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

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[Intervention Review]

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

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ABSTRACT

Background

The 8-aminoquinoline (8AQ) drugs act on *Plasmodium falciparum* gametocytes, which transmit malaria from infected people to mosquitoes. In 2012, the World Health Organization (WHO) recommended a single dose of 0.25 mg/kg primaquine (PQ) be added to malaria treatment schedules in low-transmission areas or those with artemisinin resistance. This replaced the previous recommendation of 0.75 mg/kg, aiming to reduce haemolysis risk in people with glucose-6-phosphate dehydrogenase deficiency, common in people living in malarious areas. Whether this approach, and at this dose, is effective in reducing transmission is not clear.

Objectives

To assess the effects of single dose or short-course PQ (or an alternative 8AQ) alongside treatment for people with *P. falciparum* malaria.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library; and the WHO International Clinical Trials Registry Platform (ICRTP) portal using 'malaria*', 'falciparum', 'primaquine', '8-aminoquinoline', and eight 8AQ drug names as search terms. We checked reference lists of included trials, and contacted researchers and organizations. Date of last search: 21 July 2017.

Selection criteria

Randomized controlled trials (RCTs) or quasi-RCTs in children or adults, adding PQ (or alternative 8AQ) as a single dose or short course alongside treatment for *P. falciparum* malaria.

Data collection and analysis

Two authors screened abstracts, applied inclusion criteria, and extracted data. We sought evidence on transmission (community incidence), infectiousness (people infectious and mosquitoes infected), and potential infectiousness (gametocyte measures assessed by microscopy or polymerase chain reaction [PCR]). We grouped trials into artemisinin and non-artemisinin treatments, and stratified by PQ dose (low, 0.2 to 0.25 mg/kg; moderate, 0.4 to 0.5 mg/kg; high, 0.75 mg/kg). We used GRADE, and absolute effects of infectiousness using trial control groups.

Main results

We included 24 RCTs and one quasi-RCT, comprising 43 arms. Fourteen trials evaluated artemisinin treatments (23 arms), nine trials evaluated non-artemisinin treatments (13 arms), and two trials included both artemisinin and non-artemisinin arms (three and two arms, respectively). Two trial arms used bulaquine. Seven PQ arms used low dose (six with artemisinin), 11 arms used moderate dose (seven with artemisinin), and the remaining arms used high dose. Fifteen trials tested for G6PD status: 11 excluded participants with G6PD deficiency, one included only those with G6PD deficiency, and three included all, irrespective of status. The remaining 10 trials either did not test or did not report on testing.

No cluster trials evaluating community effects on malaria transmission met the inclusion criteria.

With artemisinin treatment

Low dose PQ

Infectiousness (participants infectious to mosquitoes) was reduced (day 3 or 4: RR 0.12, 95% CI 0.02 to 0.88, 3 trials, 105 participants; day 8: RR 0.34, 95% CI 0.07 to 1.58, 4 trials, 243 participants; *low certainty evidence*). This translates to a reduction in percentage of people infectious on day 3 or 4 from 14% to 2%, and, for day 8, from 4% to 1%; the waning infectiousness in the control group by day 8 making the absolute effect smaller by day 8. For gametocytes detected by PCR, there was little or no effect of PQ at day 3 or 4 (RR 1.02, 95% CI 0.87 to 1.21; 3 trials, 414 participants; *moderate certainty evidence*); with reduction at day 8 (RR 0.52, 95% CI 0.41 to 0.65; 4 trials, 532 participants; *high certainty evidence).* Severe haemolysis was infrequent, with or without PQ, in these groups with few G6PD-deficient individuals (RR 0.98, 95% CI 0.69 to 1.39; 4 trials, 752 participants, *moderate certainty evidence)*.

Moderate dose PQ

Infectiousness was reduced (day 3 or 4: RR 0.13, 95% CI 0.02 to 0.94; 3 trials, 109 participants; day 8 RR 0.33, 95% CI 0.07 to 1.57; 4 trials, 246 participants; *low certainty evidence*). Illustrative risk estimates for moderate dose were the same as low dose. The pattern and level of certainty of evidence with gametocytes detected by PCR was the same as low dose, and severe haemolysis was infrequent in both groups.

High dose PQ

Infectiousness was reduced (day 4: RR 0.2, 95% CI 0.02 to 1.68, 1 trial, 101 participants; day 8: RR 0.18, 95% CI 0.02 to 1.41, 2 trials, 181 participants, *low certainty evidence*). The effects on gametocyte prevalence showed a similar pattern to moderate and low dose PQ. Trials did not systematically report evidence of haemolysis.

With non-artemisinin treatment

Trials with non-artemisinin treatment have been conducted only for moderate and high dose PQ. With high dose, infectiousness appeared markedly reduced on day 5 (RR 0.09, 95% CI 0.01 to 0.62; 30 participants, *very low certainty evidence*), with similar reductions at day 8. For both moderate dose (two trials with 221 people) and high dose (two trials with 30 people), reduction in gametocytes (detected by microscopy) showed similar patterns as for artemisinin treatments, with little or no effect at day 4 or 5, and larger effects by day 8. No trials with non-artemisinin partner drugs systematically sought evidence of severe haemolysis.

Two trials comparing bulaquine with PQ suggest bulaquine may have larger effects on gametocytes by microscopy on day 8 (RR 0.41, 95% CI 0.26 to 0.66; 2 trials, 112 participants).

Authors' conclusions

A single low dose of PQ (0.25 mg/kg) added to artemisinin-based combination therapy for malaria reduces infectiousness of people to mosquitoes at day 3-4 and day 8, and appears as effective as higher doses. The absolute effect is greater at day 3 or 4, and smaller at day 8, in part because of the lower infectiousness in the control group. There was no evidence of increased haemolysis at 0.25 mg/kg, but few G6PD-deficient individuals were included in the trials. The effect on infectiousness precedes the effect of PQ on gametocyte prevalence. We do not know whether single dose PQ could reduce malaria transmission at community level.

PLAIN LANGUAGE SUMMARY

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

What is the aim of this review?

To assess the effects of adding a single dose of primaquine (PQ) to treatment for falciparum malaria to reduce disease transmission. This Cochrane Review update includes 25 controlled trials. The date of latest search was 21 July 2017.

Key messages

A single low dose of PQ, at 0.25 mg/kg, which the World Health Organization (WHO) recommends adding to artemisinin-based combination therapy for malaria, reduces infectiousness (transmission from people to mosquitoes). In the trials, the percentage of people who infected mosquitoes three to four days after treatment was reduced from 14% to 2%, with a smaller effect at day 8, from 4% to 1%, with no evidence of harm.

What was studied in the review

PQ kills gametocytes (malaria transmission stages) of the falciparum malaria parasite. Gametocytes infect mosquitoes during a bite, thus perpetuating transmission. There is concern that PQ may cause red blood cells to burst (haemolysis) in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency, a genetically-determined condition common in many malaria-endemic settings, which can lead to anaemia. Recognizing concerns about the risk of haemolysis, the WHO reduced the recommended PQ dose from 0.75 mg/kg to 0.25 mg/kg in 2012.

Ideally, this approach would be tested by randomly assigning villages to standard malaria treatment, or standard treatment plus a low dose of PQ, then measuring the effect on malaria over time but this would be difficult and expensive. So, indirect indicators are used to shed light on effectiveness, including feeding studies, in which mosquitoes are allowed to feed on people (or their blood), comparing those who were assigned PQ with those who were not. Alternatively, researchers may simply monitor the presence (prevalence), number (density), and duration (time of persistence) of gametocytes in the blood of people after different treatments, assuming that gametocytes are viable irrespective of exposure to PQ.

What the research says

The 25 included trials span several decades and include a variety of treatments and PQ doses. Related to safety assessment, some trials tested participants for G6PD activity. Other trials reported results based on their G6PD status, others did not test (or did not say whether they did), and others tested and excluded people with G6PD deficiency.

There were no ideal community-level studies that would answer the question directly.

Five feeding trials with multiple arms included three low-dose, three medium-dose, and two high-dose comparisons, showing a markedly reduced proportion of people infectious who received PQ in trials with any events. Two trials using older malaria treatments and high dose PQ had similar results.

The other trials focused on indirect measures of potential infectiousness of humans to mosquitoes. In these trials, PQ shortened the period of potential infectiousness, with a lower prevalence and density of gametocytes up to day 8 after treatment. The effect was similar at all PQ dose levels.

Few serious haemolytic events occurred in these trials, but PQ did affect non-serious haemoglobin measures, even at low doses.

What are the main results of the review?

A single low dose of PQ added to an artemisinin regimen for malaria reduces infectiousness to mosquitoes and is relatively safe for most people.

PQ at WHO-recommended dose reduces infectiousness to mosquitoes on day 3-4 and day 8 with no evidence of harm. It is unclear whether this reduction would materially reduce malaria transmission in communities.

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

Low-dose primaquine (PQ) given with artemisinin combination treatment
Participants or population: adults and children with malaria being treated with artemisinin combination treatment
Settings: Mali, Burkina Faso, The Gambia, Tanzania, Senegal
Intervention: single dose PQ dose 0.2 to 0.25 mg/kg
Comparison: no PQ

Outcomes	Number of participants (trials)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		Certainty of the evidence (GRADE)	Comments
			Risk with no PQ, with artemisinin partner	Risk with single dose PQ at 0.2 to 0.25 mg/kg		
Participants infectious at day 3-4	105 (3 RCTs)	RR 0.12 (0.02 to 0.88)	14 per 100	2 per 100 (0 to 13)	⊕⊕◯◯ LOW[1] Due to imprecision	Low-dose PQ may reduce infectiousness
Participants infectious at day 8	243 (4 RCTs)	RR 0.34 (0.07 to 1.58)	4 per 100	1 per 100 (0 to 6)	⊕⊕◯◯ LOW[1] Due to imprecision	Low-dose PQ may reduce infectiousness
Participants with gametocytes at day 3 to 4 by PCR	414 (3 RCTs)	RR 1.02 (0.87 to 1.21)	52 per 100	53 per 100 (45 to 63)	⊕⊕⊕◯ MODERATE[2] Due to imprecision	Low-dose PQ probably has little or no effect on gametocytes detected by PCR at day 3 to 4
Participants with gametocytes at day 8 by PCR	532 (4 RCTs)	RR 0.52 (0.41 to 0.65)	47 per 100	25 per 100 (19 to 31)	⊕⊕⊕⊕ HIGH	Low-dose PQ reduces gametocytes detected by PCR at day 8
Participants with severe haemolysis	752 (4 RCTs)	RR 0.98 (0.69 to 1.39)	13 per 100	13 per 100 (9 to 18)	⊕⊕⊕◯ MODERATE[2] Due to imprecision	Low-dose PQ probably has little or no effect on severe haemolysis

*__The risk in the intervention group__ (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).
Abbreviations: CI: confidence interval; **PCR**: polymerase chain reaction; **RCT**: randomised controlled trial; **RR:** risk ratio; **OR:** odds ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Downgraded by 2 for imprecision: the CIs are wide; in addition, there is a large effect combined with a low number of events, which creates further uncertainty around the point estimate.
[2]Downgraded by 1 for imprecision: the CIs are wide.

BACKGROUND

Description of the condition

Malaria is a febrile illness due to infection with the *Plasmodium* parasite, and is transmitted between humans via mosquitoes (Phillips 2017). 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 (WHO 2016). The clinical illness develops due to the presence of asexual stage parasites (merozoites and schizonts) in the person's bloodstream, but transmission to mosquitoes is via sexual stage parasites (gametocytes), which develop from other blood stages at some point after infection (Phillips 2017).

Artemisinin-based combination therapies (ACTs) are currently recommended worldwide as the primary treatment for infection with *P. falciparum* (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, lumefantrine, 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 and 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, the haploid 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).

Description of the intervention

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, haemoglobinaemia, 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" (Ashley 2014). Although the haemolysis appears less likely at lower dose, there have been few studies in G6PD-deficient people at low doses of PQ (Olalekan 2017).

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:

- G6PD testing should be done more widely;
- countries already implementing single-dose PQ should reduce the dose to 0.25 mg/kg in G6PD-deficient patients; and
- 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).

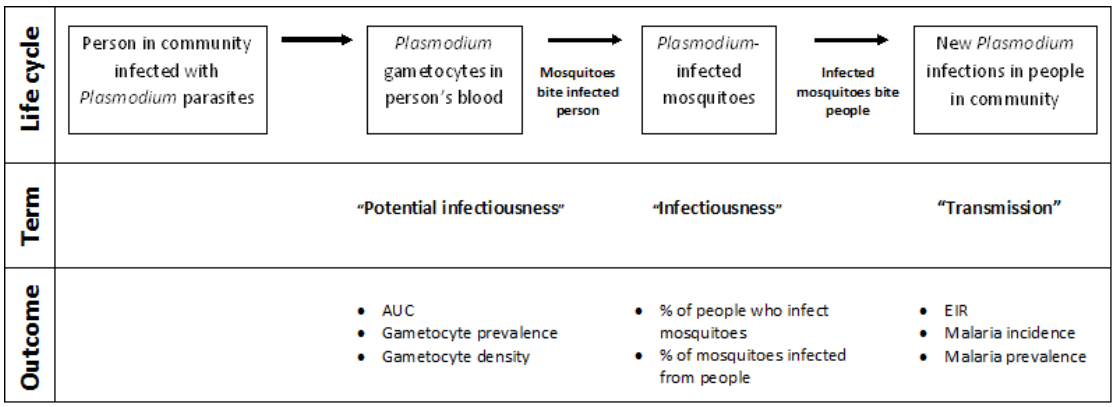
These conclusions were then incorporated into a revised WHO recommendation in treatment guidelines (WHO 2012b) for 0.25 mg/kg PQ in the above circumstances, with the goal of reducing transmissibility of treated *P. falciparum* infections (except in pregnant women, infants under six months of age, and women breast-feeding infants under six months of age). A slightly revised policy

was then included in an updated policy brief (WHO 2015a), and in the third edition of the WHO *Guidelines for the Treatment of Malaria* (WHO 2015b), which expanded the area of recommendation to all "low transmission areas"; this was a strong recommendation with low certainty evidence and it was stated that G6PD deficiency testing was not required.

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 (gametocytaemia) 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 and some direct evidence.

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. Abbreviations: AUC: area under the curve. EIR: entomological inoculation rate; PQ: primaquine.



Infectiousness to mosquitoes can be measured directly by allowing mosquitoes to feed on infected individuals (or their blood) who have been treated with and without PQ (Killeen 2006; Bousema 2012; Dicko 2016; Gonçalves 2016a; Gonçalves 2016b; Okebe 2016; Lin 2017), 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 parasitaemias 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 (Ouédraogo 2009; Bousema 2014; Stone 2015).

Recently, with the move toward a target of elimination, some policy makers are considering mass treatment strategies to reduce transmission or contain outbreaks once transmission is reduced to low levels (von Seidlein 2003; Sturrock 2013). In this situation, 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). Recent modelling has questioned the value of the additional impact of PQ to mass drug administration (MDA) (Johnston 2014; WHO 2015c).

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). While it is certainly important to urgently expand access to treatment for persons with such parasites, PQ does not act on asexual stages, which would still produce gametocytes as usual in resistant infections. Thus it is not clear how this would work, and it may actually be counterproductive (Hastings 2006).

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. It has become clear that ACTs have differing effects on gametocyte carriage following treatment, even without PQ (WWARN 2016). Therefore the 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.

OBJECTIVES

1. To summarize any reliable direct research evidence that community programmes of single low dose PQ reduce malaria transmission.

2. For currently recommended artemisinin combination treatments for *P. falciparum* infections, to summarize reliable research evidence on the effect of adding a single dose of PG/8AQ on infectiousness of infected people to mosquitoes, gametocytaemia and any evidence of haemolysis, stratified by:

- the current standard recommended dose of 0.25 mg/kg;
- previously recommended doses (up to 0.75 mg/kg).

3. To repeat the analysis of effects of single dose PQ, stratified by dose, for non-artemisinin based combination treatments for *P. falciparum* infections.

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 (at doses of 0.2 mg/kg per day or above) 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

Transmission

Any measure of community burden or incidence of malaria (entomological inoculation rate (EIR) measured in mosquitoes, incidence of new malaria infections, or prevalence of malaria infection).

Infectiousness

- Number of participants infectious (leading to infection with oocysts or sporozoites in at least one mosquito fed on them or their blood) at day 3-5 and day 8.
- Proportion of mosquitoes infected by direct or membrane feeding on blood of participants at day 3-5 and day 8.

Potential infectiousness

- Number of participants with gametocytes detected by PCR on day 3-4 and day 8.
- Number of participants with gametocyte detected by microscopy on day 3-4 and day 8.

Other measures of gametocytes including gametocyte clearance time (time to disappearance of gametocytes from the blood) and area under the curve of gametocyte density over time where reported.

Adverse effects

- Serious adverse events leading to hospital admission or death.
- Participants with severe haemolysis as defined by the trial authors. It was defined as drop of ≥ 25% (Dicko 2016; Mwaiswelo 2016), ≥ 2 g (Gonçalves 2016b), or ≥ 2 g of haemoglobin (Tine 2017) over the course of follow-up.

We also describe maximum or average absolute or percent change in haemoglobin or packed cell volume (PCV) when this is reported.
Figure 1 provides an outline of transmission of malaria to help clarify the outcomes.

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 21 July 2017 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, 2017); MEDLINE (PubMed; 1966 to 21 July 2017); Embase (OVID; 1980 to 21 July 2017); and LILACS (BIREME, 1982 to 21 July 2017). Also, we checked ClinicalTrials.gov (https://clinicaltrials.gov/ct2/home) and the WHO International Clinical Trials Registry Platform (ICTRP); http://www.who.int/ictrp/en/; both accessed 21 July 2017) 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 who were authors of some of the included and in-progress trials, other trial authors, and other experts in the field of malaria chemotherapy.

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. We listed all studies excluded after full-text assessment, and their reasons for exclusion, in the 'Characteristics of excluded studies' table. We have illustrated the study selection process in a PRISMA diagram.

Data extraction and management

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

Trial characteristics

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

Participant characteristics

- Number of participants.
- Age and sex of participants.
- Proportion with G6PD deficiency.
- Proportion with gametocytes at onset of trial.
- Inclusion criteria.
- Exclusion criteria.

Intervention characteristics

- 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, two review authors (PMG and HG) extracted data on the trial outcomes eligible for inclusion in this review for the PQ and non-PQ groups. We extracted the number of participants randomized and the numbers analysed in each treatment group for each outcome. For dichotomous data outcomes (proportion of participants infectious to mosquitoes, proportion of participants with gametocytes, proportion of mosquitoes infected), we extracted the number of participants experiencing the event of interest and the total number of participants or mosquitoes in each treatment arm of each trial. 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 genotypically (PCR). 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 review authors.

Assessment of risk of bias in included studies

Two review authors (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 judgement 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 participants 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.

