteria:                                                                 | • Age ≥ 1 year                                                                                                           |
|                                                                                     | • Weight > 10 kg                                                                                                          |
|                                                                                     | • P. falciparum mono-infection, density of at least 20 parasites/µL                                                        |
|                                                                                     | • Axillary temperature < 37.5°C                                                                                         |
|                                                                                     | • Resident in the trial area and willingness to reside for the duration of the trial                                 |
|                                                                                     | • Written informed consent (plus an assent in children > 12 years of age)                                               |
| Exclusion criteria:                                                                 | • G6PD deficiency haemoglobin < 8 g/dL                                                                                  |
|                                                                                     | • Known allergy to any of the trial medications                                                                         |
|                                                                                     | • Known pregnancy or breastfeeding                                                                                    |
|                                                                                     | • Clear/documented history of anti-malarial treatment two weeks before contact with trial team                          |
|                                                                                     | • History of blood transfusion in the previous three months                                                             |
|                                                                                     | • Any chronic or acute conditions that might interfere with the trial as judged by the research clinician              |
|                                                                                     | • History of sickle cell anaemia                                                                                       |
D'Alessandro (started 2013)  (Continued)

Interventions
1. Control: complete course of DHA-PPQ (Eurartesim)
2. Experimental: DHA-PPQ plus single dose PQ at 0.75 mg/kg body weight
3. Experimental: DHA-PPQ plus single dose PQ at 0.4 mg base/kg body weight
4. Experimental: DHA-PPQ plus single dose PQ at 0.2 mg base/kg body weight

Outcomes
Primary: Prevalence of \textit{P. falciparum} gametocyte carriers (QT-NASBA) (time frame: Day 7)
Secondary:
1. Prevalence of \textit{P. falciparum} gametocytes carriers on days 3, 10, 14, 28 and 42 as determined by QT-NASBA
2. Proportion of individuals infectious to mosquitoes (DMFA) on day 7, with direct membrane feeding assay
3. Haemoglobin change from day 0 on days 3, 7, 10, 14, 21, 28, 35 and 42, as mean (±SD) difference in haemoglobin measured between baseline (day 0) and each follow-up visit day by trial arm
4. Prevalence of infection (asexual stages) on day 3
5. Proportion of participants with recurrent infection (PCR adjusted and unadjusted) from day 7 to day 42
6. Occurrence of adverse events and serious adverse events

Starting date
August 2013; December 2014 (final data collection date for primary outcome measure)

Contact information
udalessandro@mrc.gm +220-4495442-6 ext 4001 (Umberto D'Alessandro)
jokebe@mrc.gm +220-4495442-6 ext 4009 (Joseph Okebe)

Notes
ClinicalTrials.gov identifier: NCT01838902

Gosling (recruitment ended 2014)

Trial name or title
Phase 2a Dose Escalation Study of the Efficacy, Safety, and Pharmacokinetics of Low Dose Primaquine for Gametocytocidal Activity Against \textit{P. falciparum} in Sub-Saharan Africa and South East Asia

Methods
Randomized, single blind (outcomes assessor blinded)

Participants
50 participants being recruited
Inclusion criteria:
- Male
- Age ≥ 18 years and < 50 years
- Malaria blood thick film positive
- Presence of gametocytes on thick blood film
- Agrees to admission to trial ward for 26 hours post diagnosis and available for follow-up visits
- No allergies to trial drugs
- Hemoglobin ≥ 8 g/dL
- No evidence of severe or chronic disease
- Written, informed consent

Interventions
Group 1: Active comparator: dihydroartemisinin-piperaquine (DP) only
Group 2: Experimental: DP and 0.125 mg/kg PQ
Group 3: Experimental: DP and 0.5 mg/kg PQ
**Gosling (recruitment ended 2014) (Continued)**

| Outcomes | Primary: mosquito infectivity assessed through membrane feeding at baseline, and 1, 2 and 7 days  
Secondary:  
1. Gametocyte prevalence and density, at baseline, 2, 6, 12 and 24 hours, and at 2, 3, 7, 14 and 28 days  
2. PQ pharmacokinetics - AUC of parent drug and metabolite at 1, 2, 3, 4, 6, 8, 12 and 24 hours  
3. Asexual parasite prevalence and density baseline at baseline, 2, 6, 12, and 24 hours, and at 2, 3, 7, 14 and 28 days  
4. Safety measurements including haemoglobin and signs of haemolysis baseline at baseline, 1, 2, 3, 7 14 and 28 days |
| Starting date | September 2014 (final data collection date for primary outcome measure) |
| Contact information | goslingr@globalhealth.ucsf.edu 415 597 8114 |
| Notes | ClinicalTrials.gov identifier: NCT01743820  
Sites in Mali and Thailand |

**Indonesia (started 2013)**

| Trial name or title | Surveillance and Treatment With Dihydroartemisinin-piperaquine Plus Primaquine (MTC Belu)  
Sub-title: Impact of Mass Screening and Selective Treatment With Dihydroartemisinin-piperaquine Plus Primaquine on Malaria Transmission in High Endemic Area, Belu Regency, Nusa Tenggara Timur Province, Indonesia: a Randomized Cluster Trial |
| Methods | Allocation: randomized; endpoint classification: efficacy study; intervention model: parallel assignment; masking: open label, primary purpose: treatment  
Cluster randomized. |
| Participants | Target sample size: 1488 participants  
Inclusion criteria:  
- All villagers of all the selected clusters  
Exclusion criteria:  
- Pregnant women during their first trimester  
- Single dose PQ should not be given for infants under 1 year-old, pregnant women in all trimesters of pregnancy, breast-feeding mothers and patients with G6PD deficiency  
Age minimum: N/A  
Age maximum: N/A  
Gender: Both |
| Interventions | Drug: dihydroartemisinin-piperaquine  
Drug: PQ  
1. Intervention arm of mass screening and treatment with interval of 6 weeks  
2. Intervention arm of mass screening and treatment with interval of three months  
3. Control arm without mass screening and treatment.  
The intervention arm with six weeks interval represents a new proposed method to detection malaria infections, while the intervention arm with three month interval represents the Ministry of Health current policy of active case detection in Indonesia, and the third arm will serve as the control for Ministry of Health's policy  
No arm without PQ |
| Outcomes                  | Malaria incidence (time frame: six months)  
|                         | Anaemia (time frame: six months)          |
|--------------------------|-------------------------------------------|
| Starting date            | June 2013                                  |
| Contact information      | Indonesia University/Walter and Eliza Hall Institute of Medical Research |
| Notes                    | ClinicalTrials.gov identifier: NCT01878357  
|                         | Stated to be completed                     |

| Mwaiswelo (started 2014) |
|--------------------------|
| Trial name or title      | Efficacy and Safety of a Single Low-dose Primaquine Added to Standard Artemether-lumefantrine Treatment for the Clearance of Plasmodium Falciparum Gametocytes |
| Methods                  | Phase 4, randomized, safety/efficacy study, parallel assignment, single blind (subject). Primary purpose: Prevention |
| Participants             | Target sample size (N = 220) in Tanzania  
|                         | Inclusion criteria:  
|                         | 1. Gender: Both  
|                         | 2. Age of 1 year and above and neither pregnant nor breast feeding  
|                         | 3. Weight over 10 kg  
|                         | 4. Body temperature = 37.5°C or history of fever in the last 24 hours  
|                         | 5. *P. falciparum* mono-infection  
|                         | Exclusion criteria:  
|                         | 1. Evidence of severe illness malaria or danger signs  
|                         | 2. Known allergy to study medications  
|                         | 3. Hemoglobin < 8 g/dL  
|                         | 4. Antimalarials taken within last 2 weeks  
|                         | 5. Blood transfusion within last 90 days and evidence of recent use (within 14 days) or will be taking other drugs known to cause hemolysis in G6PD-deficient subjects |
| Interventions            | Control: AL + placebo. The first dose of AL will be administered concomitantly with a single-dose placebo. A volume of normal saline will be measured based on weight bands and then will be given to patients  
|                         | Intervention: AL+PQ. All the recruited patients will be treated with a six doses, 3 days AL treatment regimen. However, patients randomized to the AL+PQ arm will be given 0.25 mg/kg single-dose PQ concomitantly with AL first dose |
| Outcomes                 | Primary outcome: Number of days per treatment arm for gametocytes to become undetectable using Quantitative nucleic acid sequence based assay (QT-NASBA) (time frame: 14 days)  
|                         | Secondary outcome: Mean maximal fall in haemoglobin (g/dL) from enrolment to day 28 of follow-up defined as mean greatest negative difference in haemoglobin per treatment arm (time frame: 28 days) |
| Starting date            | Date of registration 16 March 2014  
|                         | Date of first enrolment July 2014 |
Mwaiswelo (started 2014)  

| Contact information | richiemwai@yahoo.com +255 717 043 970 (Richard O Mwaiswelo, MSc. PE)  
|                     | Andreas Martinsson, PhD, Karolinska Institutet  
Notes | ClinicalTrials.gov identifier: NCT02090036  
|       | Primary sponsor: Muhimbili University of Health and Allied Sciences  
|       | Secondary sponsor: Karolinska Institutet  

Sarr (started 2014)  

| Trial name or title | A trial of the safety of low dose primaquine in addition to ACTs commonly used in Senegal  
| Methods | Parallel, randomized  
| Participants | 300 participants will be recruited in Senegal  
| Inclusion criteria: |  
| 1. Age minimum: 20 years old, age maximum: 50 years old  
| 2. Gender: Both  
| 3. Adult patients with acute uncomplicated P. falciparum malaria  
| 4. P. falciparum monospecific infection with parasite density ranged from 1000 to 100,000 trophozoite/µL  
| 5. Willingness to participate in the planned study investigations and to remain in the study area for the duration of the study  
| 6. Participants informed consent  
| 7. Absence of known chronic illness such as hypertension, diabetes, renal and liver disease  
| Exclusion criteria: |  
| 1. Known allergy to the study medications  
| 2. Presence of severe anaemia (haemoglobin 8 g/dL) at enrolment  
| 3. Pregnancy, or breastfeeding  
| Interventions | Control: ACT treatment, standard malaria treatment, 1 daily dose, 3 days duration (N = 150)  
| Experimental: ACT plus PQ treatment; ACT treatment 1 daily dose for 3 days, PQ single low dose 0.25 mg/kg at day 1 (N = 150)  
| Outcomes | Primary outcome  
| 1. Mean haemoglobin difference from day 0 to day 7 after treatment with ACT and PQ  
| Secondary outcomes |  
| 1. Mean haemoglobin level at day 14 of follow-up in each treatment arm  
| 2. Mean haemoglobin level at day 28 of follow-up in each treatment arm  
| Starting date | Registered 10/11/2014; Date of first enrolment 15 November 2014  
| Contact information | roger.tine@ucad.edu.sn +00 221 77 637 05 31 (Prof Roger Tine)  
|                       | bathie65@yahoo.fr +00 221 77 647 09 99 (Dr Samba Cor Sarr)  
|                       | khadimesylla@yahoo.fr +00 221 77 521 76 44 (Dr Khadime Sylla)  
Notes | Pan African Clinical Trials identifier: PACTR20141100093737  
| Primary sponsor: University Cheikh Anta DIOP of Dakar  

Primaquine or other 8-aminoquinoline for reducing Plasmodium falciparum transmission (Review)  
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**Saunders (started 2012)**

| Trial name or title | Active Surveillance for *P. falciparum* Drug Resistance With Assessment of Transmission Blocking Activity of Single Dose Primaquine in Cambodia |
|---------------------|----------------------------------------------------------------------------------------------------------------------------------|
| Methods             | Randomized, open label                                                                                                           |
| Participants        | 150 male and female participants  
Inclusion criteria:  
1. Volunteer with uncomplicated *P. falciparum* malaria (volunteers with mixed *P. falciparum* and *P. vivax* infections may be enrolled), 18 to 65 years of age  
2. Baseline asexual parasite density between 1000 to 200,000 parasites/µL  
3. Able to provide informed consent  
4. Available and agree to follow-up for anticipated trial duration including three day treatment course at the MTF and weekly follow-up for the 42-day period  
5. Authorized by local commander to participate if active duty military  
Exclusion criteria:  
1. Allergic reaction or contraindication to DHA, piperaquine or PQ  
2. Significant acute comorbidity requiring urgent medical intervention  
3. Signs or symptoms and parasitological confirmation of severe malaria  
4. Use of any antimalarial within the past 14 days.  
5. Class I or II G6PD deficiency (defined as severe) as determined at screening  
6. Pregnant or lactating female, or female of childbearing age, up to 50 years of age, who does not agree to use an acceptable form of contraception during the trial  
7. Clinically significant abnormal EKG, including a QTcF interval > 500 ms at enrolment.  
8. Known or suspected concomitant use of QTc prolonging medications.  
9. Judged by the investigator to be otherwise unsuitable for trial participation |
| Interventions       | Group 1: DHA-piperaquine 3-day course plus 45 mg single dose PQ  
Group 2: DHA-piperaquine 3-day course of DHA-piperaquine |
| Outcomes            | Primary: Efficacy rates at 42 days for DP with and without single dose PQ for uncomplicated *P. falciparum* diagnosed by positive PCR-corrected malaria microscopy  
Secondary: Efficacy of PQ to treat sexual stage gametocyte infection and prevent transmission of *P. falciparum* gametocytes to mosquitoes. |
| Starting date       | December 2012; December 2014 (final data collection date for primary outcome measure) |
| Contact information | David Saunders, MD, MPH 66-2-696-2798 david.saunders@afrims.org  
Chanthap Lon, MD, MCTM 855 23 881 845 chanthapl@afrims.org |
| Notes               | ClinicalTrials.gov identifier: NCT01849640 |

**Sawa DAPPI-1 (started 2014)**

| Trial name or title | A Double Blind Randomized Controlled Trial of Dihydroartemisinin-Piperaquine Alone and in Combination With Single Dose Primaquine to Reduce Post-treatment Malaria Transmission |
|---------------------|----------------------------------------------------------------------------------------------------------------------------------|
| Methods             | Phase 3 randomized, safety/efficacy study, parallel assignment, double blind (subject, caregiver, investigator, outcomes assessor) |
### Participants

120 participants will be recruited in Kenya

**Inclusion criteria:**
1. Microscopically detectable *P. falciparum* gametocyte carriage
2. Age 5 years to 15 years
3. Gender: both

**Exclusion criteria:**
1. Age < 5 years or > 15 years
2. Non-falciparum malaria co-infection
3. Malaria parasite density = 200,000 parasites/µL
4. Clinical symptoms indicating severe malaria
5. Axillary temperature = 39°C
6. Body Mass Index (BMI) below 16 or above 32 kg/m$^2$
7. Haemoglobin concentration below 9.5 g/dL
8. Antimalarials taken in last 2 days
9. For women: Pregnancy (assessed by clinical examination and urine pregnancy test) or lactation
10. Known hypersensitivity to DP or PQ
11. History or symptoms, or both indicating chronic illness
12. Current use of tuberculosis or anti-retroviral medication
13. Unable to give written informed consent
14. Unwillingness to participate in two membrane feeding assays
15. Travel history to Angola, Cameroon, Chad, Central African Republic, Congo, DR Congo, Equatorial Guinea, Ethiopia, Gabon, Nigeria and Sudan
16. Family history of congenital prolongation of the QTc interval or sudden death or with any other clinical condition known to prolong the QTc interval such as history of symptomatic cardiac arrhythmias, with clinically relevant bradycardia or with severe cardiac disease
17. Taking drugs that are known to influence cardiac function and to prolong QTc interval, such as class IA and III: neuroleptics, antidepressant agents, certain antibiotics including some agents of the following classes - macrolides, fluoroquinolones, imidazole, and triazole antifungal agents, certain non-sedating antihistaminics (terfenadine, astemizole) and cisapride
18. Known disturbances of electrolyte balance, eg hypokalaemia or hypomagnesaemia
19. Taking drugs which may be metabolized by cytochrome enzyme CYP2D6 (for example, flecainide, metoprolol, imipramine, amitriptyline, clomipramine)
20. Blood transfusion within last 90 days

### Interventions

**Control:** DHAP (Artekin) combination alone

**Experimental:** DHAP (Artekin) combination alone plus single-dose 0.25 mg/kg PQ

### Outcomes

**Primary outcome**
1. Gametocyte prevalence on day 7 after initiation of treatment (time frame: day 7 of follow-up)

**Secondary outcomes**
1. Gametocyte carriage during follow-up (time frame: 14 days during follow-up)
2. Gametocyte sex-ratio (time frame: 14 days of follow-up)
3. Haematological recovery (time frame: 14 days during follow-up)
4. Transmission to *An. gambiae* mosquitoes (time frame: day 3 and 7 during follow-up)

**Starting date**
Registration date 29 September 2014; first enrolment October 2014
### Sawa DAPPI-1 (started 2014)  (Continued)

| Contact information | psawa@icipe.org +254 59 22620 (Patrick Sawa MD, ICIPE)  
|                     | teun.bousema@lshtm.ac.uk +31243617574 (Teun J Bousema, PhD) |
| Notes | ClinicalTrials.gov identifier: NCT02259426  
Primary sponsor: London School of Hygiene and Tropical Medicine |

