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Primaquine at alternative dosing schedules for preventing relapse in people with *Plasmodium vivax* malaria (Review)

Milligan R, Daher A, Graves PM

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Primaquine at alternative dosing schedules for preventing relapse in people with *Plasmodium vivax* malaria.
Cochrane Database of Systematic Reviews 2019, Issue 7. Art. No.: CD012656.
DOI: 10.1002/14651858.CD012656.pub2.

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[Intervention Review]

Primaquine at alternative dosing schedules for preventing relapse in people with *Plasmodium vivax* malaria

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Editorial group: Cochrane Infectious Diseases Group
Publication status and date: Unchanged, published in Issue 7, 2019.

Citation: Milligan R, Daher A, Graves PM. Primaquine at alternative dosing schedules for preventing relapse in people with *Plasmodium vivax* malaria. *Cochrane Database of Systematic Reviews* 2019, Issue 7. Art. No.: CD012656. DOI: 10.1002/14651858.CD012656.pub2.

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ABSTRACT

Background

Malaria caused by *Plasmodium vivax* requires treatment of the blood-stage infection and treatment of the hypnozoites that develop in the liver. This is a challenge to effective case management of *P vivax* malaria, as well as being a more general substantial impediment to malaria control. The World Health Organization (WHO) recommends a 14-day drug course with primaquine, an 8-aminoquinoline, at 0.25 mg/kg/day in most of the world (standard course), or 0.5 mg/kg/day in East Asia and Oceania (high-standard course). This long treatment course can be difficult to complete, and primaquine can cause dangerous haemolysis in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency, meaning that physicians may be reluctant to prescribe in areas where G6PD testing is not available. This Cochrane Review evaluated whether more patient-friendly alternative regimens are as efficacious as the standard regimen for radical cure of*P vivax* malaria.

Objectives

To assess the efficacy and safety of alternative primaquine regimens for radical cure of *P vivax* malaria compared to the standard or high-standard 14 days of primaquine (0.25 or 0.5 mg/kg/day), as well as comparison of these two WHO-recommended regimens.

Search methods

We searched the Cochrane Infectious Diseases Group (CIDG) Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE (PubMed); Embase (Ovid); and LILACS (BIREME) up to 17 December 2018. We also searched the WHO International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov, and checked the reference lists of all studies identified by the above methods.

Selection criteria

Randomized controlled trials (RCTs) of adults and children with *P vivax* malaria using any regimen of either chloroquine or an artemisinin-based combination therapy (ACT) plus primaquine with either higher daily doses for 14 days, shorter regimens with the same total dose, or using weekly dosing regimens; compared with the usual standard regimens recommended by the WHO (0.25 or 0.5 mg/kg/day for 14 days), or a comparison of these two WHO-recommended regimens.

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Data collection and analysis

Two review authors independently assessed trial eligibility and quality, and extracted data. We calculated risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous data. We grouped efficacy data according to length of follow-up. We analysed safety data where this information was included.

Main results

High-standard 14-day course versus standard 14-day course

Two RCTs compared the high-standard 14-day regimen with the standard 14-day regimen. People with G6PD deficiency and pregnant or lactating women were excluded. We do not know if there is any difference in *P vivax* recurrences at 6 months with 0.5 mg/kg/day primaquine therapy for 14 days compared to 0.25 mg/kg/day primaquine therapy for 14 days (with chloroquine: RR 0.82, 95% CI 0.47 to 1.43, 639 participants, very low-certainty evidence; with chloroquine or an ACT: RR 1.11, 95% CI 0.17 to 7.09, 38 participants, very low-certainty evidence). No serious adverse events were reported. We do not know whether there is a difference in adverse events with the higher dosage (very low-certainty evidence).

0.5 mg/kg/day primaquine for 7 days versus standard 14-day course

Five RCTs compared 0.5 mg/kg/day primaquine for 7 days with the standard 14-day course. There may be little or no difference in *P vivax* recurrences at 6 to 7 months when using the same total dose (0.5 mg/kg/day to 210 mg) over 7 days as compared to 14 days (RR 0.96, 95% CI 0.66 to 1.39; 1211 participants; low-certainty evidence). No serious adverse events were reported. There may be little or no difference in the number of adverse events known to occur with primaquine between the primaquine shorter regimen as compared to the longer regimen (RR 1.06, 95% CI 0.64 to 1.76; 1154 participants; low-certainty evidence). We do not know whether there is any difference in the frequency of anaemia or discontinuation of treatment between groups (very low-certainty evidence). Three trials excluded people with G6PD deficiency, and two did not provide this information. Pregnant and lactating women were either excluded or no details were provided regarding their inclusion or exclusion.

0.75 mg/kg primaquine/week for 8 weeks versus high-standard course

One RCT compared weekly primaquine with the high-standard 14-day course. G6PD-deficient patients were not randomized but were included in the weekly primaquine group. Only one G6PD-deficient participant was detected during the trial. We do not know whether weekly primaquine increases or decreases recurrences of *P vivax* compared to the 14-day regimen at 11 months' follow-up (RR 3.18, 95% CI 0.37 to 27.6; 122 participants; very low-certainty evidence). No serious adverse events and no episodes of anaemia were reported.

Three other RCTs evaluated different alternative regimens and doses of primaquine, but one of these RCTs did not have results available, and two used regimens that have not been widely used and the evidence was of very low certainty.

Authors' conclusions

Although limited data were available, the analysis did not detect a difference in recurrence between the 7-day regimen and the standard 14-day regimen of 0.5 mg/kg/day primaquine, and no serious adverse events were reported in G6PD-normal participants taking 0.5 mg/kg/day of primaquine. This shorter regimen may be useful in G6PD-normal patients if there are treatment adherence concerns. Further large high-quality RCTs are needed, such as the IMPROV trial, with more standardised comparison regimens and longer follow-up to help resolve uncertainties.

16 September 2019

Update pending

Authors currently updating

The update is due to be published in December 2019.

PLAIN LANGUAGE SUMMARY

Primaquine to cure people with *Plasmodium vivax* malaria: comparing dosing schedules

Plasmodium vivax malaria can sometimes cause potentially life-threatening illness, and the infection continues to make many people unwell. The infection includes a liver stage, and this requires primaquine to eradicate it and prevent the infection recrudescing. However, the current dosing schedule requires 14 days of daily treatment.

What are the concerns about primaquine?

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Primaquine is the only drug currently recommended to treat the liver parasites in *P vivax* malaria. It can cause anaemia in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency, which is a relatively common genetic blood disorder. Shorter regimens would help reduce the risk of default with the current two-week regimen.

What does the research say?

We summarized trials that compared the World Health Organization (WHO)-recommended primaquine regimen of 15 to 30 mg per day for 14 days with the same or higher doses of primaquine given over different lengths of time to determine whether alternative regimens were as successful as the recommended courses at preventing future episodes of *P vivax* malaria. We searched for trials up to 17 December 2018, and included nine randomized controlled trials (studies in which participants are assigned to one of two or more treatment groups in a random manner) in our analysis.

When using 30 mg per day compared to 15 mg per day primaquine therapy for 14 days, we do not know if there is any difference in *P vivax* recurrences at 6 months (very low-certainty evidence). No serious side effects were reported, but it is unclear whether or not there is a difference in other side effects between doses (very low-certainty evidence).

When using 30 mg primaquine per day for 7 days compared to 15 mg per day for 14 days, there may be no difference in *P vivax* recurrences at 6 to 7 months (low-certainty evidence). No serious adverse events were reported. There may be no difference in the number of side effects known to occur with primaquine between the two treatment regimens (low-certainty evidence).

We do not know whether weekly primaquine increases or decreases recurrences of *P vivax* compared to the 14-day regimen at 11 months' follow-up (very low-certainty evidence).

Further large high-quality RCTs are needed, such as the IMPROV trial, to help improve the certainty of the evidence around alternative regimens.

How up-to-date is this review?

The review authors searched for studies up to 17 December 2018.

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SUMMARY OF FINDINGS

Summary of findings for the main comparison. 'Summary of findings' (main comparison)

0.5 mg/kg/day for 7 days versus standard 14-day regimen for radical cure of *P vivax* malaria

Patient or population: adults and children with confirmed clinical and parasitological *P vivax* malaria
Setting: India, Peru, Brazil
Intervention: 0.5 mg/kg/day primaquine for 7 days (adult dose 30 mg)
Comparison: standard 14-day course of primaquine (0.25 mg/kg/day, adult dose 15 mg)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with standard 14-day course primaquine	Risk with 0.5mg/kg/day primaquine for 7 days				
Recurrence of *P vivax* parasitaemia Follow-up: range 6 months to 7 months	89 per 1000	86 per 1000 (59 to 124)	RR 0.96 (0.66 to 1.39)	1211 (4 RCTs)	⊕⊕⊖⊖ LOW[a,b] Due to risk of bias and imprecision	There may be little or no difference between 0.5 mg/kg/day primaquine for 7 days and the standard 14-day course.
Serious adverse effects	See comment	See comment	—	1427 (5 RCTs)	—	No events reported.
Adverse events that result in the discontinuation of treatment	3 per 1000	3 per 1000 (0 to 20)	RR 1.04 (0.15 to 7.38)	1154 (4 RCTs)	⊕⊖⊖⊖ VERY LOW[c,d] due to risk of bias and imprecision	We do not know if there is any difference in adverse events that result in treatment discontinuation between 0.5 mg/kg/day primaquine for 7 days and the standard 14-day course.
Adverse effects known to occur with primaquine	44 per 1000	47 per 1000 (28 to 78)	RR 1.06 (0.64 to 1.76)	1154 (4 RCTs)	⊕⊕⊖⊖ LOW[c,e] Due to risk of bias and imprecision	There may be little or no difference in the frequency of adverse events known to occur with primaquine between 0.5 mg/kg/day primaquine for 7 days and the standard 14-day course.
Anaemia or change in haemoglobin status	0 per 1000	0 per 1000 (0 to 0)	RR 3.0 (0.51 to 174.01)	240 (1 RCT)	⊕⊖⊖⊖ VERY LOW[f,g,h]	We do not know if the occurrence of anaemia differs between the 2 treatment regimens.

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					Due to risk of bias, indirectness, and imprecision	
Adverse events known to occur with chloroquine	0 per 1000	0 per 1000 (0 to 0)	RR 9.40 (0.51 to 174.01)	779 (1 RCT)	⊕⊖⊖⊖ VERY LOW[i,j,k] Due to risk of bias, indirectness, and imprecision	We do not know if there is a difference in the number of participants experiencing adverse events known to occur with chlorquine between the 2 treatment groups.

*__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:** randomized controlled trial; **RR:** risk 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.

[a]Downgraded once for risk of bias: Rajgor 2014 IND, which contributed the most weight to the meta-analysis, was at high risk of selection bias due to no allocation concealment and high risk of attrition bias. Although Pareek 2015 IND was at risk of selection bias as well as other bias for being funded and carried out by drug company, it only contributed a small amount of weight to the meta-analysis.
[b]Downgraded once for imprecision: wide CIs - may be 34% reduction in malaria recurrences or 40% increase with 0.5 mg/kg/day primaquine for 7 days.
[c]Downgraded once for risk of bias: Rajgor 2014 IND was at high risk of selection bias due to no allocation concealment and high risk of attrition bias. Pareek 2015 IND was at risk of selection bias as well as other bias for being funded and carried out by drug company.
[d]Downgraded twice for serious imprecision: very few events (only four events occurring in one trial, Rajgor 2014 IND), very wide CIs.
[e]Downgraded once due to imprecision: wide CIs.
[f]Downgraded once due to risk of bias: Pareek 2015 IND was at risk of selection bias and other bias (funded and performed by drug company).
[g]Downgraded once for indirectness: only one study conducted in G6PD-normal adults in India (Pareek 2015 IND).
[h]Downgraded twice for serious imprecision: only one event, very wide CIs.
[i]Downgraded once for risk of bias: Rajgor 2014 IND at risk of bias selection bias due to no allocation concealment and attrition bias.
[j]Downgraded once for indirectness: only one study conducted in G6PD-normal adults in India (Rajgor 2014 IND).
[k]Downgraded twice for serious imprecision: few events, very wide CIs.

Summary of findings 2. 'Summary of findings' table 2

High-standard 14-day regimen versus standard 14-day regimen for radical cure of *P vivax* malaria

Patient or population: adults and children with confirmed clinical and parasitological *P vivax* malaria
Setting: India
Intervention: high-standard 14-day course of primaquine (0.5 mg/kg/day, adult dose 30 mg)
Comparison: standard 14-day course of primaquine (0.25 mg/kg/day, adult dose 15 mg)

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Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard 14-day course primaquine	Risk with high-standard 14-day course primaquine				
Recurrence of *P vivax* parasitaemia follow-up: range 6 months to 7 months Blood-stage treatment: chloroquine	81 per 1000	66 per 1000 (34 to 116)	RR 0.82 (0.47 to 1.43)	639 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a,b,c] due to indirectness, risk of bias, and imprecision	We do not know if there is any difference in *P vivax* recurrences between high-standard or standard 14-day courses of primaquine given with chloroquine.
Recurrence of *P vivax* parasitaemia follow-up: range 6 months Blood-stage treatment: chloroquine or an ACT	100 per 1000	111 per 1000 (17 to 709)	RR 1.11 (0.17 to 7.09)	38 (1 RCT)	⊕⊖⊖⊖ VERY LOW[d,e,f] due to indirectness, risk of bias, and imprecision	We do not know if there is any difference in *P vivax* recurrences between high-standard or standard 14-day courses of primaquine given with chloroquine or an ACT.
Serious adverse effects	0 per 1000	0 per 1000 (0 to 0)	Not estimable	816 (2 RCTs)	—	No events reported.
Adverse events that result in the discontinuation of treatment	5 per 1000	21 per 1000 (5 to 98)	RR 4.19 (0.90 to 19.60)	778 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a,b,d,g] due to indirectness, risk of bias, and imprecision	We do not know if there is any difference in adverse events resulting in treatment discontinuation between high-standard or standard 14-day courses of primaquine.
Adverse effects known to occur with primaquine	13 per 1000	34 per 1000 (12 to 95)	RR 2.72 (0.98 to 7.57)	778 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a,b,h] due to indirectness, risk of bias, and imprecision	We do not know if there is any difference in adverse events known to occur with primaquine between high-standard or standard 14-day courses of primaquine.
Adverse events known to occur with chloroquine	0 per 1000	0 per 1000 (0 to 0)	RR 9.43 (0.51 to 174.47)	778 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a,b,h] due to indirectness, risk of bias, and imprecision	We do not know if there is any difference in adverse events associated with chloroquine between the 2 treatment groups.

*__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).

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Abbreviations: ACT: artemisinin-based combination therapy; **CI:** confidence interval; **RCT:** randomized controlled trial; **RR:** risk 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.

[a]Downgraded once for indirectness: only one trial conducted in India in G6PD-normal adults (Rajgor 2014 IND).
[b]Downgraded once for risk of bias: open-label - no allocation concealment, risk of selection bias; risk of attrition bias - high percentage not completing six months' follow-up with minimal explanation.
[c]Downgraded once for imprecision: wide CIs - range of 58% reduction in malaria recurrences at 6 months with high-standard 14-day course of primaquine to 43% increase in number of malaria recurrences.
[d]Downgraded once for indirectness: only one trial conducted in India in G6PD-normal adults (Saravu 2018 IND).
[e]Downgraded once for risk of bias: no blinding, high rate of loss to follow-up.
[f]Downgraded once for imprecision: wide CIs - range of 83% reduction in malaria recurrence to 609% increase in malaria recurrences with the high-standard 14-day regimen.
[g]Downgraded once for imprecision: wide CIs 0.9 to 19.6 - range of 10% reduction in adverse events with high-standard 14-day course to 186% increase in adverse events.
[h]Downgraded once for imprecision: wide CIs.

Summary of findings 3. 'Summary of findings' table 3

0.75 mg/kg primaquine/week for 8 weeks versus high-standard 14-day regimen for radical cure of *P vivax* malaria

Patient or population: adults and children with confirmed clinical and parasitological *P vivax* malaria
Setting: Pakistan
Intervention: 0.75 mg/kg primaquine/week for 8 weeks (adult dose 45 mg)
Comparison: high-standard 14-day course primaquine (0.5 mg/kg/day, adult dose 30 mg)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with high-standard 14-day course primaquine	Risk with once-weekly 0.75 mg/kg primaquine for 8 weeks				
Recurrence of *P vivax* malaria Follow-up: 8 months	0 per 1000	0 per 1000 (0 to 0)	RR 7.00 (0.38 to 127.32)	126 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, and imprecision	We do not know if weekly primaquine reduces the risk of malaria recurrences when compared to the high-standard 14-day course.

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Recurrence of *P vivax* malaria Follow-up: 11 months	19 per 1000	59 per 1000 (7 to 511)	RR 3.18 (0.37 to 27.60)	122 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a,b,d] due to risk of bias, indirectness, and imprecision	We do not know if weekly primaquine reduces the risk of malaria recurrences when compared to the high-standard 14-day course.
Serious adverse effects	0 per 1000	0 per 1000 (0 to 0)	Not estimable	129 (1 RCT)	—	No events reported.
Anaemia (haemoglobin < 7 g/dL)	0 per 1000	0 per 1000 (0 to 0)	Not estimable	129 (1 RCT)	—	No events reported.

*__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:** randomized controlled trial; **RR:** risk 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.

[a]Downgraded by 1 for risk of bias: Leslie 2008 PAK was at high risk of bias for randomization process, allocation concealment, and incomplete outcome data.
[b]Downgraded by 1 for indirectness: only one study conducted in Pakistan, only one G6PD-deficient adult included in one trial (in weekly arm).
[c]Downgraded by 2 for serious imprecision: few events, very wide CIs.
[d]Downgraded by 2 for serious imprecision: few events, very wide CIs.

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BACKGROUND

Malaria is a potentially life-threatening disease caused by the *Plasmodium* parasite, which is transmitted by the bite of an infected female *Anopheles* mosquito. Five species of *Plasmodium* malaria parasites can cause malaria disease in humans, of which *Plasmodium vivax* and *Plasmodium falciparum* are the most important (WHO 2016). In 2017, an estimated 219 million cases of malaria occurred worldwide and an estimated 435,000 people died from the disease (WHO 2018). The World Health Organization (WHO) aims to reduce malaria case load and mortality by at least 90% by 2030 (WHO 2016).

Historically, *P vivax* infection was thought to be a milder form of malaria, and researchers have focused on *P falciparum* due to the high number of deaths it causes (Bassat 2016). In recent years, it's been shown that the morbidity and mortality of *P vivax* have been underestimated, with evidence of direct fatality and contribution to mortality in patients who have other comorbidities, such as malnutrition, HIV, or coexisting infections (Baird 2013; Bhattacharjee 2013; Rizvi 2013; Singh 2013; Battle 2014; Douglas 2014; Kochar 2014; Arévalo-Herrera 2015; Baird 2015b). Repeated *P vivax* infections through childhood and adulthood also affect personal well-being, development, and education and can thus negatively impact economic development, both for the individual and the community (Mendis 2001). *P vivax* malaria in pregnancy is associated with maternal anaemia, spontaneous abortion, stillbirth, and low birthweight, with especially poor pregnancy outcomes for women with severe infection (McGready 2012; Rijken 2012; Brutus 2013).