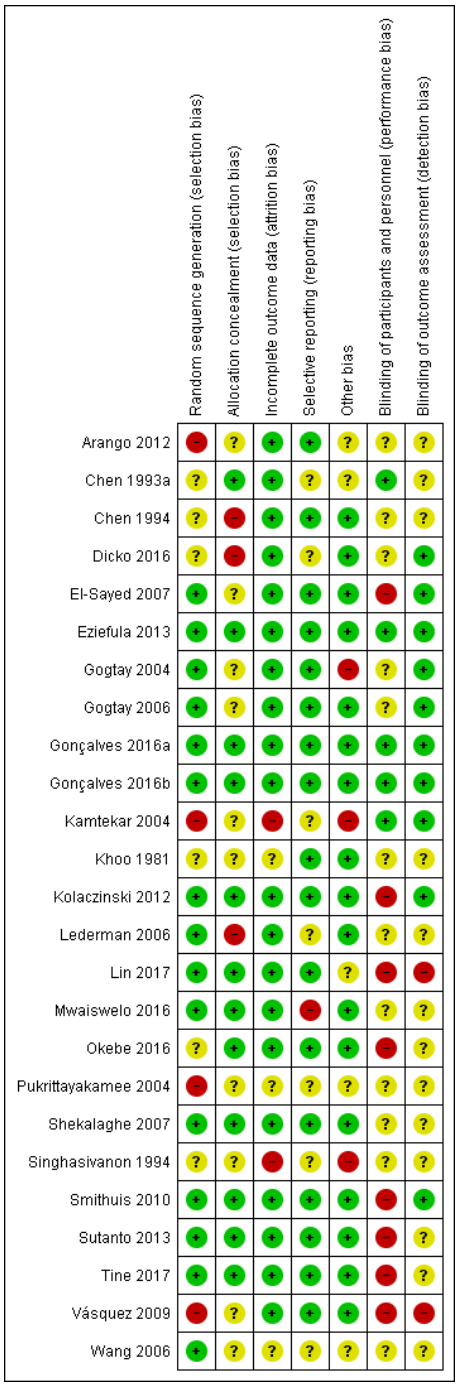
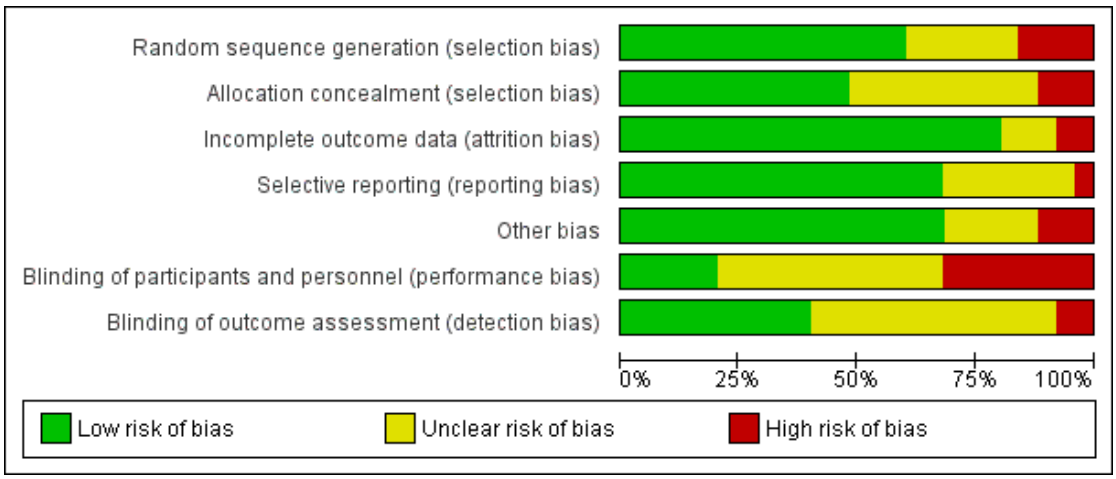


Figure 3. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included trials.



Measures of treatment effect

We analysed the data using Review Manager 5 (RevMan 5) (RevMan 2014). 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.

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 double-counting participants and falsely overestimating the precision.

Unit of analysis issues

All the included trials were individually randomized and analysed accordingly.

Dealing with missing data

Where data were missing from the trials or details were unclear, we attempted to contact the trial authors. We used complete case analysis (that is, excluding dropouts rather than 'intention to treat' 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 Chi^2 test for heterogeneity with a 10% level of significance and the I^2 statistic with a value of 50% to represent moderate levels of heterogeneity.

Assessment of reporting biases

There were insufficient trials (less than 10) within each comparison to assess the likelihood of small trial effects, such as publication bias, by examining a funnel plot for asymmetry (Higgins 2011).

Data synthesis

We prespecified subgroups for analysis by artemisinin or non-artemisinin based malaria treatment regimens and described which antimalarial drug was used for each comparison in a footnote. We prespecified strata by PQ dose category: low (0.2 to 0.25 mg/kg), medium (0.4 to 0.5 mg/kg), and high (0.75 mg/kg dose); and grouped the 8AQ drugs as PQ and other. Throughout this review, to enable standardization between trials, we designated the first day of any treatment drug 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 if not stated, we made this assumption.

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 (I^2 statistic value > 50%), we did not undertake meta-analysis but instead presented a Forest plot with the pooled effect suppressed.

Certainty of the evidence

We assessed the certainty of the evidence using the GRADE approach (Guyatt 2011). We rated each primary outcome as described by Balshem 2011 as follows.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect.
- Low: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

RCTs start as high certainty evidence but can be downgraded if there are valid reasons within the following five categories: risk of bias, imprecision, inconsistency, indirectness, and publication bias. Studies can also be upgraded if there is a large effect; a dose response effect; and if all plausible residual confounding would reduce a demonstrated effect or would suggest a spurious effect if no effect was observed (Balshem 2011). We summarized our findings in a 'Summary of findings' table.

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 inclusion to perform these analyses.

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 last published version of this review, Graves 2015, we included a total of 18 trials. There was one instance of duplicate reports of the same trial in different languages (Chen 1994). Trials frequently included arms with distinct comparisons of different malaria treatment partner drugs, doses, or schedules; thus the 18 previously included trials had 30 arms.

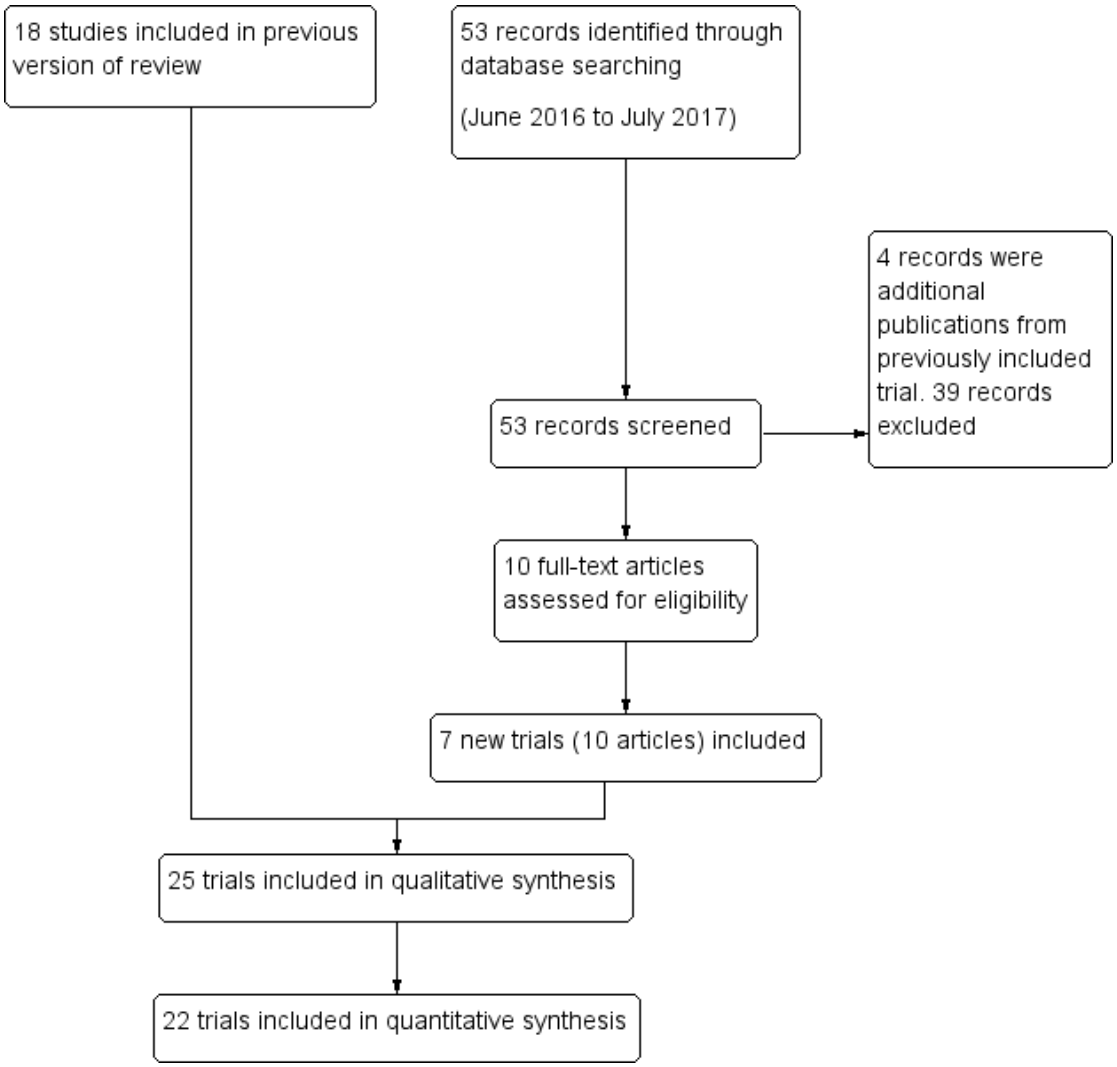
For this update, a literature search update to 21 July 2017 identified 53 new records. Four new publications (Eziefula 2013; Eziefula 2014; Pett 2014; Chang 2016) were additional reports from a previously included trial (Eziefula 2013). Of the remainder, 10 records were selected for full text review and we excluded 39 records.

Ten new publications described seven new trials published since the last revision (Dicko 2016; Gonçalves 2016a; Gonçalves 2016b; Mwaiswelo 2016; Okebe 2016; Lin 2017; Tine 2017). The Goncalves study is regarded as two trials because the two phases had different inclusion criteria (Gonçalves 2016a; Gonçalves 2016b).

The seven new trials included a total of 16 separate comparison arms. Therefore, this update now includes 25 trials which had 46 total arms (Table 1). There were 14 trials with artemisinin-only arms (seven with one arm, two with two arms, three with three arms, one with four arms, and one with five arms). There were nine trials with non-artemisinin only arms (six with one arm and three with two arms). Two trials had both artemisinin and non-artemisinin arms. Three artemisinin arms in two trials were excluded because they used doses lower than 0.2 mg/kg (Eziefula 2013; Dicko 2016), leaving 43 included arms in the 25 trials.

We updated Figure 4, which shows the flow diagram of included studies, accordingly. We still could not locate three articles that were cited in the 'Studies awaiting classification' section in the previous and this version.

Figure 4. Study flow diagram



Included studies

The 25 included trials comprised 24 individually randomized RCTs and one quasi-RCT which used alternate allocation (Arango 2012). Two trials compared PQ and bulaquine (BQ), while 23 trials compared PQ versus no PQ. One trial of PQ, Khoo 1981, did not distinguish between participants given a short or long course of PQ and therefore no outcomes are included in this review. Two trials did not include any gametocyte outcomes (Wang 2006; Mwaiswelo 2016).

Trials reporting community transmission

No cluster trials examining malaria transmission intensity in communities met the inclusion criteria.

Trials reporting infectiousness

Five trials reported on infectiousness of participants to mosquitoes by direct or membrane feeding of people given ACTs compared to ACT+PQ (Dicko 2016; Gonçalves 2016a; Gonçalves 2016b; Okebe 2016; Lin 2017). These trials were conducted in Burkina Faso (partner drug AL), Mali (DHAP), The Gambia (DHAP), and Cambodia (DHAP), respectively. In addition, Mwaiswelo 2016 planned to test infectivity in Tanzania with AL as partner drug, but no infectiousness or gametocyte outcomes were reported.

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

Trials reporting potential infectiousness

Twenty-two trials examined the impact of PQ or 8AQ on various measures of potential infectiousness, such as gametocyte prevalence or density over time in participants after treatment, gametocyte clearance time, or gametocyte circulation time. Three trials with artemisinin partners assessed gametocyte prevalence by PCR only (El-Sayed 2007; Dicko 2016; Okebe 2016). Five trials reported both microscopy and PCR gametocyte detection (Shekalaghe 2007; Eziefula 2013; Gonçalves 2016a; Gonçalves 2016b; Lin 2017), and the others with either artemisinin or non-artemsisinin partners reported gametocyte prevalence by microscopy only.

Five trials with artemisinin partners reported area under curve (AUC) or log(10)AUC as a summary combined measure of gametocyte prevalence and density over time, using PCR estimates of density (Shekalaghe 2007; Eziefula 2013; Dicko 2016; Gonçalves 2016b; Tine 2017).

Trials reporting adverse effects

Eleven trials reported adverse effects quantitatively, with 44 different types of effects reported. Nine trials included anaemia outcomes (El-Sayed 2007; Shekalaghe 2007; Eziefula 2013; Dicko 2016; Gonçalves 2016a; Mwaiswelo 2016; Okebe 2016; Lin 2017; Tine 2017), and two reported only non haemolytic effects (Wang 2006; Sutanto 2013) (Analysis 1.9 to Analysis 1.18, and Analysis 3.6).

Participants

Place of recruitment

Participants were usually people attending health clinics for treatment, but Dicko 2016 actively recruited participants from the community for a second phase of the trial when insufficient infective participants were found in phase 1.

Age

Four trials did not state the participants' ages (Khoo 1981; Chen 1993a; Chen 1994; El-Sayed 2007), and five trials included children only: Singhasivanon 1994 (five to 12 years); Shekalaghe 2007 (three to 15 years); Eziefula 2013 (one to 10 years); Gonçalves 2016a and Gonçalves 2016b (two to 15 years). Nine trials used a wide age range of children and adults: Wang 2006 (six to 60 years); Vásquez 2009 (≥ one year); Smithuis 2010 (> six months); Arango 2012 (one to 75 years); Kolaczinski 2012 (three to 70 years); Sutanto 2013 (≥ five years); Mwaiswelo 2016 (≥ one year); Okebe 2016 (> one year) and Dicko 2016 (five to 50 years). The remaining seven trials included teenagers and adults only: Gogtay 2004 (> 18 years); Kamtekar 2004 (> 16 years); Lin 2017 (18 to 65 years); Tine 2017 (18 to 74 years); Pukrittayakamee 2004 (15 to 62 years); Gogtay 2006 (> 16 years); and Lederman 2006 (≥ 15 years). See the 'Characteristics of included studies' section.

G6PD deficiency

For G6PD deficiency, two trials did not screen participants (Kamtekar 2004; Smithuis 2010), three trials screened and included all participants (Shekalaghe 2007; Mwaiswelo 2016; Tine 2017), one trial included only G6PD-deficient participants (Khoo 1981), 11 trials included only non-severely deficient participants (Gogtay 2004; Pukrittayakamee 2004; Gogtay 2006; Lederman 2006; Sutanto 2013; Eziefula 2013; Dicko 2016; Gonçalves 2016a; Gonçalves 2016b; Okebe 2016; Lin 2017), and the remaining eight studies made no comment (Chen 1993a; Chen 1994; Singhasivanon 1994; Wang 2006; El-Sayed 2007; Vásquez 2009; Arango 2012; Kolaczinski 2012); see Table 1.

Baseline infectiousness

In Dicko 2016, baseline infectiousness (proportion of persons infectious) prior to treatment in both groups combined was 58/73 (79%), with no obvious imbalance between the treatment groups. In Goncalves phase 1, no baseline infectiousness was measured (Gonçalves 2016a); in phase 2, 79 of the 149 participants were tested for infectiousness at baseline, and 30/79 (38%) were infectious (all groups combined) (Gonçalves 2016b). In Lin 2017, baseline infectiousness of participants reported on day 0 appeared unbalanced: DHAP 6/51 (12%); DHAP+PQ 1/51 (2%). This is assumed to reflect selection bias or a failure of randomization.

Interventions

Background drug

Sixteen trials (31 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 (two trials, two arms), artemether-lumefantrine (AL) (five trials, ten arms) and dihydroxyartemisinin-piperaquine (DHAP) (six trials, 11 arms). Two trials included two and one arms, respectively, with doses too low (< 0.2 mg/kg) to be included here (Eziefula 2013; Dicko 2016). One trial, Tine 2017, included arms with AL, DHAP and ASAQ, but they were combined in the paper and here for analysis.

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

Dose

Sixteen trials included the previous standard dose of 0.75 mg/kg PQ per day (adult dose 45 mg/day); see Table 1. The trials using different doses were as follows.

- Khoo 1981: adult dose of 25 mg or approximately 0.42 mg/kg/day.
- Kolaczinski 2012: (two arms) 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: 0.1 (not included in this review), 0.4 and 0.75 mg/kg.
- Dicko 2016: 0.125 (not included in this review) and 0.5 mg/kg in phase 1 and 0.0625 (not included in this review) and 0.25 mg/kg in phase 2.
- Gonçalves 2016a: 0.2 and 0.4 mg/kg.
- Gonçalves 2016b: 0.2 and 0.4 mg/kg.
- Okebe 2016: 0.2, 0.4 and 0.75 mg/kg.
- Mwaiswelo 2016: 0.25 mg/kg.
- Tine 2017: 0.25 mg/kg.

This review reports the results for clinically important doses only: 0.2 to 0.25 mg/kg, 0.4 to 0.5 mg/kg, and 0.75 mg/kg.

Schedule

We regarded the first day of any treatment as day 1. Most trials used a single dose of PQ given on the following days.

- Day 1: Chen 1993a; Chen 1994; Singhasivanon 1994; Lederman 2006 (one of two comparisons); Smithuis 2010 (five arms); Kolaczinski 2012 (one of two arms); Dicko 2016; Mwaiswelo 2016; Tine 2017 (three arms).
- Day 2: Arango 2012 (two arms).
- Day 3: Lederman 2006 (one of two arms); Vásquez 2009; Kolaczinski 2012 (one of two arms); Eziefula 2013; Sutanto 2013; Gonçalves 2016a (two arms); Gonçalves 2016b (two arms); Okebe 2016 (three arms); Lin 2017.
- Day 4: Gogtay 2004; Kamtekar 2004 (one of two arms); Gogtay 2006; El-Sayed 2007; Shekalaghe 2007.
- Day 8: Kamtekar 2004 (one of two arms).

Three trials used a longer course of PQ.

- Three days: Khoo 1981.
- Five days: Wang 2006.
- Seven days: Pukrittayakamee 2004 (three arms).

Length of follow-up

The maximum time of follow-up varied between trials. It was restricted here to eight days after treatment to enable maximum comparison between trials (some of which terminated at this point). Therefore, not all results from Kamtekar 2004 could be included since PQ was given on day 8 in one arm.

Prevalence of gametocytes at start of trial

The trials varied in inclusion criteria and hence in how representative they were of the gametocyte prevalence of the general or clinic population. Five trials included only people with microscopically detected gametocytes at onset (Chen 1993a; Chen 1994; Gogtay 2004; Gogtay 2006; Dicko 2016). In Kamtekar 2004 over 90% of participants were gametocyte positive by microscopy, but this variable was reported as "within 3 days" rather than on day 1. The Gonçalves 2016b trial had the next highest prevalence by microscopy, of 69%. The five arms of the Smithuis 2010 trial showed moderately high gametocyte prevalence (microscopy) between 29% and 38% depending on the arm. Trials with initial gametocyte prevalence between 15% and 27% by microscopy were: Pukrittayakamee 2004; Shekalaghe 2007; Vásquez 2009; Arango 2012; Kolaczinski 2012; Eziefula 2013; Gonçalves 2016a; and Sutanto 2013. The remaining three trials had low (< 15%) gametocyte prevalence by microscopy at onset (Mwaiswelo 2016; Lin 2017; Tine 2017).

Two trials reported PCR prevalence only: El-Sayed 2007, with 10.5% and Okebe 2016, with 48%. Four trials did not report the prevalence of gametocytes at onset (Khoo 1981; Singhasivanon 1994; Lederman 2006; Wang 2006).