### Shekalaghe (started 2013)

#### Trial name or title
The Optimal Timing of Primaquine to Prevent Malaria Transmission After Artemisinin-Combination Therapy

#### Methods
Randomized, open label

#### Participants
250 male and female participants  
Inclusion criteria:  
- Age 3 years to 17 years  
- Residents of research area  
- Willingness to come for complete scheduled follow-up  
- Uncomplicated malaria with *P. falciparum* mono-infection  
- Axillary temperature > 37.5°C and < 39.5°C, or history of fever in previous 48 hours  
- No history of adverse reactions to trial medication  
- Understanding of the trial procedures by parent or guardian and willing to participate by signing written informed consent forms  
Exclusion criteria:  
- Haemoglobin below 9 g/dL  
- Inability to take drugs orally  
- Known hypersensitivity to any of the drugs given  
- Reported treatment with antimalarial chemotherapy in the past two weeks  
- Evidence of chronic disease or acute infection other than malaria  
- Domicile outside the trial area  
- Signs of severe malaria (such as respiratory distress, altered consciousness deep breathing, anaemia)  
- Participating in other malaria studies conducted in the region  
- Mixed malaria parasite species infection  
- Positive pregnant test by urine (UPT) if participant is female aged above 12 years  
- G6PD deficient using the fluorescence spot test

#### Interventions
Group 1: AL 6 dose regime orally  
Group 2: AL 6 dose regime plus single dose PQ (0.75/kg) on day 0  
Group 3: AL 6 dose regimen plus single dose PQ (0.75/kg) on day 2

#### Outcomes
Primary: Gametocyte prevalence and density by microscopy and QT-NASBA on day 14  
Secondary:  
- Haemoglobin level on days 3, 7, 10 and 14  
- Proportion of infected mosquitoes on day 7 after initiation of treatment and the intensity of infection (oocyst burden) by membrane feeding assay

#### Starting date
May 2013; October 2013 (final data collection date for primary outcome measure)
### Shekalaghe (started 2013)  
*(Continued)*

| Contact information | Seif Shekalaghe, MD, PhD [sshekalaghe@ihi.or.tz +255 755 470472] |
|---------------------|---------------------------------------------------------------|
| Notes               | ClinicalTrials.gov identifier: NCT01906788  
Tanzania KCMC and Ifakara |

### Sirima SAFEPRIM (started 2014)

| Trial name or title | Evaluation of the Safety of Primaquine in Combination With Artemether-lumefantrine in Glucose-6-phosphate Dehydrogynase Deficient Males With an Asymptomatic Malaria Infection in Burkina Faso (SAFEPRIM) |
|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Methods             | Phase 2/3 randomized, safety study, parallel assignment, open label. Primary purpose: treatment |

| Participants | Target sample size (N = 70) in Burkina Faso  
Inclusion criteria:  
1. Male gender  
2. Aged ≥ 18 years to ≤ 45 years  
3. BMI ≥ 16  
4. *P. falciparum* parasitaemia at any density  
5. G6PD deficiency by Beutler Fluorescent Spot test for intervention groups and control group receiving AL only (N = 50)  
6. G6PD normal activity by Beutler Fluorescent Spot test for control groups (N = 20)  
7. Informed consent by participant  
Exclusion criteria:  
1. Enrolled in another clinical trial  
2. Fever > 37.5°C (tympanic) or history of fever in the last 24 hours  
3. Evidence of severe illness/danger signs or active infection other than malaria  
4. Known allergy to study medications  
5. Hb < 11 g/dL  
6. Antimalarials taken within the last 2 weeks  
7. PQ taken within the last 4 weeks and blood transfusion within the last 90 days  
8. Non-falciparum malaria co-infection  
9. Current use of tuberculosis or anti-retroviral medication, sulphonamides, dapsone, nitrofurantoin, nalidixic acid, ciprofloxacin, methylene blue, toluidine blue phenazopyridine and co-trimoxazole.  
10. History of severe chronic illness |
|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Interventions       | 1. AL + 0.25 mg/kg PQ  
2. AL + 0.4 mg/kg PQ  
3. AL combination |
| Outcomes            | Primary outcome: Haemoglobin concentration relative to baseline value (time frame: 28 days)  
Secondary outcome: Gametocyte clearance time (time frame: 14 days) |
| Starting date       | Date of registration 11 June 2014. Date of first enrolment October 2014 |
| Contact information | s.sirima.cnlp@fasonet.bf + 226 50 32 46 95/96 (Sodziomon Sirima, MD, PhD)  
teun.bousema@lshtm.ac.uk +31243613663 (Teun Bousema, PhD) |
### Sirima SAFEPRIM (started 2014)

**Trial name or title**  
Evaluation of DHAP with and without single dose primaquine: an open-label randomized, controlled trial in anlong Veng, Cambodia

**Methods**  
Randomized, open-label clinical trial to evaluate the safety and therapeutic efficacy of DP, and transmission blocking potential in combination with single dose primaquine (PQ) in northern Cambodia

**Participants**  
Up to 150 volunteers, including those with mild-moderate G6PD deficiency with uncomplicated *P. falciparum* or mixed malaria infections

**Interventions**  
Consecutive daily oral doses of 120/960 mg of DP with or without a single 45 mg dose of PQ

**Outcomes**  
Mosquito membrane-feeding assay  
Serial electrocardiograms and time-matched drug levels

**Starting date**  
Not known - trial registration not yet located.

**Contact information**  
M Spring

**Notes**  
Identified from preliminary results in 63rd Annual Meeting of the American Society of Tropical Medicine and Hygiene, ASTMH 2013 New Orleans

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### Spring (recruitment ended 2014)

**Trial name or title**  
Evaluation of DHAP with and without single dose primaquine: an open-label randomized, controlled trial in anlong Veng, Cambodia

**Methods**  
Randomized, open-label clinical trial to evaluate the safety and therapeutic efficacy of DP, and transmission blocking potential in combination with single dose primaquine (PQ) in northern Cambodia

**Participants**  
Up to 150 volunteers, including those with mild-moderate G6PD deficiency with uncomplicated *P. falciparum* or mixed malaria infections

**Interventions**  
Consecutive daily oral doses of 120/960 mg of DP with or without a single 45 mg dose of PQ

**Outcomes**  
Mosquito membrane-feeding assay  
Serial electrocardiograms and time-matched drug levels

**Starting date**  
Not known - trial registration not yet located.

**Contact information**  
M Spring

**Notes**  
Identified from preliminary results in 63rd Annual Meeting of the American Society of Tropical Medicine and Hygiene, ASTMH 2013 New Orleans

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### Thailand (started 2012)

**Trial name or title**  
Pharmacokinetic Study of Primaquine and Dihydroartemisinin-Piperaquine in Healthy Subjects

**Methods**  
Phase 1  
Randomized, crossover, open label safety/efficacy study. Primary purpose: treatment

**Participants**  
Target sample size (N = 16)  
Inclusion criteria:  
1. Healthy as judged by a responsible physician with no abnormality identified on a medical evaluation including medical history and physical examination.  
2. Male and female non-smokers aged between 18 years to 60 years.  
3. Males and females weight between 36 to 75 kg.  
4. A female is eligible to enter and participate in this study if she is: of non-childbearing potential including pre-menopausal females with documented (medical report verification) hysterectomy or double oophorectomy; or postmenopausal defined as 12 months of spontaneous amenorrhoea or 6 months of spontaneous amenorrhoea with serum follicle stimulating hormone levels > 40 mIU/mL or 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy; or of childbearing potential, has a...
negative serum pregnancy test at screening and prior to start the study drug in each period, and abstain from sexual intercourse or agrees to using effective contraceptive methods (for example, intrauterine device, hormonal contraceptive drug, tubal ligation or female barrier method with spermicide) during the study until completion of the follow-up procedures.

5. A male is eligible to enter and participate in this study if he: agrees to abstain from (or uses a condom during) sexual intercourse with females of childbearing potential or lactating females; or is willing to use a condom/spermicide, during the study until completion of the follow-up procedures.

6. Provide a signed and dated written informed consent prior to study participation.

7. Normal electrocardiogram (ECG) with QTc < 450 msec.

8. Willingness and ability to comply with the study protocol for the duration of the trial.

Exclusion criteria:

1. Females who are pregnant, trying to get pregnant, or are lactating.

2. The subject has evidence of active substance abuse that may compromise safety, pharmacokinetics or ability to adhere with protocol instructions.

3. A positive pre-study hepatitis B surface antigen, positive hepatitis C antibody, or positive human immunodeficiency virus-1 (HIV-1) antibody result at screening.

4. Subjects with a personal history of cardiac disease, symptomatic or asymptomatic arrhythmias, syncopal episodes or additional risk factors for torsades de points (heart failure, hypokalaemia) or with a family history of sudden cardiac death.

5. A creatinine clearance < 70 mL/min as determined by Cockcroft-Gault equation: CLcr (mL/min) = (140 - age) * wt/(72 * Scr) (multiply answer by 0.85 for females) where age is in years, weight (wt) is in kg, and serum creatinine (Scr) is in units of mg/dL (Cockcroft 1976).

6. History of alcohol or substance abuse or dependence within 6 months of the study.

7. Use of prescription or non-prescription drugs except paracetamol at doses of up to 2 g/day, including vitamins, herbal and dietary supplements (including St. John’s Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or five times the drug half-life (whichever is longer) prior to the first dose of study medication until the completion of the follow-up procedure, unless in the opinion of investigator, the medication will not interfere with the study procedures or compromise subject safety; the investigator will take advice from the manufacturer representative as necessary.

8. The subject has participated in a clinical trial and has received a drug or a new chemical entity within 30 days, or 5 half-lives, or twice the duration of the biological effect of any drug (whichever is longer) prior to the first dose of study medication.

9. The subject is unwilling to abstain from ingesting the biological effect of any drug (whichever is longer) prior to the first dose of study medication.

10. Subjects who have donated blood to the extent that participation in the study would result in more than 300 mL blood donated within a 30-day period. Note: This does not include plasma donation.

11. Subjects who have a history of allergy to the study drug or drugs of this class, or a history of drug or other allergy that, in the opinion of the investigator, contraindicates participation in the trial. In addition, if heparin is used during pharmacokinetic sampling, subjects with a history of sensitivity to heparin or heparin-induced thrombocytopenia should not be enrolled.

12. Lack of suitability for participation in this study, including but not limited to, unstable medical conditions, systemic disease manifested by tendency to granulocytopenia for example rheumatoid arthritis and lupus erythematosus that in the opinion of the investigator would compromise their participation in the trial.

13. AST or ALT > 1.5 upper limit of normal (ULN).

14. Subjects with history of renal disease, hepatic disease or cholecystectomy or both.

15. G6PD deficient detected by Beutler's dye test.

16. Abnormal methaemoglobin level.
17. History of antimalarial drugs use including but not limited to MQ, chloroquine, PQ, artesunate, piperaquine and pyronaridine treatment within 12 months.
18. Subject who received quinacrine in last 30 days.

Interventions
This study is planned to evaluate potential pharmacokinetic interaction of orally administered PQ and dihydroartemisinin-piperaquine (DHA-PQP) in healthy adult subjects. The results of these interaction studies are important in order to provide clinical guidance for the optimum combination of PQ and DHA-PQP treatment regimens in malaria infections.

Outcomes
Primary
- AUC for PQ (Time frame: 36 days; designated as safety issue: no). Area under the concentration-time curve ([AUC(0-) and AUC(0-last)]) and maximal concentration (C_max) for PQ and metabolites when given alone or together with DHA-PQP.
- AUC for dihydroartemisinin (DHA) and piperaquine (PQP) (Time frame: 36 days; designated as safety issue: no). Area under the concentration-time curve ([AUC(0-) and AUC(0-last)]) and maximal concentration (C_max) for piperaquine and dihydroartemisinin when given alone as DHA-PQP or together with PQ.

Secondary
- Clearance rate and half life of PQ and its metabolites (Time frame: 36 days; designated as safety issue: no). PQ, carboxyprimaquine (and other detectable major metabolites) elimination clearance rate (CL/F), terminal elimination half-life (t_1/2) and apparent volume of distribution (Vd).
- Dihydroartemisinin and piperaquine elimination clearance rate (CL/F), terminal elimination half-life (t_1/2) and apparent volume of distribution (Vd). Safety of dihydroartemisinin-piperaquine (DHA-PQP) (Time frame: 36 days; designated as safety issue: yes). Safety and tolerability parameters, including adverse events, clinical laboratory, and vital signs assessments, in particular QTc prolongation for DHA-PQP.
- Pharmacogenetic polymorphisms (Time frame: 36 days; designated as safety issue: yes) in the case of unusually high or low drug levels.

Starting date
June 2012

Contact information
Sasithon Pukrittayakamee, MD, Principal Investigator, Mahidol University
Salwaluk Panapipat, MBA salwaluk@tropmedres.ac

Notes
ClinicalTrials.gov identifier: NCT01525511
University of Oxford

Tiono (started 2013)

Trial name or title
Low Dose Primaquine for Clearance of Gametocytes: LOPRIM-1

Methods
Randomized, parallel assignment, double blind (subject, caregiver, investigator, outcomes assessor); safety/efficacy study

Participants
Target sample size 360 participants
Inclusion criteria
- Age > 2 and < 15 years
- Plasmodium falciparum parasitaemia > 1000 and < 200,000 parasites/µL.
- Plasmodium falciparum gametocytes
Tiono (started 2013)  (Continued)

- Normal G6PD
- Informed consent by legally acceptable representative

Exclusion criteria

- Enrolled in another study
- Fever or history of fever in last 24 hours
- Evidence of severe illness/danger signs
- Known allergy to study medications
- Hb < 8 g/dL
- Started menstruation
- Pregnancy or breastfeeding
- Antimalarials taken within last 2 days
- PQ taken within last 4 weeks
- Blood transfusion within the last 90 days
- Non-falciparum malaria co-infection

Interventions

- Group 1: AL
- Group 2: AL with a single dose of 0.25 mg/kg PQ
- Group 3: AL with a single dose of 0.4 mg/kg PQ

Outcomes

- Primary: Gametocyte carriage (time frame: 14 days during follow-up)
- Secondary:
  - Haematological recovery (time frame: 14 days during follow-up)
  - Transmission to An. gambiae mosquitoes (time frame: day 1, 3, and 7)

Starting date

- September 2013

Contact information

- t.alfred@fasonet.bf; teun.bousema@lshm.ac.uk

Notes

- ClinicalTrials.gov identifier: NCT01935882
- Burkina Faso, Centre National de Recherche et de Formation sur le Paludisme, Ougadougou, Burkina Faso
### Comparison 1. Non-artemisinin treatment regimen: PQ versus no PQ

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---------------------------|----------------|---------------------|--------------------|-------------|
| **1 Participants with gametocytes** | | | | |
| 1.1 Day 2 | 2 | 96 | Risk Ratio (M-H, Fixed, 95% CI) | 0.72 [0.46, 1.12] |
| 1.2 Day 3 | 1 | 83 | Risk Ratio (M-H, Fixed, 95% CI) | 0.75 [0.45, 1.27] |
| 1.3 Day 4 or 5 | 3 | 273 | Risk Ratio (M-H, Fixed, 95% CI) | 0.84 [0.64, 1.09] |
| 1.4 Day 8 | 5 | 402 | Risk Ratio (M-H, Fixed, 95% CI) | 0.54 [0.44, 0.65] |
| 1.5 Day 15 | 4 | 366 | Risk Ratio (M-H, Fixed, 95% CI) | 0.31 [0.22, 0.43] |
| 1.6 Day 22 | 4 | 323 | Risk Ratio (M-H, Fixed, 95% CI) | 0.30 [0.20, 0.46] |
| 1.7 Day 29 | 4 | 290 | Risk Ratio (M-H, Fixed, 95% CI) | 0.34 [0.19, 0.60] |
| 1.8 Day 36 | 1 | 81 | Risk Ratio (M-H, Fixed, 95% CI) | 0.37 [0.15, 0.94] |
| 1.9 Day 43 | 1 | 73 | Risk Ratio (M-H, Fixed, 95% CI) | 0.27 [0.04, 1.71] |
| **2 Gametocyte clearance time (days)** | | | | |
| 2.1 Day 5 | 1 | 30 | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.2 Day 8 | 1 | 30 | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.3 Day 15 | 1 | 30 | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.4 Day 22 | 1 | 30 | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| **3 Participants infectious** | | | | |
| 3.1 Day 5 | 1 | 30 | Risk Ratio (M-H, Fixed, 95% CI) | 0.06 [0.01, 0.42] |
| 3.2 Day 8 | 1 | 30 | Risk Ratio (M-H, Fixed, 95% CI) | 0.07 [0.01, 0.45] |
| 3.3 Day 15 | 1 | 30 | Risk Ratio (M-H, Fixed, 95% CI) | 0.14 [0.02, 1.04] |
| 3.4 Day 22 | 1 | 30 | Risk Ratio (M-H, Fixed, 95% CI) | 0.33 [0.02, 7.24] |
| **4 Mosquitoes infected** | | | | |
| 4.1 Day 5 | 1 | 30 | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 4.2 Day 8 | 1 | 30 | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 4.3 Day 15 | 1 | 30 | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 4.4 Day 22 | 1 | 30 | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| **5 Participants with asexual parasites at day 29** | | | | |
| 5.1 Not PCR adjusted | 1 | 209 | Risk Ratio (M-H, Fixed, 95% CI) | 0.94 [0.78, 1.15] |
| 5.2 PCR adjusted | 1 | 209 | Risk Ratio (M-H, Fixed, 95% CI) | 0.92 [0.69, 1.23] |
| **6 Asexual parasite clearance time (hrs)** | | | | |
| 6.1 Day 5 | 1 | 30 | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 6.2 Day 8 | 1 | 30 | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 6.3 Day 15 | 1 | 30 | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 6.4 Day 22 | 1 | 30 | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| **7 Adverse effects** | | | | |
| 7.1 Nausea | 1 | 30 | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 7.2 Vomiting | 1 | 30 | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 7.3 Dizziness | 1 | 30 | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 7.4 Any adverse effect | 1 | 30 | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| **8 By dose: Participants with gametocytes at day 8 (microscopy)** | | | | |
| 8.1 < 0.4 mg/kg PQ per day | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 8.2 ≥ 0.4 to < 0.6 mg/kg PQ per day | 1 | 216 | Risk Ratio (M-H, Fixed, 95% CI) | 0.60 [0.49, 0.75] |
| 8.3 ≥ 0.6 mg/kg PQ per day | 4 | 186 | Risk Ratio (M-H, Fixed, 95% CI) | 0.39 [0.25, 0.62] |
| **9 By schedule: Participants with gametocytes at day 8** | | | | |
| 9.1 Single dose day 1 or 2 | 4 | 191 | Risk Ratio (M-H, Fixed, 95% CI) | 0.64 [0.49, 0.84] |
Comparison 2. Artemisinin treatment regimen: PQ versus no PQ