Description of the condition

P vivax infection caused an estimated 7.5 million cases of malaria in 2017 (WHO 2018). The geographical distribution of*P vivax* malaria is more widespread than any of the other forms of human malaria, with around 35% of the world's population thought to be at risk (Howes 2016)). Co-infection with *P falciparum* is also common in many regions (Kumar 2007; Mueller 2009). As malaria control accelerates, the *P vivax* proportion in co-endemic areas tends to rise compared to that of *P falciparum*, which highlights the importance and challenge of this infection (John 2012).

P vivax is important because as many countries progress towards malaria elimination, the parasite becomes a roadblock to eradication (Cibulskis 2015; Bassat 2016). Despite a reported 45% reduction in *P vivax* malaria cases between 2010 and 2016 (WHO 2017), the parasite has several characteristics that enable it to evade control (Newby 2016). The early appearance of gametocytes in the blood, often prior to symptoms of malaria, increases the chance of onward transmission by mosquitoes (Mendis 2001). *P vivax* differs from *P falciparum* in that as well as having a blood-stage infection, hypnozoites develop in the liver that can be dormant for weeks to months before developing into an infection (White 2011). What triggers these relapses is not well-understood. There is difficulty in distinguishing between relapse (hypnozoite activation), recrudescence (subpar treatment of the initial blood-stage infection), and re-infection (new infection with *P vivax*) (Imwong 2007). A study in Papua New Guinea suggested that relapses cause four-fifths of *P vivax* infections (Robinson 2015), reinforcing the importance of relapse in sustaining transmission (White 2011). Parasites show high genetic diversity, even in countries that are at malaria elimination stage (Koepfli 2015). *P vivax* is likely underestimated worldwide, as the dormant liver stage is not detected in routine surveys (Gething 2012). Submicroscopic infections and asymptomatic infection reservoirs may also lead to underdiagnosis or misdiagnosis. A systematic review showed that across all study sites, the polymerase chain reaction (PCR) prevalence of *P vivax* was significantly higher than that identified by light microscopy (Cheng 2015). The effect this may have on *P vivax* malaria studies is unclear.

There are different strains of *P vivax* according to geographical region/endemicity areas, with relapse patterns that vary by latency (time to first relapse), likelihood of relapse, and frequency of relapses, which further complicates the assessment of efficacy of drugs on relapses (Battle 2014; White 2016). Strains commonly found in Southeast Asia and Oceania (including the 'Chesson' strain isolated from an individual infected in Papua New Guinea) have the shortest latency time to relapse, starting as early as three weeks after first infection (if untreated with a hypnozoiticidal drug) (Ehrman 1945). These areas correspond to zones 10 and 12 in Battle 2014. Indian and Pakistan strains (zone 8) exhibit heterogeneity in relapse latency, incidence, and frequency, while South American strains (zone 3) have a pattern of short latency to first relapse and less frequent relapses than in zones 10 and 12 (Battle 2014). The temperate strains (which include those from Korea in zone 11) relapse much more slowly (John 2012; Battle 2014). Strains of the type in zones 10 and 12, referred to here as 'East Asia and Oceania', are recommended to receive higher doses of primaquine (the high-standard course of 0.5 mg/kg/day rather than standard 0.25 mg/kg/day for 14 days) to prevent relapses (WHO 2015), apparently based on research done in the 1950s and 1960s (Coatney 1953; Jones 1953; Vivona 1961; Maffi 1971; Clyde 1977), although not all these studies were done with strains from the targeted geographic area.

Primaquine, an 8-aminoquinoline, has until very recently been the only drug available on the market for treating the hypnozoite stage of infection (Ashley 2014). One of the main barriers in *P vivax* treatment is the reluctance to use primaquine due to it potentially causing haemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. G6PD deficiency is the most common enzyme deficiency worldwide and affects red blood cells by leading to their premature lysis (Nkhoma 2009). G6PD deficiency is common in countries where *P vivax* malaria is endemic, with an estimated population prevalence of 8% (Howes 2012). Within G6PD deficiency, there are differing phenotypes, meaning some people may be mildly sensitive to primaquine, while others may be very sensitive and experience life-threatening haemolysis (Baird 2015a), which explains the varying responses to primaquine. In many areas where *P vivax* is predominant, testing for G6PD deficiency is not available locally (Baird 2015b). In 2018 the US Food and Drug Administration (FDA) approved a newer alternative, another 8-aminoquinoline known as tafenoquine (MMV 2018), which has shown promise in reducing relapses, but there are increased safety concerns in patients with undiagnosed G6PD deficiency compared to primaquine, due to its longer half-life (Rajapakse 2015).

Description of the intervention

People with *P vivax* malaria require treatment with an antimalarial drug to treat the blood-stage infection, and a drug to treat the hypnozoite stage (radical cure). The WHO recommends treatment with either chloroquine or an artemisinin-based combination therapy (ACT) for the blood-stage infection, with 0.25 to 0.5 mg/kg/day primaquine for 14 days for the liver stages (WHO 2015). Artemisinin-based combination therapies and chloroquine have been shown to

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be effective and comparable in treating the blood-stage infection of *P vivax* malaria (Gogtay 2013).

A previous Cochrane Review showed that primaquine regimens of five days or fewer had similar recurrence rates to placebo or no primaquine. Of the comparisons included in the review, a regimen of 0.25 mg/kg/day (15 mg) a day of primaquine for 14 days had the lowest recurrence rates of *P vivax* infection (Galappaththy 2013). There were no trials at that time that compared higher doses of primaquine at 14 or 7 days.

Primaquine was first made available to North American soldiers in the 1950s (Baird 2004). Its mechanism and metabolism are not widely understood, but it has a broad spectrum of activity against the *Plasmodium* parasite. As well as preventing relapse of *P vivax* malaria by targeting the latent and developing hypnozoites in the liver, it is also used in malaria prophylaxis (Baird 2003). It is absorbed from the gastrointestinal tract, has a half-life of about four to nine hours, and crosses the placenta in pregnancy (Baird 2004). New advancements in studying *P vivax* in humanized mice may lead to a greater understanding of the mechanism of action of the drug (Mikolajczak 2015).

Adverse effects of primaquine include production of methaemoglobin, an oxidated state of haemoglobin that cannot transport oxygen to tissues. Methaemoglobinaemia (an abnormal buildup of methaemoglobin) can result in cyanosis when levels exceed 10% of the usual haemoglobin level (Vale 2009). As described above, primaquine causes haemolysis in people with G6PD deficiency, which leads to anaemia (Ashley 2014). When taken on an empty stomach it can cause abdominal pain and gastrointestinal upset (Vale 2009). Safe use of primaquine during pregnancy has not been established. The radical cure with primaquine can be delayed until after pregnancy. With regard to breastfeeding patients, a recent study showed that the levels of primaquine in breast milk may not be sufficient to cause haemolysis even in a G6PD-deficient baby (Gilder 2018), but it is not recommended at this time.

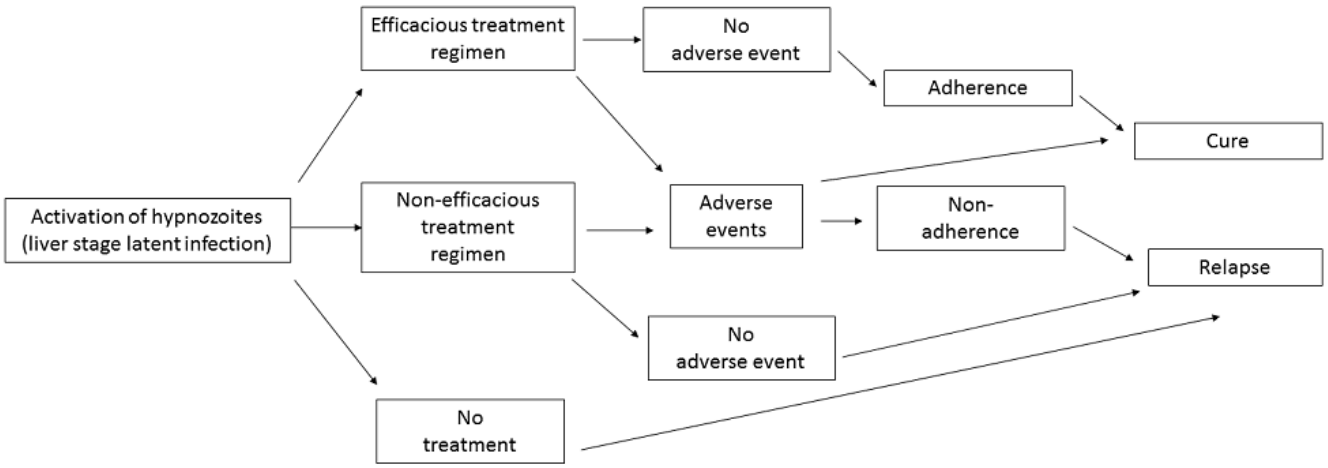
How the intervention might work

The WHO advises that 0.25 mg to 0.5 mg/kg/day of primaquine for 14 days should be used for radical cure of *P vivax* malaria in patients over six months old, excluding people with G6PD deficiency and those who are pregnant or breastfeeding (WHO 2015).

There has been suggestion of failure of the regimen of 0.25 mg/kg/day for 14 days (hereafter referred to as the 'standard 14-day regimen') of primaquine for the Chesson strain of *P vivax*, which was behind the suggestion of the increased dosing of 0.5 mg/kg/day in East Asia and Oceania (hereafter referred to as the 'high-standard 14-day regimen'). However, evidence for the choice of the high-standard regimen is not presented in the WHO treatment guidelines (WHO 2015). The previous Cochrane Review, Galappaththy 2013, found no trials that compared the high-standard 14-day regimen to the standard 14-day regimen. The WHO recommends a weekly dose of 0.75 mg/kg for eight weeks for patients with G6PD deficiency, but the evidence for this is of low quality, as there are few high-quality trials (WHO 2015).

The 14-day course of primaquine can lead to treatment adherence issues, as well as to safety concerns about haemolysis in places where G6PD testing is not available, meaning that shorter courses of primaquine are desirable. Failure to treat the hypnozoite stage of *P vivax* malaria leads to repeated relapses, morbidity, and persistent infection. The logic framework for developing efficacious and safe treatment regimens for *P vivax* is illustrated in Figure 1.

Figure 1. Logic framework: treatment outcome pathways in *Plasmodium vivax* liver hypnozoite activation.



It has long been suggested that it may be the total dose of primaquine that is important in the treatment of the hypnozoite stage rather than the length of the course (Schmidt 1977). If a higher dose of primaquine could be administered safely over a shorter period of time, it may improve adherence rates, thus reducing relapse rates and morbidity and mortality resulting from *P vivax* infection. There are small trials from the 1970s that suggest that shorter, higher-dose regimens were as efficacious as the 14-day courses (Clyde 1977; Saint-Yves 1977). At the time of the previous Cochrane Review (Galappaththy 2013), there were no recent large high-quality trials that had investigated the use of higher doses given over seven days. We planned to include any such trials in this Cochrane Review.

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Why it is important to do this review

The use of primaquine for radical cure of *P vivax* malaria continues to pose a therapeutic dilemma for healthcare providers in areas without adequate screening for G6PD status. Clinicians must either choose to give primaquine and risk haemolysis if the patient is G6PD-deficient, or withhold treatment and accept the complications of ongoing parasite infection and relapses. This is why when clinicians choose to treat with primaquine they prefer a lower dose over a more prolonged period, which then risks difficulties with adherence and thus reduced effectiveness.

We know from the previous Cochrane Review on primaquine with chloroquine for radical cure that the standard 14-day regimen of 0.25 mg/kg/day (15 mg per day or 210 mg total dose) is better than shorter regimens of similar daily doses and placebo (Galappaththy 2013). In fact, the regimen of 0.25 mg/kg/day for 5 days of primaquine did not reduce recurrences compared to treating with chloroquine alone.

A major problem with the radical cure of *P vivax* is difficulty with the adherence of the 14-day course of primaquine, which has led to many countries shortening the regimen. Peru was one such example, although a study revealed that patients often still discontinued the therapy after around three days, when they started to feel better (Grietens 2010). A study that compared directly observed therapy (DOT) for 14 days of primaquine versus non-DOT primaquine found that the *P vivax* recurrence rate was significantly lower in the DOT group (Takeuchi 2010). These problems have led to a more urgent call for shorter treatment regimens. Various trials are investigating regimens that revise dosing and duration of treatment in order to improve adherence and reduce the potential for incomplete treatment and development of resistance. As mentioned previously, the significance of the total cumulative primaquine dose given, rather than the length of the course, is one avenue of investigation. In areas where G6PD screening is present, using higher dosing regimens over shorter time periods, if at least similarly efficacious, could improve adherence and reduce morbidity associated with *P vivax* parasitaemia.

World Health Organization guidelines suggest a higher dosing regimen of primaquine for the tropical, frequent-relapsing strain of *P vivax* in East Asia and Oceania (WHO 2015), although the previous Cochrane Review, Galappaththy 2013, did not find any trials assessing this. Investigating the evidence base for this is therefore important. The 2015 WHO guidelines also suggest an alternate dosing regimen of weekly primaquine, which may be safer in patients with G6PD deficiency. As the previous Cochrane Review included data from only one trial assessing this, it is useful to investigate whether there is further evidence to substantiate this guidance.

In this Cochrane Review, we have excluded comparisons between blood-stage drug (chloroquine/ACT) with and without primaquine, as the rationale for primaquine use has been sufficiently demonstrated in a previous Cochrane Review (Galappaththy 2013). Similarly, we have not included comparisons between different blood-stage drugs in which the same dose of primaquine was used; an update to an existing Cochrane Review, Gogtay 2013, is in progress and will address this. However, we planned to stratify our results according to partner drug, as there is increasing evidence that primaquine is metabolized via the cytochrome P450 2D6 (CYP2D6) pathway (Bennett 2013), and efficacy may thus be affected if the blood-stage antimalarial drug is a CYP2D6 inhibitor (Baird 2018).

This review excluded comparisons of regimens that do not use the control of the standard or high-standard regimen of 14 days of primaquine. Also, it did not include comparisons of primaquine regimens of 0.25 mg/kg/day for less than 14 days, as Galappaththy 2013 has already assessed these shorter regimens of the same daily dose.

There is currently a lack of consensus among studies as to what the minimum time frame for follow-up of relapse in *P vivax* malaria should be. The WHO guidance on clinical trials in malaria sets out standard follow-up for blood (or schizontal) stage infection as 28 days after treatment commencement, but has no clear definition on the follow-up period for radical cure in primaquine studies. It states that "follow up varies from three months to a year in the literature, and should be adapted to regional parasite characteristics" (WHO 2009). In a recent review, John 2012 described relapse of the tropical frequently relapsing strain of *P vivax* as typically three weeks, but this varies according to blood-stage treatment: "three weeks following quinine therapy" and "six to eight weeks following chloroquine" (White 2011). With exposure to primaquine - even if radical cure is not achieved - relapses may occur at longer intervals (Sutanto 2013). In the Cochrane Review (Galappaththy 2013), the follow-up period started 30 days after completing primaquine treatment. Relapse is frequently defined as the presence of *P vivax* parasites more than 28 to 30 days after the full course of primaquine in people living in a non-endemic area (Looareesuwan 1997). Due to the varying lengths of treatment and relapse time in *P vivax* malaria, 28 days from treatment completion may not allow true assessment of radical cure. It also makes assessment of the weekly primaquine regimen difficult, as the follow-up time should start before the eight-week treatment course has finished. In this Cochrane Review we planned to assess parasitaemia at 3, 6, and 12 months' follow-up, in keeping with WHO guidance. We intended to describe the length of follow-up across studies, and then group them into meaningful lengths of follow-up, depending on the regimen.

We intended to answer the following questions by comparing the new regimens to the standard 14-day regimen of primaquine (0.25 mg/kg/day; 15 mg adult dose) or the high-standard 14-day regimen (0.5 mg/kg/day; 30 mg adult dose) recommended for East Asia/Oceania.

- Is the high-standard 14-day regimen more efficacious and safer compared to the standard 14-day course in all areas, or only in areas where it is recommended (East Asia and Oceania)?
- Are shorter, higher-dose regimens (0.5 mg/kg/day for 7 days) as efficacious and safe as the standard 14-day regimen?
- Are weekly dosing regimens (0.75 mg/kg or 45 mg adult dose/week for 8 weeks) as efficacious and safe as the standard or high-standard 14-day regimen?

OBJECTIVES

To assess the efficacy and safety of alternative primaquine regimens for radical cure of *P vivax* malaria compared to the standard or high-standard 14 days of primaquine (0.25 or 0.5 mg/kg/day), as well as comparison of these two WHO-recommended regimens.

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METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs). We excluded quasi-RCTs.

Types of participants

Adults and children with confirmed clinical and parasitological (light microscopy or PCR, or both) diagnosis of *P vivax* malaria. We included trials that excluded people with G6PD deficiency and trials that included populations that had or had not been screened for G6PD deficiency. People with mixed malaria infections were excluded.

Types of interventions

Intervention

Any regimen of either chloroquine or an artemisinin-based combination therapy (ACT) plus primaquine with any of the following.

- Daily doses higher than 0.25 mg/kg/day for 14 days.
- Shorter regimens with the same total dose.
- Weekly dosing regimens.

Control

WHO-defined standard regimen of 14 days of primaquine at 0.25 mg/kg/day (15 mg adult dose) in most areas, or high-standard regimen of 0.5 mg/kg/day (30 mg adult dose) in East Asia and Oceania, plus either chloroquine or an ACT.

We included comparisons between the two WHO recommended 14 day regimes (0.25mg/kg/day and 0.5mg/kg/day). We included trials that used chloroquine or ACT as the treatment for blood-borne infection, and we planned to stratify by the blood schizonticidal agent.

Types of outcome measures

Primary outcomes

- *P vivax* parasitaemia (detected by light microscopy or PCR, or both) at 3, 6, and 12 months' follow-up. We planned to describe this as recurrences of *P vivax* malaria due to the previously mentioned difficulties in distinguishing between relapse and re-infection.

Secondary outcomes

- *P vivax* parasitaemia (detected by light microscopy or PCR, or both) at one to three months' follow-up.

Adverse events

- Serious adverse events (fatal, life-threatening, or requiring hospitalization).
- Adverse events that result in discontinuation of treatment.
- Events known to occur with primaquine (cyanosis, leucopenia, methaemoglobinaemia, hypertension, cardiac arrhythmia, abdominal pain, nausea, vomiting, or haemolysis) or those due to a comparator drug used along with primaquine.
- Anaemia or change in haemoglobin status.
- Other adverse events.

Search methods for identification of studies

We attempted to identify all relevant studies regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

We searched the following databases using the search terms and strategy described in Appendix 1: the Cochrane Infectious Diseases Group Specialized Register (17 December 2018); the Cochrane Central Register of Controlled Trials (CENTRAL, 2018, Issue 12, published in the Cochrane Library); MEDLINE (PubMed, 1946 to 17 December 2018); Embase (Ovid, 1947 to 17 December 2018); and LILACS (Bireme, 1982 to 17 December 2018). We also searched the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/), and ClinicalTrials.gov (clinicaltrials.gov/ct2/home), for trials in progress, on 17 December 2018, using "primaquine" and "vivax" as search terms.