The details of the trial locations, malaria treatments, gametocyte prevalence at onset, 8-AQ doses, and schedules are in Table 1.

Outcomes

Transmission

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

Infectiousness

Infectiousness includes two components: proportion of participants infectious, and proportion of mosquitoes infected. Six trials intended to measure infectiousness with artemisinin partner drugs (DHAP, ASAQ, or AL) (Gonçalves 2016a; Gonçalves 2016b; Dicko 2016; Mwaiswelo 2016; Okebe 2016; Lin 2017) and five (all except Mwaiswelo 2016) provided such data. Two trials measured infectiousness with non-artemisinin drugs (in both cases MQ) with and without PQ (Chen 1993a; Chen 1994). Results are reported here for two time points after commencement of treatment. The first day of treatment is day 1. The goal was reporting at day 4 and 8, but day 4 was varied to day 3 or 5 for some trials.

Potential infectiousness

All other trials (except Wang 2006 and Mwaiswelo 2016) reported potential infectiousness: that is, the effects of PQ on gametocyte prevalence, density, or clearance time, or all three outcomes using either microscopy or PCR. The same time points are reported as for infectiousness (day 3, 4, or 5, and day 8).

Nine trials reported gametocyte clearance time (Singhasivanon 1994; Pukrittayakamee 2004; Shekalaghe 2007; Smithuis 2010; Eziefula 2013; Dicko 2016; Gonçalves 2016b; Lin 2017; Tine 2017). Four of these also reported a summary measure of potential infectiousness using area under the curve (AUC) of gametocyte density over time (Pukrittayakamee 2004; Smithuis 2010; Gonçalves 2016b; Lin 2017).

Wang 2006 and Mwaiswelo 2016 reported only asexual stage outcomes and Khoo 1981 reported data that could not be used as the length of PQ course for each participant was not clear.

Excluded studies

We have listed the reasons for exclusion of 48 trials in the 'Characteristics of excluded studies' section. Some additional details of these trials and reasons for exclusion are expanded in a previous edition of this review (Graves 2014).

We sought publications for Chinese trials cited in White 2012 and 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 were stated to be randomized (Huang 2001; Li 2007; Li 2010), 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

The 'Risk of bias' assessment for each of the 25 included trials is shown in Figure 2 with a summary by component in Figure 3. There was low risk of bias in 50% or more of trials for random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other bias. High risk of bias was present in less than 20% of the trials for these components. The trials were weakest on blinding, with low risk of bias in less than 25% for blinding of participants and personnel, and less than 50% of trials for blinding of outcome assessment. The highest risk of bias (30% of trials) was for blinding of participants and personnel. A relatively high proportion of trials (particularly older trials) did not report sufficient information to clarify the risk of bias, especially for blinding and allocation concealment ($\geq$ 30% of trials). 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** Single dose primaquine at 0.2 to 0.25 mg/kg compared to no primaquine, with artemisinin partner, for reducing *P. falciparum* transmission; **Summary of findings 2** Single dose primaquine at 0.4 to 0.5 mg/kg compared to no primaquine, with artemisinin partner, for reducing *P. falciparum* transmission; **Summary of findings 3** Single dose primaquine at 0.75 mg/kg compared to no primaquine, with artemisinin partner, for reducing *P. falciparum* transmission; **Summary of findings 4** Single dose primaquine at 0.4 to 0.5 mg/kg compared to no primaquine, with non-artemisinin partner, for reducing *P. falciparum* transmission; **Summary of findings 5** Single dose primaquine at 0.75 mg/kg compared to no primaquine, with non-artemisinin partner, for reducing *P. falciparum* transmission

We subgrouped the data by whether or not the malaria treatment was artemisinin-based, and by the gametocyte detection method. We included only one measure of gametocyte prevalence by PCR data if two different methods of PCR were reported, to avoid duplicate reporting of the same participants (Gonçalves 2016b). Results were stratified by two time points of follow-up, with the exact day depending on what was reported. The goal was reporting at day 4 and 8, but this was varied to day 3 or 5 and day 8 in some trials. Results at these time points were included only if they were after the administration of PQ. For day 3 outcomes, we excluded Sutanto 2013 since PQ was given on that day. 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).

Where reported, summary estimates of effects on gametocyte clear-

ance time over the whole period of follow-up are reported.
The day on which PQ was given varied, and is presented for each trial in Table 1 and in the footnotes to each analysis.
Results on infections acquired by mosquitoes are reported in tables only because we were not able to account for the bias due to varying numbers of mosquitoes dissected per individual.

1. PQ as part of artemisinin-based treatment regimens

Follow-up at day 3 or 4

Infectiousness of people to mosquitoes

Four trials assessed proportion of participants infectious to mosquitoes on day 3 or 4 after first treatment on day 1. Results were stratified by dose. Only one trial out of three in the low dose (0.2 to 0.25 mg/kg) group had any events (infectious people) at day 3-4 (Analysis 1.1). The proportion of people infectious to mosquitoes was reduced by 88% (95% CI 12% to 98%, 105 participants). In the moderate dose group, again only one trial had any events. The proportion of people infectious was reduced by 87% (95% CI 6% to 98%, 129 participants). At the high dose of 0.75 mg/kg (one trial), the reduction in one trial was 80% but the 95% CI was very wide and overlapped 100% (2% to 168%, 51 participants).

Infections acquired by mosquitoes

Results were also expressed as the proportion of mosquitoes infected. At baseline, before treatment with the low dose, the groups were not well matched in one trial (Dicko 2016), with 29% more mosquitoes infected in the PQ group (Table 2). With the low dose and the moderate dose, on day 3 or 4, there was a slight decrease in the proportion of mosquitoes infected (Table 3) with data available for only one trial out of three in each of the low- and moderate-dose groups. In the 0.75 mg/kg dose group, the one trial showed a slight increase in percentage of mosquitoes infected in the group without PQ.

Gametocyte prevalence by PCR

At day 3 or 4 after treatment, there was no effect at any dose on the proportion of persons with gametocytes detected by PCR (Analysis 1.2). The risk ratios (RRs) (fixed effect) were 1.02 (95% CI 0.87 to 1.21; 3 trials, 414 participants) for low dose; 1.09 (95% CI 0.93 to 1.28; 3 trials, 418 participants) for moderate dose, and 0.92 (95% CI 0.75 to 1.13; 3 trials, 394 participants) for high dose.

Gametocyte prevalence by microscopy

At day 3 or 4 after treatment, there was no reduction in proportion of persons with gametocytes detected by microscopy for the low and moderate doses (Analysis 1.3). The RRs were 0.73 (95% CI 0.21 to 2.50; 3 trials, 490 participants) for low dose, and 0.86 (95% CI 0.33 to 2.25; 2 trials, 225 participants) for moderate dose. Due to heterogeneity, a random effects RR was estimated. At the high dose, reduction of 58% was observed (RR 0.42, 95% CI 0.20 to 0.85; 3 trials, 248 participants).

Follow-up at day 8

Infectiousness of people to mosquitoes

Four trials assessed proportion of participants infectious on day 8 after first treatment on day 1. Results were stratified by dose. Three trials out of four using a low dose had events (infectious people) at day 8 (Analysis 1.4). The proportion of people infectious to mosquitoes was not significantly reduced at this time point (RR 0.34, 95% CI 0.07 to 1.58; 4 trials, 243 participants). In the moderate dose group, three of the four trials had any events. The reduction in proportion of people infectious was similar to the low dose group (RR 0.33, 0.07 to 1.57; 4 trials, 246 participants). At the high 0.75 mg/kg dose there were two trials, both with infectious events in the non-PQ group (RR 0.18, 95% CI 0.02 to 1.41; 2 trials, 181 participants). Thus the reduction in infectiousness was large but the 95% CI was very wide and overlapped one.

Infections acquired by mosquitoes

With the low and moderate dose, data on the proportion of mosquitoes infected were available for three out of four trials in each dose group (Table 4). One trial of the four in the low dose group had 29% more mosquitoes infected in the PQ than the non-PQ group (arising from one infectious individual). Otherwise, there was very little difference between PQ and no-PQ groups in the proportion of mosquitoes infected at day 8 in either the moderate dose group (four trials) or the high dose group (two trials).

Gametocyte prevalence by PCR

At day 8 after first treatment, reductions were observed in the proportion of persons with gametocytes detected by PCR (Analysis 1.5). The RRs (fixed effects) were 0.52 (95% CI 0.41 to 0.65; 4 trials, 532 participants) for low dose; 0.37 (95% CI 0.28 to 0.48; 4 trials, 758 participants) for moderate dose, and 0.31 (0.23 to 0.43; 5 trials, 793 participants) for high dose.

Gametocyte prevalence by microscopy

At day 8 after treatment, there was also a reduction in the proportion of people with gametocytes detected by microscopy for all dose groups (Analysis 1.6). The RRs (fixed effects) were 0.35 (95% CI 0.16 to 0.78; 3 trials, 491 participants) for low dose; 0.25 (95% CI 0.08 to 0.75; 2 trials, 225 participants for moderate dose, and 0.27 (95% CI 0.19 to 0.37; 6 trials (10 arms), 1433 participants) for high dose. There was moderate heterogeneity at the high dose, but not at low and moderate doses.

Additional summary measures of gametocyte persistence

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

Seven trial authors presented gametocyte clearance time (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 gametocyte carriage adjusting for intermittent periods of time without gametocytes.

Using microscopy, at low dose, Tine 2017 reported that duration of gametocyte carriage was reduced from average of 1.08 days in the ACT only group to 0.29 days in the ACT plus PQ group. In Lin 2017 (high dose), median time to clearance was reduced from 12 days in non PQ group to 1 day in the PQ group.

At low and moderate doses, Gonçalves 2016b showed that mean gametocyte clearance time (by PCR) was reduced on average by 12 days (95% CI −12.83 to −11.17) in the low dose group and by 11.5 days (−12.33 to -10.67) in the moderate dose group (Analysis 1.7).

In Eziefula 2013, also by PCR, the gametocyte clearance time was not significantly longer in 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).

Two other trials reported results for the 0.75 mg/kg dose. Gametocyte clearance time in days was presented in Shekalaghe 2007 and was significantly shorter (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). Smithuis 2010, using microscopy, also reported significantly shorter 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 (five different ACTs or formulations were tested). Although the duration of gametocyte carriage (without PQ) was significantly longer for AS+AQ, AL and DHAP than for AS+MQ, there was no 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 to 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 Shekalaghe 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 placebo group (1.97 days, 95% CI 1.64 to 2.31). than in the other two groups (0.95 and 0.98 days in the 0.4 and 0.75 mg/kg groups respectively). 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 0.75 mg/kg PQ (P < 0.001).

Area under curve of gametocyte density over time

Area under curve combines measures of density over time. Trials varied in the follow-up time completed. Using microscopy, Tine 2017 observed reduction of AUC (follow-up to day 29) from 106.7 in the ACT+PQ group to 29.5 in the ACT only group.

Gametocyte density by PCR over time was reported in four trials. For low and moderate dose, Gonçalves 2016b reported a reduction of the mean AUC (up to day 15) of −9.20 (−10.79 to −7.61) for low dose and −9.10 (−10.50 to −7.70) for moderate dose (Analysis 1.8). Eziefula 2013 also used a duration of 15 days to estimate AUC using PCR and found that the log(10)AUC in each 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, 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 0.75 mg/kg PQ than the non-PQ group, for days when gametocytes were detected (with PQ: 5.8, IQR 0.8 to 55.1; without PQ: 15.8, IQR 4.1 to 85.8). 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 0.75 mg/kg 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).

Haemolytic adverse effects

Severe haemolysis

At the low dose, four trials evaluated severe haemolysis defined as drop of ≥ 25% (Dicko 2016; Mwaiswelo 2016), or ≥ 2 g in haemoglobin (Gonçalves 2016b; Tine 2017) over the course of follow-up; only three of these trials had such events (Analysis 1.9). The results given for Gonçalves 2016b included combined data from Gonçalves 2016a as they were not reported separately. Dicko 2016 and Gonçalves 2016b excluded G6PD deficient individuals identified by fluorescent spot test (FST) or the rapid test; Mwaiswelo 2016 and Tine 2017 screened participants but did not exclude those with G6PD deficiency. Severe haemolysis as defined above was no different in frequency between the PQ group (12.3% of 381 participants) than the control group (13.2% of 371 participants).

Mwaiswelo 2016 (low dose) also reported an outcome of "acute haemolytic anaemia", experienced by 2.8% of participants in both PQ and control groups (109 participants and 108 participants respectively).

Severe haemolysis was reported for the moderate dose for two trials (Dicko 2016; Gonçalves 2016b), of which only the latter had any events (Analysis 1.9) . No difference was observed in the proportion of participants with this outcome between the PQ group (3.7% of 136 participants) and the control group (2.4% of 124 participants).

At high dose, Smithuis 2010 stated that there were no cases of severe anaemia (< 5 g/dL) or blackwater fever in any ACT or control group. 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.

Other measures of anaemia or haemoglobin

Measures of haemoglobin or PCV at day 8

No trials at low or moderate dose reported these outcomes. At high dose Shekalaghe 2007 and Sutanto 2013 found no difference between groups in mean haemoglobin at day 8. Also using high dose, El-Sayed 2007 showed that there was no difference in PCV between groups at day 8: 34.2% (15% to 44%) versus 36.2% (26% to 42%).

Maximum change in haemoglobin concentration

The maximum change in haemoglobin concentration (over all days of follow-up) was measured in three trials, two of which reported results separately by G6PD status (Eziefula 2013; Mwaiswelo 2016), while the other did not (Okebe 2016). In general, change in haemoglobin was less in the control than PQ groups (Analysis 1.10), but results were heterogenous especially at the low dose where the mean difference was 0.13 (−0.07 to 0.33) g of haemoglobin (random-effects model). The change in haemoglobin by day 8 (rather than any day) was reported in Tine 2017 and is included in Analysis 1.10. In the moderate and high dose groups, the mean difference was 0.18 (−0.08 to 0.44) and 0.05 (−0.04 to 0.14), respectively.

Percentage change in haemoglobin by day 8

Using percentage change by day 8 (rather than absolute haemoglobin concentration at that time), the low, moderate, and high dose PQ groups were not different from the control groups (Analysis 1.11), but heterogeneity was high, especially at low dose. Some trials reported this outcome separately by G6PD status, and if so, the results were presented separately (see footnotes).

Maximum percent change in haemoglobin

The maximum percent decrease in haemoglobin (by any day of follow-up) was also reported in three trials, one in each dose category (Analysis 1.12). In low and moderate dose, the maximum percent decrease was larger in the PQ group than control, but the opposite was seen for high dose.

Haemoglobinuria or dark urine

The presence of haemoglobinuria/dark urine was reported by Dicko 2016 (low and moderate dose, but with no events in the latter), Mwaiswelo 2016 (low dose), and Tine 2017 (low dose) and is shown in Analysis 1.13. These adverse effects were more than three times more likely in the PQ group (RR 3.40, 95% CI 2.15 to 5.38; 3 trials (4 arms), 527 participants) than the control group.

Other adverse effects

These outcomes were not classified by dose. Frequencies of headache, fatigue, nausea, vomiting, abdominal pain, diarrhoea, pruritis, paraesthesia, fever, cough, runny nose, muscle ache/pain, dizziness, upper respiratory infections, back pain, burning or pain with urination, bronchitis, rhinitis/rhino bronchitis, shortness of breath, whitlow, leg osteoarthritis, malaria, otitis, epistaxis, dental pain, high transaminase, palpebral inflammation, foot trauma or inflammation, skin infection or rash, pallor, pneumonia, meningitis, blurred vision, cold sore, weakness/asthenia, palpitations, cyanosis, insomnia, or unspecified other event were not increased in the PQ groups (Analysis 1.14; Analysis 1.15; Analysis 1.16; Analysis 1.17; Analysis 1.18) as reported in Wang 2006; Smithuis 2010; Dicko 2016; Gonçalves 2016a; Gonçalves 2016b; Mwaiswelo 2016; Okebe 2016; and Tine 2017, with one to 11

trial arms per event type reported. Small differences in frequencies between PQ and control groups are noted for anorexia (increased in PQ group) and wound/trauma (decreased in PQ group).

2. Comparison of low and moderate doses (artemisinin partner only)

Given the importance of confirming effectiveness of the low dose, and that fact that four trials included groups randomized to low and moderate doses, we compared these two doses directly.

Follow-up at day 3 or 4

Infectiousness of people to mosquitoes

Only one of three trials had any infectious events: one infectious person in each of the PQ and non-PQ groups, total 116 participants (Analysis 2.1). The RR was 0.93 (95% CI 0.06 to 13.54; 3 trials, 116 participants).

Gametocyte prevalence by PCR

Comparing the low and moderate groups, there was no difference in the proportion of participants with gametocytes by PCR (RR 0.93, 95% CI 0.80 to 1.09; 3 trials, 424 participants (Analysis 2.2).

Gametocyte prevalence by microscopy

In two trials (both in same location) that reported this outcome, there was also no difference in the proportion of participants with gametocytes detected by microscopy (RR 1.23, 95% CI 0.68 to 2.20; 2 trials, 231 participants; Analysis 2.3).

Follow-up at day 8

Infectiousness of people to mosquitoes

In four trials, two of which had infectious events, there was no evidence of any difference in effect on proportion of participants infectious between low and moderate doses (RR 0.95, 95% CI 0.14 to 6.48; 4 trials, 237 participants; Analysis 2.4).

Gametocyte prevalence by PCR

There were four trials reporting gametocyte prevalence by PCR at day 8. The evidence suggested the effect tended to be greater at moderate than low dose (RR 1.33, 95% CI 0.97 to 1.82; 4 trials, 559 participants; Analysis 2.5).

Gametocyte prevalence by microscopy

Two trials, both in the same site, showed the same trend as for PCR but no greater effect of moderate dose at day 8 (RR 1.80, 95% CI 0.51 to 6.38; 2 trials, 235 participants; Analysis 2.6).

3. PQ as part of non-artemisinin-based treatment regimens

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.

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 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 included only individuals with G6PD deficiency.

Follow-up at day 5

Infectiousness of people to mosquitoes

No trials tested the low or moderate dose for effect on infectiousness with non-artemisinin partners.

Using high dose, 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. The proportion of people infectious was reduced to 0% in the PQ group when measured on day 5, compared to 66.7% in the control group (RR 0.09 (95% CI 0.01 to 0.62; 2 trials, 30 participants; Analysis 3.1).

Infections acquired by mosquitoes

Chen 1994 reported the number of mosquitoes infected after feeding on trial participants. 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,

Gametocyte prevalence by PCR

No trials with non-artemisinin partners assessed gametocyte prevalence by PCR.

Gametocyte prevalence by microscopy

Two trials each at the moderate and high doses showed no difference in the gametocyte prevalence at day 4-5 (Analysis 3.2); RR 0.83 (95% CI 0.62 to 0.13; one trial (two arms), 221 participants) for moderate dose and RR 0.85 (95% CI 0.48 to 1.50; 2 trials, 52 participants) for the high dose.

Follow-up at day 8

Infectiousness of people to mosquitoes

The two Chinese trials with MQ partner using high dose showed a similar effect at day 8 as at day 5 above: the proportion of infectious people was 93% in control group and 0% in the PQ group. (Analysis 3.3). RR 0.07 (95% CI 0.01 to 0.45; 2 trials, 30 participants).

Infections acquired by mosquitoes

Chen 1994 reported the number of mosquitoes infected after feeding on trial participants. None of the mosquitoes feeding on people receiving PQ were infected, with 54% infected at day 8 after feeding on the group not receiving PQ.

Gametocyte prevalence by PCR

No trials with non-artemisinin partners assessed gametocyte prevalence by PCR.