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---------------------------|----------------|---------------------|--------------------|-------------|
| 1 Participants with gametocytes (microscopy) | 5 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 1.1 Day 4 | 4 | 971 | Risk Ratio (M-H, Random, 95% CI) | 1.00 [0.95, 1.05] |
| 1.2 Day 8 | 5 | 1071 | Risk Ratio (M-H, Random, 95% CI) | 0.21 [0.08, 0.54] |
| 1.3 Day 15 | 4 | 995 | Risk Ratio (M-H, Random, 95% CI) | 0.09 [0.04, 0.19] |
| 1.4 Day 22 | 3 | 858 | Risk Ratio (M-H, Random, 95% CI) | 0.10 [0.03, 0.32] |
| 1.5 Day 29 | 4 | 945 | Risk Ratio (M-H, Random, 95% CI) | 0.17 [0.04, 0.72] |
| 1.6 Day 36 | 3 | 838 | Risk Ratio (M-H, Random, 95% CI) | 0.21 [0.01, 4.32] |
| 1.7 Day 43 | 4 | 917 | Risk Ratio (M-H, Random, 95% CI) | 0.41 [0.04, 3.89] |
| 2 Participants with gametocytes (PCR) | 3 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 2.1 Day 8 | 3 | 627 | Risk Ratio (M-H, Random, 95% CI) | 0.42 [0.26, 0.69] |
| 2.2 Day 15 | 3 | 609 | Risk Ratio (M-H, Random, 95% CI) | 0.27 [0.11, 0.70] |
| 2.3 Day 29 | 1 | 90 | Risk Ratio (M-H, Random, 95% CI) | 0.23 [0.08, 0.62] |
| 2.4 Day 43 | 1 | 79 | Risk Ratio (M-H, Random, 95% CI) | 0.44 [0.17, 1.16] |
| 3 Participants with asexual parasites | 5 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 3.1 Day 8 | 1 | 94 | Risk Ratio (M-H, Fixed, 95% CI) | 1.28 [0.30, 5.40] |
| 3.2 Day 15 | 2 | 198 | Risk Ratio (M-H, Fixed, 95% CI) | 0.97 [0.23, 4.15] |
| 3.3 Day 29 | 3 | 747 | Risk Ratio (M-H, Fixed, 95% CI) | 0.54 [0.33, 0.88] |
| 3.4 Day 43 | 2 | 178 | Risk Ratio (M-H, Fixed, 95% CI) | 1.03 [0.59, 1.81] |
| 4 Asexual parasite clearance time (hrs) | 1 | 50 | Mean Difference (IV, Fixed, 95% CI) | -6.0 [-16.31, 4.31] |
| 5 Haemoglobin concentration | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 5.1 Day 8 | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 5.2 Day 15 | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 5.3 Day 29 | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 5.4 Day 43 | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 6 % change in haemoglobin concentration | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 6.1 Day 8 | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 6.2 Day 15 | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 6.3 Day 29 | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 6.4 Day 43 | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 7 Other adverse effects | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 7.1 Headache | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 7.2 Fatigue | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 7.3 Nausea | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 7.4 Vomiting | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 7.5 Abdominal pain | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 7.6 Diarrhea | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 7.7 Pruritis | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
Comparison 3. PQ versus no PQ; gametocytes at day 8 (microscopy or PCR); stratified by non-artemisinin versus artemisinin regimen

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---------------------------|----------------|---------------------|--------------------|-------------|
| 1 Participants with gametocytes at day 8 (microscopy or PCR) | 11 | 1994 | Risk Ratio (M-H, Random, 95% CI) | 0.38 [0.27, 0.52] |
| 1.1 Non-artemisinin-based partner drug | 5 | 402 | Risk Ratio (M-H, Random, 95% CI) | 0.54 [0.38, 0.77] |
| 1.2 Artemisinin-based partner drug | 7 | 1592 | Risk Ratio (M-H, Random, 95% CI) | 0.32 [0.20, 0.51] |

Comparison 4. PQ versus other 8AQ

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---------------------------|----------------|---------------------|--------------------|-------------|
| 1 Participants with gametocytes on day 8 | 2 | 112 | Risk Ratio (M-H, Fixed, 95% CI) | 0.41 [0.26, 0.66] |
### Analysis 1.1. Comparison 1 Non-artemisinin treatment regimen: PQ versus no PQ, Outcome 1 Participants with gametocytes.

Review: Primaquine or other 8-aminoquinoline for reducing *Plasmodium falciparum* transmission

Comparison: 1 Non-artemisinin treatment regimen: PQ versus no PQ

Outcome: 1 Participants with gametocytes

| Study or subgroup | With primaquine | Without primaquine | Risk Ratio M-H,Fixed,95% CI | Weight M-H,Fixed,95% CI |
|-------------------|-----------------|--------------------|-----------------------------|--------------------------|
| **1 Day**         |                 |                    |                             |                          |
| Chen 1993a (1)    | 6/6             | 6/6                | 27.5 % 1.00 [0.75, 1.34]    |                          |
| Kolaczynski 2012 (2) | 10/40          | 18/44              | 72.5 % 0.61 [0.32, 1.16]    |                          |
| **Subtotal (95% CI)** | **46**         | **50**             | **100.0 % 0.72 [0.46, 1.12]** |                          |
| **Total events:** | 16 (With primaquine), 24 (Without primaquine) | | | |
| **Heterogeneity:** | Chi² = 5.23, df = 1 (P = 0.02); I² = 81% | | | |
| **Test for overall effect:** | Z = 1.47 (P = 0.14) | | | |
| **2 Day 3**       |                 |                    |                             |                          |
| Kolaczynski 2012 (3) | 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 or 5**  |                 |                    |                             |                          |
| Arango 2012 (4)   | 8/20            | 7/20               | 10.5 % 1.14 [0.51, 2.55]     |                          |
| Chen 1993a (5)    | 3/6             | 6/6                | 9.8 % 0.54 [0.25, 1.16]      |                          |
| Kolaczynski 2012 (6) | 12/38          | 23/44              | 32.1 % 0.60 [0.35, 1.04]     |                          |
| Kolaczynski 2012 (7) | 32/71          | 31/68              | 47.6 % 0.99 [0.69, 1.42]     |                          |
| **Subtotal (95% CI)** | **135**        | **138**            | **100.0 % 0.84 [0.64, 1.09]** |                          |
| **Total events:** | 55 (With primaquine), 67 (Without primaquine) | | | |
| **Heterogeneity:** | Chi² = 4.01, df = 3 (P = 0.26); I² = 25% | | | |
| **Test for overall effect:** | Z = 1.30 (P = 0.19) | | | |
| **4 Day 8**       |                 |                    |                             |                          |
| Arango 2012 (8)   | 7/20            | 11/20              | 8.6 % 0.64 [0.31, 1.30]      |                          |
| Chen 1993a (9)    | 0/6             | 6/6                | 5.1 % 0.08 [0.01, 1.12]      |                          |
| Kamtekar 2004 (10) | 7/24           | 16/22              | 13.0 % 0.40 [0.20, 0.79]     |                          |
| Kolaczynski 2012 (11) | 24/36          | 37/43              | 26.3 % 0.77 [0.60, 1.01]     |                          |
| Kolaczynski 2012 (12) | 27/70          | 52/67              | 41.5 % 0.50 [0.36, 0.69]     |                          |
| Ledermann 2006 (13) | 2/28           | 2/16               | 2.0 % 0.57 [0.09, 3.68]      |                          |

(Continued...)
| Study or subgroup | With primaquine | Without primaquine | Risk Ratio | Weight |
|------------------|----------------|-------------------|------------|--------|
|                  | n/N            | n/N               | M-H,Fixed,95% CI |        |
| **Subtotal (95% CI)** | 212           | 190               | 100.0 %      | 0.54 [ 0.44, 0.65 ] |
| **Total events:** | 67 (With primaquine), 127 (Without primaquine) |
| **Heterogeneity:** | Chi$^2$ = 12.45, df = 6 (P = 0.05); I$^2$ =52% |
| **Test for overall effect:** | Z = 6.17 (P < 0.00001) |
| 5 Day 15         |                |                   |            |        |
| Chen 1993a       | 0/6           | 6/6               | 7.0 %       | 0.08 [ 0.01, 1.12 ] |
| Kamtekar 2004 (15) | 1/24          | 8/22              | 9.0 %       | 0.11 [ 0.02, 0.84 ] |
| Kamtekar 2004 (16) | 2/21          | 7/22              | 7.4 %       | 0.30 [ 0.07, 1.28 ] |
| Kolaczinski 2012 | 18/32         | 34/41             | 32.1 %      | 0.68 [ 0.48, 0.95 ] |
| Kolaczinski 2012 | 4/53          | 37/51             | 40.6 %      | 0.10 [ 0.04, 0.27 ] |
| Ledermann 2006   | 0/28          | 1/16              | 2.0 %       | 0.20 [ 0.01, 1.43 ] |
| Ledermann 2006   | 0/28          | 1/16              | 2.0 %       | 0.20 [ 0.01, 1.43 ] |
| **Subtotal (95% CI)** | 192           | 174               | 100.0 %      | 0.30 [ 0.22, 0.43 ] |
| **Total events:** | 25 (With primaquine), 94 (Without primaquine) |
| **Heterogeneity:** | Chi$^2$ = 28.69, df = 6 (P = 0.00077); I$^2$ =79% |
| **Test for overall effect:** | Z = 6.88 (P < 0.00001) |
| 6 Day 22         |                |                   |            |        |
| Chen 1993a       | 0/6           | 3/6               | 5.8 %       | 0.14 [ 0.01, 2.28 ] |
| Kamtekar 2004    | 0/24          | 6/22              | 11.3 %      | 0.07 [ 0.00, 1.19 ] |
| Kamtekar 2004    | 0/21          | 0/22              | Not estimable |
| Kolaczinski 2012 | 14/33         | 33/40             | 49.6 %      | 0.51 [ 0.34, 0.78 ] |
| Kolaczinski 2012 | 1/33          | 15/28             | 27.0 %      | 0.06 [ 0.01, 0.40 ] |
| Ledermann 2006   | 0/28          | 1/16              | 3.1 %       | 0.20 [ 0.01, 4.53 ] |
| Ledermann 2006   | 0/28          | 1/16              | 3.1 %       | 0.20 [ 0.01, 4.53 ] |
| **Subtotal (95% CI)** | 173           | 150               | 100.0 %      | 0.30 [ 0.20, 0.46 ] |
| **Total events:** | 15 (With primaquine), 59 (Without primaquine) |
| **Heterogeneity:** | Chi$^2$ = 10.52, df = 5 (P = 0.06); I$^2$ =52% |
| **Test for overall effect:** | Z = 5.61 (P < 0.00001) |
| 7 Day 29         |                |                   |            |        |
| Chen 1993a       | 0/6           | 0/6               | Not estimable |
| Kamtekar 2004    | 1/24          | 6/22              | 18.4 %      | 0.15 [ 0.02, 1.17 ] |
| Kamtekar 2004    | 0/21          | 0/22              | Not estimable |
| Kolaczinski 2012 | 7/28          | 26/38             | 64.8 %      | 0.37 [ 0.19, 0.72 ] |
| Kolaczinski 2012 | 3/20          | 5/15              | 16.8 %      | 0.45 [ 0.13, 1.59 ] |
| Ledermann 2006   | 0/28          | 0/16              | Not estimable |
| Study or subgroup | With primaquine | Without primaquine | Risk Ratio | Weight | Risk Ratio |
|------------------|----------------|--------------------|------------|--------|------------|
|                  | n/N            | n/N                | M-H,Fixed95% CI |        | M-H,Fixed95% CI |
| Ledermann 2006   | 0/28           | 0/16               | Not estimable |        |             |
| **Subtotal (95% CI)** | **155** | **135** | 100.0 % | 0.34 [ 0.19, 0.60 ] |
| **Total events:** | 11 (With primaquine), 37 (Without primaquine) | |
| **Heterogeneity:** | Chi² = 0.82, df = 2 (P = 0.66); I² = 0.0% | |
| **Test for overall effect:** | Z = 3.68 (P = 0.00023) | |
| 8 Day 36 | | |
| Kolacznik 2012 | 3/28 | 12/34 | 77.4 % | 0.30 [ 0.09, 0.97 ] |
| Kolacznik 2012 | 2/10 | 3/9 | 22.6 % | 0.60 [ 0.13, 2.82 ] |
| **Subtotal (95% CI)** | **38** | **43** | 100.0 % | 0.37 [ 0.15, 0.94 ] |
| **Total events:** | 5 (With primaquine), 15 (Without primaquine) | |
| **Heterogeneity:** | Chi² = 0.49, df = 1 (P = 0.49); I² = 0.0% | |
| **Test for overall effect:** | Z = 2.10 (P = 0.036) | |
| 9 Day 43 | | |
| Kolacznik 2012 | 0/27 | 4/34 | 77.4 % | 0.14 [ 0.01, 2.47 ] |
| Kolacznik 2012 | 1/7 | 1/5 | 22.6 % | 0.71 [ 0.06, 8.90 ] |
| **Subtotal (95% CI)** | **34** | **39** | 100.0 % | 0.27 [ 0.04, 1.71 ] |
| **Total events:** | 1 (With primaquine), 5 (Without primaquine) | |
| **Heterogeneity:** | Chi² = 0.78, df = 1 (P = 0.38); I² = 0.0% | |
| **Test for overall effect:** | Z = 1.39 (P = 0.16) | |

(1) Partner MQ: 0.75 mg/kg PQ day 1
(2) Partner SP: 0.5 mg/kg PQ day 1
(3) Partner SP: 0.5 mg/kg PQ day 1
(4) Partner AQ+SP: 0.75 mg/kg PQ day 2; outcome day 4
(5) Partner MQ: 0.75 mg/kg PQ day 1; outcome day 5
(6) Partner SP: 0.5 mg/kg PQ day 1; outcome day 4
(7) Partner CQ: 0.5 mg/kg PQ day 3; outcome day 4
(8) Partner AQ+SP: 0.75 mg/kg PQ day 2
(9) Partner MQ: 0.75 mg/kg PQ day 1
(10) Partner (CQ or (CQ+SP)): 0.75 mg/kg PQ day 4
(11) Partner SP: 0.5 mg/kg PQ day 1
(12) Partner CQ: PQ 0.5 mg/kg day 3
(13) Partner CQ+SP: 0.75 mg/kg PQ day 1
(14) Partner CQ+SP: 0.75 mg/kg PQ day 3
(15) Partner (CQ or (CQ+SP)): 0.75 mg/kg PQ day 4
(16) Partner QN: 0.75 mg/kg PQ day 8
### Analysis 1.2. Comparison 1 Non-artemisinin treatment regimen: PQ versus no PQ, Outcome 2 Gametocyte clearance time (days).