Searching other resources

We checked the reference lists of all studies identified by the above methods for additional potentially relevant studies. We contacted researchers working in the field and the WHO for unpublished and ongoing trials. We also searched the reference lists and included studies of the Cochrane Review by Galappaththy 2013.

Data collection and analysis

Selection of studies

Two review authors independently screened the titles and abstracts of the search results to identify potentially eligible trials, coding the articles as either 'retrieve' or 'do not retrieve'. We obtained the full-text reports of potentially eligible trials and assessed them for inclusion in the review using a predesigned eligibility form based on the inclusion criteria. Any discrepancies were resolved through discussion or by consulting a third review author if necessary. Where necessary, we contacted the trial authors for clarification of trial methods. We listed the excluded trials and the reasons for their exclusion in a 'Characteristics of excluded studies' table. Where there were multiple reports relating to the same trial, we planned to include all reports and collate data. We detailed the trial selection process in a PRISMA diagram.

Data extraction and management

Two review authors independently extracted data from the included trials using a data extraction form designed specifically for this review, in keeping with Cochrane guidance (Higgins 2011).

For each included trial we extracted a minimum of the following data where available.

- Study design.
- Endemicity/population demographics.
- G6PD status of participants (known/unknown).
- CYP2D6 status (if available).
- Blood-stage antimalarial drug choice.
- Dose/duration/timing of treatment arms.
- Supervised or non-supervised therapy.
- Duration of follow-up.
- Adverse events.

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- Reported outcomes.

Any differences in data extraction were resolved through discussion or by consulting a third review author if necessary. We entered the extracted data into Review Manager 5 (RevMan 2014). Where necessary, we contacted the authors of primary trials regarding missing data or methodological details of the trial. We noted any limitations in the included studies.

We grouped comparisons as illustrated in Table 1.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias of each included trial using the Cochrane 'Risk of bias' assessment tool, discussing any differences of opinion. In the case of missing or unclear information, we contacted the trial authors for clarification. We summarized the results in the 'Risk of bias' tables in the 'Characteristics of included studies' tables (Higgins 2011).

Measures of treatment effect

For dichotomous data, we compared interventions using risk ratios (RRs) to measure treatment effect. Where trial authors presented data as odds ratios, we recalculated the effect. We defined statistical significance as $P < 0.05$ and calculated 95% confidence intervals (CIs) for all results. For comparable trials, we performed meta-analyses if there were sufficient data.

Unit of analysis issues

We split trials that included more than two comparison groups and analysed them as individual pair-wise comparisons. If there was a shared control group, we split the control group so that participants were only counted once in the overall meta-analysis.

Dealing with missing data

We analysed missing data using available-case analysis if we judged the trial to be at low risk of bias for incomplete outcome data. We attempted to contact trial authors to obtain missing or unclear data. If the missing data rendered the result uninterpretable, we excluded the data from meta-analyses and clearly stated the reason for exclusion. If the missing data meant that results were interpretable but likely to be at high risk of bias, we used imputation methods to investigate the impact of the missing data. We analysed extracted data on an intention-to-treat basis where there were no missing data.

Assessment of heterogeneity

We inspected forest plots for overlapping CIs. We also applied the Chi^2 test as a statistical test for the presence of heterogeneity, with a P value of 0.10 used to indicate statistical significance, and we computed the I^2 statistic to quantify the percentage of the variability in effect estimates that was due to heterogeneity rather than sampling error (chance). We investigated possible causes of heterogeneity by subgroup analysis. If substantive heterogeneity persisted, defined as an I^2 statistic value of greater than 50%, we used a random-effects meta-analysis.

Assessment of reporting biases

We planned to examine the likelihood of reporting bias using funnel plots, however the number of included trials was insufficient to permit this.

Data synthesis

We analysed the data using Review Manager 5 (RevMan 2014). We assessed the certainty of the evidence for each outcome measure using the GRADE approach, and we constructed 'Summary of findings' tables using GRADEpro GDT (GRADEpro GDT 2015). We stratified results according to blood-stage partner drug (if different blood-stage antimalarials were used, which only occurred for one comparison). Length of follow-up varied with regimens and between studies. We described regimens and follow-up periods and defined sensible groupings for follow-up. We also performed subgroup analyses according to geographical region/endemicity and directly observed therapy (DOT) or non-DOT. We stratified results by length of follow-up. We had planned to perform a subgroup analysis according to CYP2D6 status, however data were insufficient to permit this.

Subgroup analysis and investigation of heterogeneity

We grouped the analysis by drug regimen. We described the interventions and outcomes in all included trials. We conducted an inventory of length of follow-up against each drug regimen and then grouped *P vivax* parasitaemia recurrence by appropriate groupings for length of follow-up.

Sensitivity analysis

We planned to assess the risk of bias of studies that contributed data to the meta-analyses for the prespecified outcomes with sensitivity analyses against concealment of allocation.

RESULTS

Description of studies

Results of the search

Our database search, conducted up to 17 December 2018, identified 251 studies (after removal of 3 duplicates). We excluded 214 articles during abstract screening, and selected 37 studies for full-text review. We excluded 25 studies with reasons provided; identified two trials as ongoing; and included 10 studies in the review. The search results are presented in a PRISMA diagram in Figure 2.

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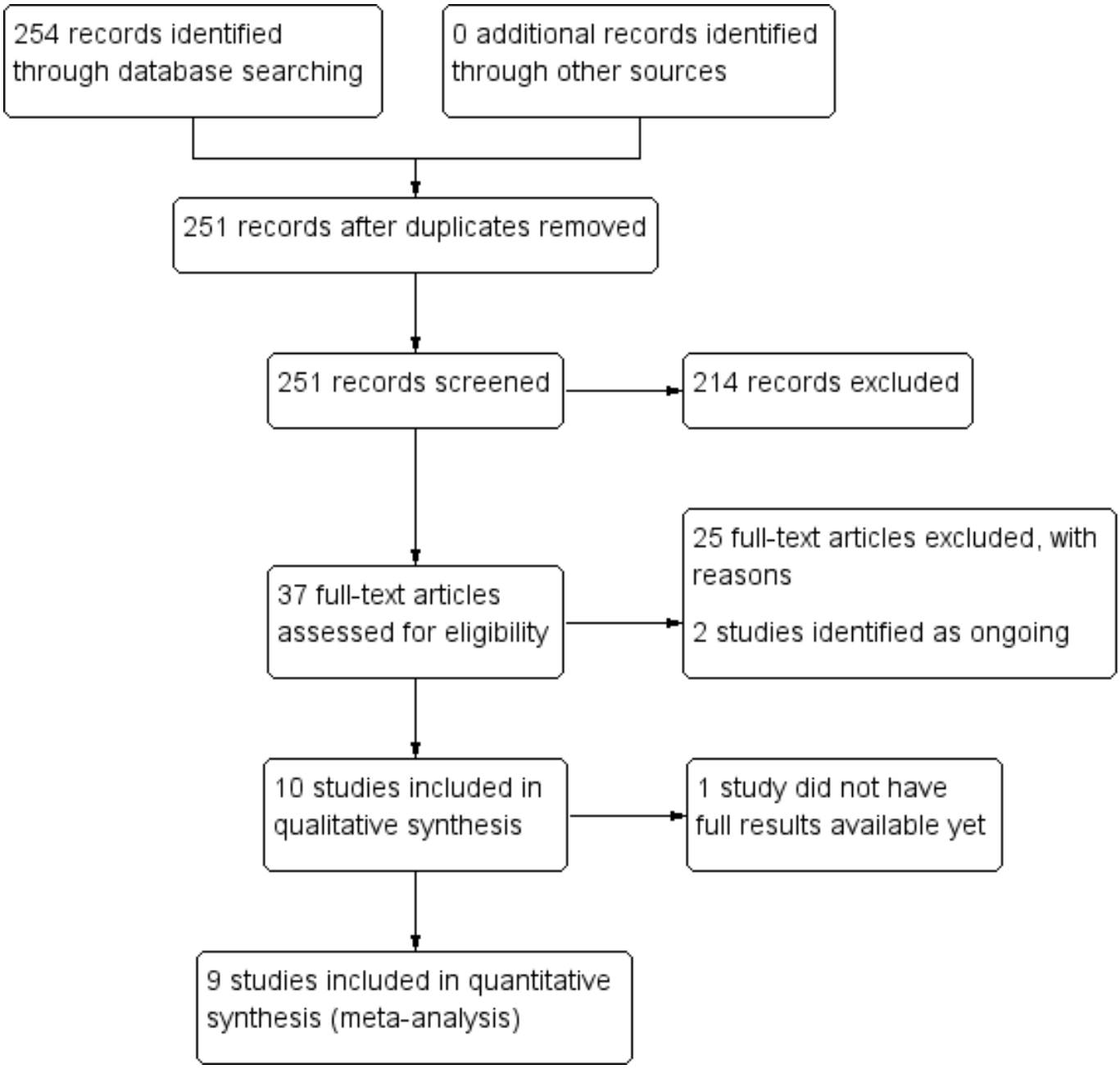
Figure 2. Study flow diagram.



Included studies

Although 10 studies (of 10 trials) met our inclusion criteria, one study was deemed ineligible for data extraction and analysis. There were only partially available results available in a conference abstract for Chu 2016 THA, meaning that we could not assess risk of bias or analyse results. We contacted the author for the full results but this was declined pending future publication. We included nine studies (of nine trials) in our quantitative analysis.

Four trials were conducted in South America: one in Colombia (Carmona-Fonseca 2009 COL), one in Brazil (Abdon 2001 BRA), and two in Peru (Solari-Soto 2002 PER; Durand 2014 PER). Five trials were conducted in Asia: one in Pakistan (Leslie 2008 PAK), one in Thailand (Bunnag 1994 THA), and three in India (Rajgor 2014 IND; Pareek 2015 IND; Saravu 2018 IND). All nine trials included data for adults, and four trials included children under the age of 10 years (Solari-Soto 2002 PER; Leslie 2008 PAK; Carmona-Fonseca 2009 COL; Durand 2014 PER). No trials had information on children under one year old.

Seven trials excluded pregnant women, and two trials did not specify whether or not pregnant women were included (Bunnag 1994 THA; Solari-Soto 2002 PER). Six trials specified that lactating women were excluded, while the remaining three trials did not provide details regarding this (Bunnag 1994 THA; Solari-Soto 2002 PER; Carmona-Fonseca 2009 COL). Only one trial included people with G6PD deficiency (Leslie 2008 PAK). Six trials excluded people with

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G6PD deficiency (Bunnag 1994 THA; Carmona-Fonseca 2009 COL; Durand 2014 PER; Rajgor 2014 IND; Pareek 2015 IND; Saravu 2018 IND), and two trials did not specify whether or not people with G6PD deficiency were included (Abdon 2001 BRA; Solari-Soto 2002 PER). All of the trials used microscopy for diagnosis of parasitaemia. Four trials carried out PCR genotyping of *vivax* parasitaemia as well (Durand 2014 PER; Rajgor 2014 IND; Pareek 2015 IND; Saravu 2018 IND).

Two trials used different doses or regimens of chloroquine within trial arms, but as both confirmed that parasitaemia had resolved following treatment, we still included them in the review (see Characteristics of included studies) (Bunnag 1994 THA; Abdon 2001 BRA). None of the included trials described the CYP2D6 status of participants.

Excluded studies

We excluded 25 studies during full-text screening; see details in Characteristics of excluded studies.

Risk of bias in included studies

A summary of the 'Risk of bias' assessments is presented in Figure 3. Full details are shown in the Characteristics of included studies tables.

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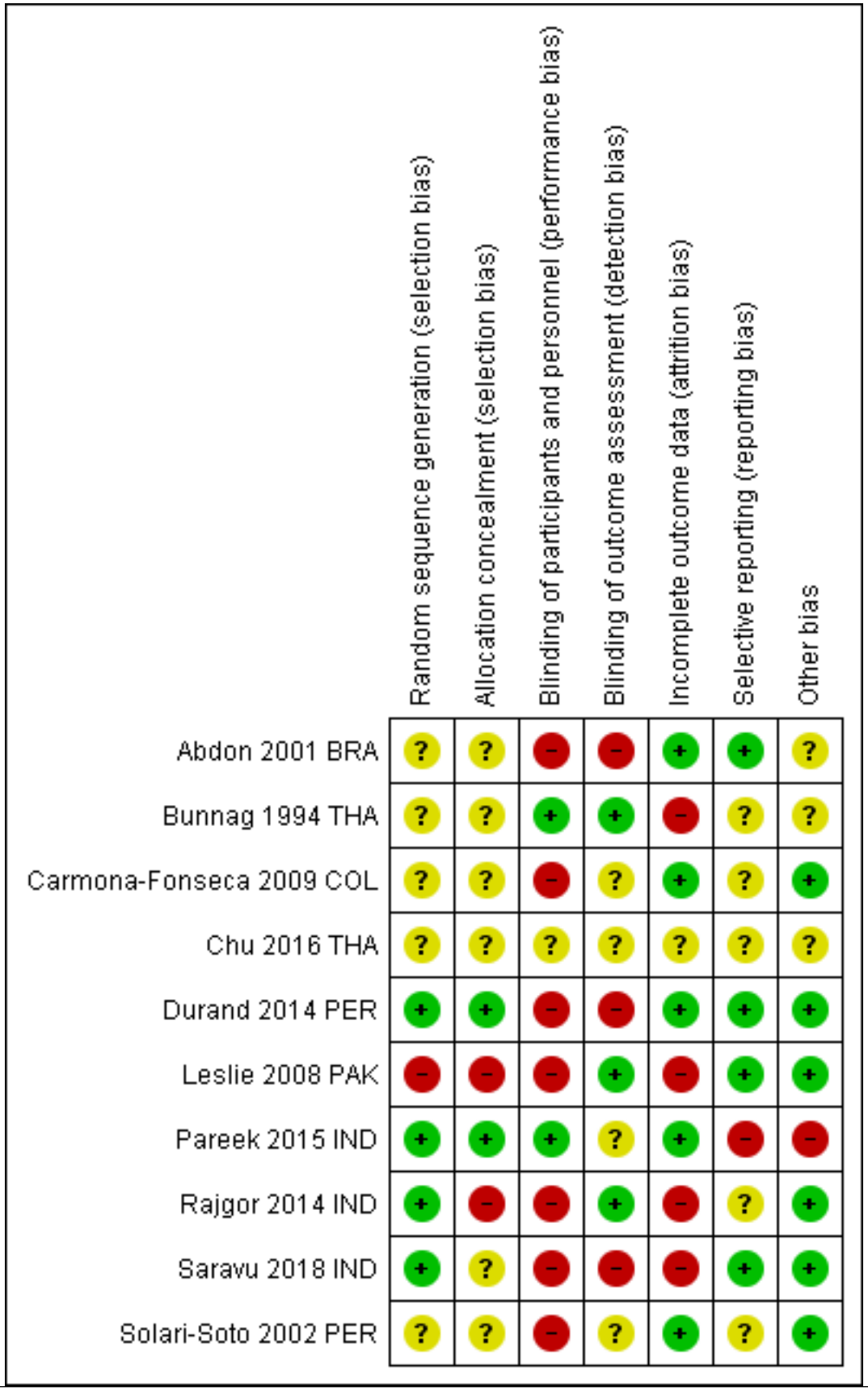
Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.



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Allocation

Four trials described adequate methods of treatment randomization and were judged to be at low risk of selection bias (Durand 2014 PER; Rajgor 2014 IND; Pareek 2015 IND; Saravu 2018 IND). We assessed one trial as being at high risk of bias as it used two different methods of randomization depending on location, using house numbers or sequential patient numbers (Leslie 2008 PAK). Four trials did not detail the randomization process (Bunnag 1994 THA; Abdon 2001 BRA; Solari-Soto 2002 PER; Carmona-Fonseca 2009 COL).

Two trials used sealed envelopes to conceal allocation and so were assessed as being at low risk of bias (Durand 2014 PER; Pareek 2015 IND). We assessed two trials with no concealment of treatment allocation as at high risk of bias (Leslie 2008 PAK; Rajgor 2014 IND), while five trials provided no information on whether or not allocation concealment was used(Bunnag 1994 THA; Abdon 2001 BRA; Solari-Soto 2002 PER; Carmona-Fonseca 2009 COL; Saravu 2018 IND).

Blinding

Seven trials were open-label and were assessed as at high risk of performance bias (Abdon 2001 BRA; Solari-Soto 2002 PER; Leslie 2008 PAK; Carmona-Fonseca 2009 COL; Durand 2014 PER; Rajgor 2014 IND; Saravu 2018 IND); two of these trials reported blinding of the microscopists who analysed the blood work (Leslie 2008 PAK; Rajgor 2014 IND). Two trials reported blinding of participants and personnel and were classified as being at low risk of bias (Bunnag 1994 THA; Pareek 2015 IND).

Incomplete outcome data

Five trials had low rates of attrition with losses accounted for and so were judged as at low risk of attrition bias (Abdon 2001 BRA; Solari-Soto 2002 PER; Carmona-Fonseca 2009 COL; Durand 2014 PER; Pareek 2015 IND). We assessed four trials as at high risk of attrition bias. Bunnag 1994 THA had unexplained, significant loss to follow-up (more than three-quarters of participants by the end of the trial), making the results uninterpretable. Leslie 2008 PAK had a higher loss to follow-up in the intervention group compared to the control group (6% loss versus 1% loss). Rajgor 2014 IND had a high percentage of missing results at six months. Saravu 2018 IND had a high percentage of loss to follow-up in both arms by six months.

Selective reporting

We judged four trials to have adequately reported on either prespecified or expected outcomes (Abdon 2001 BRA; Leslie 2008 PAK; Durand 2014 PER; Saravu 2018 IND). Risk of reporting bias was unclear for five trials as no protocols were available (Bunnag 1994 THA; Solari-Soto 2002 PER; Carmona-Fonseca 2009 COL; Rajgor 2014 IND; Chu 2016 THA). We assessed Pareek 2015 IND as being at high risk of reporting bias because compliance was added as an outcome, primaquine levels were not reported as planned, and PCR results were not well-detailed.

Other potential sources of bias

We judged Pareek 2015 IND to be at high risk of other bias as it was funded by the drug company that manufactured the primaquine preparations, and the authors were employees of the company. We assessed six trials as at low risk of other bias (Solari-Soto 2002 PER; Leslie 2008 PAK; Carmona-Fonseca 2009 COL; Durand 2014 PER; Rajgor 2014 IND; Saravu 2018 IND). We assessed two trials for which funding was not detailed as at unclear risk of other bias (Bunnag 1994 THA; Abdon 2001 BRA).

Effects of interventions

See: **Summary of findings for the main comparison** 'Summary of findings' (main comparison); **Summary of findings 2** 'Summary of findings' table 2; **Summary of findings 3** 'Summary of findings' table 3

High-standard 14-day regimen versus standard 14-day regimen

The WHO recommends higher doses of primaquine (0.5 mg/kg/day) for 14 days in East Asia and Oceania. We intended to examine whether this high-standard regimen was more efficacious in areas where it is currently recommended (because of assumed resistance - East Asia, Oceania) as well as in all other areas where resistance is not thought to occur.