Gametocyte prevalence by microscopy

At day 8 one trial (two arms) reported gametocyte prevalence at moderate dose (reduction of 40%); RR 0.60 (95% CI 0.49 to 0.75; 216 participants) and four trials (five arms) at the high dose (reduction of 61%) (RR 0.39, 95% CI 0.25 to 0.62; 4 trials, 186 participants; Analysis 3.4).

Additional summary measures of gametocyte persistence

Gametocyte clearance time or duration of gametocyte carriage (the average number of days each person has gametocytes)

The median gametocyte clearance time was reduced in Pukrittayakamee 2004 (two comparisons; partner QN) from 48 (range: six to 324) hours with low dose PQ, and from 216 (range: six to 624) hours with quinine only to 87 (range: five to 207 hours) hours with moderate dose PQ. There was no difference between the median clearance time in the two PQ arms (P = 0.45).
Using high dose, 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 3.5).

Adverse events

The trials with non-artemisinin partner 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 using high dose found no difference in frequency of reported adverse effects (nausea, vomiting or dizziness) over 28 days follow-up (Analysis 3.6).

4. Comparison of different 8AQ

Follow-up at day 8

Two small trials compared the effect of bulaquine and PQ (0.75 mg/kg) 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; 2 trials, 112 participants; Analysis 4.1). Neither trial concealed allocation.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Moderate-dose primaquine (PQ) given with artemisinin combination treatment
Participants or population: adults and children with malaria being treated with artemisinin combination treatment
Settings: Mali, Burkina Faso, The Gambia, Uganda
Intervention: single dose PQ 0.4 to 0.5 mg/kg
Comparison: no PQ

Outcomes	Number of participants (trials)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		Certainty of the evidence (GRADE)	Comments
			Risk with no PQ, with artemisinin partner,	Risk with single dose PQ at 0.4 to 0.5 mg/kg		
Participants infectious at day 3-4	109 (3 RCTs)	RR 0.13 (0.02 to 0.94)	14 per 100	2 per 100 (0 to 13)	⊕⊕◯◯ LOW[1] Due to imprecision	Medium dose PQ may reduce infectiousness
Participants infectious at day 8	246 (4 RCTs)	RR 0.33 (0.07 to 1.57)	4 per 100	1 per 100 (0 to 6)	⊕⊕◯◯ LOW[1] Due to imprecision	Medium dose PQ may reduce infectiousness
Participants with gametocytes at day 3-4, by PCR	418 (3 RCTs)	RR 1.09 (0.93 to 1.28)	52 per 100	57 per 100 (48 to 67)	⊕⊕⊕◯ MODERATE[2] Due to imprecision	Medium dose PQ probably has little or no effect on gametocytes detected by PCR on day 3 to 4
Participants with gametocytes at day 8, by PCR	758 (5 RCTs)	RR 0.37 (0.29 to 0.48)	43 per 100	16 per 100 (13 to 21)	⊕⊕⊕⊕ HIGH	Medium dose PQ reduces gametocytes detected by PCR on day 8
Participants with severe haemolysis	260 (2 RCTs)	RR 1.54 (0.38 to 6.30)	2 per 100	4 per 100 (1 to 15)	⊕⊕◯◯ LOW[3] Due to imprecision	Medium dose PQ may increase severe haemolysis

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Abbreviations: CI: confidence interval; **PCR:** polymerase chain reaction; **RCT:** randomised controlled trial; **RR:** risk ratio; **OR:** odds ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Downgraded by 2 for imprecision: the CIs are wide; in addition, there is a large effect combined with a low number of events, which creates further uncertainty around the point estimate.

[2]Downgraded by 1 for imprecision: the CIs are wide.

[3]Downgraded by 2 for imprecision: the CIs are very wide.

High-dose primaquine (PQ) given with artemisinin combination treatment
Participants or population: adults and children with malaria being treated with artemisinin combination treatment
Settings: Cambodia, Mali, Burkina Faso, The Gambia, Tanzania, Sudan, Uganda
Intervention: single dose PQ 0.75 mg/kg
Comparison: no PQ

Outcomes	Number of participants (trials)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		Certainty of the evidence (GRADE)	Comments
			Risk with no PQ, with artemisinin partner	Risk with single dose PQ at 0.75mg/kg		
Participants infectious at day 3-4	101 (1 RCT)	RR 0.20 (0.02 to 1.68)	10 per 100	2 per 100 (0 to 16)	⊕⊕◯◯ LOW[1,2] Due to imprecision	We do not know if high dose PQ may reduce infectiousness
Participants infectious at day 8	181 (2 RCTs)	RR 0.18 (0.02 to 1.41)	5 per 100	1 per 100 (0 to 8)	⊕⊕◯◯ LOW[1] Due to imprecision	High dose PQ may reduce infectiousness
Participants with gametocytes at day 3-4, by PCR	290 (2 RCTs)	RR 0.92 (0.75 to 1.13)	38 per 100	35 per 100 (29 to 43)	⊕⊕◯◯ LOW[3,4] Due to indirectness and imprecision	High dose PQ may have little or no effect on gametocytes detected by PCR
Participants with gametocytes at day 8, by PCR	793 (5 RCTs)	RR 0.31 (0.23 to 0.43)	36 per 100	11 per 100 (8 to 16)	⊕⊕⊕⊕ HIGH	High dose PQ reduces gametocytes detected by PCR
Participants with severe haemolysis	106 (1 RCT)	No estimate	Not estimable	Not estimable	No data	We don't know if high dose PQ impacts on haemolysis

*__The risk in the intervention group__ (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).
Abbreviations: CI: confidence interval; **PCR**: polymerase chain reaction; **RCT**: randomised controlled trial; **RR:** risk ratio; **OR:** odds ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Downgraded by 2 for imprecision: the CIs are wide; in addition, there is a large effect combined with a low number of events, which creates further uncertainty around the point estimate. In addition, in this one trial baseline.
[2]Baseline values for this outcome were unbalanced, but the downgrading by 2 for imprecision takes this in to account, as it could be a chance finding.
[3]Downgraded by 1 for indirectness: all the data for the results come from one trial.
[4]Downgraded by 1 for imprecision: the CIs are wide.

Moderate-dose primaquine (PQ) given with non-artemisinin treatment
Participants or population: adults and children with malaria being treated with non-artemisinin treatment
Settings: Pakistan
Intervention: single dose PQ 0.4 to 0.5 mg/kg
Comparison: no PQ

Outcomes	Number of participants (trials)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		Certainty of the evidence (GRADE)	Comments
			Risk with no PQ, with non-artemisinin partner	Risk with single dose PQ at 0.4 to 0.5 mg/kg		
Participants with gametocytes at day 4-5, by microscopy	221 (2 RCTs)	RR 0.83 (0.62 to 1.13)	48 per 100	40 per 100 (30 to 54)	⊕⊕⊕◯ MODERATE [1] Due to indirectness	Medium dose PQ probably reduces gametocytes detected by microscopy
Participants with gametocytes at day 8, by microscopy	216 (2 RCTs)	RR 0.60 (0.49 to 0.75)	81 per 100	49 per 100 (40 to 61)	⊕⊕⊕◯ MODERATE [1] Due to indirectness	Medium dose PQ probably reduces gametocytes detected by microscopy

***The risk in the intervention group** (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).
Abbreviations: CI: confidence interval; **RCT**: randomised controlled trial; **RR:** risk ratio; **OR:** odds ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Downgraded by 1 for indirectness: all the results are from one setting.

Medium-dose primaquine (PQ) given with non-artemisinin treatment
Participants or population: adults and children with malaria being treated with non-artemisinin treatment
Settings: China, Colombia, India, Indonesia
Intervention: single dose PQ 0.75 mg/kg
Comparison: no PQ

Outcomes	Number of participants (trials)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		Certainty of the evidence (GRADE)	Comments
			Risk with no PQ, with non-artemisinin partner	Risk with single dose PQ at 0.75 mg/kg		
Participants infectious at day 5	30 (2 RCTs)	RR 0.09 (0.01 to 0.62)	67 per 100	6 per 100 (1 to 41)	⊕◯◯◯ VERY LOW[1,2] Due to risk of bias and imprecision	We are uncertain whether high dose PQ reduces infectiousness
Participants infectious at day 8	30 (2 RCTs)	RR 0.07 (0.01 to 0.45)	93 per 100	7 per 100 (1 to 42)	⊕◯◯◯ VERY LOW[1,2] Due to risk of bias and imprecision	We are uncertain whether high dose PQ reduces infectiousness
Participants with gametocytes at day 5, by microscopy	52 (2 RCTs)	RR 0.85 (0.48 to 1.50)	50 per 100	43 per 100 (24 to 75)	⊕⊕◯◯ LOW[3,4] Due to risk of bias and imprecision	High dose PQ may reduce gametocytes detected by microscopy
Participants with gametocytes at day 8, by microscopy	186 (4 RCTs)	RR 0.39 (0.25 to 0.62)	48 per 100	19 per 100 (12 to 29)	⊕⊕⊕◯ MODERATE[5] Due to risk of bias	High dose PQ probably reduces gametocytes detected by microscopy

*__The risk in the intervention group__ (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).
Abbreviations: CI: confidence interval; **RCT**: randomised controlled trial; **RR:** risk ratio; **OR:** odds ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Downgraded by 1 for risk of bias: unclear risk of bias in several domains from both studies.
[2]Downgraded by 2 for imprecision: the CIs are wide; in addition, there is a large effect combined with a low number of events, which creates further uncertainty around the point estimate.
[3]Downgraded by 1 for risk of bias: Arango 2012 had serious risk for selection bias and Chen 1993a had unclear risk of bias in several domains.
[4]Downgraded by 1 for imprecision: the CIs are wide.
[5]Downgraded by 1 for risk of bias: Arango 2012 had serious risk for selection bias and Chen 1993a had unclear risk of bias in several domains. Kamtekar 2004 had serious risk of bias for several domains.

DISCUSSION

Summary of main results

We included 24 RCTs and one quasi-RCT. Sixteen trials included study arms with artemisinin-based treatments, 11 trials included study arms with non-artemisinin-based treatments, and two trials included both types of partner arms. Fifteen trials tested for G6PD status: ten then excluded participants with G6PD deficiency, one included only those with G6PD deficiency, and four 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). No trials evaluated community effects on malaria transmission.

With artemisinin combination treatment

See Summary of findings for the main comparison, Summary of findings 2 and Summary of findings 3 for low, moderate, and high dose with artemisinin partner drugs, respectively.

Low-dose PQ

Infectiousness to mosquitoes was reduced (*low certainty evidence*). For gametocytes detected by PCR, there was little or no effect of PQ at day 3 or 4 (*moderate certainty evidence*) with clear reduction at day 8 (*high certainty evidence*). Low-dose PQ probably has little or no effect on severe haemolysis (*moderate certainty evidence*).

Moderate-dose PQ

Infectiousness to mosquitoes was reduced (*low certainty evidence*). The pattern and level of certainty of evidence with gametocytes detected by PCR was the same as low dose (moderate and high at days 3 or 4 and 8 respectively, and severe haemolysis was infrequent in both groups (*low certainty evidence*).

High dose PQ

Infectiousness to mosquitoes was reduced (*low certainty evidence*). The effects on gametocyte prevalence showed a similar pattern to moderate and low dose PQ (low and high certainty at days 3 or 4 and 8 respectively). Evidence of haemolysis was not systematically sought in this dose group.

With non-artemisinin treatment

See Summary of findings 4 and Summary of findings 5 for moderate and high dose with non-artemisinin partner drugs respectively. Trials have been conducted only in the moderate- and high-dose PQ categories. Two small trials from the same laboratory in China evaluated infectiousness to mosquitoes with high dose PQ, reporting that infectiousness was reduced markedly on day 5 and on day 8 (*very low certainty evidence*).

Reduction in gametocytes, detected in this case by microscopy, showed similar patterns to the artemisinin-based treatments. For moderate dose, there was little or no effect at day 4 or 5 (*moderate certainty evidence*), and larger effect by day 8 (*moderate certainty evidence*). At high dose, findings were similar but certainly of evidence was low at day 4 to 5. No trials with non-artemisinin partners systematically sought evidence of severe haemolysis.

Two small trials comparing bulaquine with PQ suggest bulaquine may have larger effects on gametocytes (by microscopy) on day 8.

Overall completeness and applicability of evidence

What is known

This review update adds recently available evidence on infectiousness of people with falciparum malaria treated with low and moderate PQ doses in addition to primary treatment. It also includes additional evidence on the effect of PQ at different doses on gametocyte prevalence at two time points after treatment. Previously only indirect evidence was available (for example, Bunnag 1980, with no difference in gametocyte outcomes between 15 mg PQ for five days in children, and single doses of 30 mg or 45 mg PQ in adults), in narrative summaries and analyses that have proposed widespread programmatic implementation of PQ (White 2012; White 2013).

Adding PQ at around 0.25 mg/kg to treatment using artemisinin-based combination therapies reduces infectiousness to mosquitoes at day 3 to 5 and at day 8 after treatment. These data come from four trials conducted in Burkina Faso (with AL partner) (Gonçalves 2016a; Gonçalves 2016b) Gambia (DHAP) (Okebe 2016), and Mali (DHAP) (Dicko 2016). One other trial using high dose also reported on infectiousness in Cambodia with DHAP partner (Lin 2017). Two of these trials included only gametocyte carriers at screening (Dicko 2016; Gonçalves 2016b). Due to relatively low proportion of infectious individuals among treated malaria patients (even those with gametocytes), the absolute reduction in proportion of people infectious is not large. The absolute reduction in proportion of mosquitoes infected was also low. The effect on infectiousness was more marked at day 3 or 4 than day 8, which reflects the declining infectiousness in the non-PQ control groups by this time. Unlike the pattern seen in reducing infectiousness, there was little reduction by PQ with artemisinin partners in gametocyte prevalence at day 3 or 4 with the low or moderate dose. By day 8, large effects of PQ on gametocyte prevalence were seen. Reductions in gametocyte clearance time were also dramatic. The results come from trials in different epidemiological settings and with a variety of artemisinin-based treatments (Burkina Faso: AL (Gonçalves 2016a; Gonçalves 2016b); Cambodia: DHAP (Lin 2017); Colombia: AS+MQ (Vásquez 2009; Arango 2012); Gambia: DHAP (Okebe 2016); Senegal: DHAP,

AL, and ASAQ (Tine 2017); Indonesia: DHAP (Sutanto 2013); Mali: DHAP (Dicko 2016); Myanmar: AS+MQ, DHAP, AL and ASAQ (Smithuis 2010); Sudan: AS+SP (El-Sayed 2007); Tanzania: AS+SP (Shekalaghe 2007); Thailand: AS (Pukrittayakamee 2004); and Uganda: AL (Eziefula 2013)).

In terms of safety, adverse effects of PQ in people with G6PD deficiency are less common with lower doses of PQ (Olalekan 2017), although direct comparisons are few and sample sizes small. Most trials included in this review excluded individuals with G6PD deficiency, but some included them, did not test for it or did not state whether they tested; thus some trials included some G6PD deficient participants. However, few severe haematological effects were reported (Shekalaghe 2007; Dicko 2016; Gonçalves 2016b; Mwaiswelo 2016; Tine 2017).

What is unknown

While reducing infectiousness to mosquitoes and the duration and density of gametocytaemia can be assumed to reduce transmission to mosquitoes at the level of the individual, it remains unclear whether it will impact materially on community level transmission, as reliable trials have never evaluated this. We excluded from this review several older trials, which are often cited as proof of an effect on community transmission, because either: i) they lacked an adequate control group with partner drug but without PQ (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) they administered PQ alongside vector control co-interventions, which may equally be responsible for any effect seen (Hii 1987; Kaneko 2000); or iv) they administered PQ or 8AQ alone and not alongside treatment regimens (which is the policy currently recommended) (Barber 1932).

Many gametocyte carriers are asymptomatic and unlikely to seek treatment, at least in areas of moderate to high transmission where most adults have a level of acquired immunity that reduces the probability that parasitaemia will cause clinical symptoms. Therefore, since a minority of infected persons seek treatment, it is unclear whether a policy of adding PQ to malaria treatment regimens will reduce malaria transmission at a community level. Johnston 2014 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. Johnston and colleagues 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".

The relative contribution of symptomatic and asymptomatic gametocyte carriers to the infectious reservoir in the population, as well of the relative infectiousness of gametocytes detected by microscopy and PCR, are areas of active research (Stone 2015). The proportion of asymptomatic carriers varies according to the level of transmission, with low density infections comprising a large proportion of infections in low transmission areas (Gerardin 2015a). If most infectious individuals are not among the care-seeking population, they can only be reached by proactive strategies such as 'mass screen and treat' or mass treatment programmes.

Mass treatment programmes (where everyone in the community is treated at specified intervals until transmission is stopped) are a potential strategy to reach 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 additional effects of adding PQ (interrupting transmission more quickly, or at a lower coverage levels) have not been demonstrated (Poirot 2013). Gerardin 2015b modelled the impact of adding PQ to either AL or DHAP in mass treatment programs. and concluded that it would be most effective in combination with a long acting partner such as DHAP and where most of the population is protected against reinfection; otherwise, if transmission is high, the effect of adding PQ would be 'negligible'. A similar conclusion was reached by the WHO Malaria Policy Advisory Committee (MPAC) through consensus modelling (WHO 2015c).

Infectiousness of a population to mosquitoes comprises two elements: the proportion of people who are infectious, and the proportion of mosquitoes infected after feeding on an infectious person. The two factors can be multiplied together to arrive at a combined 'mosquito infection probability' (Graves 1990; Stone 2015), representing the likelihood of a mosquito acquiring infection after feeding on a member of the population. Considering only reduction in the proportion of infectious individuals may underestimate the impact of PQ, although evidence from the trials included here does not suggest large reduction in the proportion of mosquitoes infected by persons remaining infectious after treatment (Table 2; Table 3; Table 4). Larger sample sizes of infectious people are required.

The relative effect of PQ on infectiousness when added to different artemisinin drugs is not well understood and needs to be empirically studied further, since it known that there is variation between them in gametocytocidal activity (WWARN 2016). Two studies included here compared multiple ACTs (AL, AS+MQ, ASAQ, and DHAP) (Smithuis 2010; Tine 2017), but no infectiousness data were included.

The ability to metabolize PQ to active ingredients (dependent on human cytochrome P-450 enzyme (CYP2D6)) may also affect its impact, since alleles conferring low and intermediate metabolizer phenotypes are unable to reap the benefits of PQ (Bennett 2013; Meltzer 2014). In this review, Eziefula 2013 reported on the CYP2D6 phenotypes of participants. Since this may be a factor in heterogeneity of effects observed, further study of geographical distribution of these variant phenotypes affecting ability to utilize PQ is needed to determine their impact on the effectiveness of PQ on gametocytes and for reducing transmission.

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.

Quality of the evidence

In our hierarchy of study types, the strongest, most direct evidence for an effect of PQ on falciparum malaria transmission would come from trials that randomize entire communities to treatment with and without PQ and then monitor malaria prevalence over a period of years. No such trials-at any dose or with any partner drug-met the inclusion criteria. The evidence is, therefore, all indirect, requiring some untested assumptions in evaluating an effect of single dose PQ on malaria transmission.

The evidence is also predominantly for higher PQ doses than the 0.25 mg/kg currently recommended by the WHO. Out of 40 total trial arms that met the inclusion criteria and reported gametocyte outcomes, only five used a low dose (0.20 to 0.25 mg/kg). The remaining arms provide evidence, but the exact dose-response relationship that would apply to single dose PQ is not known, so again, some assumptions are needed to evaluate the relevance of this information.