Review: Primaquine or other 8-aminoquinoline for reducing *Plasmodium falciparum* transmission

Comparison: 1 Non-artemisinin treatment regimen: PQ versus no PQ

Outcome: 2 Gametocyte clearance time (days)

| Study or subgroup | With primaquine | Without primaquine | Mean Difference | Mean Difference |
|-------------------|-----------------|--------------------|-----------------|-----------------|
|                   | N   | Mean(SD) | N   | Mean(SD) | IV,Fixed | 95% CI | IV,Fixed | 95% CI |
| Singhasivanon 1994 (1) | 7   | 2.7 (2.7) | 11   | 21.9 (4.4) |          | -14.90 [ -18.18, -11.62 ] |          |       |

-100 -50 0 50 100
Favours primaquine Favours control

(1) Partner MQ+SP: 0.75 mg/kg PQ day 1
### Analysis 1.3.  Comparison 1 Non-artemisinin treatment regimen: PQ versus no PQ, Outcome 3 Participants infectious.

Review: Primaquine or other 8-aminoquinoline for reducing *Plasmodium falciparum* transmission

Comparison: 1 Non-artemisinin treatment regimen: PQ versus no PQ

Outcome: 3 Participants infectious

| Study or subgroup | Favours primaquine | Without primaquine | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|-------------------|--------------------|--------------------|-----------------------------|--------|-----------------------------|
| 1 Day 5           |                    |                    |                             |        |                             |
| Chen 1993a (1)    | 0/6 6/6            | 40.6 %             | 0.08 [0.01, 1.12]           |        |                             |
| Chen 1994 (2)     | 0/9 9/9            | 59.4 %             | 0.05 [0.00, 0.79]           |        |                             |
| **Subtotal (95% CI)** | **15** 15          | 100.0 %            | 0.06 [0.01, 0.42]           |        |                             |

Total events: 0 (Favours primaquine), 15 (Without primaquine)
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0.0%
Test for overall effect: Z = 2.85 (P = 0.0043)

| 2 Day 8           |                    |                    |                             |        |                             |
| Chen 1993a        | 0/6 6/6            | 43.3 %             | 0.08 [0.01, 1.12]           |        |                             |
| Chen 1994         | 0/9 8/9            | 56.7 %             | 0.06 [0.00, 0.89]           |        |                             |
| **Subtotal (95% CI)** | **15** 15          | 100.0 %            | 0.07 [0.01, 0.45]           |        |                             |

Total events: 0 (Favours primaquine), 14 (Without primaquine)
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² = 0.0%
Test for overall effect: Z = 2.78 (P = 0.0054)

| 3 Day 15          |                    |                    |                             |        |                             |
| Chen 1993a        | 0/6 2/6            | 35.7 %             | 0.20 [0.01, 3.46]           |        |                             |
| Chen 1994         | 0/9 4/9            | 64.3 %             | 0.11 [0.01, 1.80]           |        |                             |
| **Subtotal (95% CI)** | **15** 15          | 100.0 %            | 0.14 [0.02, 1.04]           |        |                             |

Total events: 0 (Favours primaquine), 6 (Without primaquine)
Heterogeneity: Chi² = 0.08, df = 1 (P = 0.77); I² = 0.0%
Test for overall effect: Z = 1.92 (P = 0.055)

| 4 Day 22          |                    |                    |                             |        |                             |
| Chen 1993a        | 0/6 0/6            | Not estimable      |                             |        |                             |
| Chen 1994         | 0/9 1/9            | 100.0 %            | 0.33 [0.02, 7.24]           |        |                             |
| **Subtotal (95% CI)** | **15** 15          | 100.0 %            | 0.33 [0.02, 7.24]           |        |                             |

Total events: 0 (Favours primaquine), 1 (Without primaquine)
Heterogeneity: not applicable
Test for overall effect: Z = 0.70 (P = 0.48)

---

(1) Partner MQ: 0.75 mg/kg PQ day 1
(2) Partner MQ: 0.75 mg/kg PQ day 1

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Primaquine or other 8-aminoquinoline for reducing *Plasmodium falciparum* transmission (Review)  
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### Analysis 1.4. Comparison 1 Non-artemisinin treatment regimen: PQ versus no PQ, Outcome 4 Mosquitoes infected.

**Review:** Primaquine or other 8-aminoquinoline for reducing *Plasmodium falciparum* transmission

**Comparison:** 1 Non-artemisinin treatment regimen: PQ versus no PQ

**Outcome:** 4 Mosquitoes infected

| Study or subgroup | With primaquine n/N | Without primaquine n/N | Risk Ratio M-H,Fixed 95% CI |
|------------------|---------------------|------------------------|-----------------------------|
| **1 Day**        |                     |                        |                             |
| Chen 1994 (1)    | 0/88                | 47/73                  | 0.01 [ 0.00, 0.14 ]         |
| **2 Day**        |                     |                        |                             |
| Chen 1994        | 0/62                | 49/90                  | 0.01 [ 0.00, 0.23 ]         |
| **3 Day**        |                     |                        |                             |
| Chen 1994        | 0/81                | 12/87                  | 0.04 [ 0.00, 0.71 ]         |
| **4 Day**        |                     |                        |                             |
| Chen 1994        | 0/88                | 5/64                   | 0.07 [ 0.00, 1.18 ]         |

(1) Partner MQ: 0.75 mg/kg PQ day 1; CI not corrected for unit of analysis throughout
Analysis 1.5. Comparison 1 Non-artemisinin treatment regimen: PQ versus no PQ, Outcome 5
Participants with asexual parasites at day 29.

Review: Primaquine or other 8-aminoquinoline for reducing Plasmodium falciparum transmission

Comparison: 1 Non-artemisinin treatment regimen: PQ versus no PQ

Outcome: 5 Participants with asexual parasites at day 29

| Study or subgroup | Favours primaquine | Without primaquine | Risk Ratio | Weight | Risk Ratio |
|------------------|-------------------|--------------------|------------|--------|------------|
|                  | n/N               | n/N                | M-H,Fixed,95% CI | M-H,Fixed,95% CI |
| 1 Not PCR adjusted |                   |                    |             |        |            |
| Kolaczinski 2012 (1) | 5/33              | 4/41               | 6.1 %      | 1.55 [ 0.45, 5.33 ] |
| Kolaczinski 2012 (2) | 49/67             | 55/68              | 93.9 %     | 0.90 [ 0.75, 1.09 ] |
| **Subtotal (95% CI)** | **100**           | **109**            | **100.0 %** | **0.94 [ 0.78, 1.15 ]** |
| Total events: 54 (Favours primaquine), 59 (Without primaquine) |
| Heterogeneity: Chi² = 0.83, df = 1 (P = 0.36); I² =0.0% |
| Test for overall effect: Z = 0.58 (P = 0.56) |
| 2 PCR adjusted |                   |                    |             |        |            |
| Kolaczinski 2012 | 5/33              | 4/41               | 7.9 %      | 1.55 [ 0.45, 5.33 ] |
| Kolaczinski 2012 | 36/67             | 42/68              | 92.1 %     | 0.87 [ 0.65, 1.16 ] |
| **Subtotal (95% CI)** | **100**           | **109**            | **100.0 %** | **0.92 [ 0.69, 1.23 ]** |
| Total events: 41 (Favours primaquine), 46 (Without primaquine) |
| Heterogeneity: Chi² = 0.85, df = 1 (P = 0.36); I² =0.0% |
| Test for overall effect: Z = 0.54 (P = 0.59) |
| Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.90), I² =0.0% |

(1) Partner SP: 0.5 mg/kg PQ day 1
(2) Partner CQ: 0.5 mg/kg PQ day 3
### Analysis 1.6. Comparison 1 Non-artemisinin treatment regimen: PQ versus no PQ, Outcome 6 Asexual parasite clearance time (hrs).

**Review:** Primaquine or other 8-aminoquinoline for reducing *Plasmodium falciparum* transmission

**Comparison:** 1 Non-artemisinin treatment regimen: PQ versus no PQ

**Outcome:** 6 Asexual parasite clearance time (hrs)

| Study or subgroup | With primaquine | Without primaquine | Mean Difference | Weight | Mean Difference |
|-------------------|-----------------|-------------------|----------------|--------|----------------|
| N Mean(SD)        | N Mean(SD)      | IV,Fixed,95% CI   | IV,Fixed,95% CI|
| Pukrittayakamee 2004 (1) | 29 78 (23) | 30 80 (26) | 40.1 % -2.00 [-14.52, 10.52] |
| Pukrittayakamee 2004 (2) | 37 79 (19) | 30 80 (26) | 50.6 % -1.00 [-12.14, 10.14] |
| Singhasivanon 1994 (3) | 7 93 (15) | 11 97 (39.9) | 9.2 % -4.00 [-30.07, 22.07] |
| **Total (95% CI)** | **73** | **71** | **100.0 % -1.68 [-9.60, 6.25]** |

Heterogeneity: Chi² = 0.05, df = 2 (P = 0.98); I² =0.0%

Test for overall effect: Z = 0.42 (P = 0.68)

Test for subgroup differences: Not applicable

(1) Partner QN: 0.25 mg/kg PQ days 1-7

(2) Partner QN: 0.5 mg/kg PQ days 1-7

(3) Partner MQ+SP: 0.75 mg/kg PQ day 1
### Analysis 1.7. Comparison 1 Non-artemisinin treatment regimen: PQ versus no PQ, Outcome 7 Adverse effects.

Review: Primaquine or other 8-aminoquinoline for reducing *Plasmodium falciparum* transmission

Comparison: 1 Non-artemisinin treatment regimen: PQ versus no PQ

Outcome: 7 Adverse effects

| Study or subgroup | With primaquine n/N | Without primaquine n/N | Risk Ratio M-H,Fixed,95% CI |
|-------------------|--------------------|------------------------|---------------------------|
| 1 Nausea          | 1/7                | 3/11                   | **0.52 [ 0.07, 4.09 ]**   |
| Singhasivanon 1994 (1) |                |                        |                           |
| 2 Vomiting        | 2/7                | 2/11                   | **1.57 [ 0.28, 8.74 ]**   |
| Singhasivanon 1994 |                    |                        |                           |
| 3 Dizziness       | 1/7                | 1/11                   | **1.57 [ 0.12, 21.26 ]**  |
| Singhasivanon 1994 |                    |                        |                           |
| 4 Any adverse effect | 2/7              | 3/11                   | **1.05 [ 0.23, 4.78 ]**   |
| Singhasivanon 1994 |                    |                        |                           |

(1) Partner MQ+SP: 0.75 mg/kg PQ day 1

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**Primaquine or other 8-aminoquinoline for reducing *Plasmodium falciparum* transmission (Review)**

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### Analysis 1.8. Comparison 1 Non-artemisinin treatment regimen: PQ versus no PQ, Outcome 8 By dose: Participants with gametocytes at day 8 (microscopy).

**Review:** Primaquine or other 8-aminoquinolines for reducing *Plasmodium falciparum* transmission

**Comparison:** 1 Non-artemisinin treatment regimen: PQ versus no PQ

**Outcome:** 8 By dose: Participants with gametocytes at day 8 (microscopy)

| Study or subgroup | With Primaquine | Without Primaquine | Risk Ratio | Weight | Risk Ratio |
|-------------------|-----------------|--------------------|------------|--------|------------|
|                  | n/N             | n/N                | M-H,Fixed95% CI |        | M-H,Fixed95% CI |
| **1 < 0.4 mg/kg PQ per day** | 0 | 0 | Not estimable |        |           |
| **Subtotal (95% CI)** | | | | | |
| Total events: 0 (With Primaquine), 0 (Without Primaquine) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| **2 ≥ 0.4 to < 0.6 mg/kg PQ per day** | 27/70 | 52/67 | 61.2 % | 0.50 [ 0.36, 0.69 ] | |
| Kolaczinski 2012 (1) | | | | | |
| Kolaczinski 2012 (2) | 24/36 | 37/43 | 38.8 % | 0.77 [ 0.60, 1.01 ] | |
| **Subtotal (95% CI)** | 106 | 110 | 100.0 % | 0.60 [ 0.49, 0.75 ] | |
| Total events: 51 (With Primaquine), 89 (Without Primaquine) | | | | | |
| Heterogeneity: Chi$^2$ = 4.90, df = 1 (P = 0.03); I$^2$ =80% | | | | | |
| Test for overall effect: Z = 4.64 (P < 0.00001) | | | | | |
| **3 ≥ 0.6 mg/kg PQ per day** | 7/20 | 11/20 | 26.7 % | 0.64 [ 0.31, 1.30 ] | |
| Arango 2012 (3) | 0/6 | 6/6 | 15.8 % | 0.08 [ 0.01, 1.12 ] | |
| Kamtekar 2004 (5) | 7/24 | 16/22 | 40.6 % | 0.40 [ 0.20, 0.79 ] | |
| Ledermann 2006 (6) | 2/28 | 2/16 | 6.2 % | 0.57 [ 0.09, 3.68 ] | |
| Ledermann 2006 (7) | 0/28 | 3/16 | 10.7 % | 0.08 [ 0.00, 1.53 ] | |
| **Subtotal (95% CI)** | 106 | 80 | 100.0 % | 0.39 [ 0.25, 0.62 ] | |
| Total events: 16 (With Primaquine), 38 (Without Primaquine) | | | | | |
| Heterogeneity: Chi$^2$ = 4.46, df = 4 (P = 0.35); I$^2$ =10% | | | | | |
| Test for overall effect: Z = 4.01 (P = 0.000061) | | | | | |

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1. Partner SP: 0.5 mg/kg PQ day 1
2. Partner CQ: 0.5 mg/kg PQ day 3
3. Partner AQ+SP: 0.75 mg/kg PQ day 2
4. Partner MQ: 0.75 mg/kg PQ day 1
5. Partner (CQ or (CQ+SP)): 0.75 mg/kg PQ day 4
6. Partner CQ+SP: 0.75 mg/kg PQ day 1
7. Partner CQ+SP: 0.75 mg/kg PQ day 3
Analysis 1.9. Comparison 1 Non-artemisinin treatment regimen: PQ versus no PQ, Outcome 9 By schedule: Participants with gametocytes at day 8.

Review: Primaquine or other 8-aminoquinoline for reducing Plasmodium falciparum transmission

Comparison: 1 Non-artemisinin treatment regimen: PQ versus no PQ

Outcome: 9 By schedule: Participants with gametocytes at day 8

| Study or subgroup | With primaquine | Without primaquine | Risk Ratio M-H,Fixed 95% CI | Weight | Risk Ratio M-H,Fixed 95% CI |
|------------------|-----------------|--------------------|-----------------------------|--------|-----------------------------|
| 1 Single dose day 1 or 2 | | | | | |
| Arango 2012 (1) | 7/20 | 11/20 | 19.7% | 0.64 [0.31, 1.30] | |
| Chen 1993a (2) | 0/6 | 6/6 | 11.6% | 0.08 [0.01, 1.12] | |
| Kolaczinski 2012 (3) | 24/36 | 37/43 | 60.3% | 0.77 [0.60, 1.01] | |
| Ledermann 2006 (4) | 2/28 | 5/32 | 8.4% | 0.46 [0.10, 1.71] | |
| **Subtotal (95% CI)** | **90** | **101** | | **100.0%** | **0.64 [0.49, 0.84]** |
| Total events: | 33 (With primaquine), 59 (Without primaquine) | | | | |
| Heterogeneity: | Chi² = 4.65, df = 3 (P = 0.20); I² = 36% | | | | |
| Test for overall effect: Z = 3.23 (P = 0.0012) | | | | | |
| 2 Single dose day 3 or 4 | | | | | |
| Kamtekar 2004 (5) | 7/24 | 16/22 | 22.3% | 0.40 [0.20, 0.79] | |
| Kolaczinski 2012 (6) | 27/70 | 52/67 | 70.9% | 0.50 [0.36, 0.69] | |
| Ledermann 2006 (7) | 0/28 | 5/32 | 6.9% | 0.10 [0.01, 1.79] | |
| **Subtotal (95% CI)** | **122** | **121** | | **100.0%** | **0.45 [0.33, 0.60]** |
| Total events: | 34 (With primaquine), 73 (Without primaquine) | | | | |
| Heterogeneity: | Chi² = 1.51, df = 2 (P = 0.47); I² = 0.0% | | | | |
| Test for overall effect: Z = 5.33 (P < 0.00001) | | | | | |
| 3 Multiple dose days 1 to 7 | | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **Not estimable** | |
Analysis 2.1. Comparison 2 Artemisinin treatment regimen: PQ versus no PQ, Outcome 1 Participants with gametocytes (microscopy).