Two trials compared the high-standard 14-day course with the standard (0.25 mg/kg/day) 14-day course, both carried out in adults in India (Rajgor 2014 IND; Saravu 2018 IND). Both trials excluded pregnant/lactating and G6PD-deficient patients. In Rajgor 2014 IND, participants were treated with chloroquine, with the primaquine regimen (which was supervised) given after completion of the chloroquine course. In Saravu 2018 IND, participants were treated with either chloroquine or an ACT (artesunate with doxycycline or artemether-lumefantrine), and (unsupervised) primaquine was given after completion of the blood-stage treatment. We planned to stratify results according to blood-stage treatment; however, Saravu 2018 IND combined the results for both blood-stage treatments, so we were unable to separate results according to partner drug. Only the blood-stage drugs given to participants who had recurrences were described. For this reason, results from the two studies are not combined and are presented separately.

Efficacy

In Rajgor 2014 IND, 21 participants out of 317 in the high-standard 14-day group had a recurrence of *vivax* malaria compared with 26 out of 322 in the standard 14-day group at 6 months' follow-up, giving an 18% reduction in recurrence of parasitaemia in the high-standard group (risk ratio (RR) 0.82, 95% confidence intervals (CI) 0.47 to 1.43; 639 participants; very low-certainty evidence; Analysis 1.1). *Vivax* malaria recurrences were also investigated by PCR to determine whether they were true relapses or new infections. After this adjustment, results showed an 83% increase in *vivax* malaria cases in the high-standard group (RR 1.83, 95% CI 0.62 to 5.40; Analysis 1.2).

Rajgor 2014 IND was at high risk of bias for allocation concealment. However, as we chose not to combine the data with Saravu 2018 IND for this analysis, a sensitivity analysis could not be done.

In Saravu 2018 IND, 2 out of 18 participants in the high-standard 14-day group had a recurrence of *P vivax* malaria compared to 2 out of 20 in the standard 14-day group at 6 months' follow-up (RR 1.11, 95% CI 0.17 to 7.09; Analysis 1.1). Both of the recurrences in the high-standard 14-day group were given chloroquine. Of the recurrences in the standard 14-day group, one participant received chloroquine and one participant received artesunate and doxycy-

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cline. Polymerase chain reaction genotyping suggested that all four participants had true relapses of infection.

It should be noted that because Saravu 2018 IND was a small pilot trial, if we had not stratified according to blood-stage treatment, results would have been largely the same as for Rajgor 2014 IND alone.

Adverse effects

In Rajgor 2014 IND there were no serious adverse events were reported in either study arm (778 participants). In the high-standard 14-day group, 8 out of 380 participants discontinued treatment due to adverse events, compared to 2 out of 398 in the standard 14-day group (RR 4.19, 95% CI 0.90 to 19.60; 778 participants; very low-certainty evidence; Analysis 1.4). In the high-standard arm, 13 out of 380 participants experienced adverse events known to occur with primaquine, compared to 5 out of 398 in the standard arm (RR 2.72, 95% CI 0.98 to 7.57; 778 participants; very low-certainty evidence; Analysis 1.5). In the high-standard arm, 4 out of 380 participants experienced adverse events known to occur with the blood-stage antimalarial chloroquine, compared to 0 out of 398 in the standard group (RR 9.43, 95% CI 0.51 to 174.47; 778 participants; very low-certainty evidence; Analysis 1.6). This could suggest a trend towards a higher occurrence of adverse events in the high-standard 14-day regimen.

No significant adverse events were noted in either group in Saravu 2018 IND.

0.5 mg/kg/day for 7 days versus standard 14-day regimen

This comparison aimed to investigate whether shorter, higher-dose regimens of primaquine over 7 days are as efficacious as standard treatment over 14 days to determine whether the total dose rather than the length of treatment is an important factor (total dose 210 mg).

Five trials in India and South America compared 0.5 mg/kg/day of primaquine for 7 days versus the standard (0.25 mg/kg/day) 14-day regimen (same total dose 210 mg) (Abdon 2001 BRA; Solari-Soto 2002 PER; Durand 2014 PER; Rajgor 2014 IND; Pareek 2015 IND). Pareek 2015 IND used a sustained-release preparation of primaquine in two of the study arms (0.5 mg/kg/day sustained release and 0.25 mg/kg/day sustained release) and standard primaquine at 0.25mg/kg/day in a third arm. We included the 0.5 mg/kg/day sustained release in the analysis and combined the results with the standard preparation at the same dose used for the other trials, but used only the standard-preparation group of 0.25 mg/kg/day in the study as the control group and did not include the arm of 0.25mg/kg/day sustained release preparation.

Three trials excluded people with G6PD deficiency, while two trials did not provide this information (Bunnag 1994 THA; Solari-Soto 2002 PER). All but one trial excluded women who were pregnant or lactating (Solari-Soto 2002 PER did not provide details). Participants were a mixture of adults and children over one year old. All trials used microscopy for diagnosis, and only Pareek 2015 IND did not use supervised treatment. Two trials gave chloroquine and primaquine courses simultaneously (Abdon 2001 BRA; Durand 2014 PER), while the other three trials administered primaquine following the chloroquine course. No trials stratified by age, so results were combined.

Efficacy

There was minimal difference in the number of malaria recurrences between groups at 6 to 7 months' follow-up (RR 0.96, 95% CI 0.66 to 1.39; 1211 participants; low-certainty evidence; Analysis 2.1). One trial only followed participants for two months (Solari-Soto 2002 PER), and so was not part of the main analysis.

We had planned to perform a sensitivity analysis based on risk of bias for allocation concealment (which would have involved removing Rajgor 2014 IND from the meta-analysis), but we decided that as the remaining trials were all at high risk of bias for blinding and thus quality was generally low, we would not conduct a sensitivity analysis but address these issues in our GRADE assessment.

Two trials PCR-adjusted their results to differentiate between relapses and new infections at 6 to 7 months' follow-up. In Durand 2014 PER, PCR-adjusted results showed a 31% reduction in recurrence (24% reduction with light microscopy) with the regimen of 0.5 mg/kg/day for 7 days compared with the standard 14-day course, while in Rajgor 2014 IND, PCR-adjusted results showed a 159% increase in recurrence (25% increase in recurrence with light microscopy) with the regimen of 0.5 mg/kg/day for 7 days compared to the standard 14-day regimen (Analysis 2.2). We decided that these results could not be combined in a meta-analysis, as PCR techniques can differ, and there were high levels of heterogeneity.

We performed a subgroup analysis according to geographic region (Analysis 2.3). For trials in South America, the regimen of 0.5 mg/kg/day for 7 days led to a 30% reduction in *P vivax* recurrences compared to a 19% increase in recurrences for trials in Asia, although confidence intervals were wide and included no effect for both subgroups (South America: RR 0.70, 95% CI 0.39 to 1.26; Asia: RR 1.19, 95% CI 0.73 to 1.94). Only one trial did not use directly observed therapy (DOT) (Pareek 2015 IND). Subgroup analysis (Analysis 2.4) showed that with DOT there was minimal difference in recurrences at 6 to 7 months between treatment regimens (RR 0.98, 95% CI 0.67 to 1.43) compared to a reduction of about half of recurrences with the regimen of 0.5 mg/kg/day for 7 days when treatment was not supervised (RR 0.48, 95% CI 0.04 to 5.20).

Adverse effects

No serious adverse events were reported in either group (1427 participants). The number of participants experiencing adverse events leading to discontinuation of treatment was similar in both groups (RR 1.04, 95% CI 0.15 to 7.38; 1154 participants; Analysis 2.6), as were adverse events known to occur with primaquine (RR 1.06, 95% CI 0.64 to 1.76; 1154 participants; Analysis 2.7). One trial reported on change in haemoglobin status (Pareek 2015 IND), with 1 participant out of 120 in the group receiving 0.5 mg/kg/day for 7 days becoming anaemic, versus no participants out of 120 in the standard 14-day regimen group (RR 3.0, 95% CI 0.51 to 174.01; 240 participants; very low-certainty evidence; Analysis 2.8). Only one study reported on adverse events known to occur with chloroquine (Rajgor 2014 IND), with more occurring in the group receiving 0.5 mg/kg/day for 7 days than the standard 14-day group (RR 9.40, 95% CI 0.51 to 174.01; 779 participants; very low-certainty evidence; Analysis 2.9).

0.75 mg/kg primaquine/week for 8 weeks versus high-standard 14-day regimen

This comparison aimed to investigate whether a higher once-weekly dosing regimen, which may be more beneficial for people with

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G6PD deficiency, was as efficacious as the high-standard 14-day regimen.

One trial compared weekly 0.75 mg/kg primaquine (45 mg adult dose) for 8 weeks with the high-standard 14-day regimen (0.5 mg/kg/day) (Leslie 2008 PAK). G6PD-deficient participants were not randomized but were included in the weekly group, although there only was one G6PD-deficient person included. Pregnant and lactating women were excluded. Treatment was supervised. It was not specified whether chloroquine and primaquine were given concurrently.

Efficacy

Recurrences were more common in the weekly group at 8 months' follow-up (RR 7.0, 95% CI 0.38 to 127.32; 126 participants; Analysis 3.1). Recurrences remained more common in the weekly group at 11 months' follow-up (RR 3.18, 95% CI 0.37 to 27.6; 122 participants; Analysis 3.1). Leslie 2008 PAK was at high risk of bias for allocation concealment, but a sensitivity analysis could not be done as it was the only trial found for this comparison.

Adverse effects

No serious adverse events were reported in either study arm (Analysis 3.2). No participants had anaemia defined as haemoglobin less than 7 g/dL (Analysis 3.3).

Other regimens

0.375 mg/kg/day for 14 days versus standard 14-day regimen

Bunnag 1994 THA compared 0.375 mg/kg/day (adult dose 22.5 mg) primaquine daily for 14 days with the standard regimen of 0.25 mg/kg/day for 14 days. There was a high loss to follow-up, with 167 participants enrolled and only 38 completing 18 months' follow-up, although the loss was equal in both groups at the end of follow-up. At 6 months' follow-up there were no episodes of *P vivax* in the experimental group (0/40) and two recurrences in the standard-regimen group (2/33) (RR 0.17, 95% CI 0.01 to 3.34; 73 participants; Analysis 4.1), although only about half of enrolled participants were followed up at this time point. No further recurrences were described in either group up to the end of follow-up at 18 months, but as described, the high level of unexplained dropout makes interpretation difficult.

No formal assessment of adverse events was reported, but it is mentioned in the study narrative that there was no drop in haematocrit or haemoglobinuria in either group.

1.17 mg/kg/day for 3 days versus standard 14-day regimen

One trial delivered the total dose of primaquine (1.17 mg/kg/day or 70 mg adult dose, total dose 210 mg) over 3 days versus the standard (0.25 mg/kg/day) 14-day regimen (Carmona-Fonseca 2009 COL). Recurrences of *P vivax* malaria were more common in the group receiving 1.17 mg/kg/day for 3 days than in the standard 14-day group at 4 months' follow-up (RR 3.88, 95% CI 2.11 to 7.11; 129 participants; Analysis 5.1).

Adverse events were not reported, although it was noted that there were no serious adverse events from co-administering primaquine and chloroquine.

1 mg/kg/day for 7 days versus high-standard 14-day regimen

This comparison aimed to investigate whether shorter, higher doses of primaquine over 7 days are as effective as the high-standard 14-day regimen to determine whether the total dose rather than the length of treatment is the important factor for East Asia and Oceania regimen (total dose 420 mg primaquine). Only one included trial compared 1 mg/kg/day (adult dose 60 mg) of primaquine for 7 days with the high-standard 14-day course (0.5 mg/kg/day) (Chu 2016 THA), administering the regimen with either chloroquine or an ACT (4 arms). Results are still awaited, but a conference report of the trial reports that out of 680 participants there was no difference between the two regimens. No further details are currently available.

DISCUSSION

Summary of main results

High-standard 14-day regimen versus standard 14-day regimen

See Summary of findings 2

We included 2 RCTs that compared 0.5 mg/kg/day primaquine (daily adult dose 30 mg) for 14 days with 0.25 mg/kg/day (daily adult dose 15 mg) for 14 days, both conducted in India. People with G6PD deficiency and pregnant or lactating women were excluded. One trial did not account for whether participants were given chloroquine or an ACT for blood-stage treatment. We do not know if there is any difference in *P vivax* recurrences at 6 months with the high-standard 14-day course compared to the standard 14-day course when given with chloroquine (very low-certainty evidence). We do not know if there is any difference in *P vivax* relapses at 6 months with the high-standard 14-day course compared to the standard 14-day course when given with chloroquine or an ACT (very low-certainty evidence).

No serious events were reported in either trial. We do not know whether there is a difference in adverse events between the high-standard 14-day course and the standard 14-day course (very low-certainty evidence).

0.5 mg/kg/day for 7 days versus standard 14-day regimen

See Summary of findings for the main comparison

We included 5 RCTs that compared 0.5 mg/kg/day (adult dose 30 mg) primaquine for 7 days with the standard 14-day regimen (0.25 mg/kg/day). There may be little or no difference in *P vivax* recurrences at 6 to 7 months when using the same total dose (210 mg) over 7 days as compared to 14 days (low-certainty evidence). No serious adverse events were reported. There may be little or no difference in the number of adverse events known to occur with primaquine when using the shorter regimen as compared to the longer regimen (low-certainty evidence).

We do not know whether there is any difference in the frequency of anaemia or discontinuation of treatment between groups (very low-certainty evidence). Three trials excluded people with G6PD deficiency, and two did not provide this information, so we do not know the effect of the higher daily dose regimen in this group. Pregnant and lactating women were either excluded or this information was not provided.

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0.75 mg/kg primaquine/week for 8 weeks versus high-standard 14-day regimen

See Summary of findings 3

We included 1 RCT that compared 0.75 mg/kg (daily adult dose 45 mg) weekly primaquine for 8 weeks with the high-standard 14-day regimen (0.5 mg/kg/day, daily adult dose 30 mg). G6PD-deficient participants were not randomized but were included in the weekly primaquine group. Only one G6PD-deficient participant was detected during the trial and was included in the weekly group. We do not know whether weekly primaquine reduces recurrence of *P vivax* compared to the high-standard 14-day regimen at 8 to 11 months' follow-up (very low-certainty evidence).

No serious adverse events and no episodes of anaemia were reported.

Some other included trials evaluated alternative regimens and doses of primaquine, but these regimens have not been widely used, and the evidence available from stand-alone trials was of very low certainty.

Overall completeness and applicability of evidence

We initially thought we could evaluate whether the high-standard 14-day regimen (0.5 mg/kg/day) was more effective in all areas rather than just areas where recommended by the WHO due to reported resistance or strain differences (East Asia and Oceania) (WHO 2015). However, we only found two trials that compared the high standard 14-day regimen to the standard 14-day regimen, both of which were conducted in India. A recent retrospective case review in French Guiana (also an area where the high-standard regimen is not currently recommended) found that recurrences were similar in both standard and high-standard 14-day regimens (Valdes 2018). We did not find any RCTs that evaluated whether the high-standard 14-day regimen was more effective compared to the standard 14-day regimen for the tropical, frequently relapsing strain of *P vivax* in East Asia and Oceania, so we are unable to comment on its efficacy.

A difficulty encountered in including and comparing studies was the variation in dosing and length of follow-up in studies.

In general, there were few well-conducted RCTs that used an evidence-based standard primaquine regimen (15 mg/kg/day for 14 days) as a comparator. Some trials used the high-standard 0.5 mg/kg/day for 14 days regimen as a comparator, which is recommended by the WHO in East Asia and Oceania, which is why we included these trials. However, there is limited clear evidence in this review for the increased high-standard 14-day regimen. We found two randomized clinical trials that compared its efficacy to the standard regimen, both of which were conducted in India (Rajgor 2014 IND; Saravu 2018 IND), where the regimen is not recommended.

We also found that trials continue to be conducted where placebo is used instead of an alternative primaquine regimen, which is contrary to the evidence available demonstrating its superiority for reducing recurrences (Galappaththy 2013). This may be because there is continued reluctance to use primaquine in some national programmes.

We excluded studies where individuals had mixed malaria infections so as to assess the efficacy of treatment on *P vivax* malaria alone. Areas endemic for *P vivax* malaria may also be co-endemic for *P falciparum* or *Plasmodium ovale* infection, or both. However, it should be noted that as part of our screening process we did not identify any studies where participants with mixed malaria were included, so we do not think that narrowing our search criteria impacted the directness of our results.

Although the evidence is currently of low certainty, it does appear that using 0.5 mg/kg/day with the same total dose (210 mg) over 7 days may be non-inferior to the regimen of 0.25 mg/kg/day for 14 days. It may be that these shorter regimens promote course completion. Although no serious adverse events were reported due to few reported events for any other adverse effects, it is difficult to draw conclusions as to whether there may be increased adverse events for this higher dosing until more data are available. This higher-dose regimen was not tested in G6PD-deficient patients in any of the RCTs meeting our inclusion criteria. This remains a concern in settings where testing is not available.

There was a general lack of detailed safety data for trials, which is interesting given that safety is a particular concern with primaquine use. Only one included RCT investigated the weekly primaquine regimen that is currently recommended by WHO for G6PD-deficient individuals, and only one G6PD-deficient participant was actually included in the treatment group.

Certainty of the evidence

The overall certainty of evidence for all of the outcomes was either low or very low. All results were downgraded for imprecision due to wide CIs for all of the meta-analyses performed.

The efficacy comparison for the high-standard 14-day regimen versus the standard 14-day regimen was also downgraded for indirectness. Results were based on two trials in adults in India (Rajgor 2014 IND; Saravu 2018 IND). Rajgor 2014 IND was at risk of bias as there was no allocation concealment and unexplained loss to follow-up; this study also contributed most to the meta-analysis for the comparison of 0.5 mg/kg/day for 7 days versus standard 14-day regimen, so this study was also downgraded. Saravu 2018 IND was a small pilot study where participants were given either chloroquine or an ACT for the blood stage, and which blood-stage treatment they were given was not stated. Saravu 2018 IND was downgraded for imprecision, indirectness, and risk of bias (not blinded and high rate of loss to follow-up).

We downgraded the comparison of 0.75 mg/kg weekly primaquine versus high-standard 14-day regimen for indirectness as it was based on just one study conducted in Pakistan (Leslie 2008 PAK), with only one G6PD-deficient patient participating. Leslie 2008 PAK was at risk of bias due to the randomization process used, lack of allocation concealment, and incomplete outcome data. We downgraded efficacy outcomes for this comparison for serious imprecision due to few events and very wide CIs.

Potential biases in the review process

The strictness of our inclusion criteria to not include trials where the total dose was less than the total dose of the standard regimen and the necessity of having the comparison arm be one of the WHO-recommended regimens may have meant that some relevant comparisons were excluded.

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We changed the protocol to include the high-standard 14-day regimen that WHO recommends in East Asia and Oceania as a control regimen, as we realized that some trials had used this as the comparator, and we felt that these comparisons were useful. However, this may have introduced bias, as per our results the evidence base for RCTs showing the efficacy of this regimen is limited.

The difficulty in determining between relapse and re-infection with *P vivax* remains a recognized challenge for assessing the efficacy of drugs for radical cure.

Agreements and disagreements with other studies or reviews

Our findings that 210 mg over 7 days may be as efficacious as 210 mg over 14 days are similar to the findings of other systematic reviews that examined both randomized and non-randomized studies (Carmona-Fonseca 2015; Zuluaga-Idarraga 2015). Other reviews also commented on the difficulty of comparing results due to the varying treatment regimens and length of follow-up used in clinical trials (John 2012; Carmona-Fonseca 2015; Zuluaga-Idarraga 2015).

AUTHORS' CONCLUSIONS

Implications for practice

Although limited data were available, no difference was detected for efficacy between the regimen of 0.5 mg/kg/day for 7 days and the standard (0.25 mg/kg/day) 14-day regimen in G6PD-normal patients.

No serious adverse events were reported in G6PD-normal patients taking 0.5 mg/kg/day of primaquine.

Implications for research

Further high-quality randomized controlled trials are needed with more standardized comparison regimens and length of follow-up, in particular investigating the use of the high-standard 14-day regimen, same total dose over 7 days, and weekly regimens in G6PD-deficient patients. Trials such as IMPROV will help resolve some of the uncertainties.

ACKNOWLEDGEMENTS

The Academic Editor is Professor Paul Garner.

We are grateful to Vittoria Lutje, Information Specialist of the Cochrane Infectious Diseases Group (CIDG), for help with the literature search strategy. We thank Marty Richardson, CIDG statistician, for help with the data collection and analysis strategy, and Paul Garner, CIDG Co-ordinating Editor, for help developing the research question and with data analysis.

Rachael Milligan is supported by the Research, Evidence and Development Initiative (READ-It) project. READ-It and the CIDG editorial base are funded by UK aid from the UK government for the benefit of low- and middle-income countries (project number 300342-104). The views expressed do not necessarily reflect the UK government's official policies.

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NCT01814683 {*unpublished data only***}**

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CHARACTERISTICS OF STUDIES

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

Abdon 2001 BRA

Methods	RCT July 1994 to June 1995
Participants	120 participants enrolled. Inclusion criteria: • Confirmed parasitological diagnosis for *P vivax* malaria. • Age older than 12 years. • Staying in Belém (study area) until the end of the follow-up period (180 days). Exclusion criteria • Pregnant and nursing mothers were excluded. • Patients who used antimalarials at least 2 weeks prior to the start of current treatment. • Carriers of mixed malaria. Diagnosis: microscopy G6PD status not stated No details CYP2D6 status.
Interventions	• Chloroquine 10 mg/kg single dose + primaquine 0.5 mg/kg/day for 7 days. • Chloroquine 150 mg (25 mg/kg total dose) over 3 days, 10 mg/kg day 1, 7.5 mg/kg days 2 and 3 + primaquine 15 mg/day 14 days. (Additional arm chloroquine 10 mg/kg + primaquine 0.5 mg/kg for 5 days not included as total dose (150 mg) less than standard treatment (210 mg)) Although different doses of chloroquine in the 2 arms, all participants had negative parasitaemia within 72 hours. Primaquine and chloroquine given concurrently. Supervised treatment.
Outcomes	• Relapse. • Safety.

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Abdon 2001 BRA *(Continued)*

	Follow-up 180 days
Notes	Location: Belém, state of Pará, Brazil Setting: not stated Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details supplied on randomization process.
Allocation concealment (selection bias)	Unclear risk	No details supplied on allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Low risk	One loss to follow-up as moved out of area.
Selective reporting (reporting bias)	Low risk	Unable to find protocol but relapse and standard errors (SEs) reported as would be expected.
Other bias	Unclear risk	Funding not stated.

Bunnag 1994 THA

Methods	RCT Dates not provided.
Participants	167 participants enrolled. Inclusion criteria: • 15 to 60 years. Exclusion criteria: • History of previous treatment. • G6PD deficiency. • Mixed infections. Diagnosis: microscopy No details on pregnant/breastfeeding women.

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Bunnag 1994 THA *(Continued)*

	No details CYP2D6 status.
Interventions	• Chloroquine + 22.5 mg/day primaquine for 14 days. • Chloroquine + 15 mg/day primaquine for 14 days. Open randomization to chloroquine treatment – either 300 mg or 450 mg on day 1 of admission. Re-allocated after recovery of acute symptoms (double-blind RCT). Chloroquine course completed and parasitological clearance confirmed prior to randomization to primaquine group (exact time between treatment courses not specified). Supervised treatment in hospital.
Outcomes	• Relapse. • Safety. Follow-up 6 months
Notes	Location: Thailand Setting: not stated Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	1st step chloroquine is open randomization, then PQ stage randomized. No details on randomization process.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported as double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Reported as double-blind.
Incomplete outcome data (attrition bias) All outcomes	High risk	Unexplained high loss to follow-up.
Selective reporting (reporting bias)	Unclear risk	No protocol.
Other bias	Unclear risk	Funding not disclosed.

Carmona-Fonseca 2009 COL

Methods	RCT September 2003 to September 2006

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Carmona-Fonseca 2009 COL *(Continued)*

Participants	133 patients enrolled across 2 arms (total 188 counting arms not included in review) Inclusion criteria: • Age > 2 years. • *P vivax* parasitaemia of > 1000 asexual forms/L. • Willingness to participate. • A normal quantitative G6PD screening test was required for those administered > 0.25 mg/kg/day primaquine base, and only individuals with normal G6PD levels were included in the study. Exclusion criteria: • Pregnant women. • Those with associated acute infectious diseases. • A history of antimalarials intake during the previous 2 weeks. • Presence of diarrhoea or vomiting (> 5 episodes in 24 hours). • Symptoms or signs of severe malaria (according to WHO 2006). • Hypersensitivity to antimalarials or severe undernutrition. • Exclusion from the study also followed intake of any antimalarial different from those provided by the researchers. • Failure to attend follow-up appointments. • Treatment failure during the primary episode (first 28 days of follow-up). • Consent withdrawal. Diagnosis: microscopy No details CYP2D6 status or breastfeeding mothers.
Interventions	• Chloroquine (10 mg/kg day 1, 7.5 mg/kg days 2 and 3) + primaquine 1.17 mg/kg/day for 3 days (total 210 mg). • Chloroquine (10 mg/kg day 1, 7.5 mg/kg days 2 and 3) + primaquine 0.25 mg/kg/day for 14 days. (Additional arms: 0.83 mg/kg day for 3 days (total dose 149.4 mg) and 0.58 mg/kg day for 3 days (total dose 104.4 mg) not included as total dose less than standard treatment) Primaquine given simultaneously with chloroquine. Supervised treatment.
Outcomes	• Recurrence of *P vivax* malaria (parasitaemia after day 28). Follow-up 120 days
Notes	Location: Colombia Setting: patients that attended the local health clinics in Turbo and El Bagre Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of randomization not given.
Allocation concealment (selection bias)	Unclear risk	No details supplied.

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Carmona-Fonseca 2009 COL *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention on blinding in blood smear assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 lost per group, no explanations given, but less than 5% of total across groups.
Selective reporting (reporting bias)	Unclear risk	Protocol not found. No safety data were provided (which might have been expected to have been provided).
Other bias	Low risk	Looks like government funding.

Chu 2016 THA

Methods	RCT
Participants	680 enrolled. G6PD normal. No further details
Interventions	• Chloroquine + primaquine 7 days (1 mg/kg/day). • Chloroquine + primaquine 14 days (0.5 mg/kg/day). • Dihydroartemisinin-piperaquine + primaquine 7 days (1 mg/kg/day). • Dihydroartemisinin-piperaquine + primaquine 14 days (0.5 mg/kg/day). No further details
Outcomes	• Relapse. Follow-up: 1 year
Notes	Location: Thailand Setting: no details Funding: no details

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details.
Allocation concealment (selection bias)	Unclear risk	No details.

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Chu 2016 THA *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details.
Selective reporting (reporting bias)	Unclear risk	No details.
Other bias	Unclear risk	No details.

Durand 2014 PER

Methods	RCT March 2006 to August 2008
Participants	360 participants Inclusion criteria: • Microscopy-confirmed diagnosis of monoinfection with *P vivax* between 250 and 100,000 asexual parasites/mL (determined by microscopic examination of thick and thin peripheral blood smears). • Fever defined as axillary temperature 37.5 °C or history of fever, or both. • > 1 year old. Exclusion criteria: • Pregnant and lactating women. • Patients with chronic illnesses. • Patients with symptoms of severe malaria. • Patients with G6PD deficiency. Diagnosis: light microscopy Parasite genotyping with PCR also performed - 5 microsatellite loci used to determine whether homologous relapse.
Interventions	• Chloroquine (10 mg/kg day 1 and 2, 5 mg/kg day 3) + primaquine 0.5 mg/kg/day 7 days. • Chloroquine (10 mg/kg day 1 and 2, 5 mg/kg day 3) + primaquine 0.25 mg/kg/day for 14 days. (Additional arm of chloroquine + primaquine 0.5 mg/kg/day for 5 days excluded as total dose 150 mg, which was less than standard treatment.) Supervised. Primaquine administered concurrently with chloroquine.
Outcomes	• Relapse between days 35 and 210. • Relapses (homologous only).

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Durand 2014 PER *(Continued)*

	Follow-up: 210 days
Notes	Location: Peru Setting: Padre Cocha and the San Juan Health Centers and Santa Clara Health Center The periphery of the city of Iquitos, which is located on the river bank of the Amazon River and is the largest city in the Peruvian rainforest Funding: the US Department of Defense Global Emerging Infections Surveillance and Response System (DoD-GEIS), the National Institute of Health of Peru, and the Pan-American Health Organization/US Agency for International Development (PAHO-USAID) Americas Malaria Initiative/Amazonic Network of Antimalarial Drug Resistance, AMI/RAVREDA project

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated block randomization table.
Allocation concealment (selection bias)	Low risk	The treatment allocation for each participant was placed in a sealed envelope, kept in an orderly manner, and opened only at the time of enrolment of a new participant to prevent selection bias by study physicians.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label – no mention of blood smear blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	8% to 10% loss following randomization, but all accounted for.
Selective reporting (reporting bias)	Low risk	Study protocol registered. Unable to find outcomes in protocol, but expected outcomes were reported on.
Other bias	Low risk	We did not detect any other sources of bias.

Leslie 2008 PAK

Methods	RCT September 2004 to July 2006
Participants	129 Afgan refugees Inclusion criteria: • Patients diagnosed with *P vivax* parasitaemia at study basic health units (BHUs). • Patients over 3 years of age. • Patient permanently resident in the village. Exclusion criteria:

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Leslie 2008 PAK *(Continued)*

	• Pregnancy or lactation. • Severe clinical anaemia (7 g/dL). • *P falciparum* or *P vivax* (mixed infections), or both. • Intake of any antimalarial drug in the 2 weeks prior to consultation. • Patients unavailable for the duration of follow-up (11 months). • Patients with concomitant infections or disease likely to mask treatment response. Diagnosis: microscopy
Interventions	• Chloroquine (25 mg/kg in divided doses over 3 days) + primaquine 0.75 mg/kg once weekly for 8 weeks. • Chloroquine (25 mg/kg in divided doses over 3 days) + primaquine 0.5 mg/kg/day for 14 days. (Additional arm chloroquine + weekly placebo not included) Supervised. Not specified whether primaquine given concurrently with chloroquine.
Outcomes	• *P vivax* malaria relapse. • The number of subsequent episodes and anaemia rates during and up to 2 weeks post-treatment as well as any notable adverse events. Follow-up: 9 months (11 months participation: 8 weeks treatment + 9 months follow-up)
Notes	Location: Pakistan Setting: Adizai, Baghicha, and Khagan villages, close to Peshawar, Northwest Frontier Province, Pakistan where Afghan refugees have been resident for more than 20 years Funding: UNDP/World Bank/WHO Special Program for Research in Tropical Diseases; Gates Malaria Partnership)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Two randomization methods were used. In Baghicha and Khagan villages, participants were randomized by household, whereas in Adizai, randomization was at the individual level. Randomization lists for each village were generated using a random number list (MS Excel, Microsoft Corp, Seattle, USA) by staff not involved in patient recruitment. Participants were randomized on enrolment by study staff in the BHUs based on house number or sequential patient numbers, depending on the study site.
Allocation concealment (selection bias)	High risk	Participants were randomized on enrolment by study staff in the BHUs based on house number or sequential patient numbers, depending on the study site.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blood slides were double-read by 2 microscopists working independently, who were blinded to the other's result.
Incomplete outcome data (attrition bias)	High risk	Higher loss to follow-up in intervention group (6% to 8% versus 1% to 1.8%).

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Leslie 2008 PAK *(Continued)*

All outcomes

Selective reporting (reporting bias)	Low risk	Trial protocol available, all planned outcomes reported on.
Other bias	Low risk	We did not detect any other sources of bias.

Pareek 2015 IND

Methods	RCT
Participants	358 participants Inclusion criteria: • Patients of either sex. • Aged between 18 and 65 years. • Body weight > 40 kg. • Microscopically confirmed *P vivax* malaria with ≥ 1000 asexual parasites/µL of blood. • Axillary temperature ≥ 37.5°C (≥ 99.5°F). • Presence of at least 5 of the following signs and symptoms of uncomplicated malaria: chills, nausea, vomiting, headache, malaise, diarrhoea, anorexia, abdominal cramps, myalgia, and arthralgia. Exclusion criteria: • Mixed malarial infections. • Severe or complicated malaria (as defined by the WHO). • G6PD deficiency. • Any other significant concomitant illness. • Patients with history of dark urine or significant haemoglobinuria related to previous primaquine treatment or those with history of methaemoglobinaemia. • Patients with protracted vomiting and oliguria. • Those with underlying condition compromising bone marrow function or having a tendency to granulocytopenia. • Patients taking cardioactive drug or potentially haemolytic drugs or drugs that could interact with study drugs. • Patients having history of hypersensitivity to any of the study-related drugs. • Those on another investigational drug. • History/presence of substance abuse. • Pregnant or lactating women or women of childbearing potential not using medically accepted means of birth control. Diagnosis: microscopy
Interventions	• Chloroquine (3-day course, dose not specified) + primaquine 30 mg sustained release 7 days. • Chloroquine (3-day course, dose not specified) + primaquine 15 mg 14 days. (Additional arm of chloroquine + primaquine 15 mg sustained release for 14 days not included in review) Primaquine given following completion of chloroquine course. Not supervised.
Outcomes	• Relapse. • Compliance.

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Pareek 2015 IND *(Continued)*

	• Safety. PCR genotyping done to see if true relapse (no details on genotyping method). Follow-up: 5 months (6 months participation)
Notes	Location: India Setting: multicentre, no details as to centres involved Funding: funded by drug manufacturer Ipca Laboratories Ltd. Anil Pareek and Nitin Chandurkar are the employees of Ipca Laboratories Ltd who sponsored this trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization codes were generated using computer-generated block randomization method.
Allocation concealment (selection bias)	Low risk	Patient-specific sealed boxes of medicine were provided to each study site. (Sequentially numbered, sealed, opaque envelopes (from protocol)).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details as to whether microscopy was blinded or whether there was double reading of smears.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up equal between groups. Relapses counted as discontinued patients, but numbers provided so can be assessed.
Selective reporting (reporting bias)	High risk	Compliance added as an outcome, but original outcomes also reported on. Not clear why they have concluded that compliance increased with SR, as participants had to take 3 sets of pills as did those who took dummy versions, so all participants took 3 sets of drugs. No measurement of levels of PQ (pharmacokinetics), although states that PQ SR should have therapeutic concentration over 24 hours as part of the concept. PCR results are not well-detailed.
Other bias	High risk	The study was sponsored by Ipca Laboratories Ltd, who manufactures the drugs, and the principal investigators are employees of the company.

Rajgor 2014 IND

Methods	RCT August 2001 to February 2004
Participants	1159 participants enrolled.

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Rajgor 2014 IND *(Continued)*

	Inclusion criteria: • Adult patients, male and female (18 years of age or older). • Peripheral blood smear diagnosis of *P vivax.* • Willing to undergo hospitalization for the entire duration of primaquine treatment. • Willing to provide informed consent. • Willing to undergo investigations and come for regular follow-up. • Normal G6PD. • Haemoglobin ≥ 10 g/dL. Exclusion criteria: • Mixed infection with *P falciparum.* • Pregnancy and lactation. • Evidence of significant hepatic, renal, or cardiac disease as diagnosed by history, clinical examination, and laboratory tests whenever necessary. • Any other condition that would interfere with patient's participation in the study or compliance with the treatment. Diagnosis: microscopy
Interventions	• Chloroquine (10 mg/kg day 1 and 2, 5 mg/kg day 3) + primaquine 30 mg/day 7 days. • Chloroquine (10 mg/kg day 1 and 2, 5 mg/kg day 3) + primaquine 30 mg/day 14 days. • Chloroquine (10 mg/kg day 1 and 2, 5 mg/kg day 3) + primaquine 15 mg/day 14 days. (Additional no-primaquine arm not included in analysis) Supervised treatment. Primquine treatment commenced after chloroquine treatment (day 4).
Outcomes	• Recurrence of *vivax* malaria. • Safety. Follow-up: 6 months The secondary outcome also included comparison of number of participants classified as relapse and re-infection by the 3 methods to determine the concordance between the methods used and the genetic diversity observed based on PCR sequencing method. The cases of recurrence were classified as relapse or re-infection based on the 3 methods, the month of recurrence, and the 2 genotyping methods: PCR-RFLP and PCR sequencing.
Notes	Location: Mumbai, India Setting: inpatient assessment in Mumbai Funding: Indian Council of Medical Research

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A simple, computer-generated randomization scheme was used for the randomization of participants into the 3 PQ regimen groups.
Allocation concealment (selection bias)	High risk	This was an open-label study, and no concealment of treatment allocation was followed.

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Rajgor 2014 IND *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Although the study was not blinded in terms of treatment administration, the person seeing the slides and carrying out other outcome assessments was blinded to the treatment group by coding of the samples.
Incomplete outcome data (attrition bias) All outcomes	High risk	High percentage of participants not completing 6 months' follow-up across all groups. Minimal explanation for discontinuation of participants.
Selective reporting (reporting bias)	Unclear risk	No registered protocol found - reported on expected outcomes of efficacy and adverse effects. Trial carried out 2001 to 2004 but not published until 2014.
Other bias	Low risk	We did not detect any other sources of bias.

Saravu 2018 IND

Methods	RCT, open-label, pilot study March 2017 to August 2017
Participants	50 participants enrolled. Patients presenting to Kasturba Hospital, Manipal and Dr TMA Pai Hospital, Udupi, India Inclusion criteria: • *P vivax* malaria monoinfection. • Age 18 years and over. • Fever > 37.5°C tympanic or oral, or a history of fever within previous 3 days. • Willing to give informed consent. Exclusion criteria: • Pregnant or lactating, or both. • Patients with G6PD deficiency. • Mixed infection with *P vivax* and *P falciparum.* Primaquine given after blood-stage treatment. Diagnosis: microscopy, but PCR also performed to genotype recurrences No details CYP2D6
Interventions	Blood-stage treatment: either CQ or ACT (artesunate with doxycycline or artemether-lumefantrine as per the treating clinician's judgement of severity) • Primaquine 0.5 mg/kg/day for 14 days • Primaquine 0.25 mg/kg/day for 14 days Drug therapy not supervised.
Outcomes	1. Recurrence (2. Primaquine levels in the blood at 7 days)

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Saravu 2018 IND *(Continued)*

	Follow-up 6 months
Notes	Location: Udupi district of Karnataka State, India Setting: typical tropical climatic conditions. Malaria incidence throughout the year with peaks around June to July. Urban and rural settings in catchment area. Source of funding: seed Grant Award from Manipal McGill Center for Infectious Diseases

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization – 5 blocks of 10, randomization within each block done by a lottery method.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	High risk	High percentage of loss to follow-up by 6 months in both arms – results difficult to interpret.
Selective reporting (reporting bias)	Low risk	Outcomes reported as per protocol.
Other bias	Low risk	Supported by a seed Grant Award from Manipal McGill Center for Infectious Diseases, MAHE, Manipal.

Solari-Soto 2002 PER

Methods	RCT October 1998 to January 1999
Participants	60 participants enrolled. Inclusion criteria: • Confirmed diagnosis of *P vivax* malaria (febrile and positive *P vivax* blood smear). Exclusion criteria: • Patients who had received antimalarial medication in the 4 weeks prior to diagnosis. • Children under 5 years. • Patients with severe concomitant diseases. No details about inclusion/exclusion of G6PD-deficient/pregnant/breastfeeding patients.

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Solari-Soto 2002 PER *(Continued)*

	Diagnosis: microscopy
Interventions	• Chloroquine (10 mg/kg day 1 and 2, 5 mg/kg day 3) + primaquine 0.25 mg/kg/day for 14 days. • Chloroquine (10 mg/kg day 1 and 2, 5 mg/kg day 3) + primaquine 0.5 mg/kg/day for 7 days. Directly observed therapy. Primaquine given after chloroquine course.
Outcomes	• Relapse. • Adverse events. Follow-up: 60 days (total enrolment 60 days)
Notes	Location: Peru Setting: patients treated at San Martín de Pangoa Hospital, Junín Funding: US Naval Medical Research Institute Detachment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details on randomization process.
Allocation concealment (selection bias)	Unclear risk	No details on allocation process.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Samples double-checked, but no details as to whether blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data accounted for, similar in each group.
Selective reporting (reporting bias)	Unclear risk	No details.
Other bias	Low risk	We did not detect any other sources of bias.

Abbreviations: ACT: artemisinin-based combination therapy; CQ: chloroquine; CYP2D6: cytochrome P450 2D6; G6PD: glucose-6-phosphate dehydrogenase; PCR: polymerase chain reaction; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; PQ: primaquine; RCT: randomized controlled trial; SE: standard error; SR: sustained release; WHO: World Health Organization.

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

Study	Reason for exclusion
Adak 2001	No PQ comparison group.

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Study	Reason for exclusion
Alvarez 2006	Comparison regimens are of a lower total dose than the control (15 mg/day for 3 days or 7 days) – shown to be inferior in Galappaththy 2013.
Alvarez Sanchez 2007	Low-dose, shorter regimens of PQ.
Betuela 2012	Only one treatment group received primaquine.
Chu 2017	Wrong outcomes: primary outcome of this analysis was the fractional haematocrit reduction up to day 14 after enrolment.
Chu 2018	No primaquine comparison arm.
Clyde 1977	Not an RCT, observational single-arm trial.
Contacos 1974	Not an RCT.
da Silva 1984	Not properly randomized (randomized according to whether the end of the notes code is odd or even), low-dose comparison PQ group.
Gogtay 1999	Low-dose 15 mg for shorter time period (5 days) – shown to be ineffective in Galappaththy 2013.
Goller 2007	Not an RCT – logistic regression using already-published RCTs and observational studies (not primary trial).
Kim 2012	Wrong comparator: low-dose for 5 days - shown to be ineffective in Galappaththy 2013.
Kimura 1996	Not an RCT.
Krudsood 2008	Artesunate only as blood-stage treatment (does not meet inclusion criteria) and follow-up only 28 days.
Leslie 2004	No PQ comparison group: supervised versus unsupervised therapy.
Leslie 2008b	Duplicate of Leslie 2008 PAK; conference abstract title only for session at ASTMH 57th Annual Meeting.
Maneeboonyang 2011	Not randomized, participants were sequentially allocated into either the directly observed therapy (DOT) group or the self-administered therapy (SAT) group. No PQ comparison group, supervised versus non-supervised therapy.
Miller 1974	Not an RCT.
Pasaribu 2013	No PQ comparison group.
Pukrittayakamee 2000	No PQ comparison group.
Sabchareon 1981	No blood-stage antimalarial treatment used in primaquine comparison group according to inclusion criteria.
Saint-Yves IF 1977	Presumptive treatment of 45 mg PQ given to all participants before randomization.
Takeuchi 2010	No PQ comparison group: supervised versus non-supervised therapy.
Villalobos-Salcedo 2000	Wrong comparator: lower dose of PQ in comparison group (total dose 150 mg) - shown to be ineffective in Galappaththy 2013.

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Study	Reason for exclusion
Warrasak 2018	No primaquine comparison arm, ophthalmological outcomes.

Abbreviations: PQ: primaquine; RCT: randomized controlled trial.

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

NCT01814683

Trial name or title	Improving the radical cure of *vivax* malaria: a multicentre randomised comparison of short and long course primaquine regimens
Methods	RCT, multicentre Participant, care provider, and investigator blinding
Participants	Aged 6 months and older. Inclusion criteria: • Participant (or parent/guardian of children below age of consent) is willing and able to give written informed consent to participate in the trial; verbal consent in the presence of a literate witness is required for illiterate patients. In addition, written assent (or verbal assent in the presence of a literate witness for illiterates) from children 12 to 17 years as per local practice. • Monoinfection with *P vivax* of any parasitaemia in countries that use chloroquine as blood schizonticidal therapy. Mixed infections with *P vivax* and *P falciparum* can be enrolled in countries that use an artemisinin combination therapy. • Diagnosis based on rapid diagnostic tests. • Over 6 months of age. • Weight 5 kg or greater. • Fever (axillary temperature 37.5°C) or history of fever in the last 48 hours. • Able (in the investigator's opinion) and willing to comply with the study requirements and follow-up. Exclusion criteria: • Female participant who is pregnant, lactating, or planning pregnancy during the course of the study. • Inability to tolerate oral treatment. • Previous episode of haemolysis or severe haemoglobinuria following primaquine. • Signs/symptoms indicative of severe/complicated malaria or warning signs requiring parenteral treatment - haemoglobin concentration less than 9 g/dL. • Known hypersensitivity or allergy to the study drugs. • Blood transfusion in last 90 days, since this can mask G6PD-deficient status. • A febrile condition due to diseases other than malaria (for example, measles, acute lower respiratory tract infection, severe diarrhoea with dehydration). • Presence of any condition which in the judgement of the investigator would place the participant at undue risk or interfere with the results of the study (for example, serious underlying cardiac, renal, or hepatic disease; severe malnutrition; HIV/AIDS; or severe febrile condition other than malaria); co-administration of other medication known to cause haemolysis or that could interfere with the assessment of antimalarial regimens. • Currently taking medication known to interfere significantly with the pharmacokinetics of primaquine and the schizonticidal study drugs. • Prior antimalarial medications in the previous 7 days. Locations: Afghanistan, Ethiopia, Indonesia, Vietnam

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NCT01814683 *(Continued)*

	Estimated enrolment: 3150 participants
Interventions	1. Standard blood schizonticidal therapy plus 7 days of supervised primaquine (7 mg/kg total dose) administered once per day (1.0 mg/kg once daily) followed by 7 days of placebo 2. Standard blood schizonticidal therapy plus 14 days of supervised primaquine (7 mg/kg total dose) administered once per day (0.5 mg/kg) (3. Standard blood schizonticidal therapy plus 14 days placebo)
Outcomes	• Incidence rate (per person-year) and risk of symptomatic recurrent *P vivax* [Time Frame: 12 months]. The incidence rate (that is, per person-year) of symptomatic recurrent *P vivax* parasitaemia (detected by microscopy) over 12 months of follow-up in the 7- versus 14-day primaquine groups for all sites combined and stratified by site • Incidence rate (per person-year) of recurrent *P vivax* parasitaemia; haematological recovery; serious adverse drug reaction, primaquine tolerability, risk of severe anaemia in G6PD-deficient arm, cost-effective analysis with respect to the use of G6PD tests
Starting date	July 2014
Contact information	Ric Price, University of Oxford; ric.price@ndm.ox.ac.uk
Notes	Esimated completion date: December 2019 Protocol published (see IMPROV Study Group 2015; listed under NCT01814683) clinicaltrials.gov/ct2/show/NCT01814683

NCT01837992

Trial name or title	Evaluation of safety and efficacy of two primaquine dosing regimens for the radical treatment of *Plasmodium vivax* malaria in Vanuatu and Solomon Islands
Methods	RCT, open-label
Participants	Children and adults aged 12 months to 60 years. Solomon Islands and Vanuatu. Inclusion criteria: • Age 12 months to 60 years. • Melanesian background and living in local area. • Microscopically (based on field microscopy) or RDT-confirmed *P vivax* regardless of parasite density. Mixed infections (*P falciparum-P vivax* and *P malariae-P vivax*) can be included. Exclusion criteria: • Any signs of severe malaria (see WHO definitions) including: impaired consciousness, respiratory distress, severe anaemia (haemoglobin < 5), multiple seizures, frequent vomiting/inability to swallow tablets, prostration, jaundice, hypotension, abnormal bleeding, or hypoglycaemia. • Clinical evidence of non-malarial illness (such as pneumonia or otitis media). • Severe malnutrition (weight-for-age nutritional Z score < 60th percentile). • Permanent disability that prevents or impedes study participation. • Treatment with primaquine in the previous 14 days. • Residence or planned travel outside the study area during the follow-up period (precluding supervised treatment and follow-up procedures). • Known or suspected pregnancy. • Currently breastfeeding.

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NCT01837992 *(Continued)*	• A positive rapid test for G6PD deficiency (Binax or Carestart RDT).
Interventions	1. Primaquine dose of 0.5 mg/kg/day for 14 consecutive days and standard age-based dosage 3-day course of artemether-lumefantrine 2. Primaquine dose of 0.25 mg/kg for 14 consecutive days and standard age-based dosage 3-day course of artemether-lumefantrine (3. Participants will receive a standard 3-day treatment course of artemether-lumefantrine at the standard age-based dosage, but will not receive primaquine until the time of confirmed recurrent parasitaemia or completion of 3 months follow-up)
Outcomes	• Efficacy: numbers of *P vivax* relapses per person-years of follow-up [Time Frame: 12 months]. Total number of microscopically diagnosed (including both symptomatic and asymptomatic infections), PCR-confirmed relapses with *P vivax* in participants in each treatment arm over the 3-month follow-up period, expressed as number of relapses per person-years of follow-up. • Safety and toxicity: mild, moderate, and severe adverse events, haemolysis, methaemoglobinaemia.
Starting date	May 2013
Contact information	Dr Ivo Mueller; mueller@wehi.edu.au
Notes	Estimated completion date May 2015. Contacted for results - no response. Protocol available at clinicaltrials.gov/ct2/show/NCT01837992

Abbreviations: G6PD: glucose-6-phosphate dehydrogenase; RCT: randomized controlled trial; RDT: rapid diagnostic test; WHO: World Health Organization.

DATA AND ANALYSES

Comparison 1. High-standard 14-day regimen versus standard 14-day regimen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrence at 6 months' follow-up	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 6 months (chloroquine blood-stage treatment)	1	639	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.47, 1.43]
1.2 6 months (chloroquine or ACT blood-stage treatment)	1	38	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.17, 7.09]
2 Recurrence (PCR-adjusted)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 6 to 7 months	1	639	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [0.62, 5.40]
3 Serious adverse effects	1	778	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Adverse events that result in discontinuation of treatment	1	778	Risk Ratio (M-H, Fixed, 95% CI)	4.19 [0.90, 19.60]

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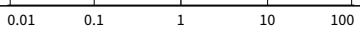
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Adverse effects known to occur with primaquine	1	778	Risk Ratio (M-H, Fixed, 95% CI)	2.72 [0.98, 7.57]
6 Adverse events known to occur with chloroquine	1	778	Risk Ratio (M-H, Fixed, 95% CI)	9.43 [0.51, 174.47]

Analysis 1.1. Comparison 1 High-standard 14-day regimen versus standard 14-day regimen, Outcome 1 Recurrence at 6 months' follow-up.

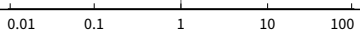
Study or subgroup	0.5mg/kg/ day PQ 14 days n/N	0.25mg/kg/ day PQ 14 days n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 6 months (chloroquine blood-stage treatment)					
Rajgor 2014 IND	21/317	26/322		100%	0.82[0.47,1.43]
Subtotal (95% CI)	**317**	**322**		**100%**	**0.82[0.47,1.43]**
Total events: 21 (0.5mg/kg/day PQ 14 days), 26 (0.25mg/kg/day PQ 14 days)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.7(P=0.48)					
1.1.2 6 months (chloroquine or ACT blood-stage treatment)					
Saravu 2018 IND	2/18	2/20		100%	1.11[0.17,7.09]
Subtotal (95% CI)	**18**	**20**		**100%**	**1.11[0.17,7.09]**
Total events: 2 (0.5mg/kg/day PQ 14 days), 2 (0.25mg/kg/day PQ 14 days)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.11(P=0.91)					
Test for subgroup differences: Chi^2=0.09, df=1 (P=0.76), I^2=0%					



Favours 0.5mg/kg/day PQ 14 days | Favours 0.25mg/kg/day PQ 14 days

Analysis 1.2. Comparison 1 High-standard 14-day regimen versus standard 14-day regimen, Outcome 2 Recurrence (PCR-adjusted).

Study or subgroup	0.5mg/kg/ day PQ 14 days n/N	0.25mg/kg/ day PQ 14 days n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 6 to 7 months					
Rajgor 2014 IND	9/317	5/322		100%	1.83[0.62,5.4]
Subtotal (95% CI)	**317**	**322**		**100%**	**1.83[0.62,5.4]**
Total events: 9 (0.5mg/kg/day PQ 14 days), 5 (0.25mg/kg/day PQ 14 days)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.09(P=0.27)					



Favours 0.5mg/kg/day PQ 14 days | Favours 0.25mg/kg/day PQ 14 days

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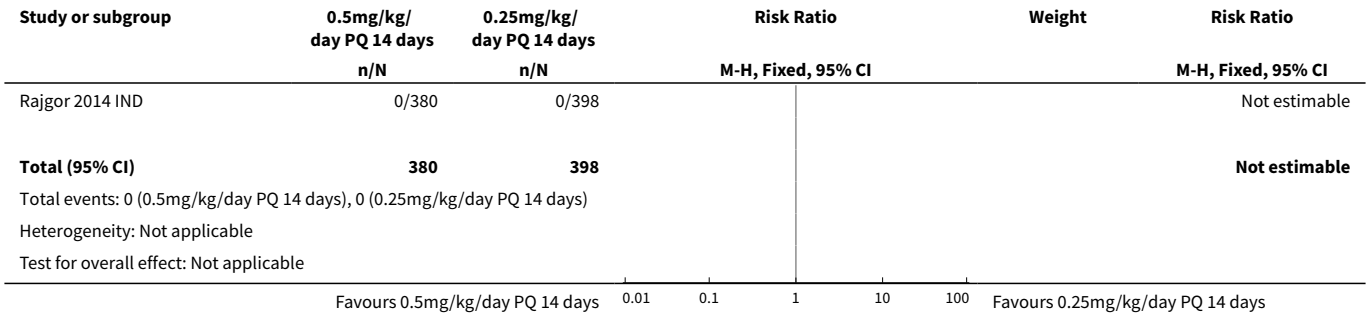
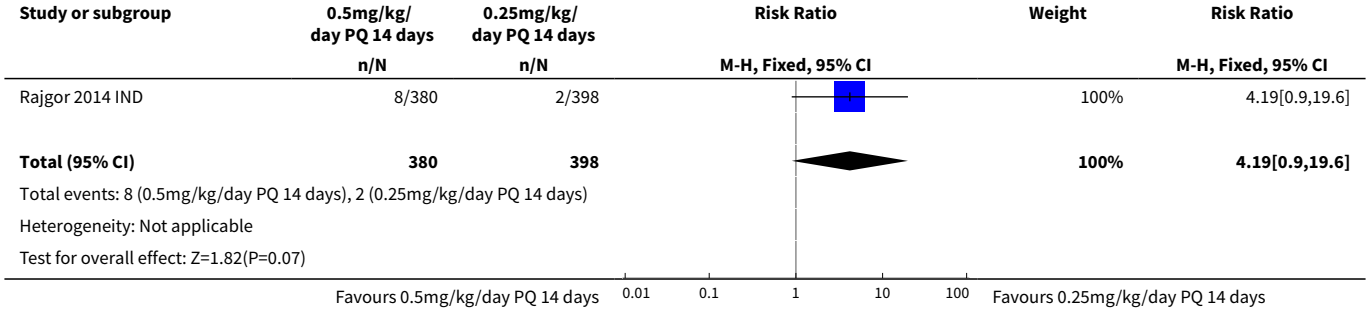
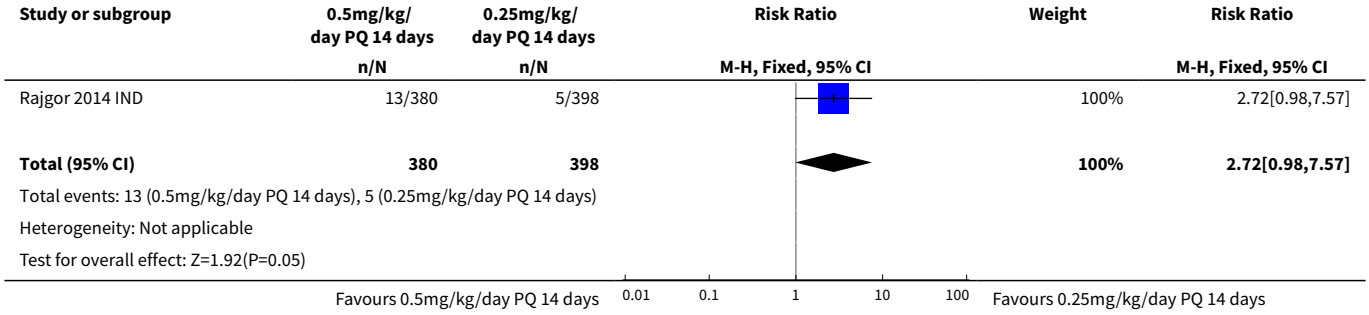
Analysis 1.3. Comparison 1 High-standard 14-day regimen versus standard 14-day regimen, Outcome 3 Serious adverse effects.



Analysis 1.4. Comparison 1 High-standard 14-day regimen versus standard 14-day regimen, Outcome 4 Adverse events that result in discontinuation of treatment.



Analysis 1.5. Comparison 1 High-standard 14-day regimen versus standard 14-day regimen, Outcome 5 Adverse effects known to occur with primaquine.



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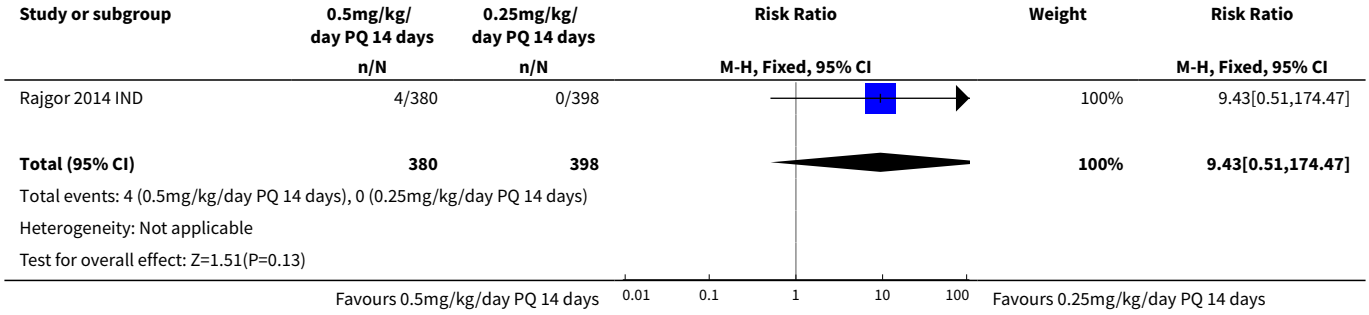
Analysis 1.6. Comparison 1 High-standard 14-day regimen versus standard 14-day regimen, Outcome 6 Adverse events known to occur with chloroquine.



Comparison 2. 0.5 mg/kg/day for 7 days versus standard 14-day regimen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrence by 6 to 7 months' follow-up	4	1211	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.66, 1.39]
2 Recurrence by 6 to 7 months' follow-up (PCR-adjusted)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Recurrence by 6 to 7 months subgrouped by geographical region	4	1211	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.66, 1.39]
3.1 South America	2	397	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.39, 1.26]
3.2 Asia	2	814	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.73, 1.94]
4 Recurrence by 6 to 7 months subgrouped by directly observed therapy (DOT) versus non-DOT	4	1211	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.66, 1.39]
4.1 DOT	3	1017	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.67, 1.43]
4.2 Non-DOT	1	194	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.04, 5.20]
5 Serious adverse effects	5	1427	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Adverse events that result in discontinuation of treatment	5	1427	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.15, 7.38]
7 Adverse effects known to occur with primaquine	4	1154	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.64, 1.76]
8 Anaemia or change in haemoglobin status	1	240	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.12, 72.91]
9 Adverse events known to occur with chloroquine	1	779	Risk Ratio (M-H, Fixed, 95% CI)	9.40 [0.51, 174.01]

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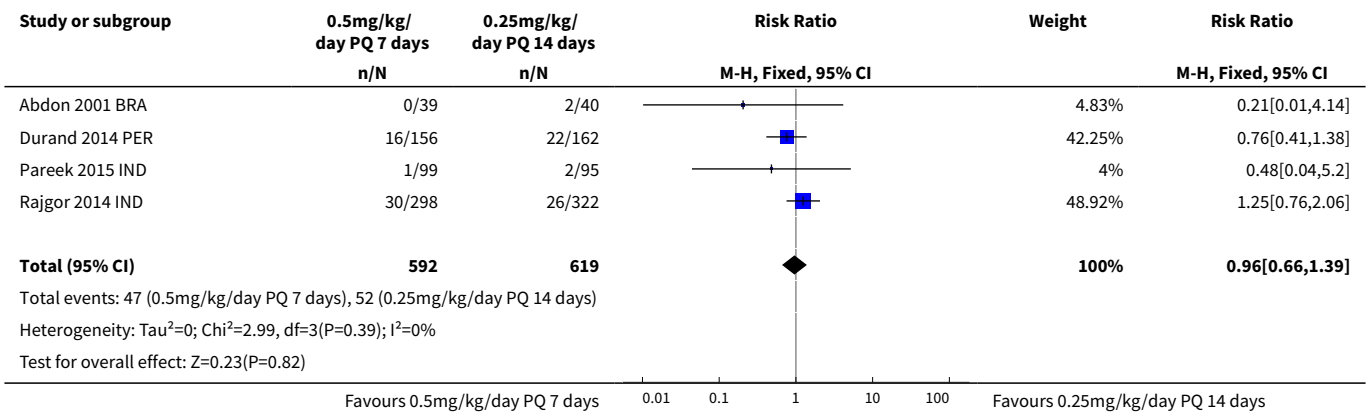
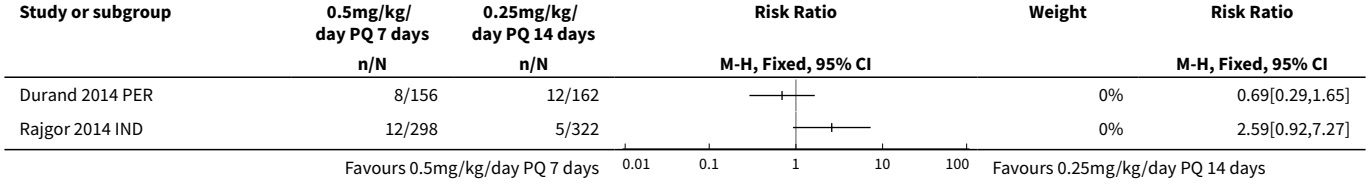
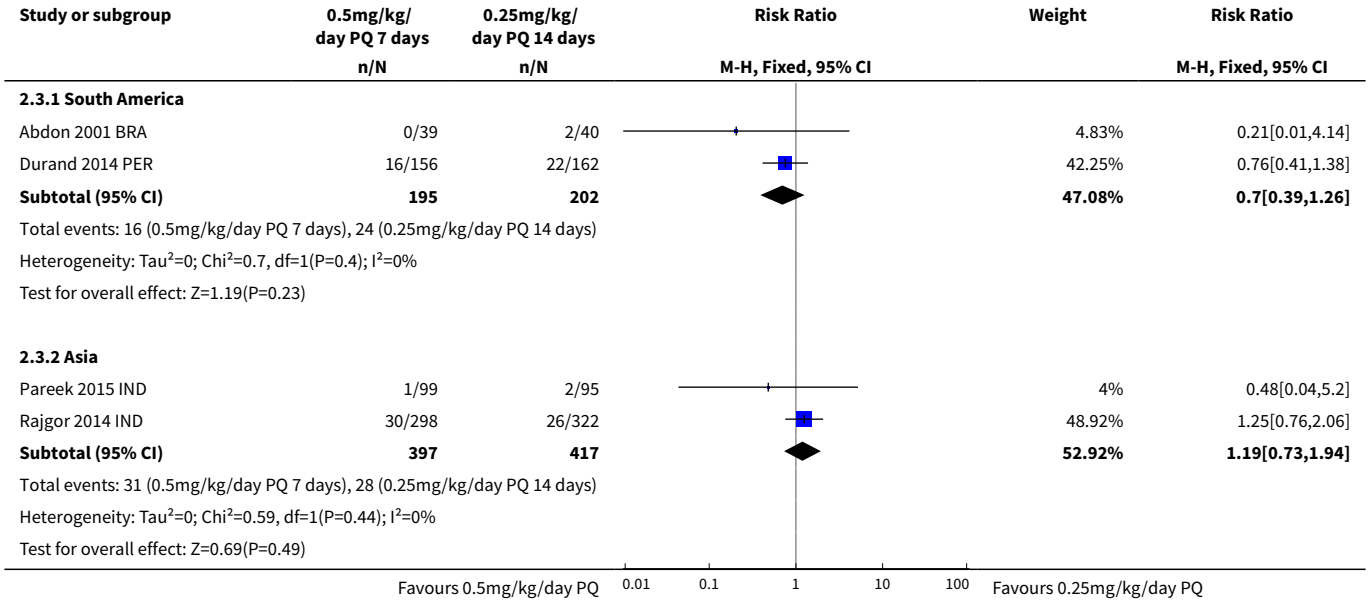
Analysis 2.1. Comparison 2 0.5 mg/kg/day for 7 days versus standard 14-day regimen, Outcome 1 Recurrence by 6 to 7 months' follow-up.



Analysis 2.2. Comparison 2 0.5 mg/kg/day for 7 days versus standard 14-day regimen, Outcome 2 Recurrence by 6 to 7 months' follow-up (PCR-adjusted).



Analysis 2.3. Comparison 2 0.5 mg/kg/day for 7 days versus standard 14-day regimen, Outcome 3 Recurrence by 6 to 7 months subgrouped by geographical region.



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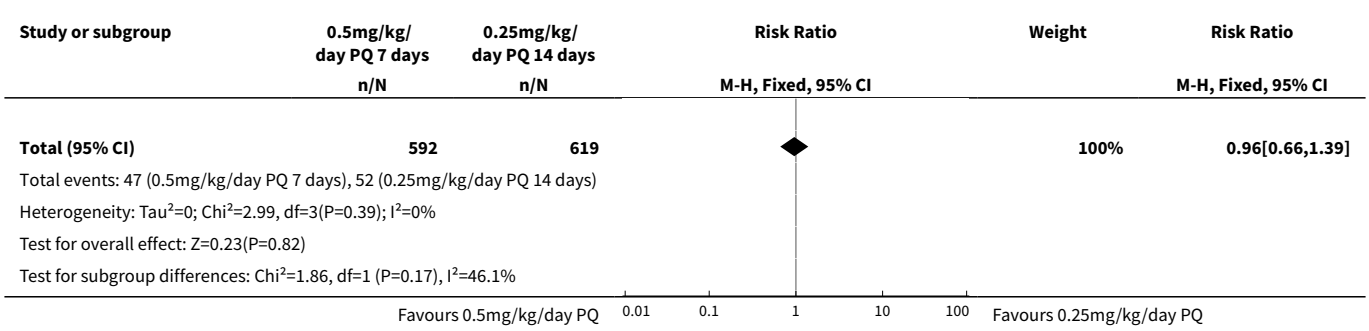
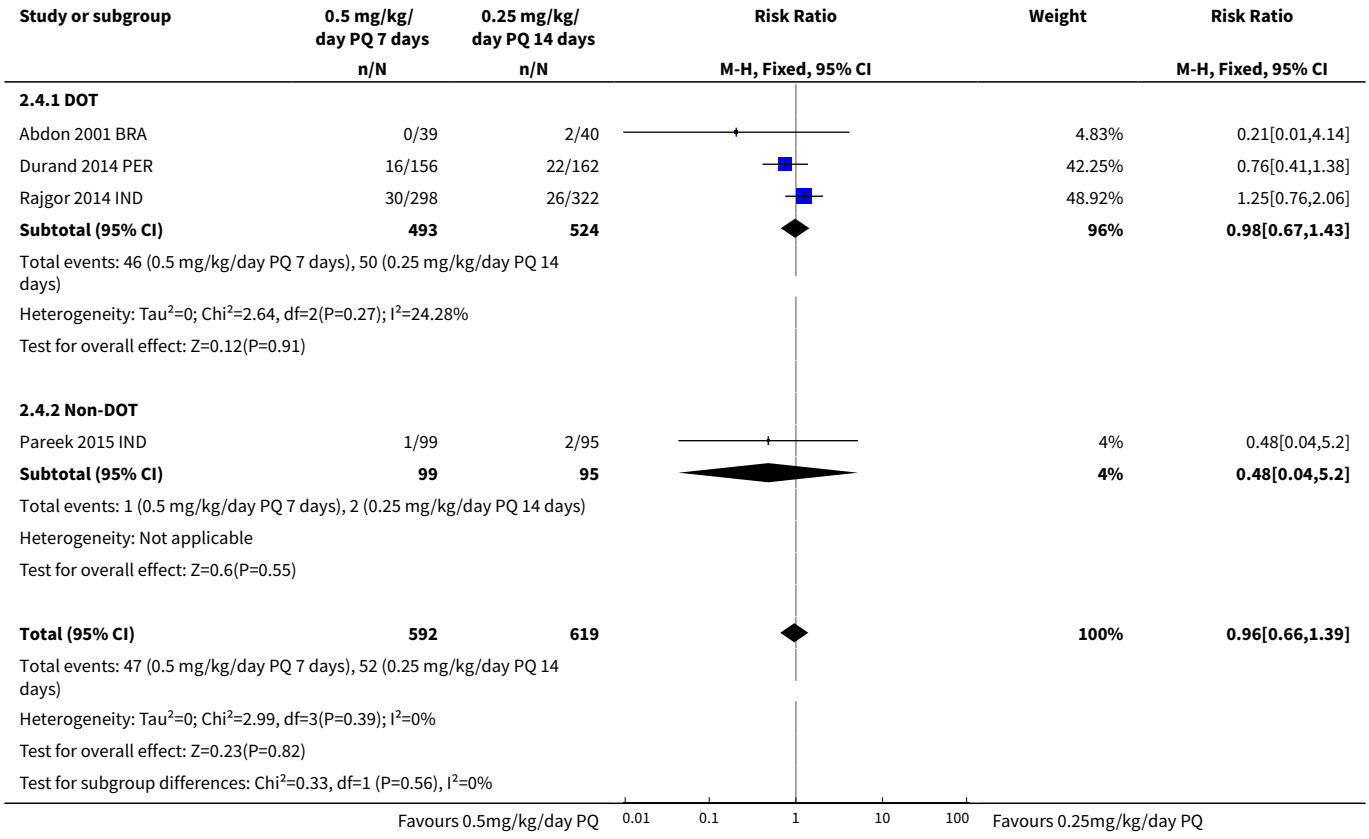
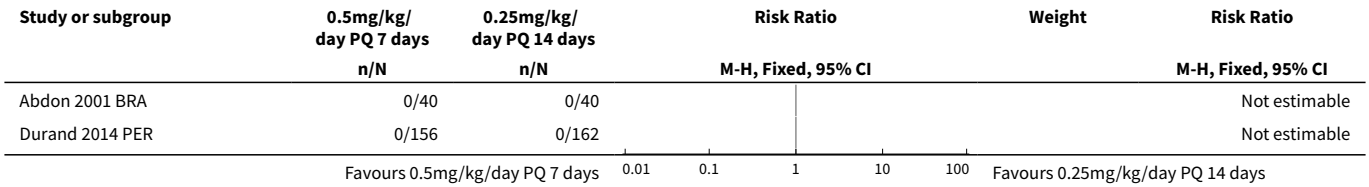


Analysis 2.4. Comparison 2 0.5 mg/kg/day for 7 days versus standard 14-day regimen, Outcome 4 Recurrence by 6 to 7 months subgrouped by directly observed therapy (DOT) versus non-DOT.



Analysis 2.5. Comparison 2 0.5 mg/kg/day for 7 days versus standard 14-day regimen, Outcome 5 Serious adverse effects.



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Study or subgroup	0.5mg/kg/ day PQ 7 days n/N	0.25mg/kg/ day PQ 14 days n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Pareek 2015 IND	0/99	0/95			Not estimable
Rajgor 2014 IND	0/381	0/398			Not estimable
Solari-Soto 2002 PER	0/28	0/28			Not estimable
Total (95% CI)	**704**	**723**			**Not estimable**
Total events: 0 (0.5mg/kg/day PQ 7 days), 0 (0.25mg/kg/day PQ 14 days)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours 0.5mg/kg/day PQ 7 days 0.01 0.1 1 10 100 Favours 0.25mg/kg/day PQ 14 days

Analysis 2.6. Comparison 2 0.5 mg/kg/day for 7 days versus standard 14-day regimen, Outcome 6 Adverse events that result in discontinuation of treatment.

Study or subgroup	0.5mg/kg/ day PQ 7 days n/N	0.25mg/kg/ day PQ 14 days n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Abdon 2001 BRA	0/40	0/40			Not estimable
Durand 2014 PER	0/156	0/162			Not estimable
Pareek 2015 IND	0/99	0/95			Not estimable
Rajgor 2014 IND	2/381	2/398		100%	1.04[0.15,7.38]
Solari-Soto 2002 PER	0/28	0/28			Not estimable
Total (95% CI)	**704**	**723**		**100%**	**1.04[0.15,7.38]**
Total events: 2 (0.5mg/kg/day PQ 7 days), 2 (0.25mg/kg/day PQ 14 days)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.04(P=0.97)					

Favours 0.5mg/kg/day PQ 7 days 0.01 0.1 1 10 100 Favours 0.25mg/kg/day PQ 14 days

Analysis 2.7. Comparison 2 0.5 mg/kg/day for 7 days versus standard 14-day regimen, Outcome 7 Adverse effects known to occur with primaquine.

Study or subgroup	0.5mg/kg/ day PQ 7 days n/N	0.25mg/kg/ day PQ 14 days n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Abdon 2001 BRA	6/39	11/40		42.18%	0.56[0.23,1.36]
Pareek 2015 IND	11/120	10/120		38.83%	1.1[0.49,2.49]
Rajgor 2014 IND	10/381	5/398		18.99%	2.09[0.72,6.06]
Solari-Soto 2002 PER	0/28	0/28			Not estimable
Total (95% CI)	**568**	**586**		**100%**	**1.06[0.64,1.76]**
Total events: 27 (0.5mg/kg/day PQ 7 days), 26 (0.25mg/kg/day PQ 14 days)					
Heterogeneity: $Tau^2=0$; $Chi^2=3.54$, df=2(P=0.17); $I^2=43.55\%$					
Test for overall effect: Z=0.22(P=0.82)					

Favours 0.5mg/kg/day PQ 7 days 0.01 0.1 1 10 100 Favours 0.25mg/kg/day PQ 14 days

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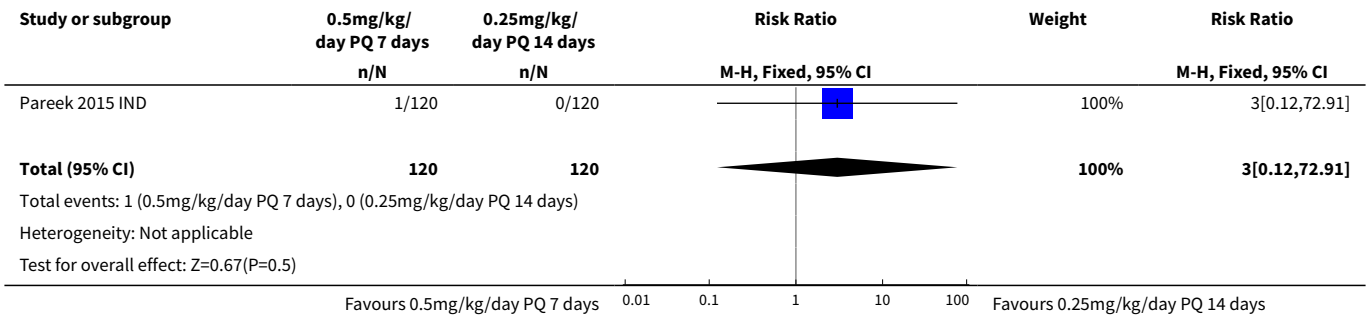
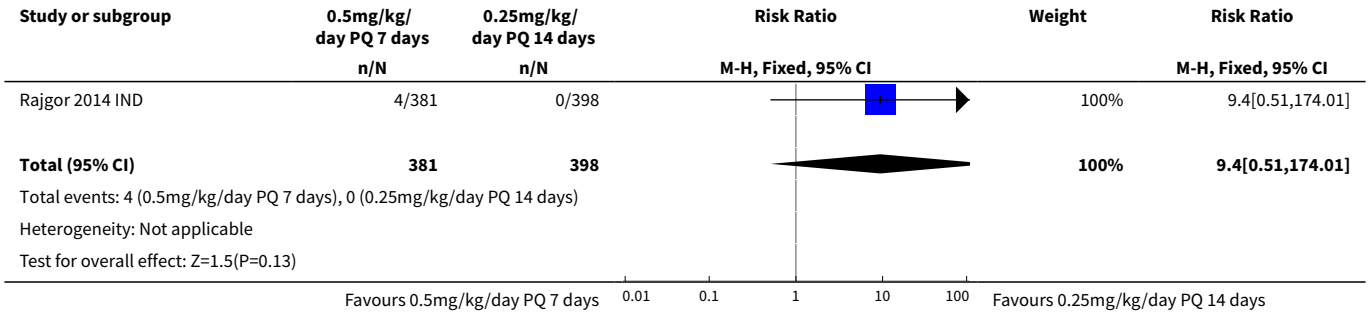
Analysis 2.8. Comparison 2 0.5 mg/kg/day for 7 days versus standard 14-day regimen, Outcome 8 Anaemia or change in haemoglobin status.



Analysis 2.9. Comparison 2 0.5 mg/kg/day for 7 days versus standard 14-day regimen, Outcome 9 Adverse events known to occur with chloroquine.



Comparison 3. 0.75 mg/kg primaquine/week for 8 weeks versus high-standard 14-day regimen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrence	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 5 months	1	129	Risk Ratio (M-H, Fixed, 95% CI)	5.23 [0.28, 99.15]
1.2 8 months	1	126	Risk Ratio (M-H, Fixed, 95% CI)	7.0 [0.38, 127.32]
1.3 11 months	1	122	Risk Ratio (M-H, Fixed, 95% CI)	3.18 [0.37, 27.60]
2 Serious adverse effects	1	129	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Anaemia (haemoglobin < 7 g/dL)	1	129	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

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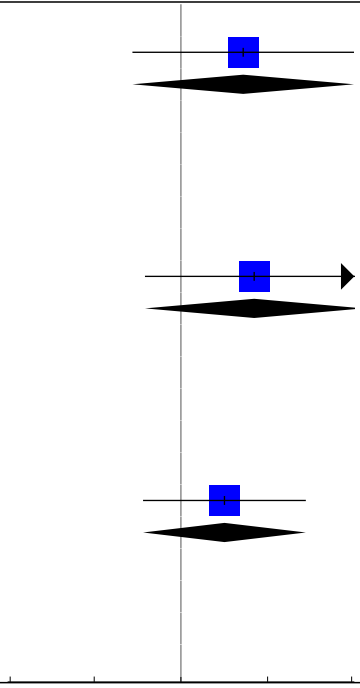
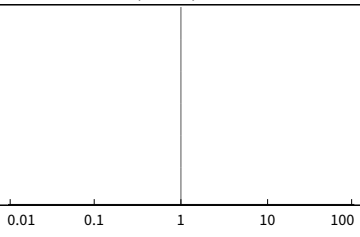
Analysis 3.1. Comparison 3 0.75 mg/kg primaquine/week for 8 weeks versus high-standard 14-day regimen, Outcome 1 Recurrence.

Study or subgroup	0.75mg/kg PQ weekly 8wks n/N	0.5mg/kg/ day PQ 14 days n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 5 months					
Leslie 2008 PAK	3/74	0/55		100%	5.23[0.28,99.15]
Subtotal (95% CI)	**74**	**55**		**100%**	**5.23[0.28,99.15]**
Total events: 3 (0.75mg/kg PQ weekly 8wks), 0 (0.5mg/kg/day PQ 14 days)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.1(P=0.27)					
3.1.2 8 months					
Leslie 2008 PAK	4/71	0/55		100%	7[0.38,127.32]
Subtotal (95% CI)	**71**	**55**		**100%**	**7[0.38,127.32]**
Total events: 4 (0.75mg/kg PQ weekly 8wks), 0 (0.5mg/kg/day PQ 14 days)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.31(P=0.19)					
3.1.3 11 months					
Leslie 2008 PAK	4/68	1/54		100%	3.18[0.37,27.6]
Subtotal (95% CI)	**68**	**54**		**100%**	**3.18[0.37,27.6]**
Total events: 4 (0.75mg/kg PQ weekly 8wks), 1 (0.5mg/kg/day PQ 14 days)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.05(P=0.29)					
Test for subgroup differences: Chi^2=0.2, df=1 (P=0.91), I^2=0%					



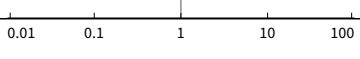
Analysis 3.2. Comparison 3 0.75 mg/kg primaquine/week for 8 weeks versus high-standard 14-day regimen, Outcome 2 Serious adverse effects.

Study or subgroup	0.75mg/kg PQ weekly 8wks n/N	0.5mg/kg/ day PQ 14 days n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Leslie 2008 PAK	0/74	0/55			Not estimable
Total (95% CI)	**74**	**55**			**Not estimable**
Total events: 0 (0.75mg/kg PQ weekly 8wks), 0 (0.5mg/kg/day PQ 14 days)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



Analysis 3.3. Comparison 3 0.75 mg/kg primaquine/week for 8 weeks versus high-standard 14-day regimen, Outcome 3 Anaemia (haemoglobin < 7 g/dL).

Study or subgroup	0.75mg/kg PQ weekly 8wks n/N	0.5mg/kg/ day PQ 14 days n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Leslie 2008 PAK	0/74	0/55			Not estimable



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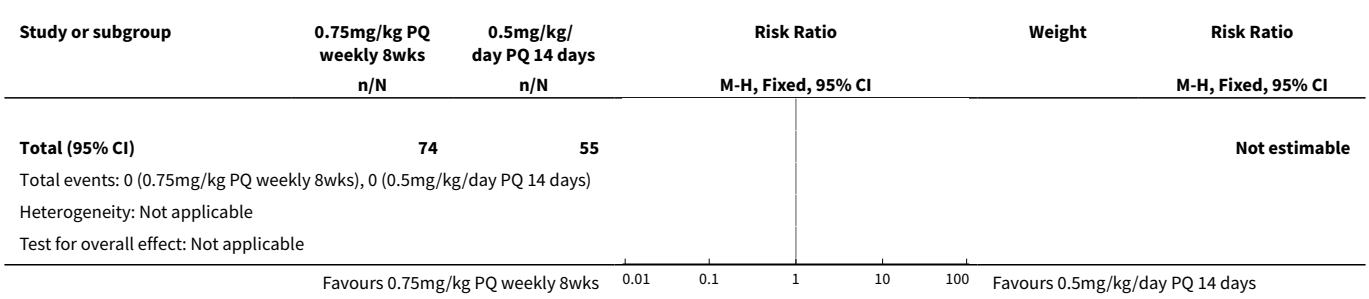
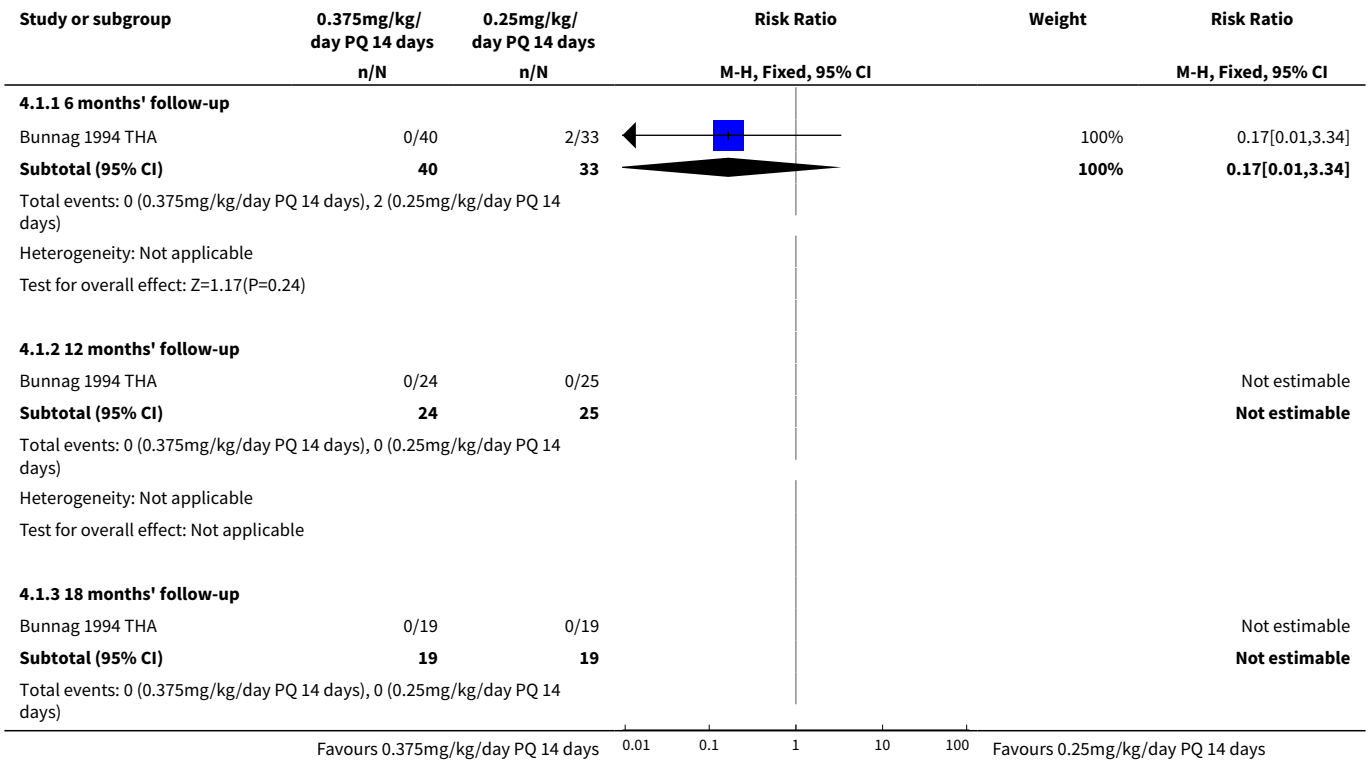


Comparison 4. 0.375 mg/kg/day primaquine for 14 days versus standard 14-day regimen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrence	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 6 months' follow-up	1	73	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.01, 3.34]
1.2 12 months' follow-up	1	49	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 18 months' follow-up	1	38	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 4.1. Comparison 4 0.375 mg/kg/day primaquine for 14 days versus standard 14-day regimen, Outcome 1 Recurrence.



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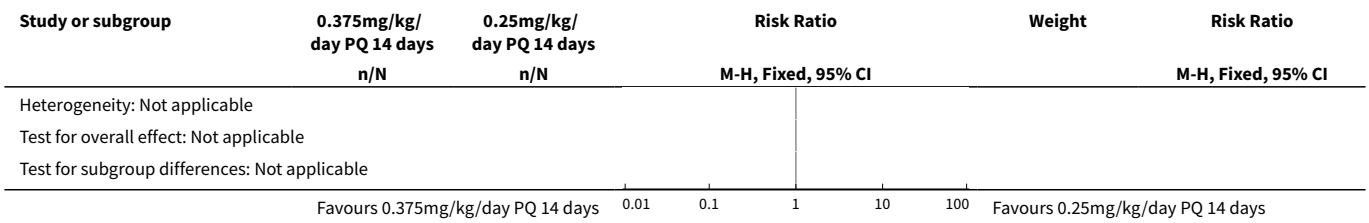
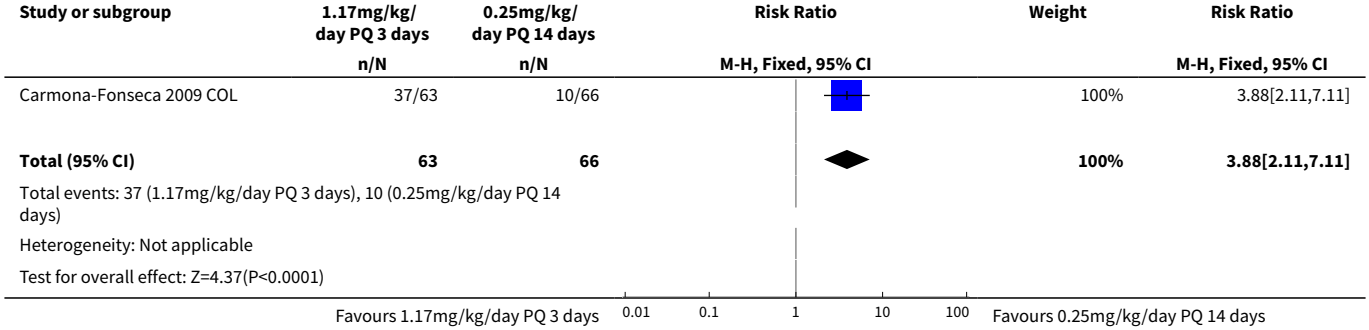


Comparison 5. 1.17 mg/kg/day primaquine for 3 days versus standard 14-day regimen; follow-up 4 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrence	1	129	Risk Ratio (M-H, Fixed, 95% CI)	3.88 [2.11, 7.11]

Analysis 5.1. Comparison 5 1.17 mg/kg/day primaquine for 3 days versus standard 14-day regimen; follow-up 4 months, Outcome 1 Recurrence.



ADDITIONAL TABLES

Table 1. Data extraction: grouping of comparisons to address the review's objectives

Objective	Intervention	Control
Are higher doses (0.5 mg/kg/day or 30 mg/day primaquine for 14 days) more effective in all areas, or only in areas where they are standard treatment (East Asia and Oceania)?	Blood-stage antimalarial drug with primaquine 0.5 mg/kg/day (adult dose 30 mg) for 14 days (total dose 420 mg). Both intervention and control groups must have received the same treatment for the blood-borne stage of infection, that is, either CQ or ACT.	Blood-stage antimalarial drug with standard 14-day course primaquine (0.25 mg/kg/day, adult dose 15 mg, total dose 210 mg). Both intervention and control groups must have received the same treatment for the blood-borne stage of infection, that is, either CQ or ACT.
Are shorter, higher-dose regimens of primaquine over 7 days as effective as treatment over 14 days (is the total dose	Blood-stage antimalarial drug with primaquine 0.5 mg/kg/day (adult dose 30 mg) for 7 days (total dose 210 mg) or 1 mg/kg/day (adult dose 60 mg) for 7 days (total dose 420 mg).	Blood-stage antimalarial drug with standard 14-day course primaquine (0.25 mg/kg/day, adult dose 15 mg, total dose 210 mg) or high-standard 14-day course primaquine (0.5 mg/kg/day, adult dose 30 mg, total dose 420 mg).

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Table 1. Data extraction: grouping of comparisons to address the review's objectives *(Continued)*

rather than the length of treatment the important factor)?	Both intervention and control groups must have received the same treatment for the blood-borne stage of infection, that is, either CQ or ACT.	Both intervention and control groups must have received the same treatment for the blood-borne stage of infection, that is, either CQ or ACT.
Are weekly dosing regimens (0.75 mg/kg/week or 45 mg/week for 8 weeks) as effective?	Blood-stage antimalarial drug with primaquine 0.75/kg (45 mg) per week for 8 weeks (total dose 360 mg)	Blood-stage antimalarial drug with standard 14-day course primaquine (0.25 mg/kg/day, adult dose 15 mg, total dose 210 mg) or high-standard 14-day course primaquine (0.5 mg/kg/day, adult dose 30 mg, total dose 420 mg). Both intervention and control groups must have received the same treatment for the blood-borne stage of infection, that is, either CQ or ACT.

Abbreviations: ACT = artemisinin-based combination therapy; CQ = chloroquine.

APPENDICES

Appendix 1. Detailed search strategies

PubMed	MEDLINE
1	primaquine [Title/Abstract]
2	"Primaquine"[Mesh]
3	1 or 2
4	"plasmodium vivax" [Title/Abstract]
5	"Plasmodium vivax"[Mesh]
6	"vivax malaria " [Title/Abstract]
7	"Malaria, Vivax"[Mesh]
8	4 or 5 or 6
9	3 and 8
10	"Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type]
11	randomized or placebo [Title/Abstract]
12	randomly or trial or groups [Title/Abstract]
13	"drug therapy" [Subheading]
14	10 or 11 or 12 or 13
15	9 and 14

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Issue 12 2018

ID Search

#1 primaquine: ti,ab,kw: (Word variations have been searched)

#2 MeSH descriptor: [Primaquine] explode all trees

#3 #1 or #2

#4 "plasmodium vivax": ti, ab,kw (Word variations have been searched)

#5 MeSH descriptor : [Malaria, Vivax] explode all trees

#6 MeSH descriptor: [Plasmodium vivax] explode all trees

#7 #4 or #5 or #6

#8 #3 and #7

Embase

1947-Present, updated daily

---

1 "primaquine".mp.

2 primaquine/

3 1 or 2

4 plasmodium vivax.mp. or Plasmodium vivax/

5 malaria vivax.mp. or Plasmodium vivax malaria/

6 4 or 5 or 6

7 controlled clinical trial.mp. or Controlled Clinical Trial/

8 randomized controlled trial.mp. or Randomized Controlled Trial/

9 (randomized or placebo or double-blind* or single-blind*).mp.

10 randomization/

11 crossover procedure/

12 7 or 8 or 9 or 10 or 11

13 3 and 6 and 12

LILACS

Search on : primaquine [Words] and malaria vivax or plasmodium vivax [Words]

ClinicalTrials.gov and WHO ICTRP

primaquine and vivax

CONTRIBUTIONS OF AUTHORS

Rachael Milligan (RM): data collection and management, analysis and interpretation of results, review writing.

Andre Daher (AD): data collection and management, analysis and interpretation of results, review writing.

Patricia Graves (PMG): interpretation of results, review writing.

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All review authors read and approved the final manuscript.

DECLARATIONS OF INTEREST

RM has no known conflicts of interest.
AD has no known conflicts of interest.
PMG has no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.

External sources

- Department for International Development, UK.

  Project number 300342-104

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the inclusion criteria for trials to add 30 mg (0.5 mg/kg/day) for 14 days, as this is a World Health Organization-recommended regimen, and some trials use it as the control group for this reason.

INDEX TERMS

Medical Subject Headings (MeSH)

Antimalarials [administration & dosage] [*therapeutic use]; Drug Administration Schedule; Malaria, Vivax [*drug therapy]; Primaquine [administration & dosage] [*therapeutic use]; Primary Prevention; Randomized Controlled Trials as Topic; Recurrence

MeSH check words

Humans

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