Second in our evidence hierarchy were trials of the infectiousness of treated individuals to mosquitoes, of which there were four at the low dose of PQ. However, all four trials did not report all key data. Summing up, the infectiousness results for the low dose are based mainly on the results from only one trial (Dicko 2016), which observed one versus seven infectious events at day 3, and 0 versus 3 events at day 8 in the PQ and non-PQ groups respectively. Thus, despite the inclusion of several new trials with infectiousness data in this update, the evidence for reduction is inconsistent and based on a very small number of trials and events. The three infectiousness trials at higher PQ doses reported significant declines, but once again, the relevance to lower doses is uncertain.

Most of the included trials were on the next rung of the hierarchy: the effect of PQ on circulating gametocytes in people treated with and without PQ (potential infectiousness). The included trial arms span decades of research, including many conducted before the artemisinin era. Out of 40 arms, 16 were with non-artemisinin partners (which also used higher PQ doses). Artemisinin drugs themselves have some impact on gametocytes, so how well the earlier evidence reflects the impact of an artemisinin derivative plus PQ is also unknown. Nonetheless, results of these trials were generally consistent. Differences in gametocyte detection method (microscopy or PCR) made synthesis somewhat difficult, but potential infectiousness is the most convincing and robust evidence for a possible effect on transmission, under the right conditions.

The included trials do not provide sufficient evidence to evaluate the safety of this intervention. Many trials did not test for G6PD deficiency, and of those that did, most excluded deficient individuals. The trials were, by and large, not designed for safety evaluations.

Overall, the evidence of efficacy is limited in both quality and quantity, and it is all indirect, to varying degrees.

Potential biases in the review process

We have identified three potential biases or deficiencies in the search and review processes.

First, three trials could not be located. Two were earlier trials (publication dates 1993 and 2006) in Chinese; one was a conference abstract from 2009. Second, we restricted follow-up only to day 8 because most persons were non-infectious by then. Third, we stratified by artemisinin/non-artemisinin drugs, since the former are the recommended treatments in the majority of malaria-endemic areas. We believe these decisions should have no material impact on the results, but could be challenged.

Agreements and disagreements with other studies or reviews

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. 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).

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, it appears that the effect on infectiousness and gametocytes is preserved at lower doses of 0.2 to 0.25 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, sources of data and comparisons are not clearly specified, but the authors argue this provides evidence that PQ decreases infectivity much faster than the effect on gametocytes would suggest. The current review supports this view that the effect of PQ on infectiousness appears earlier (day 3-5) than the effect on gametocyte presence, at least for artemisinin partners. However the effect on infectiousness wanes by day 8 due to declining infectiousness in both PQ and control groups.

Also in the *Malaria Journal*, White 2014 urged stratification of trials by dose, which has now been further accomplished with the newly included trials at lower doses. The overall conclusion of White 2014 endorses the conclusions of all earlier editions of this Cochrane Review: there is a need for more mosquito-feeding studies for "the assessment of transmission-blocking, dose-response relationships". This updated review now includes several trials that report reduction in infectiousness soon after treatment, and hence improve on earlier recommendations based only on indirect measures. However, although there were five new trials aiming to study infectiousness included here, all trials except two had no or very few infection events. Overall infectiousness of patients attending for malaria treatment is very low and wanes quickly, despite a large proportion having PCR detectable gametocytes.

In relation to current WHO guidelines, evidence is available from this systematic review to support the currently recommended 0.25 mg/kg dose as 1) effective in potentially reducing transmission from individuals to mosquitoes and 2) probably safer than higher doses for those without G6PD deficiency and possibly for those with the deficiency. This review of all available evidence sheds minimal light on the question of whether PQ at any dose will materially affect transmission in communities (WHO 2012b; WHO 2015b). The amount of evidence on infectiousness of treated malaria patients to mosquitoes remains low, and evidence of the impact of treating malaria patients on transmission at a community level completely absent.

AUTHORS' CONCLUSIONS

Implications for practice

Current policy recommendations are that 0.25 mg/kg PQ should be added as a single dose to primary treatment for *P. falciparum* malaria in areas of low transmission to reduce infectiousness of treated individuals to mosquitoes, under the assumption that this will contribute to reducing malaria prevalence.

This Cochrane Review of all reliable data supports the idea of reducing infectiousness of people to mosquitoes, but provides very little evidence on the question of whether this reduction is of any material value in reducing community prevalence. It is consistent with the recommendation that PQ not be used in high endemicity areas, where the dilutional effects of a large part of the population carrying asymptomatic infections would likely outweigh a potential benefit. In a low endemicity area, what might be important is whether most people with parasitaemia are likely to be treated. If PQ is used systematically, monitoring malaria prevalence in a well-designed programme might provide useful information on its effectiveness.

If PQ is to be used, then it should be implemented as early as possible during treatment as the effects on infectivity appear to be maximal early in the treatment course.

Risk of harm at the currently recommended dose of 0.25 mg/kg was low in the study participants, relatively few of whom were G6PD-deficient. However, the emphasis in the included trials, hence in this systematic review, is on the efficacy of PQ, and evidence from these sources is insufficient to comment definitively on safety in all affected populations.

Implications for research

The totality of the evidence from the trials included in this review does not provide a clear answer about whether, or under what circumstances, low-dose PQ could materially reduce the community malaria burden. We do not envision direct evidence being generated that will fill this high-level gap; to do so would require many large cluster-randomized trials at different endemicity levels, conducted over many years. A realistic approach would combine evidence from randomized trials and possibly some observational data in robust mathematical models to predict the impact of PQ on malaria transmission at the community level across the range of endemicity levels. This Cochrane Review is the first step toward determining whether the existing information is sufficient to inform modelling studies and, if not, what specific questions must be addressed in further field or laboratory research to generate evidence that can be used for sound future recommendations.

A next step could be the collaborative evaluation of current evidence by recent randomized trialists, mathematical modelers who are working on this question, and others involved with malaria control policy. It would be important to examine key parameter estimates (and the relevant variability in those parameter estimates) in relation to the question of whether low-dose PQ should be implemented in combination with antimalarial treatment of acute episodes of malaria illness and, if yes, when and under what circumstances. A consensus could be reached about whether results from additional trials would provide missing information. This

determination would guide decisions on the need for further trials and if needed, precisely what endpoints should be sought.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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 • Uncomplicated malaria. • *P. falciparum* only. • Not pregnant. • Voluntary consent. Colombia 82 participants, 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 • AQ+SP. • AQ+SP+PQ. • MQ+AS. • 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) All outcomes	Low risk	No evidence of incomplete data.

Arango 2012 (*Continued*)

Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Unclear risk	No information given.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not discussed.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not discussed.

Chen 1993a

Methods	RCT
Participants	18 participants, healthy adults with *P. falciparum* and positive for gametocytes Setting: China
Interventions	A: MQ 750 mg. B: MQ 750 mg + SP (1500 mg/75 mg). C: MQ 750 mg + PQ 45 mg. 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 but no details given in the text
Allocation concealment (selection bias)	Low risk	Supervisor who oversaw patients taking the drug opened a sealed envelope then saying what drug it was
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were followed up.
Selective reporting (reporting bias)	Unclear risk	No information in the text.

Chen 1993a (*Continued*)

Other bias	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated to be double blind in the text.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information in the text.

Chen 1994

Methods	Possibly individually RCT (stated to be randomized but no information given) Dates of trial not reported.
Participants	27 participants 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	• Artemisinin: 1200 mg per day for 5 days (not included in review). • MQ 750 mg single dose day 1 (reported as day 0). • MQ 750 mg single dose + PQ 45 mg single dose day 1 (reported as day 0).
Outcomes	• 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. • Percentage of participants infectious to *An. dirus:* days 5, 8, 15, and 22 (reported as days 4, 7, 14, and 21). • 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 asexual 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.

Chen 1994 (*Continued*)

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.

Dicko 2016

Methods	Individually RCT
Participants	81 men aged 5 to 50 years All gametocyte carriers by microscopy (≥ 32 gametocytes/µL) - at least 2 gametocytes/500 wbcs on thick film Hb ≥ 8 g/dL Normal G6PD by colorimetric classification Oulessbougoue, near MRTC Mali Exclusion criteria • Malaria drugs in last 7 days. • Known allergies to study drugs. • Serious or chronic illness. • Diagnosed cardiac arrhythmias.
Interventions	DHAP daily for 3 days, by weight to closest whole tablet; tablets were 320 mg DHA and 40 mg piperaquine 13 kg to < 24 kg: 1 tablet; 24 kg to < 36 kg: 2 tablets; 36 kg to < 75 kg: 3 tablets; 75 to 100 kg: 4 tablets DHAP plus PQ on day 1 at 0.125 and 0.5 mg/kg in Phase 1 DHAP plus PQ on day 1 at 0.065 and 0.25 mg/kg in Phase 2 PQ dissolved in water and given orally, observed.
Outcomes	People infective to mosquitoes on day 1 (pretreatment), 2, 3, and 8 Mosquitoes infected on day 1 (pretreatment), 2, 3, and 8 by membrane feeding Mean within-person change in mosquito infectivity (in all participants, and only those who were infectious on day 1) Hb on day 1, 2, 3, 4, 8, 15, 29 Mean within-person change in Hb after treatment on day 1, 2, 3, 4, 8, 15, 29 Adverse events (mild, moderate, severe) on day 2, 3, 4, 8, 15, 29 Gametocyte prevalence and density by microscopy day 1 (pretreatment), 2 hours, 6 hours, 12 hours, and days 2, 3, 4, 8, 15, 29

Dicko 2016 (*Continued*)

	Gametocyte prevalence and density by qRT-PCR, same time points CYP2D^ genotype and metabolizers phenotype AUC gametocyte density (qt-PCR) over time to day 29
Notes	Study was halted after 8 participants enrolled in phase 1, due to low infection rate in mosquitoes before treatment. Protocols were optimized and the study restarted 6 months later

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Study was in two phases: phase 1 was RCT (in blocks of 6) and phase 2 was not randomized (alternate allocation?)
Allocation concealment (selection bias)	High risk	Sealed opaque envelopes in phase 1. In phase 2 "participants were enrolled first into 0.25 mg/kg group and then 0.0625 mg/kg group when full"
Incomplete outcome data (attrition bias) All outcomes	Low risk	79/81 (97.5%) had at least one follow-up visit; 68/81 (84%) completed all follow-up to day 29
Selective reporting (reporting bias)	Unclear risk	Gametocyte density by microscopy is not reported except at baseline and in summary form for intervention and control groups combined at day 3 and 8 in the discussion
Other bias	Low risk	None known.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study participants were allowed to ask which group they were in. PQ taste is distinctive. Unlikely that participants knowledge of their status could influence infectivity or gametocyte prevalence
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators and outcome assessors were blinded.

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: 2 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.

El-Sayed 2007 (*Continued*)

Interventions	• 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. • As for 1. above plus PQ 0.75 mg/kg day 4 (reported as day 3).
Outcomes	• Proportion of people with *P. falciparum* parasites by PCR days 4, 8 and 15 (reported as days 3, 7, and 14). • Proportion of people with gametocytes by RT-PCR days 8 and 15 (reported as days 7 and 14). • Adverse events days 2, 3, 4, 8 and 15 (reported as days 1, 2, 3, 7, and 14). • 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
Random sequence generation (selection bias)	Low risk	"The list of carriers was sorted according to village and age to ensure that the treatment groups were balanced with respect to these two variables. The random allocation of this ordered list into the treatment arms was then created using restricted randomization with a block size of 12 in STATA v7"
Allocation concealment (selection bias)	Unclear risk	No information given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 3/104 participants did not complete follow-up.
Selective reporting (reporting bias)	Low risk	No obvious selective reporting.
Other bias	Low risk	No indication of other bias.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients and health staff were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory staff doing PCR were blinded.

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 Setting: Uganda Inclusion criteria • *P. falciparum* mono infection with parasite density lower than 500,000 parasites/ μL • Normal G6PD enzyme function • Fever or history of fever in past 24 hours Exclusion criteria • Signs of severity. • Haemoglobin concentration < 80 g/L. • Known allergy to the trial drugs. • Antimalarials taken within the past 2 days. • PQ taken within the past 4 weeks. • Blood transfusion within the past 90 days.
Interventions	• AL standard three day (twice per day) course + placebo (given with 5th AL dose, that is, with 1st dose on 3rd day of treatment). • AL + 0.1 mg/kg PQ. • AL + 0.4 mg/kg PQ. • 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 Mean absolute and relative change in Hb on day 3, 7, 10 stratified by G6PD status Gametocyte prevalence on day 7 stratified by CYP2D6 metabolism status
Notes	G6PD enzyme function based on a fluorescence spot test (R&D Diagnostics, Aghia Paraskevi, Greece) and on genotyping of G6PD A-; 202A and 376G. CYP2D6 genotyped by QuantSudio 12K Flex system and 32SNP Open Array and Copy number variation assays (N = 247)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated 4-digit treatment assignment codes and allocated these to random dose groups in block sizes of 16

Eziefula 2013 (*Continued*)

Allocation concealment (selection bias)	Low risk	Only the pharmacist was aware of allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 8% of participants 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) All outcomes	Low risk	"Masking syrup" added to all treatments to mask taste of drug
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded.

Gogtay 2004

Methods	Allocated by "simple, computer-generated randomization code"
Participants	Twenty-two patients in Mumbai, India Inclusion criteria • > 18 years. • Normal G6PD. • > 55 *P. falciparum* gametocytes/μL on admission. Exclusion criteria • Complicated malaria.
Interventions	• Quinine days 1 to 7: 30 mg/kg/day + PQ (45 mg). • 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.

Gogtay 2004 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of incomplete data.
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) All outcomes	Unclear risk	Not reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory technician reading blood smears was blinded.

Gogtay 2006

Methods	Randomized (computer-generated) to PQ or bulaquine (1:2 ratio) after primary treatment with quinine + doxycycline
Participants	93 participants in India Inclusion criteria • > 16 years. • Male. • Uncomplicated *P. falciparum* only. • > 55 *P. falciparum* gametocytes/μL on admission. Exclusion criteria • Antimalarial treatment in previous two weeks. • Allergy to trial drug. • G6PD deficient.
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 • PQ. • Bulaquine.
Outcomes	Gametocyte prevalence, density and viability on days 1, 4, 15, 22, and 29 Adverse events
Notes	Gametocyte viability assessed by Shute's technique (ex flagellation)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Gogtay 2006 (*Continued*)

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 (2 bulaquine, 1 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.

Gonçalves 2016a

Methods	Individually RCT. This is Phase 1 of the trial.
Participants	Children aged 2 to 15 years Asymptomatic Normal G6PD by BinaxNOW RDT Carrying patent *P. falciparum* asexual parasites or gametocytes (1000 to 200,000 parasites/µl) Weigh ≥ 10 kg Living in Balonghin, Sapone, Burkina Faso, an area of seasonal malaria transmission Exclusion criteria: Hb < 8 g/dL, fever or history or fever in last 24 hours, antimalarials in last 48 hours, PQ use in last 4 weeks, blood transfusion in last 90 days, non-*P. falciparum* infection at screening.
Interventions	AL: half a tablet (20 mg artemether and 120 mg of lumfantrine) per 5 kg body weight in 6 doses over 3 days + placebo AL+PQ: 0.25 and 0.4 mg/kg given on day 3 with the 5th dose of AL
Outcomes	Gametocyte clearance time Gametocyte prevalence by microscopy days 4, 8, 11, and 15 Proportion of mosquitoes infected Oocyst counts Max fall in Hb during follow-up (to day 15) Number of participants needing blood transfusion Max % decrease in Hb Proportion of participants with Hb below 5 g/dL

Gonçalves 2016a (*Continued*)

	Serious adverse events
Notes	Phase 1: children who are asymptomatic *P. falciparum* carriers (Gonçalves 2016a): N = 210 Phase 1: children who infect mosquitoes: no baseline feeding experiments Confirmed *P. falciparum* gametocyte carriers in Phase 2 (Gonçalves 2016b): N = 150 Phase 2: children who infected mosquitoes: 30/79 38%)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	RCT stratified by gender and blocks of 6 (3 study arms and two feeding schedules)
Allocation concealment (selection bias)	Low risk	Sealed envelopes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Phase 1: 205/210 (97.6%) completed follow-up to day 14.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes appear to have been reported.
Other bias	Low risk	None noted.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo controlled; syrup was added to mask taste of PQ.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Participants, investigators and staff were blinded to study arm allocation"

Gonçalves 2016b

Methods	Individually RCT. This is Phase 2 of the trial where inclusion criteria were modified to increase probability of infecting mosquitoes
Participants	Children aged 2 to 15 years Asymptomatic Normal G6PD by BinaxNOW RDT Carrying patent P.falciparum gametocytes (1000 to 200,000 parasites/µl) Weigh ≥ 10 kg Living in Balonghin, Sapone, Burkina Faso, an area of seasonal malaria transmission Exclusion criteria: Hb < 8 g/dL, fever or history or fever in last 24 hours, antimalarials in last 48 hours, PQ use in last 4 weeks, blood transfusion in last 90 days, non-*P. falciparum* infection at screening.

Gonçalves 2016b (*Continued*)

Interventions	AL: half a tablet (20 mg artemether and 120 mg of lumfantrine) per 5 kg body weight in 6 doses over 3 days + placebo AL+PQ: 0.25 and 0.4 mg/kg given on day 3 with the 5th dose of AL
Outcomes	Gametocyte clearance time Gametocyte prevalence by microscopy days 4, 8, 11, and 15 Proportion of mosquitoes infected Oocyst counts Max fall in Hb during follow-up (to day 15) Number of participants needing blood transfusion Max % decrease in Hb Proportion of participants with Hb below 5 g/dL Serious adverse events
Notes	Asymptomatic *P. falciparum* carriers in Phase 1 (Gonçalves 2016a): N = 210 Confirmed *P. falciparum* gametocyte carriers in Phase 2 (Gonçalves 2016b): N = 150

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	RCT stratified by gender and blocks of 6 (3 study arms and two feeding schedules)
Allocation concealment (selection bias)	Low risk	Sealed envelopes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Phase 2: 146/150 (97.3%) completed follow-up to day 14.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes appear to have been reported.
Other bias	Low risk	None noted.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo controlled; syrup was added to mask taste of PQ.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Participants, investigators and staff were blinded to study arm allocation"

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. Gametocytaemic within first 72 hrs with > 55 *P. falciparum* gametocytes/μL Site: urban areas of Mumbai, India. Exclusion criteria: pregnant or lactating, treatment for malaria within last 2 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	• Proportion of people with gametocytes, days 1, 4, 8, 15, 22, and 29. • Proportion of people with viable gametocytes (exflagellation), days 1, 4, 8, 15, 22, and 29. • 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

Kamtekar 2004 (*Continued*)

		were (a) 22 and 24 (b) 22 and 21
Selective reporting (reporting bias)	Unclear risk	No obvious selective reporting.
Other bias	High risk	It was not clear why some patients got SP and others did not, and the numbers in each group are not given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial used a placebo for PQ. Patients and health workers were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Slide readers were blinded.

Khoo 1981

Methods	Individually 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	• CQ: 1.5 g CQ over 3 days for *P. falciparum*, *P. vivax* or mixed, less for children. • 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. • SP (not included in this review): 1.5 g S and 75 mg P, single dose.
Outcomes	• Haemolysis. • Proportion cleared parasites by 72 hours. • Need for blood transfusion. • Renal failure.
Notes	The participants are not divided by *P. falciparum*, *P. vivax*, or mixed, so it is not possible to use the data.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"those found G6PD deficient were randomly assigned".
Allocation concealment (selection bias)	Unclear risk	No information given.

Khoo 1981 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information given.
Selective reporting (reporting bias)	Low risk	No apparent selective reporting.
Other bias	Low risk	No indication of other bias.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.