Review: Primaquine or other 8-aminoquinoline for reducing Plasmodium falciparum transmission

Comparison: 2 Artemisinin treatment regimen: PQ versus no PQ

Outcome: 1 Participants with gametocytes (microscopy)

| Study or subgroup | Favours primaquine | Without primaquine | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|-------------------|--------------------|-------------------|---------------------------|--------|---------------------------|
| 1 Day 4           |                    |                   |                           |        |                           |
| Arango 2012 (1)   | 3/19               | 7/23              | 0.2 %                     | 0.52 [ 0.15, 1.74 ] |                           |
| Smithuis 2010 (2) | 26/71              | 27/84             | 1.5 %                     | 1.14 [ 0.74, 1.76 ] |                           |
| Smithuis 2010 (3) | 25/78              | 29/84             | 1.5 %                     | 0.93 [ 0.60, 1.44 ] |                           |
| Smithuis 2010 (4) | 24/86              | 26/83             | 1.3 %                     | 0.89 [ 0.56, 1.42 ] |                           |
| Smithuis 2010 (5) | 21/79              | 25/82             | 1.2 %                     | 0.87 [ 0.53, 1.42 ] |                           |
| Smithuis 2010 (6) | 27/83              | 24/78             | 1.4 %                     | 1.06 [ 0.67, 1.67 ] |                           |
| Sutanto 2013 (7)  | 41/41              | 31/31             | 93.0 %                    | 1.00 [ 0.95, 1.06 ] |                           |
| Vasquez 2009 (8)  | 2/25               | 4/24              | 0.1 %                     | 0.48 [ 0.10, 2.38 ] |                           |
| Subtotal (95% CI) | 482                | 489               | 100.0 %                   | 1.00 [ 0.95, 1.05 ] |                           |

Total events: 169 (Favours primaquine), 173 (Without primaquine)

Heterogeneity: Tau² = 0.0; Chi² = 5.80, df = 7 (P = 0.56); I² =0.0%

Test for overall effect: Z = 0.13 (P = 0.90)

2 Day 8

| Study or subgroup | Favours primaquine | Without primaquine | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|-------------------|--------------------|-------------------|---------------------------|--------|---------------------------|
| Arango 2012       | 1/19               | 3/23              | 8.6 %                     | 0.40 [ 0.05, 3.57 ] |                           |
| Shekalaghe 2007 (9)| 0/53               | 6/53              | 6.5 %                     | 0.08 [ 0.00, 3.33 ] |                           |

Continued...
| Study or subgroup | Favours primaquine | Without primaquine | Risk Ratio | Weight |
|------------------|-------------------|-------------------|------------|--------|
| Smithuis 2010    | 3/71              | 24/84             | 12.7 %     | 0.15 [ 0.05, 0.47 ] |
| Smithuis 2010    | 1/78              | 28/84             | 9.4 %      | 0.04 [ 0.01, 0.28 ] |
| Smithuis 2010    | 3/84              | 17/83             | 12.6 %     | 0.17 [ 0.05, 0.57 ] |
| Smithuis 2010    | 3/77              | 18/80             | 12.6 %     | 0.17 [ 0.05, 0.56 ] |
| Smithuis 2010    | 3/83              | 24/78             | 12.7 %     | 0.12 [ 0.04, 0.37 ] |
| Sutanto 2013     | 22/41             | 25/31             | 15.3 %     | 0.67 [ 0.48, 0.93 ] |
| Vasquez 2009     | 2/25              | 2/24              | 9.7 %      | 0.96 [ 0.15, 6.28 ] |
| **Subtotal (95% CI)** | **531**         | **540**           | **100.0 %**| **0.21 [ 0.08, 0.54 ]** |

Total events: 38 (Favours primaquine), 147 (Without primaquine)
Heterogeneity: Tau² = 1.52; Chi² = 44.75, df = 8 (P<0.00001); I² =82%
Test for overall effect: Z = 3.22 (P = 0.0013)

3 Day 15

| Study or subgroup | Favours primaquine | Without primaquine | Risk Ratio | Weight |
|------------------|-------------------|-------------------|------------|--------|
| Shekalaghe 2007  | 0/52              | 2/52              | 6.4 %      | 0.20 [ 0.01, 4.07 ] |
| Smithuis 2010    | 1/67              | 18/83             | 14.8 %     | 0.07 [ 0.01, 0.50 ] |
| Smithuis 2010    | 1/73              | 8/81              | 13.8 %     | 0.14 [ 0.02, 1.08 ] |
| Smithuis 2010    | 0/81              | 4/80              | 6.9 %      | 0.11 [ 0.01, 2.01 ] |
| Smithuis 2010    | 0/73              | 4/77              | 6.9 %      | 0.12 [ 0.01, 2.14 ] |
| Smithuis 2010    | 2/80              | 24/76             | 29.4 %     | 0.08 [ 0.02, 0.32 ] |
| Sutanto 2013     | 1/41              | 17/31             | 15.2 %     | 0.04 [ 0.01, 0.32 ] |
| Vasquez 2009     | 0/25              | 2/23              | 6.5 %      | 0.18 [ 0.01, 3.65 ] |
| **Subtotal (95% CI)** | **492**         | **503**           | **100.0 %**| **0.09 [ 0.04, 0.19 ]** |

Total events: 5 (Favours primaquine), 79 (Without primaquine)
Heterogeneity: Tau² = 0.0; Chi² = 1.33, df = 7 (P = 0.99); I² =0.0%
Test for overall effect: Z = 6.16 (P < 0.00001)

4 Day 22

| Study or subgroup | Favours primaquine | Without primaquine | Risk Ratio | Weight |
|------------------|-------------------|-------------------|------------|--------|
| Smithuis 2010    | 0/58              | 15/74             | 18.0 %     | 0.04 [ 0.00, 0.67 ] |
| Smithuis 2010    | 1/69              | 5/79              | 31.2 %     | 0.23 [ 0.03, 1.91 ] |
| Smithuis 2010    | 0/84              | 0/79              | Not estimable |
| Smithuis 2010    | 0/70              | 0/72              | Not estimable |
| Smithuis 2010    | 0/78              | 15/76             | 17.9 %     | 0.03 [ 0.00, 0.52 ] |
| Sutanto 2013     | 1/41              | 6/31              | 32.9 %     | 0.13 [ 0.02, 0.99 ] |
| Vasquez 2009     | 0/25              | 0/22              | Not estimable |
| **Subtotal (95% CI)** | **425**         | **433**           | **100.0 %**| **0.10 [ 0.03, 0.32 ]** |

Total events: 2 (Favours primaquine), 41 (Without primaquine)
Heterogeneity: Tau² = 0.0; Chi² = 1.89, df = 3 (P = 0.59); I² =0.0%
### Primaquine or other 8-aminoquinoline for reducing *Plasmodium falciparum* transmission (Review)

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| Study or subgroup | Favours primaquine | Without primaquine | Risk Ratio M-H Random 95% CI | Weight |
|-------------------|--------------------|--------------------|-----------------------------|--------|
| Shekalaghe 2007   | 2/51               | 3/52               | 40.0% 0.68 [0.12, 3.90]     | 0.68   |
| Smithuis 2010     | 0/54               | 8/75               | 20.2% 0.08 [0.00, 1.38]     | 0.08   |
| Smithuis 2010     | 0/69               | 0/78               | Not estimable               |        |
| Smithuis 2010     | 0/82               | 0/76               | Not estimable               |        |
| Smithuis 2010     | 0/67               | 0/70               | Not estimable               |        |
| Smithuis 2010     | 0/75               | 10/77              | 20.3% 0.05 [0.00, 0.82]     | 0.05   |
| Sutanto 2013      | 0/41               | 4/31               | 19.6% 0.08 [0.00, 1.52]     | 0.08   |
| Vasquez 2009      | 0/25               | 0/22               | Not estimable               |        |

**Subtotal (95% CI)**

464 481 [100.0% 0.17 [0.04, 0.72]]

Total events: 2 (Favours primaquine), 25 (Without primaquine)

Heterogeneity: Tau² = 0.52; Chi² = 3.96, df = 3 (P = 0.27); I² = 24%

Test for overall effect: Z = 2.42 (P = 0.015)

| Study or subgroup | Favours primaquine | Without primaquine | Risk Ratio M-H Random 95% CI | Weight |
|-------------------|--------------------|--------------------|-----------------------------|--------|
| Smithuis 2010     | 0/55               | 0/76               | Not estimable               |        |
| Smithuis 2010     | 0/70               | 0/74               | Not estimable               |        |
| Smithuis 2010     | 0/80               | 0/79               | Not estimable               |        |
| Smithuis 2010     | 0/69               | 0/70               | Not estimable               |        |
| Smithuis 2010     | 0/71               | 2/75               | 100.0% 0.21 [0.01, 4.32]    | 0.21   |
| Sutanto 2013      | 0/41               | 0/31               | Not estimable               |        |
| Vasquez 2009      | 0/25               | 0/22               | Not estimable               |        |

Subtotal (95% CI)

411 427 [100.0% 0.21 [0.01, 4.32]]

Total events: 0 (Favours primaquine), 2 (Without primaquine)

Heterogeneity: not applicable

Test for overall effect: Z = 1.01 (P = 0.31)

### 7 Day

| Study or subgroup | Favours primaquine | Without primaquine | Risk Ratio M-H Random 95% CI | Weight |
|-------------------|--------------------|--------------------|-----------------------------|--------|
| Shekalaghe 2007   | 0/50               | 0/52               | Not estimable               |        |
| Smithuis 2010     | 0/50               | 1/74               | 50.0% 0.49 [0.02, 11.80]    | 0.49   |
| Smithuis 2010     | 0/62               | 0/75               | Not estimable               |        |
| Smithuis 2010     | 0/79               | 0/76               | Not estimable               |        |
| Smithuis 2010     | 0/69               | 1/71               | 50.0% 0.34 [0.01, 8.27]     | 0.34   |
| Smithuis 2010     | 0/71               | 0/69               | Not estimable               |        |
| Sutanto 2013      | 0/41               | 0/31               | Not estimable               |        |
| Vasquez 2009      | 0/25               | 0/22               | Not estimable               |        |
| Study or subgroup | Favours primaquine | Without primaquine | Risk Ratio | Weight | Risk Ratio |
|------------------|-------------------|-------------------|------------|--------|------------|
|                  | n/N               | n/N               | M-H,Random,95% CI |        | M-H,Random,95% CI |
| Subtotal (95% CI) | 447               | 470               | 100.0 %    | 0.41 [0.04, 3.89] |

Total events: 0 (Favours primaquine), 2 (Without primaquine)

Heterogeneity: Tau² = 0.0; Chi² = 0.02, df = 1 (P = 0.88); I² = 0.0%

Test for overall effect: Z = 0.78 (P = 0.44)

(1) Partner MQ+AS: 0.75 mg/kg PQ day 2
(2) Partner AS+AQ: 0.75 mg/kg PQ day 1
(3) Partner AL: 0.75 mg/kg PQ day 1
(4) Partner AS+MQ (fixed): 0.75 mg/kg PQ day 1
(5) Partner AS+MQ (loose): 0.75 mg/kg PQ day 1
(6) Partner DHAP: 0.75 mg/kg PQ day 1
(7) Partner DHAP: 0.75 mg/kg PQ on day 4
(8) Partner AS+MQ: 0.75 mg/kg PQ day 3
(9) Partner AS+SP: 0.75 mg/kg PQ day 4
### Analysis 2.2. Comparison 2 Artemisinin treatment regimen: PQ versus no PQ, Outcome 2 Participants with gametocytes (PCR).

Review: Primaquine or other 8-aminoquinoline for reducing *Plasmodium falciparum* transmission

Comparison: 2 Artemisinin treatment regimen: PQ versus no PQ

Outcome: 2 Participants with gametocytes (PCR)

| Study or subgroup | Favours primaquine | Without primaquine | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|-------------------|--------------------|--------------------|-------------------------------|--------|-------------------------------|
| 1 Day 8           |                    |                    |                               |        |                               |
| El-Sayed 2007 (1) | 4/48               | 3/46               | 9.0%                          | 1.28   | [0.30, 5.40]                  |
| Ezefula 2013 (2)  | 25/108             | 13/38              | 24.9%                         | 0.68   | [0.39, 1.18]                  |
| Ezefula 2013 (3)  | 11/104             | 13/38              | 20.9%                         | 0.31   | [0.15, 0.63]                  |
| Ezefula 2013 (4)  | 15/104             | 14/39              | 23.0%                         | 0.40   | [0.21, 0.75]                  |
| Shekalaghe 2007 (5)| 8/51               | 36/51              | 22.2%                         | 0.22   | [0.11, 0.43]                  |
| **Subtotal (95% CI)** | **415** | **212** | **100.0%** | **0.42** | **[0.26, 0.69]** |
| Total events: 63 (Favours primaquine), 79 (Without primaquine) |
| Heterogeneity: Tau² = 0.18; Chi² = 9.44, df = 4 (P = 0.05); I² = 58% |
| Test for overall effect: Z = 3.40 (P = 0.00067) |
| 2 Day 15          |                    |                    |                               |        |                               |
| El-Sayed 2007     | 3/47               | 2/45               | 15.8%                         | 1.44   | [0.25, 8.20]                  |
| Ezefula 2013      | 6/103              | 5/35               | 23.1%                         | 0.41   | [0.13, 1.25]                  |
| Ezefula 2013      | 2/103              | 5/35               | 17.3%                         | 0.14   | [0.03, 0.67]                  |
| Ezefula 2013      | 6/106              | 6/35               | 23.9%                         | 0.33   | [0.11, 0.96]                  |
| Shekalaghe 2007   | 2/51               | 30/49              | 19.8%                         | 0.06   | [0.02, 0.25]                  |
| **Subtotal (95% CI)** | **410** | **199** | **100.0%** | **0.27** | **[0.11, 0.70]** |
| Total events: 19 (Favours primaquine), 48 (Without primaquine) |
| Heterogeneity: Tau² = 0.67; Chi² = 9.84, df = 4 (P = 0.04); I² = 59% |
| Test for overall effect: Z = 2.72 (P = 0.0066) |
| 3 Day 29          |                    |                    |                               |        |                               |
| Shekalaghe 2007   | 4/46               | 17/44              | 100.0%                        | 0.23   | [0.08, 0.62]                  |
| **Subtotal (95% CI)** | **46**   | **44**   | **100.0%** | **0.23** | **[0.08, 0.62]** |
| Total events: 4 (Favours primaquine), 17 (Without primaquine) |
| Heterogeneity: not applicable |
| Test for overall effect: Z = 2.90 (P = 0.0037) |
| 4 Day 43          |                    |                    |                               |        |                               |
| Shekalaghe 2007   | 5/40               | 11/39              | 100.0%                        | 0.44   | [0.17, 1.16]                  |
| **Subtotal (95% CI)** | **40**   | **39**   | **100.0%** | **0.44** | **[0.17, 1.16]** |

(Continued...)
| Study or subgroup | Favours primaquine | Without primaquine | Risk Ratio M-H, Random, 95% CI | Weight |
|------------------|--------------------|--------------------|--------------------------------|--------|
|                  | n/N                | n/N                | M-H, Random, 95% CI            |        |
|                  |                    |                    |                                |        |
| Total events: 5 (Favours primaquine), 11 (Without primaquine) |                    |                    |                                |        |
| Heterogeneity: not applicable |                    |                    |                                |        |
| Test for overall effect: Z = 1.66 (P = 0.097) |                    |                    |                                |        |

(Continued)

Analysis 2.3. Comparison 2 Artemisinin treatment regimen: PQ versus no PQ, Outcome 3 Participants with asexual parasites.

Review: Primaquine or other 8-aminoquinoline for reducing *Plasmodium falciparum* transmission

Comparison: 2 Artemisinin treatment regimen: PQ versus no PQ

Outcome: 3 Participants with asexual parasites

| Study or subgroup | With primaquine | Without primaquine | Risk Ratio M-H, Fixed, 95% CI | Weight |
|------------------|-----------------|--------------------|--------------------------------|--------|
|                  | n/N             | n/N                | M-H, Fixed, 95% CI             |        |
|                  |                 |                    |                                |        |
| 1 Day 8          |                 |                    |                                |        |
| El-Sayed 2007 (1) | 4/48            | 3/46               | 100.0 %                        | 1.28 [0.30, 5.40] |
| Subtotal (95% CI)| 48              | 46                 | 100.0 %                        | 1.28 [0.30, 5.40] |
| Total events: 4 (With primaquine), 3 (Without primaquine) |                   |                    |                                |        |
| Heterogeneity: not applicable |                   |                    |                                |        |
| Test for overall effect: Z = 0.33 (P = 0.74) |                   |                    |                                |        |
| 2 Day 15         |                 |                    |                                |        |
| El-Sayed 2007    | 3/47            | 2/45               | 57.7 %                         | 1.44 [0.25, 8.20] |
| Shekalaghe 2007 (2) | 0/53             | 1/53              | 42.3 %                         | 0.33 [0.01, 8.00] |
| Subtotal (95% CI)| 100             | 98                 | 100.0 %                        | 0.97 [0.23, 4.15] |

(Continued . . .)
| Study or subgroup | With primaquine n/N | Without primaquine n/N | Risk Ratio M-H,Fixed 95% CI | Weight M-H,Fixed 95% CI |
|-------------------|---------------------|------------------------|-----------------------------|------------------------|
| Total events: 3 (With primaquine), 3 (Without primaquine) | 3 (With primaquine) | 3 (Without primaquine) | 3.9 % 2.20 [0.28, 17.28] | 2.20 [0.28, 17.28] |
| Heterogeneity: Chi² = 0.63, df = 1 (P = 0.43); I² = 0.0% | 3 Day 29 | Ezefula 2013 (3) | 7/108 1/34 | 5.8 % 0.11 [0.00, 2.62] |
| Test for overall effect: Z = 0.04 (P = 0.97) | | Ezefula 2013 (4) | 0/106 1/34 | 7.8 % 0.77 [0.35, 1.63] |
| | | Ezefula 2013 (5) | 5/111 2/34 | 30.7 % 0.75 [0.35, 1.63] |
| | | Shekalaghe 2007 | 9/53 12/53 | 51.7 % 0.29 [0.12, 0.70] |
| | | Wang 2006 (6) | 6/108 20/106 | 100.0 % 0.54 [0.33, 0.88] |
| Subtotal (95% CI) | 486 | 261 | 100.0 % 0.54 [0.33, 0.88] |
| Total events: 27 (With primaquine), 36 (Without primaquine) | 4 Day 43 | Shekalaghe 2007 | 17/53 15/53 | 86.8 % 1.13 [0.63, 2.03] |
| Heterogeneity: Chi² = 5.50, df = 4 (P = 0.24); I² = 27% | | Sutanto 2013 (7) | 1/41 2/31 | 132.3 % 0.38 [0.04, 3.98] |
| Test for overall effect: Z = 2.46 (P = 0.014) | Subtotal (95% CI) | 94 | 84 | 100.0 % 1.03 [0.59, 1.81] |
| Total events: 18 (With primaquine), 17 (Without primaquine) | | | | |
| Heterogeneity: Chi² = 0.80, df = 1 (P = 0.37); I² = 0.0% | | | | |
| Test for overall effect: Z = 0.12 (P = 0.91) | | | | |

(1) Partner AS+SP: 0.75 mg/kg PQ day 4
(2) Partner AS+SP: 0.75 mg/kg day 4
(3) Partner AL: 0.1 mg/kg PQ day 3
(4) Partner AL: 0.4 mg/kg PQ day 3
(5) Partner AL: 0.75 mg/kg PQ day 3
(6) Partner AS: 0.38 mg/kg PQ days 1-5
(7) Partner DHAP: 0.75 mg/kg PQ day 4
### Analysis 2.4. Comparison 2 Artemisinin treatment regimen: PQ versus no PQ, Outcome 4 Asexual parasite clearance time (hrs).

**Review:** Primaquine or other 8-aminoquinoline for reducing *Plasmodium falciparum* transmission

**Comparison:** 2 Artemisinin treatment regimen: PQ versus no PQ

**Outcome:** 4 Asexual parasite clearance time (hrs)

| Study or subgroup | With primaquine | Without primaquine | Mean Difference | Weight | Mean Difference |
|-------------------|-----------------|--------------------|----------------|--------|----------------|
|                   | N   | Mean(SD) | N   | Mean(SD) | IV,Fixed,95% CI | IV,Fixed,95% CI |
| Pukrittayakamee 2004 (1) | 27  | 63 (18) | 23  | 69 (19) | -6.00 [-16.31, 4.31] |
| Total (95% CI)    | 27  |          | 23  |          | 100.0 % -6.00 [-16.31, 4.31] |

Heterogeneity: not applicable

Test for overall effect: Z = 1.14 (P = 0.25)

Test for subgroup differences: Not applicable

---

(1) Partner AS: 0.5 mg/kg PQ days 1-7
## Analysis 2.5. Comparison 2 Artemisinin treatment regimen: PQ versus no PQ, Outcome 5 Haemoglobin concentration.

**Review:** Primaquine or other 8-aminoquinoline for reducing *Plasmodium falciparum* transmission

**Comparison:** 2 Artemisinin treatment regimen: PQ versus no PQ

**Outcome:** 5 Haemoglobin concentration

| Study or subgroup | With primaquine | Without primaquine | Mean Difference | Mean Difference |
|-------------------|-----------------|--------------------|----------------|----------------|
|                   | N               | Mean(SD)           | N              | Mean(SD)       | IV/Fixed 95% CI | IV/Fixed 95% CI |
| 1 Day 8           | 10.0965 (1.643201) | 52 | 53 | 10.48 (1.544036) | -0.39 [-1.00, 0.22] |
| Shekalaghe 2007 (1) | 10.686 (1.16135)  | 53 | 53 | 10.73 (1.379669) | -0.04 [-0.53, 0.44] |
| 2 Day 15          | 11.448 (1.30371) | 53 | 52 | 11.19 (1.3591)  | 0.26 [-0.25, 0.77] |
| Shekalaghe 2007   | 11.79718 (1.625543) | 51 | 52 | 11.85 (1.273753) | -0.05 [-0.61, 0.52] |

(1) Partner AS+SP, 0.75 mg/kg PQ day 4

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Primaquine or other 8-aminoquinoline for reducing *Plasmodium falciparum* transmission (Review)  
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**Analysis 2.6. Comparison 2 Artemisinin treatment regimen: PQ versus no PQ, Outcome 6 % change in haemoglobin concentration.**

Review: Primaquine or other 8-aminoquinoline for reducing *Plasmodium falciparum* transmission

Comparison: Artemisinin treatment regimen: PQ versus no PQ

Outcome: 6 % change in haemoglobin concentration

| Study or subgroup | With primaquine | Without primaquine | Mean Difference | Mean Difference |
|-------------------|----------------|-------------------|----------------|----------------|
|                   | Mean(SD)       | Mean(SD)          | IV/Fixed,95% CI| IV/Fixed,95% CI|
| 1 Day 8           |                |                   |                |                |
| Shekalaghe 2007   | -0.0513034 (0.1411953) | 51 50 0.01 (0.0922952) | -0.06 [-0.11, -0.02] |
| 2 Day 15          | 0.0148362 (0.134191) | 52 50 0.04 (0.1272108) | -0.03 [-0.08, 0.02] |
| 3 Day 29          | 0.0930569 (0.1671262) | 52 49 0.09 (0.1698335) | 0.00 [-0.06, 0.07] |
| 4 Day 43          | 0.1164377 (0.1546697) | 50 49 0.15 (0.1973936) | -0.03 [-0.10, 0.04] |

(1) Partner AS+SP: 0.75 mg/kg PQ day 4

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**Primaquine or other 8-aminoquinoline for reducing *Plasmodium falciparum* transmission (Review)**

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Analysis 2.7. Comparison 2 Artemisinin treatment regimen: PQ versus no PQ, Outcome 7 Other adverse effects.

Review: Primaquine or other 8-aminoquinoline for reducing *Plasmodium falciparum* transmission

Comparison: 2 Artemisinin treatment regimen: PQ versus no PQ

Outcome: 7 Other adverse effects

| Study or subgroup | With primaquine | Without primaquine | Risk Ratio M-H,Fixed,95% CI |
|-------------------|-----------------|--------------------|-----------------------------|
|                   | n/N             | n/N                |                             |
| 1 Headache        |                 |                    |                             |
| Sutanto 2013 (1)  | 13/97           | 18/96              | 0.71 [0.37, 1.38]           |
| 2 Fatigue         |                 |                    |                             |
| Sutanto 2013      | 13/93           | 11/96              | 1.22 [0.58, 2.58]           |
| 3 Nausea          |                 |                    |                             |
| Sutanto 2013      | 1/139           | 4/150              | 0.27 [0.03, 2.38]           |
| 4 Vomiting        |                 |                    |                             |
| Sutanto 2013      | 1/163           | 1/168              | 1.03 [0.07, 16.34]          |
| 5 Abdominal pain  |                 |                    |                             |
| Sutanto 2013      | 4/156           | 4/170              | 1.09 [0.28, 4.28]           |
| 6 Diarrhea        |                 |                    |                             |
| Sutanto 2013      | 1/163           | 3/172              | 0.35 [0.04, 3.35]           |
| 7 Pruritis        |                 |                    |                             |
| Sutanto 2013      | 0/170           | 0/177              | Not estimable               |
| 8 Paresthesia     |                 |                    |                             |
| Sutanto 2013      | 2/170           | 2/161              | 0.95 [0.14, 6.64]           |
| 9 Unspecified     |                 |                    |                             |
| Wang 2006 (2)     | 7/108           | 6/106              | 1.15 [0.40, 3.30]           |

(1) Partner DHAP: 0.75 mg/kg PQ on day 4

(2) Partner AS: 0.38 mg/kg PQ days 1-5
Analysis 2.8. Comparison 2 Artemisinin treatment regimen: PQ versus no PQ, Outcome 8 By dose: Participants with gametocytes at day 8 (microscopy or PCR).

**Review:** Primaquine or other 8-aminoquinoline for reducing *Plasmodium falciparum* transmission

**Comparison:** 2 Artemisinin treatment regimen: PQ versus no PQ

**Outcome:** 8 By dose: Participants with gametocytes at day 8 (microscopy or PCR)

| Study or subgroup | With Primaquine | Without Primaquine | Risk Ratio | Weight | Risk Ratio |
|-------------------|-----------------|--------------------|------------|--------|------------|
|                   | n/N             | n/N                | M-H,Fixed95% CI |        | M-H,Fixed95% CI |
| 1 < 0.4 mg/kg PQ per day | 25/108 | 40/115 |                         | 100.0 % | 0.67 [ 0.44, 1.02 ] |
| Eziefu 2013 (1)    | 25/108 | 40/115 |                         | 100.0 % | 0.67 [ 0.44, 1.02 ] |
| **Subtotal (95% CI)** | 108 | 115 |               | 100.0 % | 0.67 [ 0.44, 1.02 ] |
| Total events: 25 (With Primaquine), 40 (Without Primaquine) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 1.88 (P = 0.060) | | | | |
| 2 ≥ 0.4 to < 0.6 mg/kg PQ per day | | | | |
| Eziefu 2013 (2)    | 11/104 | 40/115 |                         | 100.0 % | 0.30 [ 0.16, 0.56 ] |
| **Subtotal (95% CI)** | 104 | 115 |               | 100.0 % | 0.30 [ 0.16, 0.56 ] |
| Total events: 11 (With Primaquine), 40 (Without Primaquine) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 3.81 (P = 0.00014) | | | | |
| 3 ≥ 0.6 mg/kg PQ per day | | | | |
| Arango 2012 (3)    | 1/19 | 3/23 |                         | 1.2 % | 0.40 [ 0.05, 3.57 ] |
| El-Sayed 2007 (4)  | 4/48 | 3/46 |                         | 1.4 % | 1.28 [ 0.30, 5.40 ] |
| Eziefu 2013 (5)    | 15/104 | 40/115 |                         | 17.4 % | 0.41 [ 0.24, 0.71 ] |
| Shekailaghe 2007 (6) | 8/51 | 36/51 |                         | 16.5 % | 0.22 [ 0.11, 0.43 ] |
| Smithuis 2010 (7)  | 3/71 | 24/84 |                         | 10.1 % | 0.15 [ 0.05, 0.47 ] |
| Smithuis 2010 (8)  | 3/78 | 28/84 |                         | 12.3 % | 0.04 [ 0.01, 0.28 ] |
| Smithuis 2010 (9)  | 3/84 | 17/83 |                         | 7.8 % | 0.17 [ 0.05, 0.57 ] |
| Smithuis 2010 (10) | 3/77 | 18/80 |                         | 8.1 % | 0.17 [ 0.05, 0.56 ] |
| Smithuis 2010 (11) | 3/83 | 24/78 |                         | 11.3 % | 0.12 [ 0.04, 0.37 ] |
| Sutanto 2013 (12)  | 22/41 | 25/31 |                         | 13.0 % | 0.67 [ 0.48, 0.93 ] |
| Vasquez 2009 (13)  | 2/25 | 2/24 |                         | 0.9 % | 0.96 [ 0.15, 6.28 ] |
| **Subtotal (95% CI)** | 681 | 699 |               | 100.0 % | 0.29 [ 0.22, 0.37 ] |
| Total events: 65 (With Primaquine), 220 (Without Primaquine) | | | | |
| Heterogeneity: Chi$^2$ = 41.58, df = 10 (P<0.00001); I$^2$ =76% | | | | |
| Test for overall effect: Z = 9.79 (P < 0.00001) | | | | |

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Favours experimental Favours control
(1) Partner AL: 0.1 mg/kg PQ day 3; PCR
(2) Partner AL: 0.4 mg/kg PQ day 3; PCR
(3) Partner MQ+AS: 0.75 mg/kg PQ day 2; Microscopy
(4) Partner AS+SP: 0.75 mg/kg PQ day 4; PCR
(5) Partner AL: 0.75 mg/kg PQ day 3; PCR
(6) Partner AS+SP: 0.75 mg/kg PQ day 4; PCR
(7) Partner AS+AQ: 0.75 mg/kg PQ day 1; Microscopy
(8) Partner AL: 0.75 mg/kg PQ day 1; Microscopy
(9) Partner AS+MQ (fixed): 0.75 mg/kg PQ day 1; Microscopy
(10) Partner AS+MQ (loose): 0.75 mg/kg PQ day 1; Microscopy
(11) Partner DHAP: 0.75 mg/kg PQ day 1; Microscopy
(12) Partner DHAP: 0.75 mg/kg PQ day 4; Microscopy
(13) Partner AS+MQ: 0.75 mg/kg PQ day 3; Microscopy
### Analysis 2.9. Comparison 2 Artemisinin treatment regimen: PQ versus no PQ, Outcome 9 By schedule: Participants with gametocytes at day 8 (microscopy or PCR).

Review: Primaquine or other 8-aminoquinoline for reducing *Plasmodium falciparum* transmission

Comparison: 2 Artemisinin treatment regimen: PQ versus no PQ

Outcome: 9 By schedule: Participants with gametocytes at day 8 (microscopy or PCR)

| Study or subgroup | With primaquine | Without primaquine | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|-------------------|-----------------|--------------------|-----------------------------|--------|-----------------------------|
| **1 Single dose day 1 or 2** | | | | | |
| Arango 2012 (1) | 1/19 | 3/23 | 2.4 % | 0.40 [ 0.05, 3.57 ] | |
| Smithuis 2010 (2) | 3/71 | 24/84 | 19.8 % | 0.15 [ 0.05, 0.47 ] | |
| Smithuis 2010 (3) | 3/84 | 17/83 | 15.4 % | 0.17 [ 0.05, 0.57 ] | |
| Smithuis 2010 (4) | 1/78 | 28/84 | 24.2 % | 0.04 [ 0.01, 0.28 ] | |
| Smithuis 2010 (5) | 3/83 | 24/77 | 22.4 % | 0.12 [ 0.04, 0.37 ] | |
| Smithuis 2010 (6) | 3/77 | 18/80 | 15.9 % | 0.17 [ 0.05, 0.56 ] | |
| **Subtotal (95% CI)** | **412** | **431** | | **100.0 %** | **0.13 [ 0.07, 0.22 ]** |
| **Total events**: 14 (With primaquine), 114 (Without primaquine) | | | | | |
| Heterogeneity: Chi² = 3.08, df = 5 (P = 0.69); I² =0.0% | | | | | |
| Test for overall effect: Z = 7.46 (P < 0.00001) | | | | | |
| **2 Single dose day 3 or 4** | | | | | |
| El-Sayed 2007 (7) | 4/48 | 3/46 | 2.4 % | 1.28 [ 0.30, 5.40 ] | |
| Eziefula 2013 (8) | 11/104 | 13/38 | 14.8 % | 0.31 [ 0.15, 0.63 ] | |
| Eziefula 2013 (9) | 25/108 | 14/39 | 16.0 % | 0.64 [ 0.37, 1.11 ] | |
| Eziefula 2013 (10) | 15/104 | 13/38 | 14.8 % | 0.42 [ 0.22, 0.80 ] | |
| Shekalaghe 2007 (11) | 8/51 | 36/51 | 28.1 % | 0.22 [ 0.11, 0.43 ] | |
| Sutanto 2013 (12) | 22/41 | 25/31 | 22.2 % | 0.67 [ 0.48, 0.93 ] | |
| Vasquez 2009 (13) | 2/25 | 2/24 | 1.6 % | 0.96 [ 0.15, 6.28 ] | |
| **Subtotal (95% CI)** | **481** | **267** | | **100.0 %** | **0.47 [ 0.37, 0.59 ]** |
| **Total events**: 87 (With primaquine), 106 (Without primaquine) | | | | | |
| Heterogeneity: Chi² = 14.36, df = 6 (P = 0.03); I² =58% | | | | | |
| Test for overall effect: Z = 6.34 (P < 0.00001) | | | | | |
| **3 Multiple dose days 1 to 7** | | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | Not estimable | | |
| **Total events**: 0 (With primaquine), 0 (Without primaquine) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| Test for subgroup differences: Chi² = 18.55, df = 1 (P = 0.00), I² =95% | | | | | |

*Primaquine or other 8-aminoquinoline for reducing* *Plasmodium falciparum* transmission (Review)