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	• CQ: 3 days 25 mg/kg. • CQ+PQ: CQ as in 1; PQ on day 3 (0.5 mg/kg). • SP: 25(S)/1.25(P) mg/kg in single dose. • SP+PQ: SP as in 3; PQ on same day (0.5 mg/kg).
Outcomes	• Clinical treatment failure (PCR non-adjusted and adjusted). • Gametocytes on day 8. • Gametocyte density on days 1 to 8 of follow-up. • Genotyping of resistant strains for CQ and SP-specific mutations.
Notes	Also included CQ + AS and SP + AS arms, compared with CQ ± PQ and SP ± PQ arms, respectively

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients numbered sequentially at enrolment. Random numbers with treatment assignment from Excel-generated lists, then paired with patient numbers

Kolaczinski 2012 (*Continued*)

Allocation concealment (selection bias)	Low risk	Patient number concealed until after enrolment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	209 of 237 randomized completed treatment and at least one follow-up test. 47 (13%) of those randomized did not contribute data. Variable numbers tested during follow-up (see analyses)
Selective reporting (reporting bias)	Low risk	None detected.
Other bias	Low risk	None noted.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Identified in report as "single-blind". Manager (gave Rx) not blinded; patients, microscopists and health workers "partially blinded" due to different drug appearance and times of follow-up. No placebos used, but vitamin given to those in non-PQ arms
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Implied only.

Lederman 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 < 40 kg, G6PD deficiency, history of antimalarial or antibiotic in last 7 days, severe or complicated malaria, history or allergy or adverse reaction to trial medications, *P. vivax* or mixed infection.
Interventions	• CQ only (not included in this review). • 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). • CQ+SP as for group 2 above plus PQ 45 mg on day 1 (reported as day 0). • CQ+SP as for group 2 above plus PQ 45 mg on day 3 (reported as day 2).
Outcomes	• 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) • Fever clearance time at days 2, 3, 4, 5, 8, 12, 15, 19, 22, 29 • Proportion of people with gametocytes (from chart) days 1 to 29

Lederman 2006 (*Continued*)

	• 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.

Lin 2017

Methods	Individually RCT
Participants	101 adults aged 18 to 65 years, 97% male presenting or referred with uncomplicated *P. falciparum* or mixed *P. falciparum*/*P. vivax* infection diagnosed with microscopy and confirmed with qPCR, had mild or moderate G6PD deficiency Setting: Cambodia
Interventions	DHAP: daily for 3 days; tablets containing 40mg DHA and 320 mg piperaquine each PQ: single dose 45mg at day 3
Outcomes	The proportion of individuals infecting at least 1 mosquito out of 50, at 1 and 2 weeks post-treatment in the 2 arms The effect of the 2 treatment regimens on the risk of gametocyte carriage as measured

Lin 2017 (*Continued*)

	by microscopy and RT-PCR. This was done by comparing gametocyte prevalence at weekly timepoints post-treatment and the time to gametocyte clearance in the 2 arms The number of infected mosquitos per treatment arm, the relationship of gametocytaemia to mosquito infectivity, and within-person changes in haemoglobin 4 days post-PQ treatment among volunteers with G6PD-deficiency
Notes	Baseline infectivity of participants (day 0): DHAP 6/51 (12%); DHAP+PQ 1/51 (2%)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block size 2, randomization scheme and codes prepared in advance
Allocation concealment (selection bias)	Low risk	Sealed envelopes offered to patients to choose from.
Incomplete outcome data (attrition bias) All outcomes	Low risk	less than 10% loss to follow-up by day 8; >10% at day 15.
Selective reporting (reporting bias)	Low risk	Not detected.
Other bias	Unclear risk	Baseline infectivity between the groups probably chance.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded.

Mwaiswelo 2016

Methods	Individually RCT
Participants	Yombo primary health facility, Bagamoyo town, an area of high year round transmission in Tanzania with two seasonal peaks 220 participants Inclusion criteria • Gender: both. • Age of 1 year and above and neither pregnant nor breast feeding. • Weight over 10 kg. • Body temperature = 37.5°C or history of fever in the last 24 hours. • *P. falciparum* mono-infection. Exclusion criteria • Evidence of severe illness malaria or danger signs. • Known allergy to study medications.

	• Haemoglobin < 8 g/dL. • Antimalarials taken within last 2 weeks. • Blood transfusion within last 90 days and evidence of recent use (within 14 days) of or will be taking other drugs known to cause haemolysis in G6PD-deficient subjects.
Interventions	AL standard doses by weight, six doses over 3 days. Placebo given with dose 1 AL+PQ (0.25 mg/kg) with dose 1, thereafter AL only.
Outcomes	No gametocyte outcomes were reported. Original planned outcomes: Primary outcome planned: 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) Actually reported: PCR-adjusted asexual parasite outcomes (parasitological cure) Mean relative reduction in Hb between day 1 and 8
Notes	ClinicalTrials.gov identifier: NCT02090036 Primary sponsor: Muhimbili University of Health and Allied Sciences Secondary sponsor: Karolinska Institutet Patients were admitted during treatment

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sex-stratified block randomization with 4 blocks, 2 per treatment arm using Research Randomizer v4
Allocation concealment (selection bias)	Low risk	Opaque envelopes with pre-determined treatment codes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	211 out of 220 (95.9%) completed the follow-up.
Selective reporting (reporting bias)	High risk	Trial was designed to look at gametocyte clearance but this was not reported because only one enrolled patient had gametocytes at baseline
Other bias	Low risk	None known.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Single blind. Nurses giving treatment opened the envelopes. Patients were blinded but could have noticed extra tablet. Glucose syrup masked the taste
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.

Okebe 2016

Methods	Individual RCT
Participants	694 asymptomatic malaria-infected (RDT, then microscopy, > 20 parasites/µl) G6PD normal individuals aged ≥ 1 year Upper and Central River Regions, The Gambia, in an area with seasonal transmission peaking between Sept and Nov Age ≥ 1 year and weight > 10 kg G6PD normal Hb > 8 g/dL No known allergy to study drugs Not pregnant or breastfeeding No malaria treatment in last 2 weeks No blood transfusion in last 3 months No history of sickle cell anaemia No chronic or acute conditions that might interfere with the study 170 participants in membrane feeding studies.
Interventions	• DHAP only. • DHAP 3 days + 0.2 mg/kg PQ on day 3 (reported as 2). • DHAP 3 days + 0.4 mg/kg PQ on day 3 (reported as 2). • DHAP 3 days + 0.75 mg/kg PQ on day 3 (reported as 2).
Outcomes	Participants with gametocytes on day 1, 4, 8, 11, 15 (reported as 0, 3, 7, 10, 14) by QT-NASBA Participants infectious to mosquitoes on day 8 (reported as 7) Mosquitoes infected on day 8 (reported as 7) Adverse events Clinical follow-up to day 43
Notes	ClinicalTrials.gov NCT01838902

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomization list generated by the trial statistician using STATA 13. 1:1:1:1 ratio using blocks of varying size to ensure a balance between the 4 groups. A separate randomization sequence was used to select participants for membrane feeding
Allocation concealment (selection bias)	Low risk	Sequentially numbered opaque envelopes prepared from randomization list by non-study physician
Incomplete outcome data (attrition bias) All outcomes	Low risk	647/694 (93.2%) of participants completed follow-up.
Selective reporting (reporting bias)	Low risk	Not detected.
Other bias	Low risk	Not detected.

Okebe 2016 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label: staff involved in clinical care including the trial drugs were aware of assigned groups
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Those involved in sample processing and data analysis are blinded

Pukrittayakamee 2004

Methods	Individually RCT Dates of trial not stated.
Participants	176 patients with acute uncomplicated *P. falciparum*. After exclusion of QN+tetracycline group: 146. Age 14 to 62. All male. Site: Hospital for Tropical Diseases, Bangkok, Thailand. Exclusion criteria: severe malaria, mixed malaria infection, history of drug hypersensitivity, any antimalarial within last 48 hrs, urine positive for sulfonamide or 4AQ People with G6PD deficient phenotype were excluded from receiving PQ
Interventions	• QN: QN sulfate (300 mg salt/tab) at 10 mg salt/kg, three times per day for 7 days. • QN+tetracycline (excluded from this review). • 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. • 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. • 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. • AS+PQ (high dose): AS as above plus PQ 0.5 mg/kg base daily on days 1 to 7.
Outcomes	• Parasite clearance time: measured at 12 hrs until clearance. • Gametocyte clearance time: median, 12 hrs until clearance. • Fever clearance time (measured every 4 hr at first and then every 6 to 12 hrs until resolution of fever). • Parasite reduction ratio at 48 hrs. • Reappearance of infection *P. falciparum*/*P. vivax* up to 28 days. • Prevalence of gametocytes on admission/after treatment/total. • 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

Pukrittayakamee 2004 (*Continued*)

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

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 2 weeks, evidence of chronic disease or acute infection other than malaria, domicile outside trial area, signs of severe malaria, eligible for other malaria studies

Shekalaghe 2007 (*Continued*)

Interventions	• AS+SP: AS: 4 mg/kg once daily for 3 days; SP: S 25 mg/kg and P: 1.125 mg/kg. • AS+SP+PQ: As above for AS and SP plus PQ base 0.75 mg/kg on the third day.
Outcomes	• Proportion of people with gametocytes (by microscopy) days 1, 4, 8, 15, 29 and 43 (reported as 0, 3, 7, 14, 28, and 42). • Proportion with gametocytes (by PCR), same time points. • Gametocyte density by PCR. • AUC for gametocyte presence. • Adverse events. • Adequate clinical and parasitological response. • Haemoglobin.
Notes	Hb outcome assessed with respect to G6PD variant.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Generated in STATA 8.0 using restricted randomization with block size of 20
Allocation concealment (selection bias)	Low 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	Individual RCT Dates of trial: not stated.
Participants	23 people with uncomplicated *P. falciparum* malaria, parasitaemia between 1 to 5 per 1000 RBC.

Singhasivanon 1994 (*Continued*)

	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	• MSP: MQ 20 mg/kg; S 40 mg base/kg; P 2 mg/kg; single dose. • MSP + PQ: As above plus PQ 0.75 mg/kg single dose. MSP+PQ crushed and mixed with 30 mL syrup (83% dextrose).
Outcomes	• Gametocyte clearance time (days) (assessed twice daily until negative, then once daily, by blood slide). • Adverse drug reactions, assessed once daily in first week then once a week. • Parasite clearance time (hrs). • Fever clearance time (hrs). • Cure rate.
Notes	Those who vomited within 3 hours of Rx were excluded - this is a post-randomization exclusion

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information given.
Allocation concealment (selection bias)	Unclear risk	No information given.
Incomplete outcome data (attrition bias) All outcomes	High risk	Outcomes only reported for 18 of the 23 participants.
Selective reporting (reporting bias)	Unclear risk	No information given.
Other bias	High risk	Those who vomited within 3 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 9 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 • L 19.8 mg/kg in two divided doses each day for 3 days • Advised to consume fatty food or breast feed before each dose 5+6. AS plus MQ, fixed-dose combination: 25 mg/55 mg or 100 mg/220 mg tablets (artesunate: Guilin, Lariam: Hoffman-La Roche) • AS 4 mg/kg once daily for 3 days • MQ 8.8 mg/kg once daily for 3 days 7+8. Artesunate plus MQ, loose combination (artesunate: Guilin, Lariam: Hoffman-La Roche) • AS 4 mg/kg once daily for 3 days • MQ 25 mg base/kg as a single dose on day 1 (reported as day 0) 9+10. DHAP, fixed-dose combination: 40 mg/320 mg or 20 mg/160 mg tablets (Artekin: Holleykin) • DHA 2.5 mg/kg once daily for 3 days • P 20 mg/kg once daily for 3 days First dose supervised, all others unsupervised.
Outcomes	• Recurrent parasitaemia at day 15, 29, 43 and 64 (reported as days 14, 28, 42, and 63). • Treatment failure due to *P. falciparum.* • Gametocytaemia prevalence. • Person-gametocyte weeks. • Haemoglobin on days 1 and 64. • Adverse events (monitoring not described).
Notes	Funding: Médecins sans Frontières (Holland).
Risk of bias	

Smithuis 2010 (*Continued*)

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) All outcomes	Low risk	Attrition is low in absolute numbers and unlikely to have introduced significant bias
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No indication of other bias.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label trial for patients and medical staff.
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 • Parasite density $\geq$ 1000 parasites/μL.

	• Age ≥ 5 years. • Normal glucose-6-phosphate dehydrogenase (G6PD) enzyme levels based on a qualitative test. • Haemoglobin level ≥ 8 g/dL. • Negative pregnancy test (assessed by human chorionic gonadotropin urine test) or not breastfeeding. • No signs of severe malnutrition. • No other chronic diseases. • No history of allergy to the trial drugs. • Ability to return for 42 days of follow-up.
Interventions	• Standard 3-day DHAP (fixed-dose tablets of 40 mg dihydroartemisinin and 320 mg piperaquine; D-ARTEPP, Guilin Pharmaceutical Co, Ltd). • 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	• Gametocyte prevalence-days 7, 14, 21, 28, 35, and 42. • Gametocyte clearance rates by day 42 in patients with gametocytes on day 3. • Recurrence of asexual stages of *P. falciparum*, PCR adjusted and unadjusted for reinfections. • Gametocyte development by day 42 in patients who were gametocyte free on day 3. • Gametocyte densities between days 3 and 42 inclusive. • Asexual infection recurrence by PCR. • Haemoglobin on days 7, 42. • Adverse events.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated sequences in blocks of 4.
Allocation concealment (selection bias)	Low risk	Opaque envelopes used in order at the health centre.
Incomplete outcome data (attrition bias) All outcomes	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) All outcomes	High risk	No blinding, no PQ placebo.

Sutanto 2013 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information.

Tine 2017

Methods	Individually RCT
Participants	Adult patients > 18 years of age presenting with falciparum malaria with a parasite density of 1000 to 100,000 trophozoites/μL Setting: Senegal, Deggo health post, Pikine, Dakar Number of participants: 274 randomized (over two transmission seasons) Exclusion criteria • Pregnant (confirmed by urine testing). • Breastfeeding. • History of hypersensitivity to any of the study drugs. • Severe malaria. • Moderately severe anaemia (haemoglobin < 8 g/dL). • Had a chronic illness.
Interventions	• AL: twice daily; tablets containing 20 mg artemether and 120 mg lumefantrine. • DHAP: daily for 3 days; tablets containing 40 mg DHA and 320 mg piperaquine. • ASAQ: daily for 3 days, 2 tablets containing 100 mg artesunate plus 270 mg amodiaquine. • PQ: single dose 15mg given on the first day of treatment with the ACT in the intervention arm. • PQ +AL was given with biscuits.
Outcomes	• Change in Hb from day 0 to day 7. • Change in Hb by day 3, day 14, day 21, and day 28. • Anaemia (Hb < 11 g/dL) at any time up to day 28. • Clinical adverse events up to day 28. • Prevalence and density of gametocyte carriage during follow-up.
Notes	Patients were withdrawn from the study and treated with quinine if they vomited for a second time within 30 minutes of taking each treatment dose

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomization of 18, to 6 treatment groups.
Allocation concealment (selection bias)	Low risk	Numbered sealed opaque envelopes opened by study pharmacist at time of treatment

Tine 2017 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	4% loss to follow-up.
Selective reporting (reporting bias)	Low risk	None detected.
Other bias	Low risk	None detected.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Trial assessors not blinded, although microscopists and laboratory technicians were not aware of allocation

Vásquez 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 1 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 4 weeks Setting: Colombia
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 As above plus PQ: 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. • Clinical recurrence. • Parasitemia prevalence. • Parasite density. • Fever resolution. • Prevalence of gametocytes. • Density of gametocytes. • Adverse effects.
Notes	

Vásquez 2009 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Seems to be alternate allocation following order of arrival ("segun el orden de llegada")
Allocation concealment (selection bias)	Unclear risk	Not clear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts noted.
Selective reporting (reporting bias)	Low risk	No evidence of bias.
Other bias	Low risk	No suggestion of other bias.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Does not seem to be blinded ("con determination no ciega del efecto en grupos iguales")
Blinding of outcome assessment (detection bias) All outcomes	High risk	Does not seem to be blinded ("con determination no ciega del efecto en grupos iguales")

Wang 2006

Methods	Individually RCT
Participants	Number of participants: 214 (no dropouts mentioned) Gabon International Tropical Medicine Institute Age range: 6 to 60 All had *P. falciparum* malaria clinical symptoms and blood smear positive. • Trial group: 108, male 50, female 58, age 16.4 ± 10.5. • Control group: 106, male 52, female 54, age 18.2 ± 9.4. Exclusion criteria: N/A
Interventions	• 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. • Only artesunate IM injection daily for 5 days, 1.2 mg/kg each dose, the first dose double total 5 days.
Outcomes	• Fever clearance time: (hrs) below 37°C continuously measured 4 times. • Clinical cure rate at day 7. • Adverse events (not specified). • 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	Not stated.
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.

Abbreviations: 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; PQ = primaquine; QN = quinine; RCT = randomized controlled trial; SP = sulfadoxine-pyrimethamine.

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.

(*Continued*)

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 participants and not controlled
Clyde 1971	Individual before-and-after study, but small number of participants 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)
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.

(*Continued*)

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 PQ
Mapanawang 2016	Pharmacokinetic study of PQ in 12 patients. Not randomized and no gametocyte measures
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
Santana 2007	Study of 14 day regimen of 15 mg PQ. Some *P. falciparum* cases were included but study did not distinguish between the patients with *P. falciparum* and *P. vivax*. Study was a comparison of association between methaemoglobinaemia after 14 day PQ in people with and without G6PD deficiency
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

(*Continued*)

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	AS + 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 *P. falciparum* patients.

Abbreviations: 8AQ = 8-aminoquinoline; AS = artesunate; CQ = chloroquine; CV8 = combination of dihydroartiemisin, piperaquine, trimethoprim, and PQ; G6PD = glucose-6-phosphate dehydrogenase; ITN = insecticide treated net; MDA= mass drug administration; MQ = mefloquine; PQ = primaquine; QN = quinine; RCT = randomized controlled trial; SP = sulfadoxine-pyrimethamine.

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

Chen 1993b

Methods	
Participants	
Interventions	
Outcomes	
Notes	Study not yet located

Ishii 2009

Methods	Unclear
Participants	Residents of trial villages in Solomon Islands (number not given)
Interventions	Testing of clinical malaria patients for G6PD and addition of single dose PQ to other malaria treatment if appropriate

Ishii 2009 (*Continued*)

Outcomes	Village prevalence of malaria
Notes	Abstract only with no results

Li 2006

Methods	
Participants	
Interventions	
Outcomes	
Notes	Study not yet located

Abbreviations: G6PD = glucose-6-phosphate dehydrogenase; PQ = primaquine.