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(1) Partner MQ+AS: 0.75 mg/kg PQ day 2; Microscopy
(2) Partner ASAQ: 0.75 mg/kg PQ; Microscopy
(3) Partner AS+MQ (fixed dose): 0.75 mg/kg; Microscopy
(4) Partner AL: 0.75 mg/kg PQ; Microscopy
(5) Partner DHAP: 0.75 mg/kg PQ; Microscopy
(6) Partner AS+MQ (loose): 0.75 mg/kg PQ; Microscopy
(7) Partner AS+SP: 0.75 mg/kg PQ day 4; PCR
(8) Partner AL: 0.4 mg/kg PQ day 3; PCR
(9) Partner AL: 0.1 mg/kg PQ day 3; PCR
(10) Partner AL: 0.75 mg/kg PQ day 3; PCR
(11) Partner AS+SP: PQ 0.75 mg/kg day 4; PCR
(12) Partner DHAP: 0.75 mg/kg PQ day 3; Microscopy
(13) Partner AS+MQ: 0.75 mg/kg day 3; Microscopy
### Analysis 3.1. Comparison 3 PQ versus no PQ: gametocytes at day 8 (microscopy or PCR); stratified by non-artemisinin versus artemisinin regimen, Outcome 1 Participants with gametocytes at day 8 (microscopy or PCR)

**Review:** Primaquine or other 8-aminoquinoline for reducing *Plasmodium falciparum* transmission

**Comparison:** 3 PQ versus no PQ; gametocytes at day 8 (microscopy or PCR); stratified by non-artemisinin versus artemisinin regimen

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

| Study or subgroup | with PQ | without PQ | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|-------------------|---------|------------|-----------------------------|--------|-----------------------------|
| 1 Non-artemisinin-based partner drug |         |            |                             |        |                             |
| Arango 2012 (1)   | 7/20    | 11/20      | 6.6 % 0.64 [0.31, 1.30]     |        |                             |
| Chen 1993a (2)    | 0/6     | 6/6        | 1.3 % 0.08 [0.01, 1.12]     |        |                             |
| Kamtekar 2004 (3) | 7/24    | 16/22      | 6.8 % 0.40 [0.20, 0.79]     |        |                             |
| Kolaczninski 2012 (4) | 24/36  | 37/43      | 9.0 % 0.77 [0.60, 1.01]     |        |                             |
| Kolaczninski 2012 (5) | 27/70  | 52/67      | 8.7 % 0.50 [0.36, 0.69]     |        |                             |
| Ledermann 2006 (6) | 2/28    | 3/16       | 2.7 % 0.38 [0.07, 2.04]     |        |                             |
| Ledermann 2006 (7) | 0/28    | 2/16       | 1.1 % 0.12 [0.01, 2.30]     |        |                             |
| **Subtotal (95% CI)** | **212** | **190** | **36.3 % 0.54 [0.38, 0.77]** |        |                             |
| **Total events:** | 67 (with PQ), 127 (without PQ) |

Heterogeneity: Tau² = 0.09; Chi² = 12.04, df = 6 (P = 0.06); I² = 50%

Test for overall effect: Z = 3.38 (P = 0.00072)

| 2 Artemisinin-based partner drug |         |            |                             |        |                             |
| Arango 2012 (8)   | 1/19    | 3/23       | 1.8 % 0.40 [0.05, 3.57]     |        |                             |
| El-Sayed 2007 (9) | 4/48    | 3/46       | 3.4 % 1.28 [0.30, 5.40]     |        |                             |
| Eziefula 2013 (10) | 25/108  | 13/38      | 7.5 % 0.68 [0.39, 1.18]     |        |                             |
| Eziefula 2013 (11) | 11/104  | 13/38      | 6.6 % 0.31 [0.15, 0.63]     |        |                             |
| Eziefula 2013 (12) | 15/104  | 14/39      | 7.1 % 0.40 [0.21, 0.75]     |        |                             |
| Shekalaghe 2007 (13) | 8/51    | 36/51      | 69 % 0.22 [0.11, 0.43]      |        |                             |
| Smithuis 2010 (14) | 3/71    | 24/84      | 44 % 0.15 [0.05, 0.47]      |        |                             |
| Smithuis 2010 (15) | 3/84    | 17/83      | 43 % 0.17 [0.05, 0.57]      |        |                             |
| Smithuis 2010 (16) | 1/78    | 28/84      | 22 % 0.04 [0.01, 0.28]      |        |                             |
| Smithuis 2010 (17) | 3/77    | 18/80      | 43 % 0.17 [0.05, 0.56]      |        |                             |
| Smithuis 2010 (18) | 3/83    | 24/78      | 44 % 0.12 [0.04, 0.37]      |        |                             |
| Sutanto 2013 (19) | 22/41   | 25/31      | 8.7 % 0.67 [0.48, 0.93]      |        |                             |

(Continued...)
| Study or subgroup | with PQ | without PQ | Risk Ratio M-H, Random, 95% CI | Weight |
|-------------------|---------|------------|-------------------------------|--------|
| Vasquez 2009 (20) | 2/25    | 2/24       | 2.3% 0.96 [0.15, 6.28]        | 2.3 %  |

**Subtotal (95% CI)** 893 699 63.7% 0.32 [0.20, 0.51]

Total events: 101 (with PQ), 220 (without PQ)
Heterogeneity: Tau² = 0.46; Chi² = 44.91, df = 12 (P = 0.00001); I² = 73%
Test for overall effect: Z = 4.73 (P < 0.00001)

**Total (95% CI)** 1105 889 100.0% 0.38 [0.27, 0.52]

Total events: 168 (with PQ), 347 (without PQ)
Heterogeneity: Tau² = 0.30; Chi² = 69.13, df = 19 (P<0.00001); I² = 73%
Test for overall effect: Z = 5.81 (P < 0.00001)
Test for subgroup differences: Chi² = 3.09, df = 1 (P = 0.08), I² = 68%

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(1) Partner AQ+SP: 0.75 mg/kg PQ day 2; microscopy
(2) Partner MQ: 0.75 mg/kg PQ day 1; microscopy
(3) Partner CQ or (CQ+SP): 0.75 mg/kg PQ day 4; microscopy
(4) Partner SP: 0.5 mg/kg PQ day 1; microscopy
(5) Partner CQ: 0.5 mg/kg PQ day 3; microscopy
(6) Partner CQ+SP: 0.75 mg/kg PQ day 1; microscopy
(7) Partner CQ+SP: 0.75 mg/kg PQ day 3; microscopy
(8) Partner MQ+AS: 0.75 mg/kg PQ day 2; microscopy
(9) Partner AS+SP: 0.75 mg/kg PQ day 4; PCR
(10) Partner AL: 0.1 mg/kg PQ day 3; PCR
(11) Partner AL: 0.4 mg/kg PQ day 3; PCR
(12) Partner AL: 0.75 mg/kg PQ day 3; PCR
(13) Partner AS+SP: PQ 0.75 mg/kg day 4; PCR
(14) Partner AS+AQ: 0.75 mg/kg PQ day 1; microscopy
(15) Partner AS+MQ (fixed): 0.75 mg/kg PQ day 1; microscopy
(16) Partner AL: 0.75 mg/kg PQ day 1; microscopy
(17) Partner AS+MQ (loose): 0.75 mg/kg PQ day 1; microscopy
(18) Partner DHAP: 0.75 mg/kg PQ day 1; microscopy
(19) Partner DHAP: 0.75 mg/kg PQ day 4; microscopy
(20) Partner AS+MQ: 0.75 mg/kg PQ day 3; microscopy
Analysis 4.1. Comparison 4 PQ versus other 8AQ, Outcome 1 Participants with gametocytes on day 8.

Review: Primaquine or other 8-aminoquinoline for reducing *Plasmodium falciparum* transmission

Comparison: 4 PQ versus other 8AQ

Outcome: 1 Participants with gametocytes on day 8

| Study or subgroup | Bulaquine n/N | Primaquine n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|-------------------|--------------|---------------|-----------------------------|--------|-----------------------------|
| Gogtay 2004 (1)   | 1/9          | 10/13         |                             | 23.8 % | 0.14 [ 0.02, 0.94 ]         |
| Gogtay 2006 (2)   | 19/59        | 20/31         |                             | 76.2 % | 0.50 [ 0.32, 0.79 ]         |
| **Total (95% CI)** | **68**      | **44**        |                             | 100.0 %| 0.41 [ 0.26, 0.66 ]         |

Total events: 20 (Bulaquine), 30 (Primaquine)

Heterogeneity: Chi² = 1.86, df = 1 (P = 0.17); I² =46%

Test for overall effect: Z = 3.74 (P = 0.00018)

Test for subgroup differences: Not applicable

(1) Partner QN+doxycycline: 0.75 mg/kg PQ or 75mg BQ day 4
(2) Partner QN+doxycycline: 0.75mg/kg PQ or 75mg BQ day 4

**ADDITIONAL TABLES**

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

| Comparator | Trial | Comparison | Place | G6PD status | Parasite species | Partner or alternative drug | Proportion with gametocytes at onset (by microscopy unless noted) | PQ day(s) * | Target dose per day |
|------------|-------|------------|-------|--------------|-----------------|-----------------------------|------------------------------------------------------------------|------------|-------------------|
| Non-artemisinin partner |       |            |       |              |                 |                             |                                                                  |            |                   |
| CQ or (CQ+SP) Kamtekar 2004 | a | India (Mumbai) | Not screened | Pf only | CQ days 1 to 3 or CQ days 1 to 3 + SP day 1 | 100% (within days) (N = 46) | day 4 | 3 | 45 mg (~0.75 mg/kg) |
| Study                | Country                | G6PD status | Partner drugs | Gametocyte status at onset | PQ dose and treatment schedule |
|----------------------|------------------------|-------------|---------------|----------------------------|--------------------------------|
| Khoo 1981            | Malaysia (Sabah)       | Only deficient (method: Brewer’s methaemoglobin reduction test) | Pf, Pv or mixed | CQ days 1 to 3 | Not reported | days 1 to 3 | 25 mg (~0.42 mg/kg) |
| Kolaczynski 2012     | Pakistan (3 Afghan refugee camps) | Not reported | Pf only | CQ days 1 to 3 | 17.8% (N = 152) | day 3 | 0.5 mg/kg |
| Ledermann 2006       | Indonesia (Central Java) | Only non-deficient (method: semiquantitative glucose-6-phosphate dehydrogenase (G6PD) assay) | Pf only | CQ days 1 to 3 + SP day 1 | Not reported (N = 60) | day 1 | 45 mg (~0.75 mg/kg) |
| Ledermann 2006       | Indonesia (Central Java) | Only non-deficient (method: semiquantitative glucose-6-phosphate dehydrogenase (G6PD) assay) | Pf only | CQ days 1 to 3 + SP day 1 | Not reported (N = 60) | day 3 | 45 mg (~0.75 mg/kg) |
| SP                   | Kolaczynski 2012       | Pakistan (2 Afghan refugee camps) | Not reported | Pf only | SP day 1 | 27.1% (N = 85) | day 1 | 0.5 mg/kg |
| AQ+SP                | Arango 2012            | Colombia | Not reported | Pf only | AQ days 1 to 3 + SP day 1 | 22.5% (N = 40) | day 2 | 0.75 mg/kg |
| MQ or (MQ+SP)        | Chen 1993a             | China | Not reported | Pf only | MQ day 1 | 100% (N = 12) | day 1 | 45 mg (~0.75 mg/kg) |
| Study                         | Country          | Region          | G6PD status          | Partner drugs  | Gametocyte status at onset | PQ dose and treatment schedule |
|-------------------------------|------------------|-----------------|----------------------|----------------|----------------------------|--------------------------------|
| Chen, 1994                    | China            | Hainan province | Not reported         | Pf only        | MQ day 1                   | 45 mg (~0.75 mg/kg)            |
| Singhasivananon, 1994         | Thailand         | Bangkok         | Not reported         | Pf only        | MQ+SP fixed day 1          | 0.75 mg/kg                     |
| Kamtekar, 2004 a, b           | India            | Mumbai          | Not screened         | Pf only        | QN i.v. days 1 to 2 and orally days 1 to 7 | 18.6% (N = 59)  |
| Pukrit-tayakamee, 2004 a, b   | Thailand         |                 | Patients with G6PD deficiency were excluded from getting PQ (method not reported) | Pf only        | QN days 1 to 7              | 22.4% (N = 67)  |
| Arango, 2012                 | Colombia         |                 | Not reported         | Pf only        | AS+MQ days 1 to 3          | 17.1% (N = 42)  |
| El-Sayed, 2007              | Sudan (east)     |                 | Not reported         | Pf only        | AS+SP days 1 to 3          | 3.8% (N = 104)  |

Artemisinin-based partner

| Study                         | Country          | Region          | G6PD status          | Partner drugs  | Gametocyte status at onset | PQ dose and treatment schedule |
|-------------------------------|------------------|-----------------|----------------------|----------------|----------------------------|--------------------------------|
| Arango, 2012                 | Colombia         |                 | Not reported         | Pf only        | AS+MQ days 1 to 3          | 0.75 mg/kg                     |
| El-Sayed, 2007              | Sudan (east)     |                 | Not reported         | Pf only        | AS+SP days 1 to 3          | 0.75 mg/kg                     |
Table 1. G6PD status, partner drugs, gametocyte status at onset, and PQ dose and treatment schedule  

| Study                | Country     | Criteria                                                                 | Drug Regimen | Gametocyte Status at Onset | PQ Dose and Treatment Schedule |
|----------------------|-------------|---------------------------------------------------------------------------|--------------|----------------------------|--------------------------------|
| Eziefula 2013        | Uganda      | Patients without normal G6PD were excluded (method: fluorescence spot test) | AL days 1 to 3 | 24.3% (N = 115) 86.7% PCR (N = 113) | day 3 0.1 mg/kg |
| Eziefula 2013        | Uganda      | Patients without normal G6PD were excluded (method: fluorescence spot test) | AL days 1 to 3 | 20.4% (N = 113) 78.7% PCR (N = 108) | day 3 0.4 mg/kg |
| Eziefula 2013        | Uganda      | Patients without normal G6PD were excluded (method: fluorescence spot test) | AL days 1 to 3 | 22.4% (N = 116) 82.0% PCR (N = 111) | day 3 0.75 mg/kg |
| Pukrittayakamee 2004 | Thailand    | Patients with G6PD deficiency were excluded from getting PQ (method not reported) | AS days 1 to 7 | 26.0% (N = 50) | days 1 to 7 0.5 mg base/kg |
| Shekalaghe 2007      | Tanzania    | Screened and all included (method:                                   | AS+SP days 1 to 3 | 22.6% (N = 106) 87.7% | day 4 0.75 mg/kg |
Table 1. G6PD status, partner drugs, gametocyte status at onset, and PQ dose and treatment schedule  

| Study          | Region (states)           | PCP screened | Partner drugs | Gametocyte status at onset | PCR (N) | Day 1 dose | kg   |
|---------------|---------------------------|--------------|---------------|---------------------------|---------|------------|------|
| Smithuis 2010 | Myanmar (3 states)        | Not screened | Pf or mixed   | AS+AQ days 1 to 3         | 34% (N = 155) | day 1 | 0.75 mg/ |
| Smithuis 2010 | Myanmar (3 states)        | Not screened | Pf or mixed   | AL days 1 to 3            | 33% (N = 152) | day 1 | 0.75 mg/ |
| Smithuis 2010 | Myanmar (3 states)        | Not screened | Pf or mixed   | AS+MQ fixed dose days 1 to 3 | 30% (N = 169) | day 1 | 0.75 mg/ |
| Smithuis 2010 | Myanmar (3 states)        | Not screened | Pf or mixed   | AS days 1 to 3 + MQ day 1 loose | 29% (N = 161) | day 1 | 0.75 mg/ |
| Sutanto 2013  | Indonesia (south Sumatra) | Screened and only normals included (method: qualitative) | Pf only | DHAP days 1 to 3 | 38% (N = 161) | day 1 | 0.75 mg/ |

Note: PCR = polymerase chain reaction, PCP = Plasmodium falciparum, AS = artesunate, AQ = amodiaquine, AL = atovaquone/螺旋霉素, MQ = mefloquine, DHAP = doxycycline, Primaquine or other 8-aminoquinoline for reducing Plasmodium falciparum transmission (Review)
**Table 1. G6PD status, partner drugs, gametocyte status at onset, and PQ dose and treatment schedule (Continued)**

| Test | Vasquez 2009 | Colombia (Antioquia) | Not reported | Pf only | AS+MQ days 1 to 3 (MQ only on day 2 for children < 6) | 20.0% (N = 50) | day 3 | 45 mg (~0.75 mg/kg) |
|------|--------------|----------------------|-------------|---------|-------------------------------------------------|----------------|------|-------------------|
|      | Wang 2006    | Gabon                | Not reported| Pf      | AS i.m. days 1 to 5 (N = 204)                    | 22.5 mg (~0.38 mg/kg) | |

**Comparison of different 8AQ**

| PQ versus Bulaquine | Gogtay 2004 | India (Mumbai) | Only non-deficient (method: not stated) | Pf | QN + doxycycline days 1 to 7 + BQ day 4 | 100% (N = 22) | day 4 | 45 mg (~0.75 mg/kg) |
|---------------------|-------------|----------------|----------------------------------------|---|-------------------------------------|----------------|------|-------------------|
|                     | Gogtay 2006 | India          | Only non-deficient (method: not stated) | Pf | QN + doxycycline days 1 to 7 + BQ day 4 | 100% (N = 93) | day 4 | 45 mg (~0.75 mg/kg) |

* first day of any treatment = day 1

Abbreviations: G6PD = glucose-6-phosphate dehydrogenase; PQ = primaquine; CQ = chloroquine; SP = sulfadoxine-pyrimethamine; MQ = mefloquine; QN = quinine; AS = artesunate; ACT = artemisinin-based combination therapy; 8AQ: 8-aminoquinoline; AQ = amodiaquine; AL = artemether-lumefantrine; DHAP = dihydroxyartemisinin-piperaquine; BQ = bulaquine; i.v. = intravenous injection; i.m. = intramuscular injection; Pf = P. falciparum; Pv = P. vivax.