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

ISRCTN11594437

Trial name or title	Assessing the tolerability and safety of single low dose primaquine in African children with acute uncomplicated falciparum malaria and glucose 6 phosphate dehydrogenase deficiency in Africa. Primaquine in African Children (PAC study)
Methods	Multi-centre double blind open randomised parallel safety trial (Treatment)
Participants	Democratic Republic of Congo and Uganda Inclusion criteria: • Aged six months to 11 years old • Clinically uncomplicated disease • Fever (= 37.5°C aural) or history of fever within the previous 72 hours • Positive malaria RDT (Uganda only) • Positive malaria slide for P. falciparum (mono or mixed infection) of any parasitaemia (Kinshasa only) • Informed consent provided by patient or relative/legal guardian Exclusion criteria: • Malaria danger signs, sign(s) of severe malaria, or decompensated anaemia, including: an inability to take or retain fluids or oral medications, confusion, prostration, convulsions, respiratory distress, passing of red or cola-coloured urine (putative "blackwater fever") • Severe anaemia (Hb < 6 g/dL) • Comorbid illness that requires treatment in hospital (physician's judgement) • Patients on drugs known to cause haemolysis in G6PDd e.g. dapsone, nalidixic acid • Known to be allergic to PQ, AL, or DHAPP • Previous enrolment in the current trial or current enrolment in another trial

ISRCTN11594437 (*Continued*)

Interventions	Participants are allocated to either the G6PDd group or the G6PD normal group based on their the results of a G6PD rapid diagnostic test (RDT) Participants are then randomly allocated as to which dosing group they receive using a computer generated randomisation list generated for each site. Treatment allocation is placed in a sealed envelope which is opened once participants receive their study number. The treatment allocation described the Artemisinin based combination treatment (ACT) to be given and the number of PQ/placebo pack The four dosing groups are the following: • Artemether lumefantrine (AL) + single low-dose primaquine (SLDPQ) • AL + SLDPQ placebo • Dihydroartemisinin-piperaquine (DHAPP) + single low-dose primaquine (SLDPQ) • DHAPP + SLDPQ placebo The dosages for primaquine depends vary with age and the dosing for AL vary with weight (in kg). DHAPP+SLDPQ dosages are given daily for three days and vary with body weight (in kg). Those who receive the primaquine/placebo receive it once only at baseline. Follow up continues until day 42
Outcomes	Primary outcomes • Profound anaemia (Hb concentration < 4 g/dL) is measured using the HemoCue machine during the first days 21 days of follow-up • Severe anaemia (Hb < 5 g/dL) with clinical features of severe malaria is measured using the HemoCue machine during the first 21 days of follow-up
Starting date	01/09/2017
Contact information	Bob Taylor, Mahidol Oxford Tropical Medicine Clinical Research Unit (MORU) Mahidol University 420/6 Rajvithi Road Rajthevee 10400 Bangkok Thailand
Notes	http://isrctn.com/ISRCTN11594437

NCT01906788

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

NCT01906788 (*Continued*)

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

NCT02259426

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 • Microscopically detectable*P. falciparum* gametocyte carriage • Age 5 years to 15 years • Gender: both Exclusion criteria • Age < 5 years or > 15 years • Non-falciparum malaria co-infection • Malaria parasite density = 200,000 parasites/μL • Clinical symptoms indicating severe malaria • Axillary temperature = 39°C • Body Mass Index (BMI) below 16 or above 32 kg/m² • Haemoglobin concentration below 9.5 g/dL

NCT02259426 (*Continued*)

	• Antimalarials taken in last 2 days • For women: pregnancy (assessed by clinical examination and urine pregnancy test) or lactation • Known hypersensitivity to DP or PQ • History or symptoms, or both indicating chronic illness • Current use of tuberculosis or anti-retroviral medication • Unable to give written informed consent • Unwillingness to participate in two membrane feeding assays • Travel history to Angola, Cameroon, Chad, Central African Republic, Congo, DR Congo, Equatorial Guinea, Ethiopia, Gabon, Nigeria and Sudan • 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 • 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 • Known disturbances of electrolyte balance, for example, hypokalaemia or hypomagnesaemia • Taking drugs which may be metabolized by cytochrome enzyme CYP2D6 (for example, flecainide, metoprolol, imipramine, amitriptyline, clomipramine) • 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 • Gametocyte prevalence on day 7 after initiation of treatment (time frame: day 7 of follow-up) Secondary outcomes • Gametocyte carriage during follow-up (time frame: 14 days during follow-up) • Gametocyte sex-ratio (time frame: 14 days of follow-up) • Haematological recovery (time frame: 14 days during follow-up) • 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
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

NCT02431650

Trial name or title	Effectiveness of OZ439 as a gametocytocidal and transmission blocking agent (OZGAM)
Methods	Allocation: randomized Intervention model: parallel assignment Masking: no masking Primary purpose: treatment

NCT02431650 (*Continued*)

	Each participant in the cohort will be inoculated on Day 0 with ~2800 viable parasites of *P. falciparum*-infected human erythrocytes (BSPC) administered intravenously. when PCR quantification of all participants is ≥ 5000 parasites/mL, they will receive a single dose of 480 mg of piperaquine phosphate to clear blood stage parasitaemia. When gametocytaemia is at the peak (approximately 15 days after administration of piperaquine), participants will be randomized to receive either OZ439 or a control group (PQ treatment)
Participants	12 adults aged 18 to 55 years
Interventions	Experimental: OZ439 Active Comparator: PQ
Outcomes	Primary outcome • Infection success of vector mosquitoes (time frame: from day 10 to 21 post-piperaquine dosing) assessing the transmissibility by oocyst detection in mosquito midgut preparations following direct and membrane (indirect) feeding.
Starting date	April 2015
Contact information	Q-Pharm Clinics Herston, Queensland, Australia, 4006 Prof James McCarthy QIMR Berghofer Medical Research Institute
Notes	

NCT02434952

Trial name or title	The tolerability and safety of low dose PQ for transmission blocking in symptomatic falciparum infected Cambodians
Methods	Allocation: randomized Intervention model: parallel assignment Masking: open label Primary purpose: treatment
Participants	Cambodia Inclusion criteria: • Age ≥ 1 year • Presentation with a confirmed fever (≥ 38 °C axilla or ≥ 37.5°C aural) or history of fever in previous 48 hours ± other clinical features of uncomplicated malaria • *P. falciparum* monoinfection ≥ 1 asexual form / 500 white blood cells • Informed consent (written/verbal) provided by patient or relative/legal guardian • Signed assent form for children aged 12 to < 18 years Exclusion criteria: • Clinical signs of severe malaria or danger signs • Pregnant or breast feeding • Unable or unwilling to take a pregnancy test (for women of child-bearing age) • Women intending to become pregnant in the next 3 months

NCT02434952 (*Continued*)

	• Allergic to PQ or DHA PP • Patients taking drugs known to cause acute intravascular haemolytic anaemia (AIHA) in G6PD deficiency e.g. dapsone, nalidixic acid • Patients on treatment for a significant illness e.g. HIV, tuberculosis (TB) treatment, steroids • On drugs that could interfere with anti-malarial pharmacokinetics like antiretrovirals, cimetidine, ketoconazole, antiepileptic drugs, rifampicin
Interventions	Experimental: DHA PP plus PQ, G6PD deficiency Active comparator: DHA PP plus PQ, G6PD normal Active comparator: DHA PP alone, G6PD deficiency Active comparator: DHA PP alone, G6PD normal
Outcomes	Primary outcomes: • Haemoglobin concentration [Time Frame: Day 7] Compare haemoglobin concentrations in g/dL between the G6PD deficient arm given DHA PP plus PQ, and the G6PD normal arm receiving the same regimen
Starting date	October 2014
Contact information	Dysoley Lek, MD, National Centre for Parasitology, Entomology and Malaria Control, Cambodia
Notes	https://clinicaltrials.gov/ct2/show/NCT02434952

NCT02831023

Trial name or title	Phase 2 efficacy study of primaquine and methylene blue: efficacy, safety, and pharmacokinetics of sulphadoxine-pyrimethamine-amodiaquine (SP-AQ), SP-AQ plus primaquine, dihydroartemisinin-piperaquine (DP), DP plus methylene blue for preventing transmission of *P. falciparum* gametocytes in Mali
Methods	Interventional Allocation: randomized; endpoint classification: safety/efficacy study; intervention model: parallel assignment; masking: single blind (outcomes assessor), primary purpose: treatment Phase 2
Participants	Mali Inclusion criteria: • Glucose-6-phosphate dehydrogenase (G6PD) normal defined by CareStart™ G6PD rapid diagnostic test (RDT) or the OSMMR2000 G6PD semi-qualitative test • Absence of symptomatic falciparum malaria, defined by fever upon enrolment • Presence of P. falciparum gametocytes on thick blood film at a density > 30 gametocytes/µL (i.e. = 2 gametocytes recorded in the thick film against 500 white blood cells) • No allergies to study drugs • No self-reported use of antimalarial drugs over the past 7 days (as reported by the participant) • Haemoglobin = 10 g/dL • Individuals weighing < 80 kg • No evidence of severe or chronic disease • Written, informed consent Exclusion criteria:

NCT02831023 (*Continued*)

	• Age < 5 years or > 50 years • Female gender • Blood thick film negative for sexual stages of malaria • Previous reaction to study drugs/known allergy to study drugs • Signs of severe malaria, including hyperparasitaemia, defined as asexual parasitemia >100,000 parasites/µL) • Signs of acute or chronic illness, including hepatitis • Use of other medications (with the exception of paracetamol and/or aspirin) - Consent not given Age minimum: 5 Years Age maximum: 50 Years Gender: Male
Interventions	Drug: 0.25 mg/kg PQ Drug: Amodiaquine Drug: Dihydroartemisinin-piperaquine Drug: Methylene blue Drug: Sulphadoxine-pyrimethamine
Outcomes	Primary: Mosquito infectivity assessed through membrane feeding assays (time frame: 7 day)
Starting date	July 2016
Contact information	Alassane Dicko, MD adicko@icermali.org; Ingrid Chen, PhD ingrid.chen@ucsf.edu
Notes	https://clinicaltrials.gov/show/NCT02831023

NCT02851108

Trial name or title	Methylene blue against falciparum malaria in Burkina Faso BlueACTn Safety of artesunate-amodiaquine combined with methylene blue or PQ for falciparum malaria treatment in African children: a randomised controlled trial
Methods	Interventional Allocation: randomized; endpoint classification: safety/efficacy study; intervention model: parallel assignment; masking: open label; primary purpose: treatment Phase 2
Participants	Burkina Faso Inclusion criteria: • Weight = 6 kg • Uncomplicated malaria caused by *P. falciparum* • Asexual parasites = 2 000/µL and = 100,000/µL • Axillary temperature = 37.5°C or a history of fever during the last 24 hours • Burkinabe nationality • Permanent residence in the study area with no intention of leaving during the surveillance period • Written informed consent of parents or care takers Exclusion criteria: • Severe malaria

NCT02851108 (*Continued*)

	• Mixed malaria infection • Vomiting (> 2 times within 24 hours before the visit) • Any apparent significant disease, including severe malnutrition • A history of a previous, significant adverse reaction or known allergy to one or more of the study drugs • Anaemia (haemoglobin < 7 g/dL) • Treated in the same trial before • All modern antimalarial treatment prior to inclusion (last 7 days) • Therapy with serotonin reuptake inhibitors (e.g. citalopram, escitalopram, fluoxetine, Paroxetine, Sertraline) • Simultaneous participation in another investigational study • Patients with known HIV/AIDS disease • Therapy with drugs known to inhibit the liver enzymes cytochrome 2A6 (e.g. methoxsalen, pilocarpine, tranylcypromine) and/or cytochrome 2C8 (e.g. trimethoprim, • ketoconazole, ritonavir, saquinavir, lopinavir, gemfibrozil, montelukast) Age minimum: 6 months Age maximum: 59 months Gender: Both
Interventions	Drug: methylene blue Drug: PQ
Outcomes	Primary: Change in haemoglobin compared to the baseline (time frame: 7 days)
Starting date	October 2016
Contact information	Olaf Müller, Prof. Dr. olaf.mueller@urz.uni-heidelberg.de
Notes	https://clinicaltrials.gov/show/NCT02851108

PACTR201611001859416

Trial name or title	Addition of low dose primaquine to artemether-lumefantrine for the treatment of uncomplicated malaria
Methods	RCT Parallel: different groups receive different interventions at same time during study, Randomized Random number generation, stratified by clinic, prepared by an independent statistician using a valid system, Sealed opaque envelopes,
Participants	South Africa Inclusion criteria: • *P. falciparum* positive by RDT • Age b 2 years • Weight over 10 kg • Prescribed artemether-lumefantrine according to standard practice • Informed consent (by legally acceptable representative if under 18 years of age) • Assent in children aged 7 and above • Intention to remain in the study area for the duration of the follow-up period

PACTR201611001859416 (*Continued*)

	Exclusion criteria: • Evidence of severe illness/danger signs • Known allergy to study medications • Medical history of haemolysis, rheumatoid arthritis, lupus erythematosus or cardiac disease • In patients receiving concurrently other drugs that are cause haemolysis, bone marrow suppression, or QTc interval prolongation • Hb 7 g/dL • A decrease in Hb of b 2 g/dL between day 0 and day 3 prior to PQ dose • Currently menstruating • Pregnant or breastfeeding • History of any antimalarials (including PQ) taken within the last 4 weeks • Blood transfusion within the last 90 days Age minimum: 2 years Age maximum: 100 years Gender: both
Interventions	PQ plus standard of care (AL) Standard of care (AL)
Outcomes	Primary: Change in mean haemoglobin (Hb) as measured by HemoCue on day 3 Changes in gametocyte prevalence on days 7 and 14 using RT-PCR
Starting date	2016-11-18
Contact information	Jaishee Raman, jaishreer@nucd.ac.za ; Karen Barnes karen.barnes@uct.ac.za
Notes	www.pactr.org/ATMWeb/appmanager/atm/atmregistry?dar=true&tNo=PACTR201611001859416

Abbreviations: AL = artemether-lumefantrine; BSPC = blood stage *Plasmodium falciparum* challenge; DHA = dihydroartemisinin; DHAP = dihydroartemisinin-piperaquine; DHAPP = Dihydroartemisinin-piperaquine; DP = dihydroartemisinin-piperaquine; G6PD = glucose-6-phosphate dehydrogenase; Hb = haemoglobin; PCR = polymerase chain reaction; PP = piperaquine phosphate; PQ = primaquine; QT-NASBA = real-time quantitative nucleic acid sequence-based amplification; RT-PCR = real time PCR; SLDPQ = single low-dose primaquine; SP-AQ = sulphadoxine-pyrimethamine-amodiaquine.

DATA AND ANALYSES

Comparison 1. Artemisinin treatment regimen: PQ versus no PQ

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants infectious, day 3 or 4, by dose	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 0.2 to 0.25 mg/kg	3	105	Risk Ratio (M-H, Fixed, 95% CI)	0.12 [0.02, 0.88]
1.2 0.4 to 0.5 mg/kg	3	109	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.02, 0.94]
1.3 0.75 mg/kg	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.02, 1.68]
2 Participants with gametocytes (PCR), day 3 or 4, by dose	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 0.2 to 0.25 mg/kg	3	414	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.87, 1.21]
2.2 0.4 to 0.5 mg/kg	3	418	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.93, 1.28]
2.3 0.75 mg/kg	2	394	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.75, 1.13]
3 Participants with gametocytes (microscopy), day 3 or 4, by dose	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 0.2 to 0.25 mg/kg	3	490	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.21, 2.50]
3.2 0.4 to 0.5 mg/kg	2	225	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.33, 2.25]
3.3 0.75 mg/kg	3	248	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.20, 0.85]
4 Participants infectious, day 8, by dose	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 0.2 to 0.25 mg/kg	4	243	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.07, 1.58]
4.2 0.4 to 0.5 mg/kg	4	246	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.07, 1.57]
4.3 0.75 mg/kg	2	181	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.02, 1.41]
5 Participants with gametocytes (PCR), day 8, by dose	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 0.2 to 0.25 mg/kg PQ	4	532	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.41, 0.65]
5.2 0.4 to 0.5 mg/kg PQ	5	758	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.29, 0.48]
5.3 0.75 mg/kg PQ	5	793	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.23, 0.43]
6 Participants with gametocytes (microscopy), day 8, by dose	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 0.2 to 0.25 mg/kg	3	491	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.16, 0.78]
6.2 0.4 to 0.5 mg/kg	2	225	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.08, 0.75]
6.3 0.75 mg/kg	6	1443	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.19, 0.37]
7 Gametocyte clearance time (PCR), by dose	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 0.2 to 0.25 mg/kg	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 0.4 to 0.5 mg/kg	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Area under curve of gametocytes (PCR), days 1 to 15, by dose	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 0.2 to 0.25 mg/kg	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 0.4 to 0.5 mg/kg	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Participants with severe haemolysis, by dose	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 0.2 to 0.25 mg/kg	4	752	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.69, 1.39]
9.2 0.4 to 0.5 mg/kg	2	260	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.38, 6.30]

9.3 0.75 mg/kg	1	102	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Mean max change in haemoglobin concentration, by dose	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
10.1 0.2 to 0.25 mg/kg	2	435	Mean Difference (IV, Random, 95% CI)	0.13 [-0.07, 0.33]
10.2 0.4 to 0.5 mg/kg	2	475	Mean Difference (IV, Random, 95% CI)	0.18 [-0.08, 0.44]
10.3 0.75 mg/kg	3	538	Mean Difference (IV, Random, 95% CI)	0.05 [-0.04, 0.14]
11 Percent change in haemoglobin, day 8, by dose	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
11.1 0.2 to 0.25 mg/kg	2	492	Mean Difference (IV, Random, 95% CI)	0.25 [-0.99, 1.50]
11.2 0.4 to 0.5 mg/kg	1	230	Mean Difference (IV, Random, 95% CI)	0.43 [-3.40, 4.26]
11.3 0.75 mg/kg	2	334	Mean Difference (IV, Random, 95% CI)	1.46 [-1.70, 4.63]
12 Max percent change in haemoglobin, by dose	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12.1 0.2 to 0.25 mg/kg	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 0.4 to 0.5 mg/kg	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.3 0.75 mg/kg	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Haemoglobinuria/dark urine	3	527	Odds Ratio (M-H, Fixed, 95% CI)	3.40 [2.15, 5.38]
14 Other adverse effects (CNS symptoms)	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 Headache	5	1706	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.66, 1.36]
14.2 Paresthesia	1	331	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.13, 6.80]
14.3 Dizziness	4	1335	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.74, 1.23]
14.4 Meningitis	1	441	Odds Ratio (M-H, Fixed, 95% CI)	0.08 [0.00, 2.13]
14.5 Blurred vision	1	217	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.12]
14.6 Insomnia	1	808	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.64, 1.47]
15 Other adverse effects (systemic)	6	4142	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.74, 1.24]
15.1 Fatigue	2	236	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.46, 2.19]
15.2 Pruritis	1	347	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.3 Fever	4	1056	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.65, 1.55]
15.4 Muscle ache/pain	2	398	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.12, 3.55]
15.5 Skin rash	3	921	Odds Ratio (M-H, Fixed, 95% CI)	1.51 [0.46, 5.01]
15.6 Pallor	2	704	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.59, 1.54]
15.7 Weakness/asthenia	2	480	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.43, 1.49]
16 Other adverse effects (respiratory symptoms)	5		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 Cough	2	488	Odds Ratio (M-H, Fixed, 95% CI)	1.39 [0.77, 2.54]
16.2 Runny nose	1	47	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.07, 3.61]
16.3 URTI/respiratory infection	2	488	Odds Ratio (M-H, Fixed, 95% CI)	2.57 [0.68, 9.72]
16.4 Bronchitis	1	351	Odds Ratio (M-H, Fixed, 95% CI)	2.34 [0.50, 10.87]
16.5 Rhinitis/rhinobronchitis	2	398	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.10, 5.83]
16.6 Shortness of breath	1	47	Odds Ratio (M-H, Fixed, 95% CI)	0.16 [0.01, 4.45]
16.7 Otitis	1	351	Odds Ratio (M-H, Fixed, 95% CI)	2.36 [0.11, 50.02]
16.8 Epistaxis	1	351	Odds Ratio (M-H, Fixed, 95% CI)	1.41 [0.06, 35.04]
16.9 Pneumonia	1	441	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.05, 2.24]
16.10 Cold sores	1	217	Odds Ratio (M-H, Fixed, 95% CI)	1.33 [0.29, 6.10]
16.11 Cyanosis	1	263	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Other adverse effects (gastrointestinal symptoms)	7		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 Nausea	5	1624	Odds Ratio (M-H, Fixed, 95% CI)	1.20 [0.88, 1.64]
17.2 Vomiting	7	2459	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.65, 1.56]