**Table 2. AUC of gametocyte density over time, days 1 to 15 after treatment**

| Other malaria treatment type | Trial       | Malaria treatment | Dose PQ mg/kg | AUC with PQ days 1 to 15 | AUC without PQ days 1 to 15 | % reduction AUC days 1 to 15 | log(10) AUC with PQ days 1 to 15 | log(10) AUC without PQ days 1 to 15 | % reduction log(10) AUC days 1 to 15 |
|-----------------------------|-------------|-------------------|---------------|-------------------------|-----------------------------|-------------------------------|----------------------------------|-----------------------------------|-------------------------------------|
| Non-artemisinin-based       | Kolaczinski 2012 | a: CQ           | 0.5           | 485.26                  | 4266.61                     | 88.6                          | 2.69                             | 3.63                              | 26.0                                |
Table 2. AUC of gametocyte density over time, days 1 to 15 after treatment (Continued)

| Therapy Type          | Trial          | Malaria treatment | Dose PQ mg/kg | AUC with PQ days 1 to 29 | AUC without PQ days 1 to 29 | % Reduction AUC days 1 to 29 | log(10) AUC with PQ days 1 to 29 | log(10) AUC without PQ days 1 to 29 | % Reduction log(10) AUC days 1 to 29 |
|-----------------------|----------------|-------------------|---------------|--------------------------|-----------------------------|-------------------------------|---------------------------------|---------------------------------|----------------------------------|
| Artemisinin-based     | Kolaczynski 2012 | b: SP             | 0.5           | 924.87                   | 5964.77                     | 84.5                          | 2.97                           | 3.78                           | 21.4                             |
| Shekalaghe 2007       | AS+SP          | 0.75              | 40.15         | 65.06                    | 38.3                        | 1.60                          | 1.81                           | 11.6                            |
| Smithuis 2010         | a: AS+AQ       | 0.75              | 140.35        | 428.51                   | 67.3                        | 2.15                          | 2.63                           | 18.4                            |
| Smithuis 2010         | b: AL          | 0.75              | 196.24        | 242.86                   | 19.2                        | 2.29                          | 2.39                           | 3.9                             |
| Smithuis 2010         | c: AS+MQ fixed | 0.75              | 237.78        | 510.03                   | 53.4                        | 2.38                          | 2.71                           | 12.2                            |
| Smithuis 2010         | d: AS+MQ loose | 0.75              | 183.51        | 293.28                   | 37.4                        | 2.26                          | 2.47                           | 8.3                             |
| Smithuis 2010         | e: DHAP        | 0.75              | 295.24        | 709.60                   | 58.4                        | 2.47                          | 2.85                           | 13.4                            |
| Sutanto 2013          | DHAP           | 0.75              | 1252.48       | 2355.84                  | 46.8                        | 3.10                          | 3.37                           | 8.1                             |
| Vasquez 2009          | AS+MQ          | 0.75              | 500.40        | 305.67                   | -63.7                       | 2.70                          | 2.49                           | -8.6                            |

Abbreviations: AUC = area under curve; PQ = primaquine; CQ = chloroquine; SP = sulfadoxine-pyrimethamine; AS = artesunate; AQ = amodiaquine; AL = artemether-lumefantrine; MQ = mefloquine; DHAP = dihydroxyartemisinin-piperaquine.

Table 3. AUC of gametocyte density over time, days 1 to 29 after treatment

| Other malaria treatment type | Trial          | Malaria treatment | Dose PQ mg/kg | AUC with PQ days 1 to 29 | AUC without PQ days 1 to 29 | % reduction AUC days 1 to 29 | log(10) AUC with PQ days 1 to 29 | log(10) AUC without PQ days 1 to 29 | % reduction log(10) AUC days 1 to 29 |
|-----------------------------|----------------|-------------------|---------------|--------------------------|-----------------------------|-------------------------------|---------------------------------|---------------------------------|----------------------------------|
| Non-artemisinin-based       | Kolaczynski 2012 | a: CQ             | 0.5           | 732.98                   | 8777.24                     | 91.7                          | 2.87                           | 3.94                           | 27.3                             |
|                             | b: SP           | 0.5               | 2111.55       | 12847.37                 | 83.6                        | 3.32                          | 4.11                           | 19.1                            |

Primaquine or other 8-aminoquinoline for reducing Plasmodium falciparum transmission (Review)
Table 3. AUC of gametocyte density over time, days 1 to 29 after treatment (Continued)

| Treatment type       | Trial                | Malaria treatment | Dose PQ | AUC with PQ days 1 to 43 | AUC without PQ days 1 to 43 | % reduction AUC 1 to 43 | log(10) AUC with PQ days 1 to 43 | log(10) AUC without PQ days 1 to 43 | % reduction log(10) AUC 1 to 43 |
|----------------------|----------------------|-------------------|---------|--------------------------|-----------------------------|-------------------------|---------------------------------|---------------------------------|----------------------------------|
| Artemisinin-based    | Shekalaghe 2007      | AS+SP             | 0.75    | 40.30                    | 87.69                       | 54.0                    | 1.61                            | 1.94                            | 17.4                             |
|                      | Smithuis 2010 a:     | AS+AQ             | 0.75    | 141.08                   | 649.46                      | 78.3                    | 2.15                            | 2.81                            | 23.6                             |
|                      | Smithuis 2010 b:     | AL                | 0.75    | 197.57                   | 318.23                      | 37.9                    | 2.3                             | 2.5                             | 8.3                              |
|                      | Smithuis 2010 c:     | AS+MQ fixed       | 0.75    | 240.79                   | 535.40                      | 55.0                    | 2.38                            | 2.73                            | 12.7                             |
|                      | Smithuis 2010 d:     | AS+MQ loose       | 0.75    | 183.51                   | 321.96                      | 43.0                    | 2.26                            | 2.51                            | 9.7                              |
|                      | Smithuis 2010 e:     | DHAP              | 0.75    | 307.14                   | 952.93                      | 67.8                    | 2.49                            | 2.98                            | 16.5                             |
|                      | Sutanto 2013         | DHAP              | 0.75    | 1363.10                  | 3108.05                     | 56.1                    | 3.13                            | 3.49                            | 10.3                             |
|                      | Vasquez 2009         | AS+MQ             | 0.75    | 526.40                   | 349.04                      | -50.8                   | 2.72                            | 2.54                            | -7.0                             |

Abbreviations: AUC = area under curve; PQ = primaquine; CQ = chloroquine; SP = sulfadoxine-pyrimethamine; AS = artesunate; AQ = amodiaquine; AL = artemether-lumefantrine; MQ = mefloquine; DHAP = dihydroxyartemisinin-piperaquine.

Table 4. AUC of gametocyte density over time, days 1 to 43 after treatment

| Other malaria treatment type | Trial                | Malaria treatment | Dose PQ | AUC with PQ days 1 to 43 | AUC without PQ days 1 to 43 | % reduction AUC 1 to 43 | log(10) AUC with PQ days 1 to 43 | log(10) AUC without PQ days 1 to 43 | % reduction log(10) AUC 1 to 43 |
|-----------------------------|----------------------|-------------------|---------|--------------------------|-----------------------------|-------------------------|---------------------------------|---------------------------------|----------------------------------|
| Non-artemisinin-based       | Kolaczynski 2012     | CQ                | 0.5     | 71.02                    | 279.13                      | 74.6                    | 1.85                            | 2.45                            | 24.3                             |
|                             |                      | SP                | 0.5     | 85.47                    | 445.65                      | 80.8                    | 1.93                            | 2.65                            | 27.1                             |
| Artemisinin-based           | Shekalaghe 2007      | AS+SP             | 0.75    | 1.16                     | 3.22                        | 64.1                    | 0.06                            | 0.51                            | 87.5                             |
|                             | Smithuis 2010        | AS+AQ             | 0.75    | 3.36                     | 19.29                       | 82.6                    | 0.53                            | 1.29                            | 59.1                             |
|                             |                      | AL                | 0.75    | 4.70                     | 8.12                        | 42.1                    | 0.67                            | 0.91                            | 26.1                             |

Primaquine or other 8-aminoquinoline for reducing Plasmodium falciparum transmission (Review)

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Table 4. AUC of gametocyte density over time, days 1 to 43 after treatment (Continued)

| Abbreviation | AS+MQ fixed | AS+MQ loose | DHAP | Sutanto 2013 | Vasquez 2009 |
|--------------|-------------|-------------|------|--------------|--------------|
|              | 0.75        | 5.73        | 12.75| 55.0         | 0.76         |
|              | 0.75        | 4.37        | 7.74 | 43.5         | 0.64         |
|              | 0.75        | 7.38        | 25.49| 71.1         | 0.87         |
|              | 0.75        | 32.73       | 83.15| 60.6         | 1.51         |
|              | 0.75        | 12.53       | 8.87 | -41.3        | 1.10         |
|              |             |             | 8.87 | -41.3        | 1.10         |
|              |             |             |      | 1.10         | 0.95         |
|              |             |             |      |              | -15.8        |

Abbreviations: AUC = area under curve; PQ = primaquine; CQ = chloroquine; SP = sulfadoxine-pyrimethamine; AS = artemunate; AQ = amodiaquine; AL = artemether-lumefantrine; MQ = mefloquine; DHAP = dihydroxyartemisinin-piperaquine.

**APPENDICES**

Appendix 1. Search strategy

| Search set | CIDG SR\(^1\) | CENTRAL | MEDLINE\(^2\) | EMBASE\(^2\) | LILACS\(^2\) |
|------------|----------------|---------|---------------|---------------|--------------|
| 1          | malaria        | MALARIA, FALCIPARUM/DRUG THERAPY | MALARIA, FALCIPARUM/DRUG THERAPY | MALARIA FALCIPARUM/DRUG THERAPY | Malaria AND falciparum |
| 2          | primaquine OR primaquine OR plasmoquine OR plasmochin OR plasmocide OR rhodoquine OR plasmocid OR quinocine OR pentaquine OR isopentaquine OR bulaque OR tafenoquine OR 8-aminoquinoline* | Malaria AND falciparum ti, ab | Malaria AND falciparum ti, ab | Malaria AND falciparum ti, ab | primaquine OR primaquine OR plasmoquine OR plasmochin OR plasmocide OR rhodoquine OR plasmocid OR quinocine OR pentaquine OR isopentaquine OR bulaque OR tafenoquine OR 8-aminoquinoline$ |
| 3          | 1 and 2        | 1 or 2  | 1 or 2        | 1 or 2        | 1 and 2      |

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Primaquine or other 8-aminoquinoline for reducing *Plasmodium falciparum* transmission (Review)

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**WHAT’S NEW**

Last assessed as up-to-date: 5 January 2015.

| Date               | Event                                                                 | Description                                                                                                                                                                                                 |
|--------------------|----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 4 February 2015    | New citation required but conclusions have not changed              | Search updated and minor errors corrected.                                                                                                                                                                 |
| 4 February 2015    | New search has been performed                                        | Search updated to 5 January 2015. We simplified the text. We corrected data extraction errors in one study and corrected the results and ‘Summary of findings’ table. We adjusted the wording around “evidence of no effect”. We took into account comments and criticisms received. These criticisms were also published in the Malaria Journal in 2014, so this revision corrects the minor data extraction errors pointed out in this article. The conclusions are not changed |
**HISTORY**

Protocol first published: Issue 4, 2009

Review first published: Issue 9, 2012

| Date         | Event                                         | Description                                                                 |
|--------------|-----------------------------------------------|----------------------------------------------------------------------------|
| 24 June 2014 | New search has been performed                 | New studies added.                                                         |
| 24 June 2014 | New citation required and conclusions have changed | We stratified the analysis by dose or primaquine and added new studies. We clarified the excluded studies and adjusted the conclusions |

**CONTRIBUTIONS OF AUTHORS**

2015 edition: PMG, HG and PG contributed to adjusting the data and updating the text.

Graves 2014: PMG and HG added the new studies. PG helped rewrite the review. All review authors contributed to the interpretation of the results and the conclusions drawn.

Graves 2012: Two review authors (PMG and HG) independently screened all abstracts, applied inclusion criteria and extracted data. PG helped structure the review and contributed to the logic framework of the 'Summary of findings' tables. All review authors contributed to the writing of the review, the interpretation of the results and the conclusions drawn.

**DECLARATIONS OF INTEREST**

We have no affiliations with or involvement in any organization or entity with a direct financial interest in the subject matter of the review (for example, employment, consultancy, stock ownership, honoraria or 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.

PMG is a member of the WHO Malaria Policy Advisory Committee, to provide independent strategic advice in forming WHO policies in malaria. PG is a member of the WHO Guidelines for the Treatment of Malaria Group that made the recommendation for PQ to reduce *P. falciparum* malaria transmission.

None of the review authors are investigators on any of the included trials.

**SOURCES OF SUPPORT**
Differences Between Protocol and Review

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

Changes to primary outcomes:

- Proportion of participants with gametocytes: we added: by microscopy and PCR;
- We added: Proportion of participants infectious;
- We included: Gametocyte density (by microscopy and PCR);
- We added: Gametocyte clearance time and duration of gametocyte carriage.

We arranged the primary outcomes to capture the three categories: transmission intensity, infectiousness and potential infectiousness.

Changes to secondary outcomes:

- We deleted AUC of asexual parasite density over time. We did not identify any relevant data;
- We added asexual clearance time.

Changes to Adverse events:

- We 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);
- We modified haemolysis or drop in haemoglobin or PCV (as assessed/defined in each trial) by deleting reference to G6PD since these outcomes occur in non-G6PD people too. We also added PCV since this was used in some trials as a measure of anaemia.

2. In the first version of the review, we deleted the objective: “To compare the effects of different doses and schedules of PQ given to reduce infectiousness” and we modified the definition of control in comparisons accordingly. We only included controls without PQ. We deleted the comparison of different doses of PQ with identical other treatment regimens since it does not answer the important question of whether adding PQ is effective. We included one trial with two arms using different doses of PQ with same other treatment regimens as two separate arms within the same comparison.

In the June 2014 update, we reversed this decision.

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, we changed the groups, added some, and combined some for the following reasons:
a. some trials combined two types of malaria treatment regimens, not distinguishing the patients who received each one (for example, 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. We also grouped combinations of an artemisinin derivative with SP here.

3. There were no eligible cluster-RCTs so we deleted how we would manage them from the Methods section. If we include any cluster-RCTs 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 attempt 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 \( \text{DEff} = 1 + (m-1) \times \text{ICC} \). This assumes that the necessary information is reported, 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-RCTs using a range of estimates for the ICC to see if clustering could influence the individual trial's result.

NOTES

We received comments from Professor Nick White, who has published extensively on using PQ to prevent transmission. Professor White sent some helpful comments on the use of the data and its interpretation. These were considered by the authorship team and disaggregated into key points that needed to be addressed by the review. The Cochrane Contact Editor moderated the process. The main points raised and addressed were:

1. The lack of effect in low dose categories of PQ does not mean there is no effect and the data suggests a dose response relationship. Response: we have adjusted the wording within the review.

2. Data from Pukrittayakamee 2004 has been incorrectly extracted/interpreted. Response: Two review authors working independently assumed “after treatment” meant after the seven day course, and it was helpful to have it clarified that this was not the case. Therefore we excluded the data for day 8 gametocyte prevalence from this analysis. We inserted additional text on the gametocyte clearance time and duration of gametocyte carriage to the Results section.

Professor White's comments subsequently appeared in a publication about the topic (White 2014). We have corrected all points of factual detail in this current review version.

INDEX TERMS

Medical Subject Headings (MeSH)
Antimalarials [*administration & dosage]; Artemisinins [therapeutic use]; Chloroquine [therapeutic use]; Drug Combinations; Glucosephosphate Dehydrogenase Deficiency [diagnosis]; Malaria, Falciparum [*prevention & control; transmission]; Mefloquine [therapeutic use]; Plasmodium falciparum [*drug effects]; Primaquine [*administration & dosage]; Pyrimethamine; Quinine [therapeutic use]; Randomized Controlled Trials as Topic; Sulfadoxine

MeSH check words
Humans