17.3 Abdominal pain	7	2453	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.86, 1.51]
17.4 Diarrhoea/dysentery/ stooling	7	2462	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.50, 1.10]
17.5 Anorexia/loss of appetite	3	1296	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.45, 0.95]
18 Other adverse effects (Miscellaneous)	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 Back pain	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.04, 2.05]
18.2 Burning with urination	1	47	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.06, 29.31]
18.3 Pain with urination	1	47	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.06, 29.31]
18.4 Whitlow	1	47	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.06, 29.31]
18.5 Leg osteoarthritis	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 4.14]
18.6 Uncomplicated malaria	1	351	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.12, 4.04]
18.7 Dental pain	1	351	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 3.67]
18.8 High transaminase	1	351	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 3.67]
18.9 Palpebral inflammation	1	351	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 3.67]
18.10 Wound/trauma	2	792	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.12, 0.97]
18.11 Foot trauma	1	351	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.06, 33.01]
18.12 Foot inflammation	1	351	Risk Ratio (M-H, Fixed, 95% CI)	1.4 [0.06, 33.83]
18.13 Skin infection	1	441	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.30, 2.29]
18.14 Palpitations	1	808	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.80, 1.37]
18.15 Unspecified	2	655	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.46, 1.96]

Comparison 2. Artemisinin treatment regimen: PQ 0.25 versus 0.50 mg/kg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants infectious, day 3 to 4	3	116	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.06, 13.54]
2 Participants with gametocytes (PCR), day 3 to 4	3	424	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.80, 1.09]
3 Participants with gametocytes (microscopy), day 3 to 4	2	231	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.68, 2.20]
4 Participants infectious, day 8	4	237	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.14, 6.48]
5 Participants with gametocytes (PCR), day 8	4	559	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.97, 1.82]
6 Participants with gametocytes (microscopy), day 8	2	235	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [0.51, 6.38]

Comparison 3. Non-artemisinin treatment regimen: PQ versus no PQ

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants infectious, day 5, by dose	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 0.75 mg/kg	2	30	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 0.62]
2 Participants with gametocytes (microscopy), day 4 to 5, by dose	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 0.4 to 0.5 mg/kg	1	221	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.62, 1.13]
2.2 0.75 mg/kg	2	52	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.48, 1.50]
3 Participants infectious, day 8, by dose	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 0.75 mg/kg PQ	2	30	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.01, 0.45]
4 Participants with gametocytes (microscopy), day 8, by dose	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 0.4 to 0.5 mg/kg PQ	1	216	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.49, 0.75]
4.2 0.75 mg/kg PQ	4	186	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.25, 0.62]
5 Gametocyte clearance time	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6 Adverse effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Nausea	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Vomiting	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Dizziness	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.4 Any adverse effect	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 4. PQ versus other 8AQ

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with gametocytes (microscopy), day 8	2	112	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.26, 0.66]

ADDITIONAL TABLES

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

Comparator	Trial	Arm	Place	G6PD status	Parasite species	Partner or alternative drug	Proportion with gametocytes at onset (control group)	Proportion with gametocytes at onset (experimental group)	Day(s)* PQ given	Target PQ dose per day
	Dicko 2016	a	Mali	Only non-deficient included[1]	Pf only	DHAP days 1 to 3	100% Mic (N = 15)	100% Mic (N = 16)	day 1	0.0625 mg/kg**
		b						100% Mic (N = 16)	day 1	0.125 mg/kg**
		c						100% Mic (N = 15)	day 1	0.25 mg/kg
		d						100% Mic (N = 17)	day 1	0.5 mg/kg
	El-Sayed 2007		Sudan (east)	Not reported	Pf only	AS+SP days 1 to 3	11.5% PCR (N = 52) Table 2	11.5% PCR (N = 52)	day 4	0.75 mg/kg
	Eziefula 2013	a	Uganda	Only non-deficient included[2] (PCR testing of those included after FST)	Pf only	AL days 1 to 3	23.1% Mic (N = 117) 79.8% PCR (N = 114) Table 1	24.3% MIc (N = 115) 86.7% PCR (N = 113)	day 3	0.1 mg/kg**
		b						20.4% Mic (N = 113) 78.7% PCR (N = 108)	day 3	0.4 mg/kg
		c						22.4% Mic (N = 116) 82.0%	day 3	0.75 mg/kg

Table 1. Trial locations, partner drugs, gametocyte status at onset, G6PD status, and PQ dose and treatment schedule (*Continued*)

							PCR (N = 111)		
	Gonçalves 2016a	a	Burkina Faso	Only non-deficient included[3]	Pf only	AL days 1 to 3	17.7% Mic (N = 62) Table 2	32% Mic (N = 75) 92.9% PCR (N = 70)	day 3	0.25 mg/kg
		b						20.5% Mic (N = 73) 85.5% PCR (N = 62)	day 3	0.4 mg/kg
	Gonçalves 2016b	a	Burkina Faso	Only non-deficient included[3]	Pf only	AL days 1 to 3	69.4% Mic (N = 49) Table 2	55.3% Mic (N = 47) 93.7% PCR (N = 48)	day 3	0.25 mg/kg
		b						83.3% Mic (N = 46) 100.0% PCR (N = 46)	day 3	0.4 mg/kg
	Lin 2017		Cambodia	Screened and severely deficient excluded[4]	Pf or Pf+Pv	DHAP days 1 to 3	10% Mic 44% PCR (N = 51) Table 1	8% Mic 49% PCR (N = 50) Table 1	day 3	0.75 mg/kg
	Mwaiswelo 2016		Tanzania	Screened and all included[5]	Pf only	AL days 1 to 3	1 patient had gametocytes at recruitment but treatment group not given	0.5% Mic (N = 220) both groups	day 1	0.25 mg/kg
	Okebe 2016	a	The Gambia	Only non-deficient included[2]	Pf only	DHAP days 1 to 3	47.7% PCR (N = 153) Table 1	53.4% PCR (N = 148)	day 3	0.2 mg/kg

Table 1. Trial locations, partner drugs, gametocyte status at onset, G6PD status, and PQ dose and treatment schedule (*Continued*)

		b					54.6% PCR (N = 152)	day 3	0.4 mg/kg
		c					53.4% PCR (N = 146)	day 3	0.75 mg/kg
	Pukrittayakamee 2004	c	Thailand	Only non-deficient included[10]	Pf only	AS days 1 to 7	26.1% Mic (N = 23) Table 3	26.0% Mic (N = 50)	days 1 to 7	0.5 mg/kg
	Shekalaghe 2007		Tanzania (North east)	Screened and all included[6]	Pf only	AS+SP days 1 to 3	26.4% Mic (N = 63) 88.2% PCR (N = 51) Table 1	18.9% Mic (N = 53) 90.6% PCR (N = 53)	day 3	0.75 mg/kg
	Smithuis 2010	a	Myanmar (3 states)	Not screened	Pf or mixed	AS+AQ days 1 to 3	32.1% Mic (N = 84)	36.6% Mic (N = 71)	day 1	0.75 mg/kg
		b				AL days 1 to 3	34.5% Mic (N = 84)	32.1% Mic (N = 78)	day 1	0.75 mg/kg
		c				AS+MQ fixed dose days 1 to 3	31.3% Mic (N = 83)	27.9%% Mic (N = 86)	day 1	0.75 mg/kg
		d				AS days 1 to 3 + MQ day 1 loose	30.5% Mic (N = 82)	26.6% Mic (N = 79)	day 1	0.75 mg/kg
		e				DHAP days 1 to 3	43.6% Mic (N = 78)	32.5% Mic (N = 83)	day 1	0.75 mg/kg
	Sutanto 2013		Indonesia (south Sumatra)	Only non-deficient included[7]	Pf only	DHAP days 1 to 3	17.4% Mic (N = 178) Figure 1	24.0% Mic (on day 3) (N = 171)	day 4	0.75 mg/kg

Table 1. Trial locations, partner drugs, gametocyte status at onset, G6PD status, and PQ dose and treatment schedule (*Continued*)

	Tine 2017	a	Senegal	Screened and all included[5]	Pf only	AL days 1 to 3	6.7% Mic (N = 135) Table 5	7.9% Mic (N = 139) Table 5	day 1	0.25 mg/kg
		b				DHAP days 1 to 3				
		c				AS+AQ days 1 to 3				
	Vásquez 2009		Colombia (Antioquia)	Not reported	Pf only	AS+MQ days 1 to 3 (MQ only on day 2 for children < 6)	16% Mic (N = 25) Figure 1 estimated	24.0% Mic (N = 25)	day 3	45 mg (~0.75 mg/kg)
	Wang 2006		Gabon	Not reported	Pf	AS i.m. days 1 to 5	Not reported (N = 106)	Not reported (N = 108)	days 1 to 5	22.5 mg (~0.38 mg/kg)
Non-artemisinin partner										
CQ or (CQ+SP)	Kamtekar 2004	a	India (Mumbai)	Not screened	Pf only	CQ days 1 to 3 or CQ	100% Mic (N = 44)	100% Mic (within 3 days)	day 4	45 mg (~0.75 mg/kg)
	Khoo 1981		Malaysia (Sabah)	Only deficient included[8]	Pf, Pv or mixed	CQ days 1 to 3	Not reported	Not reported	days 1 to 3	25 mg (~0.42 mg/kg)
	Kolaczinski 2012	a	Pakistan (3 Afghan refugee camps)	Not reported	Pf only	CQ days 1 to 3	17.6% Mic (N = 239) Table 2 (combined CQ, CQ+AS, SP, SP+AS groups)	19.7% Mic (N = 76)	day 3	0.5 mg/kg
	Lederman 2006	a	Indonesia (Central Java)	Only non-deficient included[9]	Pf only	CQ days 1 to 3 + SP day 1	8.2% Mic (N = 61) Figure 3 est (combined CQ,	25% Mic (N = 28) Figure 3 est	day 1	45 mg (~0.75 mg/kg)

Table 1. Trial locations, partner drugs, gametocyte status at onset, G6PD status, and PQ dose and treatment schedule (*Continued*)

							CQ+SP groups)			
		b						14.3% (N = 28) Figure 3 est	day 3	45 mg (~0.75 mg/kg)
SP	Kolaczinski 2012	b	Pakistan (2 Afghan refugee camps)	Not reported	Pf only	SP day 1	See above under Kolaczinski 2012 a	27.1% Mic (N = 85)	day 1	0.5 mg/kg
AQ+SP	Arango 2012	a	Colombia	Not reported	Pf only	AQ days 1 to 3 + SP day 1	15% Mic (N = 20) Table 3	30% Mic (N = 20)	day 2	0.75 mg/kg
MQ or (MQ+SP)	Chen 1993a		China	Not reported	Pf only	MQ day 1	100% Mic (N = 6)	100% Mic (N = 6)	day 1	45 mg (~0.75 mg/kg)
	Chen 1994		China (Hainan province)	Not reported	Pf only	MQ day 1	100% Mic (N = 9) MQ group only	100% Mic (N = 9)	day 1	45 mg (~0.75 mg/kg)
	Singhasivanon 1994		Thailand (Bangkok)	Not reported	Pf only	MQ+SP fixed day 1	Not reported (N = 11)	Not reported (N = 7)	day 1	0.75 mg/kg
QN	Kamtekar 2004	b	India (Mumbai)	Not screened	Pf only	QN i.v. days 1 to 2 and orally days 1 to 7	88.6% Mic (N = 44)	100% Mic (within 3 days)	day 8	45 mg (~0.75 mg/kg)
	Pukrittayakamee 2004	a	Thailand	Only non-deficient included[10]	Pf only	QN days 1 to 7	23.3% Mic (N = 60) QN, QN+TC groups	18.6% Mic (N = 59)	days 1 to 7	0.25 mg base/kg
		b						22.4% Mic (N = 67)	days 1 to 7	0.5 mg base/kg
Comparison of different 8AQ										

Table 1. Trial locations, partner drugs, gametocyte status at onset, G6PD status, and PQ dose and treatment schedule (*Continued*)

PQ versus Bulaquine	Gogtay 2004		India (Mumbai)	Only non-deficient included[10]	Pf	QN + doxycycline days 1 to 7 + BQ day 4	No control group without 8-AQ	100% Mic (N = 22)	day 4	45 mg (~0.75 mg/kg)
	Gogtay 2006		India	Only non-deficient included [10]	Pf	QN + doxycycline days 1 to 7 + BQ day 4	No control group without 8-AQ	100% Mic (N = 93)	day 4	45 mg (~0.75 mg/kg)

*first day of any treatment = day 1
**arm excluded as dose < 0.2 mg/kg
[1]G6PD colorimetric method, R&D diagnostics, Papagos, Greece.
[2]G6PD by fluorescence spot test.
[3]G6PD by Binax Now Alere rapid test.
[4]G6PD by fluorescent spot test (R&D diagnostics, Greece) and quantitative enzyme activity testing (Trinity Biotech, Ireland).
[5]G6PD (phenotypic) by CareStart ™ Access Bio test; (genotypic) by PCR and RFLP digestion for the two most common Afrcian G6PD polymorphisms.
[6]G6PD by detection of single nucleotide polymorphisms (G202A, A376G) by PCR and ELISA.
[7]G6PD by qualitative test.
[8]G6PD by Brewer's methaemoglobin reduction test.
[9]G6PD by semi-quantitative G6PD assay.
[10]G6PD method not reported.
Abbreviations: G6PD = glucose-6-phosphate dehydrogenase; FST = fluorescent spot test; 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; Mic = microscopy; Pf = *P. falciparum*; Pv = *P. vivax*.

Table 2. Infectivity to mosquitoes baseline

Dose	Study	With PQ			Without PQ			Absolute difference (reduction or increase) in % of mosquitoes infected in PQ group	Average number of mosquitoes dissected per participant (both arms combined)
		Total number	Number of in-	Average % of	Total number of	Number of in-	Average % of		

Table 2. Infectivity to mosquitoes baseline (*Continued*)

		of participants	fectious people	mosquitoes infected	participants	fectious people	mosquitoes infected		
0.25 mg/kg	Dicko 2016	15	14	35.5	14	10	6.7	+28.8	143.1
	Gonçalves 2016b	27	8	4.5	32	15	14.8	−10.3	44.0
0.4 to 0.5 mg/kg	Dicko 2016	14	12	11.0	14	10	6.7	+4.3	136.6
	Gonçalves 2016b	20	7	8.9	32	15	14.8	−5.8	44.3
0.75 mg/kg	Lin 2017	50	1	1.4	51	6	5.3	−3.9	50

Abbreviations: PQ: primaquine.

Table 3. Infectivity to mosquitoes day 3-4

Dose	Study	With PQ			Without PQ			Absolute difference (reduction or increase) in % of mosquitoes infected in PQ group	Average number of mosquitoes dissected per participant (both arms combined)
		Total number of participants	Number of infectious people	Average % of mosquitoes infected	Total number of participants	Number of infectious people	Average % of mosquitoes infected		
0.25 mg/kg	Dicko 2016	15	1	0.6	13	7	8.1	−7.5	71.6
	Gonçalves 2016a	27	0	0.0	32	0	0.0	0.0	26.9
	Gonçalves 2016b	23	0	0.0	19	0	0.0	0.0	45.6
0.4 to 0.5 mg/kg	Dicko 2016	14	1	0.3	13	7	8.1	−7.8	70.2
	Gonçalves 2016a	20	0	0.0	32	0	0.0	0.0	33.4

Table 3. Infectivity to mosquitoes day 3-4 (*Continued*)

	Gonçalves 2016b	28	0	0.0	19	0	0.0	0.0	45.6
0.75 mg/kg	Lin 2017	50	1	1.4	51	5	6.6	-5.2	50

Abbreviations: PQ: primaquine.

Table 4. Infectivity to mosquitoes day 8

Dose	Study	With PQ			Without PQ			Absolute difference (reduction or increase) in % of mosquitoes infected in PQ group	Average number of mosquitoes dissected per participant (both arms combined)
		Total number of participants	Number of infectious people	Average % of mosquitoes infected	Total number of participants	Number of infectious people	Average % of mosquitoes infected		
0.2 to 0.25 mg/kg	Dicko 2016	15	0	0.0	13	3	3.7	−3.7	72.8
	Gonçalves 2016a	27	0	0.0	32	0	0.0	0.0	26.6
	Gonçalves 2016b	49	0	0.0	49	1	0.2	−0.2	43.7
	Okebe 2016[1]	44	1	29.2	46	1	1.3	+27.9	80
0.4 to 0.5 mg/kg	Dicko 2016	14	1	0.1	13	3	3.7	−3.6	71
	Gonçalves 2016a	20	0	0.0	32	0	0.0	0.0	31.4
	Gonçalves 2016b	46	0	0.0	49	1	0.2	−0.2	43.4
	Okebe 2016	42	0	0.0	46	1	1.3	−1.3	80
0.75 mg/kg	Lin 2017	48	0	0.0	48	4	6.9	−6.9	50

Table 4. Infectivity to mosquitoes day 8 (*Continued*)

	Okebe 2016[1]	39	0	0.0	46	1	1.3	−1.3	80

[1]Okebe 2016 reported the median number of mosquitoes per person.
Abbreviations: PQ: primaquine.

WHAT'S NEW

Last assessed as up-to-date: 21 July 2017.

Date	Event	Description
9 February 2018	Amended	PLS title corrected to 'A single dose of primaquine added to malaria treatment to prevent malaria transmission'

HISTORY

Protocol first published: Issue 4, 2009

Review first published: Issue 9, 2012

Date	Event	Description
1 February 2018	New search has been performed	Search updated to 21 July 2017. We included seven new trials (Dicko 2016; Gonçalves 2016a; Gonçalves 2016b; Mwaiswelo 2016; Okebe 2016; Lin 2017; Tine 2017) and four additional publications from a previously included trial (Eziefula 2013).The new trials included direct measures of infectiousness of people to mosquitoes and these data were included
1 February 2018	New citation required and conclusions have changed	This is an update of a review last updated in 2015.
4 February 2015	New citation required but conclusions have not changed	New citation.
4 February 2015	New search has been performed	Search updated to 5 January 2015. No new trials were included. 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 re-

(*Continued*)

		vision corrects the minor data extraction errors pointed out in this article. The conclusions are not changed
24 June 2014	New citation required and conclusions have changed	We stratified the analysis by dose of primaquine and added new studies. We clarified the excluded studies and adjusted the conclusions
24 June 2014	New search has been performed	New studies added.

CONTRIBUTIONS OF AUTHORS

2018 update

PMG and HG screened the abstracts, added the new studies, and extracted the data. LC and PG revised the GRADE analysis and 'Summary of findings' tables. All authors contributed to interpretation of results and rewriting the review.
Graves 2015: 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. 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.

PMG was a member from 2012 to 2016 of the WHO Malaria Policy Advisory Committee, which provides independent strategic advice in forming WHO policies in malaria.

HG and LC have no known conflicts of interest.

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

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Internal sources

- Liverpool School of Tropical Medicine, UK.

External sources

- Department for International Development, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2012 version

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 summarized. 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.

2014 version

In the June 2014 update, we reversed this decision. 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 sulphadoxine + 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 DEff=1+(m-1)*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.

2015 version

5. Comments on the review were addressed (see below). An updated search did not identify any new trials for inclusion.

2018 version

6. In 2018 we removed some secondary outcomes including our AUC calculations, asexual stage outcomes, and gametocyte prevalence outcomes at time periods after day 8, given new higher priority evidence and comparisons. AUC if reported by trials is still included. We removed the following secondary outcomes that were in the 2015 version:

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

We also restricted infectiousness and gametocyte prevalence outcomes to day 8 of follow-up. We excluded any trial arms with < 0.2 mg/kg PQ (three arms). We converted analysis figures of infections acquired by mosquitoes to tables.

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 corrected all points of factual detail in the 2015 review version.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans