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

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[Intervention Review]

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

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ABSTRACT

Background

Plasmodium vivax liver stages (hypnozoites) may cause relapses, prolonging morbidity, and impeding malaria control and elimination. The World Health Organization (WHO) recommends three schedules for primaquine: 0.25 mg/kg/day (standard), or 0.5 mg/kg/day (high standard) for 14 days, or 0.75 mg/kg once weekly for eight weeks, all of which can be difficult to complete. Since primaquine can cause haemolysis in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency, clinicians may be reluctant to prescribe primaquine without G6PD testing, and recommendations when G6PD status is unknown must be based on an assessment of the risks and benefits of prescribing primaquine. Alternative safe and efficacious regimens are needed.

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-day courses.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE (PubMed); Embase (Ovid); LILACS (BIREME); WHO International Clinical Trials Registry Platform and ClinicalTrials.gov up to 2 September 2019, and checked the reference lists of all identified studies.

Selection criteria

Randomized controlled trials (RCTs) of adults and children with *P vivax* malaria using either chloroquine or artemisinin-based combination therapy plus primaquine at a total adult dose of at least 210 mg, compared with the WHO-recommended regimens of 0.25 or 0.5 mg/kg/day for 14 days.

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, partner drug, and trial location. We analysed safety data where included.

Main results

0.5 mg/kg/day for seven days versus standard 0.25 mg/kg/day for 14 days

There may be little or no difference in *P vivax* recurrences at six to seven months when using the same total dose (210 mg adult dose) over seven days compared to 14 days (RR 0.96, 95% CI 0.66 to 1.39; 4 RCTs, 1211 participants; low-certainty evidence). No serious adverse events were reported. We do not know if there is any difference in the number of adverse events resulting in discontinuation of primaquine (RR 1.04, 95% CI 0.15 to 7.38; 5 RCTs, 1427 participants) or in the frequency of anaemia (RR 3.00, 95% CI 0.12 to 72.91, 1 RCT, 240 participants) between the shorter and longer regimens (very low-certainty evidence). Three trials excluded people with G6PD deficiency; two did not provide this information. Pregnant and lactating women were either excluded or no details were provided.

High-standard 0.5 mg/kg/day for 14 days versus standard 0.25 mg/kg/day for 14 days

There may be little or no difference in *P vivax* recurrences at six months with 0.5 mg/kg/day primaquine for 14 days compared to 0.25 mg/kg/day for 14 days (RR 0.84 (95% CI 0.49 to 1.43; 2 RCTs, 677 participants, low-certainty evidence). No serious adverse events were reported. We do not know whether there is a difference in adverse events resulting in discontinuation of treatment with the high-standard dosage (RR 4.19, 95% CI 0.90 to 19.60; 1 RCT, 778 participants, very low-certainty evidence). People with G6PD deficiency and pregnant or lactating women were excluded.

0.75 mg/kg/week for eight weeks versus high-standard 0.5 mg/kg/day for 14 days

We do not know whether weekly primaquine increases or decreases recurrences of *P vivax* compared to high-standard 0.5 mg/kg/day for 14 days, at 11 months' follow-up (RR 3.18, 95% CI 0.37 to 27.60; 1 RCT, 122 participants; very low-certainty evidence). No serious adverse events and no episodes of anaemia were reported. G6PD-deficient patients were not randomized but included in the weekly primaquine group (only one patient detected).

1 mg/kg/day for seven days versus high standard 0.5 mg/kg/day for 14 days

There is probably little or no difference in *P vivax* recurrences at 12 months between 1.0 mg/kg/day primaquine for seven days and the high-standard 0.5 mg/kg/day for 14 days (RR 1.03, 95% CI 0.82 to 1.30; 2 RCTs, 2526 participants; moderate-certainty evidence). There may be moderate to large increase in serious adverse events in the 1.0 mg/kg/day primaquine for seven days compared with the high-standard 0.5 mg/kg/day for 14 days, during 42 days follow-up (RR 12.03, 95% CI 1.57 to 92.30; 1 RCT, 1872 participants, low-certainty evidence). We do not know if there is a difference between 1.0 mg/kg/day primaquine for seven days and high-standard 0.5 mg/kg/day for 14 days in adverse events that resulted in discontinuation of treatment (RR 2.50, 95% CI 0.49 to 12.87; 1 RCT, 2526 participants, very low-certainty evidence), nor if there is difference in frequency of anaemia by 42 days (RR 0.93, 95% CI 0.62 to 1.41; 2 RCTs, 2440 participants, very low-certainty evidence). People with G6PD deficiency were excluded.

Other regimens

Two RCTs evaluated other rarely-used doses of primaquine, one of which had very high loss to follow-up. Adverse events were not reported. People with G6PD deficiency and pregnant or lactating women were excluded.

Authors' conclusions

Trials available to date do not detect a difference in recurrence between the following regimens: 1) 0.5 mg/kg/day for seven days versus standard 0.25 mg/kg/day for 14 days; 2) high-standard 0.5 mg/kg/day for 14 days versus standard 0.25 mg/kg/day for 14 days; 3) 0.75 mg/kg/week for eight weeks versus high-standard 0.5 mg/kg/day for 14 days; 4) 1 mg/kg/day for seven days versus high-standard 0.5 mg/kg/day for 14 days. There were no differences detected in adverse events for Comparisons 1, 2 or 3, but there may be more serious adverse events with the high seven-day course in Comparison 4.

The shorter regimen of 0.5 mg/kg/day for seven days versus standard 0.25 mg/kg/day for 14 days may suit G6PD-normal patients. Further research will help increase the certainty of the findings and applicability in different settings.

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 recurring. However, the current dosing schedule requires 14 days of daily treatment.

What are the concerns about primaquine?

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 mg to 30 mg per day for 14 days with the same (210 mg) or higher total 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 2 September 2019 and included 11 randomized controlled trials (RCTs) (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 primaquine per day for seven days compared to 15 mg per day for 14 days, there may be little or no difference in *P vivax* recurrences at six to seven months (low-certainty evidence). No serious adverse events were reported. We do not know if there is a difference in the number of adverse events that cause people to stop taking the drug (low-certainty evidence).

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 six months (very low-certainty evidence). No serious adverse events were reported, but it is unclear whether or not there is a difference between doses in other adverse events that cause people to stop taking the drug (very low-certainty evidence).

We do not know whether primaquine at 45 mg once per week for eight weeks increases or decreases recurrences of *P vivax* compared to the high standard 30 mg per day for 14-days, at 11 months' follow-up (very low-certainty evidence).

There is probably little or no difference for recurrence using high dose 60 mg per day for seven days compared to the high standard 30 mg per day for 14 days, but there may be an increase in serious adverse events in the high-dose shorter course regimen group.

Further RCTs will 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 2 September 2019.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings table 1 (main comparison)

0.5 mg/kg primaquine/day for 7 days versus standard 0.25 mg/kg/day for 14 days 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/day, total dose 210 mg)
Comparison: standard 14-day course primaquine (0.25 mg/kg/day, adult dose 15 mg/day; total dose 210 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	84 per 1000	81 per 1000 (55 to 117)	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 events	Not estimable (0 events in 723 participants)	Not estimable (0 events in 704 participants)	Not estimable	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)	1427 (5 RCTs)	⊕⊖⊖⊖ VERY LOW[c,d] due to risk of bias and serious 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.
Anaemia or change in haemoglobin status	Not estimable (0 events in 120 participants)	Not estimable (1 event in 120 participants)	RR 3.0 (0.12 to 72.91)	240 (1 RCT)	⊕⊖⊖⊖ VERY LOW[e,f,g] due to risk of bias, indirectness, and serious imprecision	We do not know if the occurrence of anaemia differs between the 2 treatment regimens.

*__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 seven 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 risk of bias: Pareek 2015 IND was at risk of selection bias and other bias (funded and performed by drug company).
[f]Downgraded once for indirectness: only one study that excluded G6PD-deficient adults measured this safety outcome (Pareek 2015 IND).
[g]Downgraded twice for serious imprecision: only one event (in the 0.5 mg/kg/day primaquine for seven days group), very wide CIs.

Summary of findings 2. Summary of findings table 2

High standard 0.5 mg/kg primaquine /day for 14 days versus standard 0.25 mg/kg/day for 14 days 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 primaquine (0.5 mg/kg/day, adult dose 30 mg/day; total dose 420 mg)
Comparison: standard 14-day course primaquine (0.25 mg/kg/day, adult dose 15 mg/day; total dose 210 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 high-standard 14-day course primaquine				
Recurrence of *P vivax* parasitaemia follow-up: range 6 months to 7 months	82 per 1000	69 per 1000 (40 to 117)	RR 0.84 (0.49 to 1.43)	677 (2 RCTs)	⊕⊕⊖⊖ LOW[a,b] due to risk of bias and imprecision	There may be little or no difference in *P vivax* recurrences between high-standard or standard 14-day courses of primaquine given with chloroquine or an ACT.

Serious adverse events	Not estimable (0 events in 398 participants)	Not estimable (0 events in 380 participants)	Not estimable	778 (1 RCT)	—	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[c,d,e] 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.

*__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: 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 risk of bias: one study was open-label with no allocation concealment (risk of selection bias) and risk of attrition bias due to high percentage not completing six months' follow-up with minimal explanation; the other study had no blinding and a high rate of loss to follow-up.
[b]Downgraded once for imprecision: wide CIs - range of 51% reduction in malaria recurrences at six months with high-standard 14-day course of primaquine to 43% increase in number of malaria recurrences.
[c]Downgraded once for indirectness: only one trial that excluded G6PD-deficient adults measured this safety outcome (Rajgor 2014 IND).[d]Downgraded once for risk of bias: open-label with no allocation concealment (risk of selection bias) and risk of attrition bias due to high percentage not completing six months' follow-up with minimal explanation.
[e]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.

Summary of findings 3. Summary of findings table 3

0.75 mg/kg primaquine /week for 8 weeks versus high-standard 0.5 mg/kg/day for 14 days 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/week; total dose 360 mg)
Comparison: high-standard 14-day course primaquine (0.5 mg/kg/day, adult dose 30 mg/day; total dose 420 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: 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] due to risk of bias and serious 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 events	Not estimable (0 events in 55 participants)	Not estimable (0 events in 74 participants)	Not estimable	129 (1 RCT)	—	No events reported.
Anaemia (haemoglobin < 7 g/dL)	Not estimable (0 events in 55 participants)	Not estimable (0 events in 74 participants)	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 once for risk of bias: Leslie 2008 PAK was at high risk of bias for randomization process, allocation concealment, and incomplete outcome data.
[b]Downgraded twice for serious imprecision: few events, very wide CIs that incorporated a potential large beneficial effect and a potential large harmful effect.

Summary of findings 4. Summary of findings table 4

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

Patient or population: adults and children with confirmed clinical and parasitological *P vivax* malaria

Settings: Afghanistan, Ethiopia, Indonesia, Thailand, and Vietnam

Intervention: 1.0 mg/kg/day primaquine for 7 days (adult dose 60 mg/day; total dose 420mg)

Comparison: high-standard 14-day course primaquine (0.5 mg/kg/day, adult dose 30 mg/day; total dose 420mg)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of Participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with	Risk with 1.0 mg/kg/				

	high-standard 14-day course primaquine	day primaquine for 7 days				
Recurrence of *P vivax* parasitaemia Follow-up: 12 months	104 per 1000	107 per 1000 (85 to 135)	RR 1.03 (0.82 to 1.30)	2526 (2 RCTs)	⊕⊕⊕⊖[a] MODERATE due to risk of bias	There is probably little or no difference between 1.0 mg/kg/day primaquine for 7 days and the high-standard 0.5 mg/kg/day for 14 days course
Serious adverse events Follow-up: up to 42 days	1 per 1000	13 per 1000 (2 to 99)	RR 12.03 (1.57 to 92.30)	1872 (1 RCT)	⊕⊕⊖⊖[b,c] LOW due to indirectness and imprecision	There may be a moderate to large increase in serious adverse events in the 1.0 mg/kg/day primaquine for 7 days compared with the high-standard 0.5 mg/kg/day Chu 2019 THA provides overall narrative results only, see Effects of interventions text.
Adverse events the resulted in discontinuation of treatment	2 per 1000	4 per 1000 (1 to 20)	RR 2.50 (0.49 to 12.87)	2526 (2 RCTs)	⊕⊖⊖⊖[a,b,d] VERY LOW due to risk of bias, indirectness and serious imprecision	We do not know if there is any difference in adverse events resulting in treatment discontinuation between 1.0 mg/kg/day primaquine for 7 days and the high-standard 0.5 mg/kg/day for 14 days course.
Anaemia Follow-up: between 3 and 42 days follow-up	35 per 1000	33 per 1000 (22 to 50)	RR 0.93 (0.62 to 1.41)	2440 (2 studies)	⊕⊖⊖⊖[a,b,e] VERY LOW due to risk of bias, indirectness and imprecision	We do not know if there is any difference in anaemia between 1.0 mg/kg/day primaquine for 7 days and the high-standard 0.5 mg/kg/day for 14 days course.

*__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).
CI: Confidence interval; **DHA-PPQ**: dihydroartemisinin-piperaquine; **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: Chu 2019 THA was an open-label trial with high risk of performance and detection bias; although drop-outs were balanced between groups the proportion of drop-outs after one year was high in both trials (30-40%).
[b]Downgraded once for indirectness: G6PD-deficient children and adults were excluded from the two trials that measured this outcome (Chu 2019 THA; Taylor 2019 MULTI).
[c]Downgraded once for imprecision: few events.
[d]Downgraded twice for imprecision: few events and a very wide 95% CI that incorporated a potential large beneficial effect and a potential large harmful effect.
[e]Downgraded once for imprecision: few events and a wide 95% CI that incorporated a potential moderate beneficial effect and a potential moderate harmful effect.

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 2018, an estimated 228 million cases of malaria occurred worldwide and an estimated 405,000 people died from the disease (WHO 2019). 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 has 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 2018 (WHO 2019). 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 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) and is gametocytocidal (Graves 2018). 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 events observed with 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 (standard) to 0.5 mg/kg/day (high standard) of primaquine for 14 days (total dose 210 mg or 420 mg) 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). Citing the review previous Cochrane Review of this topic (Galappaththy 2013), the WHO notes that the standard regimen reduced relapses during 15 months of follow-up by about 40% compared to placebo or no primaquine (high-quality evidence), and reduced relapses during six months follow-up by over 50% compared to seven days primaquine (low-quality evidence) (WHO 2015). The increased dosing in the high standard 0.5 mg/kg/day regimen was previously recommended in East Asia and Oceania based on suggestion of failure of the standard regimen of 0.25 mg/kg/day for 14 days for strains of *P vivax* in these areas (including the Chesson strain). The guidelines note that "no direct comparison has been made of higher doses (0.5 mg/kg bw for 14 days) with the standard regimen (0.25 mg/kg bw for 14 days)". Given that the 15 trials included in the WHO assessment excluded G6PD-deficient persons (12 trials) or did not comment on their exclusion, WHO guidelines also stated "in the absence of evidence to recommend alternatives, the guidelines development group consider 0.75 mg/kg bw primaquine given once weekly for 8 weeks to be the safest regimen for people with mild to moderate G6PD deficiency", but no trials of this regimen were included in the WHO guidance (WHO 2015).

The 14-day course of primaquine at any dose, as well as the eight-week course, 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.

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 the same total dose as the standard regimen (210 mg), or higher total doses, given over either shorter or longer periods. We planned to include any such trials in this Cochrane Review.

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 five 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 to 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 strains 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 that do not use the standard (0.25 mg/kg/day) or high-standard (0.5 mg/kg/day) regimens of 14 days of primaquine in the control groups. 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 at this 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 three, six, 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.

Attention is needed to the problems of lack of completion of long treatment courses and potential insufficient dosing in some geographical areas, while maintaining daily doses within a safe range. We compare the efficacy and safety of alternative schedules to those currently recommended, or those with insufficient evidence in current recommendations. Specifically, we intended to answer the following questions by comparing alternative regimens with total adult dose of over 210 mg to the standard 14-day regimen of primaquine (0.25 mg/kg/day,15 mg adult daily dose, total dose 210 mg), or the high-standard 14-day regimen (0.5 mg/kg/day,30 mg adult daily dose, total dose 420 mg).

- Is a shorter, higher daily dose regimen with same or higher total dose, given over seven days, as (or more) efficacious and safe as the standard or high standard regimens given over 14 days? (Comparisons 1 and 4)
- Is the high-standard 14-day regimen, with higher daily and total dose, as (or more) efficacious and safe as the standard 14-day course, in all areas and/or where it was formerly recommended (East Asia and Oceania)? (Comparison 2)
- Is a weekly dosing regimen with higher daily dose given one day a week and with either higher or lower total dose, as (or more) efficacious and safe as the standard or high-standard 14-day regimens? (Comparison 3)

OBJECTIVES

To assess the efficacy and safety of alternative primaquine regimens with total adult dose >210 mg for radical cure of *P vivax* malaria compared to the standard or high-standard 14 days of primaquine (0.25 mg/kg/day or 0.5 mg/kg/day, total adult dose 210 mg or 420 mg), as well as comparison of these two WHO-recommended regimens.

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 at total adult dose >210 mg in any of the following categories.

Daily doses higher than 0.25 mg/kg/day (15 mg daily adult dose, total dose 210 mg) for 14 days.

- Shorter regimens with the same or higher total dose than the regimen they are being compared to i.e. standard or high standard regimen.
- Weekly dosing regimens.

Control

WHO-defined standard regimen of 14 days of primaquine at 0.25 mg/kg/day (15 mg daily adult dose, total dose 210 mg), or high-standard regimen of 0.5 mg/kg/day for 14 days (30 mg adult daily dose, total dose 420 mg), plus either chloroquine or an ACT as the treatment for blood-borne infection. Where possible, we stratified 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.
- 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 (2 September 2019); the Cochrane Central Register of Controlled Trials (CENTRAL, 2018, Issue 12, published in the Cochrane Library); MEDLINE (PubMed, 1946 to 2 September 2019); Embase (Ovid, 1947 to 2 September 2019); and LILACS (Bireme, 1982 to 2 September 2019). 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 2 September 2019, 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 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.
- 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 5) (Review Manager 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.

We also extracted measures of rate ratio and hazard ratio when reported by trials, and summarized these in appendices.

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 planned to use 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 RevMan 5 (Review Manager 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 grouped the analyses by drug regimen and stratified results according to blood-stage partner drug (if different blood-stage antimalarials were used). Length of follow-up varied with regimens and between studies. 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 and stratified data accordingly.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses according to geographical region/endemicity and directly observed therapy (DOT) or non-DOT. We had planned to perform a subgroup analysis according to CYP2D6 status, however data were insufficient to permit this.

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.

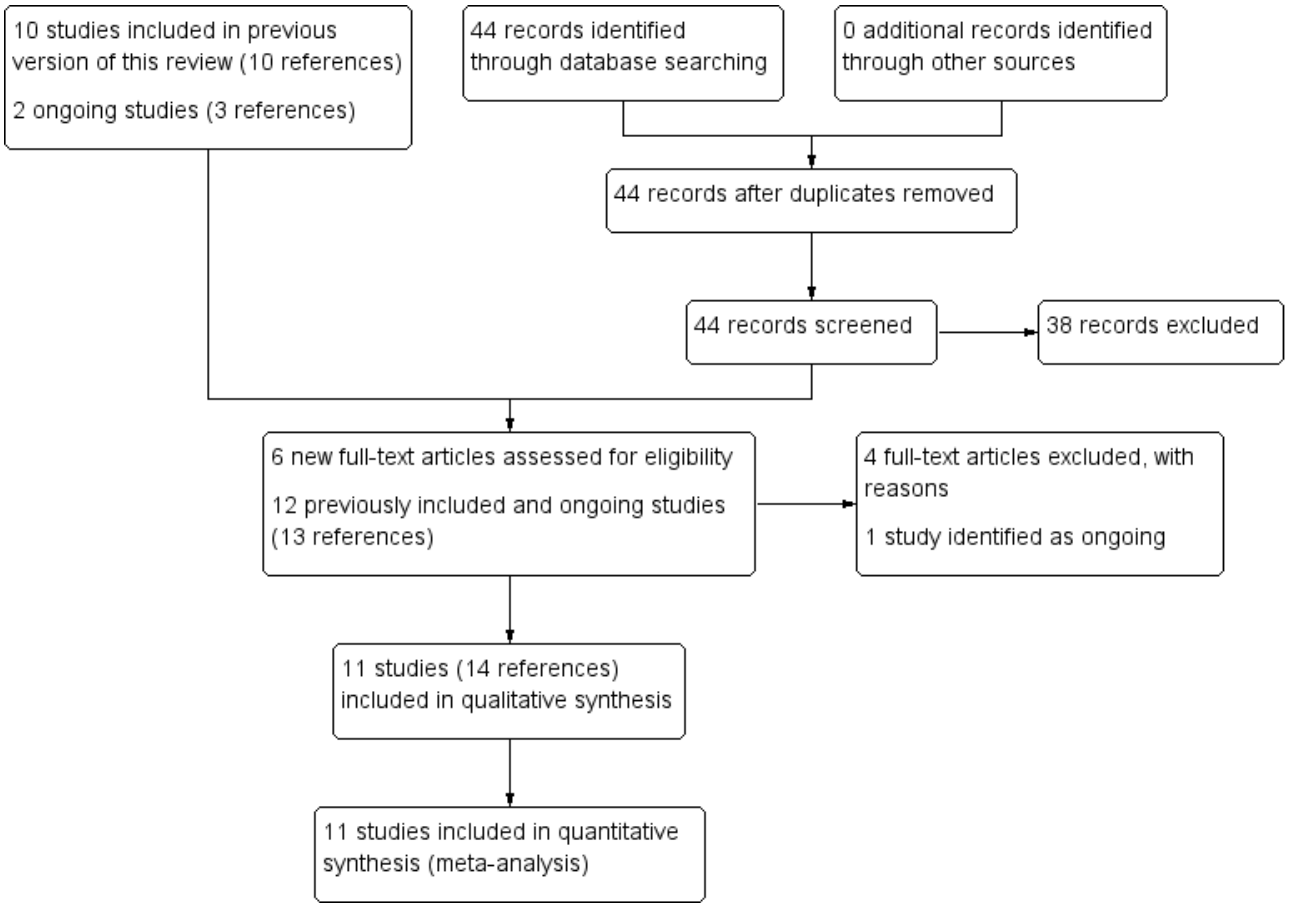
RESULTS

Description of studies

Results of the search

Our database update search, conducted up to 2 September 2019, identified 44 studies. We excluded 38 articles during abstract screening, and selected six studies for full-text review. We excluded four studies with reasons provided, and included one new reference with outcome data for a previously ongoing study (Taylor 2019 MULTI) ,and one new reference with outcome data for an already included study that had not provided any data in the previous version of this review (Chu 2019 THA). Following this update search, this review now contains 11 included studies, 29 excluded studies and one ongoing study. The search results and screening process for this update are presented in a PRISMA diagram in Figure 1.

Figure 1. Study flow diagram.



Included studies

We included 11 studies (of 11 trials) in our quantitative analysis.

One trial was multinational and conducted in Africa (Ethiopia) and Asia (Afghanistan, Indonesia, and Vietnam) (Taylor 2019 MULTI). 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). Six trials were conducted in Asia: one in Pakistan (Leslie 2008 PAK), two in Thailand (Bunnag 1994 THA; Chu 2019 THA), and three in India (Rajgor 2014 IND; Pareek 2015 IND; Saravu 2018 IND).

Eight trials were funded by not for profit organizations, government agencies, or academia. One trial was funded by the drug manufacturer (Pareek 2015 IND), and two trials did not report their source of funding (Bunnag 1994 THA; Abdon 2001 BRA).

All 11 trials included data for adults, and six trials included children under the age of 10 years (Solari-Soto 2002 PER; Leslie 2008 PAK; Carmona-Fonseca 2009 COL; Durand 2014 PER; Chu 2019 THA; Taylor 2019 MULTI). Two trials (Chu 2019 THA; Taylor 2019 MULTI) included children from the age of six months.

Nine trials excluded pregnant women, and two trials did not specify whether or not pregnant women were included (Bunnag 1994 THA; Solari-Soto 2002 PER). Eight 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). Eight trials excluded people with G6PD deficiency (Bunnag 1994 THA; Carmona-Fonseca 2009 COL; Durand 2014 PER; Rajgor 2014 IND; Pareek 2015 IND; Saravu 2018 IND; Chu 2019 THA; Taylor 2019 MULTI), 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 polymerase chain reaction (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.

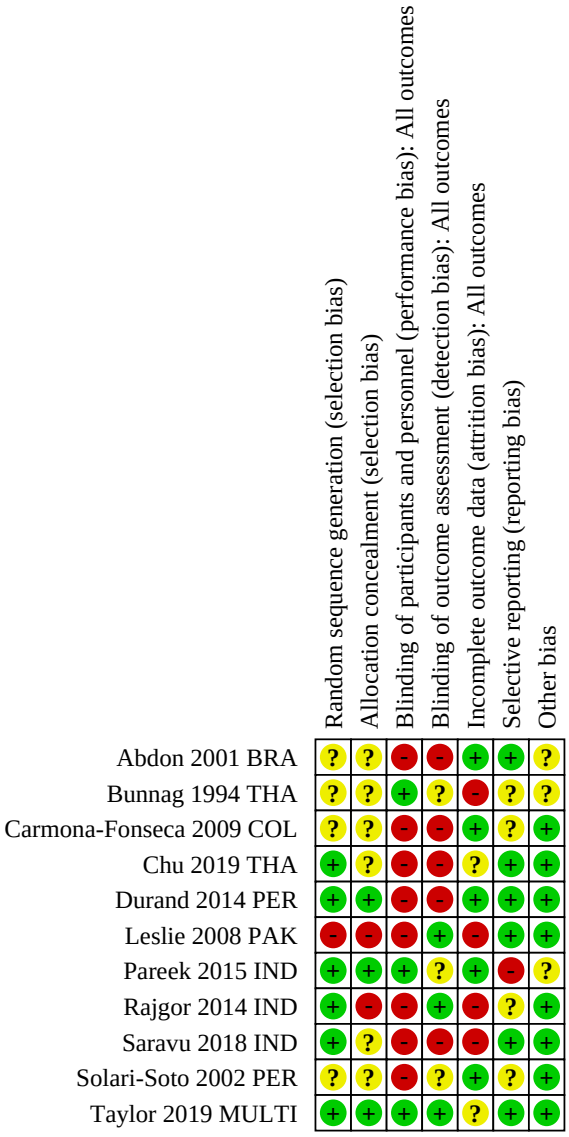
Excluded studies

We excluded 29 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 2. Full details are shown in the Characteristics of included studies tables.

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



Allocation

Six 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; Chu 2019 THA; Taylor 2019 MULTI). 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 (Durand 2014 PER; Pareek 2015 IND) and an independent statistician held the group assignments in one trial (Taylor 2019 MULTI), so these three trials were assessed as being at low risk of bias. We assessed

two trials with no concealment of treatment allocation as at high risk of bias (Leslie 2008 PAK; Rajgor 2014 IND), while six 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; Chu 2019 THA).

Blinding

Eight 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; Chu 2019 THA). The remaining three trials reported blinding of participants and personnel, and were classified as being at low risk of performance bias (Bunnag 1994 THA; Pareek 2015 IND; Taylor 2019 MULTI). FIve trials were at high risk of detection bias (Abdon 2001 BRA; Carmona-Fonseca 2009 COL; Durand 2014 PER; Saravu 2018 IND; Chu 2019 THA); they were all open-label trials that did not report any details of blinding outcome assessment. Three trials were at unclear risk of detection bias. They were either double-blind trials that did not report any details as to whether microscopy was blinded or whether there was double reading of smears (Bunnag 1994 THA; Pareek 2015 IND), or an open-label trial that mentioned double-checking of smears but did not clarify whether outcome assessment was blinded (Solari-Soto 2002 PER). Three trials were at low risk of detection bias; they reported blinding of the microscopists who read the slides (Leslie 2008 PAK; Rajgor 2014 IND; Taylor 2019 MULTI).

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. Two trials were assessed as at unclear risk of attrition bias (Chu 2019 THA; Taylor 2019 MULTI), both had high rates of dropouts, but this was after one year and rates were balanced between groups and reasons for dropping out were provided.

Selective reporting

We judged six trials to have adequately reported on either prespecified or expected outcomes (Abdon 2001 BRA; Leslie 2008 PAK; Durand 2014 PER; Saravu 2018 IND; Chu 2019 THA; Taylor 2019 MULTI). Risk of reporting bias was unclear for four trials as no protocols were available (Bunnag 1994 THA; Solari-Soto 2002 PER; Carmona-Fonseca 2009 COL; Rajgor 2014 IND). 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 assessed eight 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; Chu 2019 THA; Taylor 2019 MULTI). We assessed Pareek 2015 IND to be at unclear 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. Another two trials, for which funding was not detailed, were also assessed as at unclear risk of other bias (Bunnag 1994 THA; Abdon 2001 BRA).

Effects of interventions

See: **Summary of findings 1** Summary of findings table 1 (main comparison); **Summary of findings 2** Summary of findings table 2; **Summary of findings 3** Summary of findings table 3; **Summary of findings 4** Summary of findings table 4

Comparison 1: 0.5 mg/kg/day for seven days versus standard 0.25 mg/kg/day for 14 days

This comparison aimed to investigate whether a shorter, higher-dose regimen of primaquine over seven days is 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 seven 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 0.25 mg/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 0.25 mg/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 six to seven months' follow-up (risk ratio (RR) 0.96, 95% confidence interval (CI) 0.66 to 1.39; 4 trials, 1211 participants; low-certainty evidence; Analysis 1.1). 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 six to seven 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 seven 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 seven days compared to the standard 14-day regimen (Analysis 1.2). 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 1.3). For trials in South America, the regimen of 0.5 mg/kg/day for seven days led to a 30% reduction in *P vivax* recurrences compared to a 19% increase in recurrences for trials in Asia, although CIs were wide and included no effect for both subgroups (South America: RR 0.70, 95% CI 0.39 to 1.26; 2 trials, 397 participants; Asia: RR 1.19, 95% CI 0.73 to 1.94; 2 trials, 814 participants). Only one trial did not use directly observed therapy (DOT) (Pareek 2015 IND). Subgroup analysis (Analysis 1.4) showed that with DOT there was minimal difference in recurrences at six to seven months between treatment regimens (RR 0.98, 95% CI 0.67 to 1.43; 1017 participants) compared to a reduction of about half of recurrences with the regimen of 0.5 mg/kg/day for seven days when treatment was not supervised (RR 0.48, 95% CI 0.04 to 5.20; 194 participants).

Adverse events

No serious adverse events were reported in either group (5 trials, 1427 participants, Analysis 1.5). The number of participants experiencing adverse events leading to discontinuation of treatment was similar in both groups (very low-certainty evidence, RR 1.04, 95% CI 0.15 to 7.38; 5 trials, 1427 participants; Analysis 1.6). Only one study reported on adverse events during chloroquine administration (Rajgor 2014 IND), with more occurring in the group receiving 0.5 mg/kg/day for seven days than the standard 14-day group (RR 9.40, 95% CI 0.51 to 174.01; one trial, 779 participants; Analysis 1.7). There was no difference in adverse events occurring during primaquine administration (RR 1.64, CI 0.75 to 3.57; 2 trials,1019 participants; Analysis 1.8). There was no difference between arms in other adverse events (RR 0.56, 95% CI 0.23 to 1.36; 2 trials,135 participants; Analysis 1.9).

One trial reported on change in haemoglobin status (Pareek 2015 IND), with one participant out of 120 in the group receiving 0.5 mg/kg/day for seven days becoming anaemic, versus no participants out of 120 in the standard 14-day regimen group (very low-certainty evidence, RR 3.00, 95% CI 0.12 to 72.91; 240 participants; Analysis 1.10).

Durand 2014 PER noted that the arms with higher daily primaquine dose did not present significantly higher frequency of the five symptoms (fever, chills, headache, muscular pain, and dark urine) monitored during treatment.

Details on the nature of the adverse events are reported in Appendix 2.

Comparison 2: high-standard 0.5 mg/kg/day for 14 days versus standard 0.25 mg/kg/day for 14 days

The World Health Organization (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 (East Asia and Oceania), as well as in all other areas where it has been used due to perceived resistance or strain differences.

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 women 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 artemisinin-based combination therapy (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. Results from the two studies are presented separately in subgroups, but are also combined.

Efficacy

The combined estimate for both trials suggests little or no difference between the arms: (RR 0.84, 95% CI 0.49 to 1.43; 2 trials, 677 participants, low-certainty evidence, test for subgroup differences, $I^2 = 0\%$).

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 six-month follow-up, giving an 18% reduction in recurrence of parasitaemia in the high-standard group (RR 0.82, 95% CI 0.47 to 1.43; 639 participants; Analysis 2.1). *P 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 *P vivax* malaria cases in the high-standard group (RR 1.83, 95% CI 0.62 to 5.40; Analysis 2.2). Rajgor 2014 IND was at high risk of bias for allocation concealment.

Saravu 2018 IND was a small open-label pilot trial in which participants were given either chloroquine or ACT depending on clinician's judgement of severity. 78% of participants were given chloroquine (76% in the standard arm and 80% in the high-standard arm). In Saravu 2018 IND, two out of 18 participants in the high-standard 14-day group had a recurrence of *P vivax* malaria compared to two out of 20 in the standard 14-day group at six months' follow-up (RR 1.11, 95% CI 0.17 to 7.09; Analysis 2.1). Polymerase chain reaction (PCR) genotyping suggested that all four participants had true relapses of infection.

Adverse events

In Rajgor 2014 IND there were no serious adverse events reported in either study arm (778 participants). In the high-standard 14-day group, eight out of 380 participants discontinued treatment due to adverse events (one participant discontinued chloroquine

and seven participants discontinued primaquine), compared to two out of 398 in the standard 14-day group (both participants discontinued primaquine) (RR 4.19, 95% CI 0.90 to 19.60; 778 participants; Analysis 2.4). In the high-standard arm during chloroquine treatment, four out of 380 participants experienced adverse events compared to zero out of 398 in the standard group (RR 9.43, 95% CI 0.51 to 174.47; 778 participants; Analysis 2.5). In the high-standard arm during primaquine treatment, 13 out of 380 participants experienced adverse events known to occur with primaquine, compared to five out of 398 in the standard arm (RR 2.72, 95% CI 0.98 to 7.57; 778 participants; Analysis 2.5). These results could suggest a trend towards higher occurrence of adverse events in the high-standard 14-day regimen. Details on the nature of the adverse events are reported in Appendix 2.

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

Comparison 3: 0.75 mg/kg/week for eight weeks versus high-standard 0.5 mg/kg/day for 14 days

This comparison aimed to investigate whether a higher once-weekly dosing regimen, which may be more beneficial for people with 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 eight 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 eight months' follow-up (RR 7.00, 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 27.60; 122 participants; very low-certainty evidence; 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 events

No serious adverse events (Analysis 3.2) or notable non-serious adverse events (Analysis 3.4) were reported in either study arm. No participants had anaemia defined as haemoglobin less than 7 g/dL (Analysis 3.3).

Comparison 4: 1 mg/kg/day for seven days versus high-standard 0.5 mg/kg/day for 14 days

This comparison aimed to investigate whether shorter, higher doses of primaquine over seven days are as effective as the high-standard 14-day regimen; i.e. to determine whether the total dose rather than the length of treatment is the important factor (total dose 420 mg primaquine). Two trials conducted in Ethiopia, Afghanistan, Indonesia, Thailand, and Vietnam compared 1 mg/kg/day (adult dose 60 mg) of primaquine for seven days with the high-standard 14-day course (0.5 mg/kg/day, adult dose 30 mg/day) (Chu 2019 THA; Taylor 2019 MULTI), administering the regimen with either chloroquine or an ACT (dihydroartemisinin-piperaquine (DHA-PPQ). We stratified the results accordingly. Both trials excluded people with G6PD deficiency, however, both trials included those with G6PD deficiency in parallel observational cohorts. Women who were pregnant or lactating were excluded. Participants were a mixture of adults and children over six months old. Both trials used microscopy for diagnosis, and both trials used supervised treatment. Taylor 2019 MULTI gave chloroquine or DHA-PPQ and primaquine courses simultaneously, while Chu 2019 THA did not specify whether primaquine was given concurrently, before, or after blood-stage drug. No trials stratified by age, so results were combined.

Efficacy

Primary outcome

Little or no difference was detected in recurrence of *P vivax* malaria after 12 months between 1 mg/kg/day for seven days compared with the high-standard 14-day regimen in two trials (RR 1.03, 95% CI 0.82 to 1.30; 2526 participants, moderate-certainty evidence, Analysis 4.1). Rate ratios and hazard ratios support the RR estimate and are reported in Appendix 3 The results were similar for the chloroquine subgroup (RR 0.91, 95% CI 0.67 to 1.22; 1404 participants) and for the DHA-PPQ subgroup (RR 1.24, 95% CI 0.87 to 1.77; 1122 participants). Results were also similar for subgroups by geographical region (Analysis 4.2).

Only one trial (Chu 2019 THA) reported risk ratios at six and three months. There was little or no difference detected in recurrence of *P vivax* malaria after six months (RR 1.10, 95% CI 0.61 to 1.97; 1 RCT, 474 participants; Analysis 4.3) and after three months (RR 0.94, 95% CI 0.41 to 2.14; 1 RCT, 522 participants; Analysis 4.4). Results subgrouped by blood-stage drug were similar, but results were imprecise due to wide 95% CIs.

Taylor 2019 MULTI did not report risk ratios at six and three months that could be pooled with the main results. Rate ratios from this study are presented in Appendix 3, and they also show little or no difference in recurrences between the two arms.

Secondary outcome

Taylor 2019 MULTI reported on short-term follow-up of *P vivax* parasitaemia. Little or no difference was detected for *P vivax* parasitaemia after 28 days (RR 0.67, 95% CI 0.11 to 3.99; 1872 participants; Analysis 4.5), and after 42 days (RR 1.00, 95% CI 0.35 to 2.85; 1872 participants; Analysis 4.5). The estimates are uncertain due to very wide 95% CIs.

Adverse events

There may be moderate to large increase in serious adverse events in the 1.0 mg/kg/day primaquine for seven days group compared with the high-standard 0.5 mg/kg/day at 42 days (RR 12.03, 95% CI 1.57 to 92.30; 1872 participants; low-certainty evidence; Analysis 4.6), and at one year follow-up (RR 3.61, 95% CI 1.35 to 9.68; 1872 participants; Analysis 4.6). The absolute numbers reported by Taylor 2019 MULTI at 42 days and one year were 12 and 18 serious adverse events in the primaquine 1 mg/kg/day for seven days group among 935 participants compared to one and five in the control arm among 937 participants, respectively. Of the 12 serious adverse events reported at 42 days in the 1 mg/kg/day group, nine were regarded as being possibly, probably, or definitely related to primaquine (details of each event from Taylor

2019 MULTI supplementary files are given in Appendix 2). At one year, an additional six serious adverse events deemed unrelated to primaquine were reported in the 1 mg/kg/day group. Only one of the five serious adverse events in the high-standard 14 day regimen (observed by 42 days) was deemed probably related to primaquine (Appendix 2).

Chu 2019 THA only provides a narrative summary and does not report serious adverse events per group. The authors noted that there were 30 serious adverse events reported; most common were methaemoglobinaemia (n = 10), haemolysis (n = 3), and presumed bacterial infection (n = 10). Four deaths occurred. None was considered related to the study drugs (follow-up, up to 42 days).

There is probably no difference in adverse events leading to discontinuation of treatment between both groups (RR 2.50, 95% CI 0.49 to 12.87; 2 trials, 2526 participants; very low-certainty evidence; Analysis 4.7). However, the evidence is very uncertain due to risk of bias and wide 95% CIs.

Taylor 2019 MULTI reported 1819 adverse events among the 935 participants in the seven-day primaquine group and 1732 events among the 937 participants in the 14-day primaquine group; Chu 2019 THA reported 169 events among the 327 participants in the seven-day primaquine group and 173 events among the 327 participants in the 14-day primaquine group (Analysis 4.8).

Full details on the nature of adverse events are reported in Appendix 2.

There is probably no difference in haemoglobin status between both groups (RR 0.93, CI 95% 0.62 to 1.41; 2 trials, 2440 participants; very low-certainty evidence; Analysis 4.9). However, the evidence is very uncertain due to risk of bias and wide 95% CIs.

Comparisons 5 and 6: 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 six 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 5.1), 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 patients tolerated the medication well and no serious adverse effect was seen in either group.There was no drop in haematocrit, or haemoglobinuria in either group.

1.17 mg/kg/day for three 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 three 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 three 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 6.1).

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

DISCUSSION

Summary of main results

Comparison 1 (main comparison): 0.5 mg/kg/day for seven days versus standard 0.25 mg/kg/day for 14 days

See Summary of findings 1

We included five randomised controlled trials (RCTs) that compared 0.5 mg/kg/day (adult dose 30 mg) primaquine for seven days with the standard 14-day regimen (0.25 mg/kg/day). There may be little or no difference in *P vivax* recurrences at six to seven months when using the same total dose (210 mg) over seven 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 during primaquine treatment when using the shorter regimen as compared to the longer regimen.

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.

Comparison 2: high-standard 0.5 mg/kg for 14 days versus standard 0.25 mg/kg/day for 14 days

See Summary of findings 2

We included two 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. The total dose differed between arms, being 420 mg in the high standard arm and 210 mg in the standard arm. People with G6PD deficiency and pregnant or lactating women were excluded. One trial did not account for whether participants were given chloroquine or an artemisinin-based combination therapy (ACT) for blood-stage treatment.

There may be little or no difference in *P vivax* recurrences at six months with the high-standard 14-day course compared to the standard 14-day course when given with chloroquine or an ACT. No differences were observed when primaquine was given either with chloroquine, or with chloroquine or ACT.

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

Comparison 3: 0.75 mg/kg/week for eight weeks versus high-standard 0.5 mg/kg/day for 14 days

See Summary of findings 3

We included one RCT that compared 0.75 mg/kg (daily adult dose 45 mg) weekly primaquine for eight weeks with the high-standard 14-day regimen (0.5 mg/kg/day, daily adult dose 30 mg). The total dose was 360 mg in the weekly arm versus 420 mg in the high-standard arm. 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 eight to 11 months' follow-up (very low-certainty evidence).

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

Comparison 4: 1.0 mg/kg/day for seven days versus high-standard 0.5 mg/kg/day for 14 days

See Summary of findings 4

We included two RCTS (one a large multicentre trial) that compared a new high dose of 1 mg/kg/day for seven days with the high-standard course. The total dose of 420 mg was the same for both arms. G6PD-deficient participants were excluded from one trial; in the other trial, patients with G6PD deficiency were excluded from the randomised trial, but were enrolled into a parallel observational group receiving weekly primaquine.

There is probably little or no difference in recurrences between 1.0 mg/kg/day primaquine for seven days and the high-standard 0.5 mg/kg/day for 14 days course at 12 months follow-up (moderate-certainty evidence). No differences were observed when primaquine was given with chloroquine or dihydroartemisinin-piperaquine (DHA-PPQ).

There may be moderate to large increase in serious adverse events with 1.0 mg/kg/day primaquine for seven days compared with the high-standard 0.5 mg/kg/day, as reported by one trial (Taylor 2019 MULTI) at 42 days and one-year follow-up (low-certainty evidence); the other trial reported narrative summary only (Chu 2019 THA). We do not know if there is difference in anaemia at 42 days follow-up or in adverse events leading to discontinuation (very low-certainty evidence).

Comparisons 5 and 6: other regimens

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 limited.

Overall completeness and applicability of evidence

Although the evidence is currently of low certainty, it appears from Comparison 1 that using 0.5 mg/kg/day with the same total dose (210 mg) over seven days may be non-inferior to the regimen of 0.25 mg/kg/day for 14 days. It is likely that this shorter regimen would promote course completion. No serious adverse events were reported in the five trials in this comparison. However, this seven-day 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.

We initially planned to evaluate whether the high-standard 14-day regimen (0.5 mg/kg/day) was more effective in areas where recommended by the World Health Organization (WHO) due to reported resistance or strain differences (East Asia and Oceania), as well as in other areas (WHO 2015). However, the two randomized clinical trials that compared the efficacy of high-standard to the standard regimen were both conducted in India (Rajgor 2014 IND; Saravu 2018 IND), where the high-standard regimen is not recommended. 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.

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 trial.

We found two trials of a new high dose 1.0 mg/kg/day for seven days compared to the high standard 0.5 mg/kg/day for 14 days. There is probably no difference in frequency of recurrences between these two regimens. However one of these trials reported increased serious adverse events in the seven-day arm.

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 (0.25 mg/kg/day for 14 days) as a comparator. Some trials used the high-standard 0.5 mg/kg/day for 14 days regimen, which is recommended by the WHO in East Asia and Oceania, as a comparator. However, as noted above, there is limited clear evidence in this review that the high-standard 0.5 mg/kg/day 14-day regimen is better than the standard 0.25 mg/kg/day for 14 days.

We 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 *Plasmodium 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.

There was a lack of detailed safety data for some trials, despite the fact that safety is a particular concern with primaquine use. Although more recent trials have paid more attention to this issue, they do not all report the adverse events by arm.

Certainty of the evidence

The overall certainty of evidence for most of the outcomes was either low or very low. Most results were downgraded for

imprecision due to wide confidence intervals (CIs) in the meta-analyses performed. The exception is the recent Comparison 4 using high dose 1 mg/kg/day versus high-standard course for the efficacy outcomes, where evidence for non-inferiority was moderate certainty.

The efficacy comparison for Comparison 2 (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 by outcome (although appeared balanced between arms). 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 3 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.

Comparison 4 of high-dose 1 mg/kg for seven days versus high-standard 14-day regimen was downgraded because one of the two trials was open-label (Chu 2019 THA).

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.

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 the evidence base for RCTs (including our results) showing the relative 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

Three previous meta-analyses (John 2012; Carmona-Fonseca 2015; Zuluaga-Idarraga 2015) of this topic have been published. John 2012 did not explicitly compare short and long schedules, and none of the reviews included the recent high-dose 1 mg/kg/day seven-day course trials which are evaluated here.

Our findings that 210 mg over seven days may be as efficacious as the standard course of 210 mg over 14 days (Comparison 1) are consistent with findings of other systematic reviews that examined both randomized and non-randomized studies (Carmona-Fonseca 2015; Zuluaga-Idarraga 2015). The other reviews also confirm the lack of comparative evidence for the high-standard versus standard regimens (Comparison 2), whether in the recommended geographical area or not. However we included additional recent RCTs using the standard and high-standard schedules that were not included in Carmona-Fonseca 2015 or Zuluaga-Idarraga 2015. Only Carmona-Fonseca 2015 included weekly schedules, and like us identified only a single study (with one G6PD deficient participant) evaluating 0.75 mg/kg/day once a week for eight weeks compared to high-standard 14-day regimen (Comparison 3). Comparison 4 includes trials that are not in the other reviews.

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.

The systematic review and individual patient data analysis of Commons 2019 showed that the adverse haematological effects of primaquine (when given with chloroquine) may be outweighed by the effect of preventing anaemia due to malaria relapses by day 42. We have not been able to investigate such a trade-off using the studies in this review.

AUTHORS' CONCLUSIONS

Implications for practice

Trials available to date do not detect a difference in efficacy between the regimen of 0.5 mg/kg/day for seven days and the standard (0.25 mg/kg/day) 14-day regimen in G6PD-normal patients. Thus, clinicians wanting to prescribe a shorter regimen to improve treatment completion with the same as standard overall dose could use this regimen, and no serious adverse events were reported in G6PD-normal patients taking 0.5 mg/kg/day of primaquine for seven days. Clinicians considering the regimen of 1 mg/kg/day for seven days should take into account the elevated numbers of severe adverse events observed.

Implications for research

Further high-quality randomized controlled trials will help improve the certainty in different settings. Particularly useful would be studies of the 0.5 mg/kg/day seven-day and high-standard 14-day regimens in East Asia and Oceania (where the high standard course is current recommended), and studies testing modified or weekly regimens in G6PD-deficient patients.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Abdon 2001 BRA

Study characteristics

Methods	RCT

Abdon 2001 BRA *(Continued)*

	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 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.

Abdon 2001 BRA *(Continued)*

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

Study characteristics	
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. 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

Bunnag 1994 THA *(Continued)*

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	Unclear risk	Reported as double-blind but there were no details as to whether microscopy was blinded or whether there was double reading of smears.
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

Study characteristics

Methods	RCT September 2003 to September 2006
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.

Carmona-Fonseca 2009 COL *(Continued)*

	• 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: Colciencias (government agency), Dirección Seccional de Salud de Antioquia (DSSA), Universidad de Antioquia

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.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded and 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	Government and academic funding.

Chu 2019 THA

Study characteristics	
Methods	RCT February 2012 to July 2015
Participants	680 participants enrolled. Inclusion criteria • ≥6 months • ≥7 kg • uncomplicated *P vivax* monoinfection Exclusion criteria • G6PD deficient by the fluorescent spot test • Pregnant or breastfeeding an infant ≤ 6 months • Hematocrit ≤25% • Blood transfusion within 3 months Diagnosis: microscopy No details CYP2D6
Interventions	• Chloroquine 3 days + primaquine 7 days (1 mg/kg/day). • Chloroquine 3 days + primaquine 14 days (0.5 mg/kg/day). • Dihydroartemisinin-piperaquine 3 days + primaquine 7 days (1 mg/kg/day). • Dihydroartemisinin-piperaquine 3 days + primaquine 14 days (0.5 mg/kg/day). Supervised treatment. Not specified whether primaquine given concurrently with chloroquine/dihydroartemisinin-piperaquine.
Outcomes	• *P vivax* recurrence • Adverse events Follow-up: 3 months, 4 months, 6 months, 8 months, 1 year
Notes	Location: Thailand Setting: Clinics along the Thailand-Myanmar border Source of funding: The Wellcome Trust Authors were contacted and provided 3-month and 6-month recurrence data for Analysis 4.3 and Analysis 4.4

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: “Randomization was computer generated in blocks of 20”

Chu 2019 THA *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open 2-way randomized controlled trial"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label and no mention of blood smear blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Overall, 40% left the study before the end of 1-year follow-up. 4% of enrolled participants did not receive blood-stage treatment and were not included in any analyses. A further 20% had left the study at 6 months and another 17% after 1 year. No imputations were used to account for participants that left the study early. However, dropouts were balanced between groups and reasons for leaving the study were provided.
Selective reporting (reporting bias)	Low risk	NCT record (NCT01640574) reports little information on outcomes, however all are reported in the study
Other bias	Low risk	We did not detect any other sources of bias.

Durand 2014 PER

Study characteristics	
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.

Durand 2014 PER *(Continued)*

	(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) 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

Study characteristics

Methods	RCT

Leslie 2008 PAK *(Continued)*

	September 2004 to July 2006
Participants	129 Afghan 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 • 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.

Leslie 2008 PAK *(Continued)*

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) All outcomes	High risk	Higher loss to follow-up in intervention group (6% to 8% versus 1% to 1.8%).
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

Study characteristics	
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.

Pareek 2015 IND *(Continued)*

	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 • 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.

Pareek 2015 IND *(Continued)*

		PCR results are not well-detailed.
Other bias	Unclear 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

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

Rajgor 2014 IND *(Continued)*

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.
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 events. 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

Study characteristics

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.

Saravu 2018 IND *(Continued)*

	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 level in the blood at 7 days) 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

Study characteristics

Solari-Soto 2002 PER *(Continued)*

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. 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.

Solari-Soto 2002 PER *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No details.
Other bias	Low risk	We did not detect any other sources of bias.

Taylor 2019 MULTI

Study characteristics	
Methods	RCT, multicentre July 2014 to November 2018
Participants	2336 participants were randomised. 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 schizontocidal 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. Diagnosis: microscopy Patients with G6PD deficiency were excluded from the randomised trial, but were enrolled into a parallel observational group and treated with chloroquine or dihydroartemisinin-piperaquine plus supervised primaquine (0.75 mg/kg) once a week for 8 weeks.

Taylor 2019 MULTI *(Continued)*

	No details CYP2D6 status.
Interventions	• 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. • Standard blood schizonticidal therapy plus 14 days of supervised primaquine (7 mg/kg total dose) administered once per day (0.5 mg/kg). (Additional arm Standard blood schizonticidal therapy plus 14 days placebo was not included in the review; no primaquine was administered to participants in this arm). Supervised treatment. Primaquine and blood schizonticidal therapy given concurrently. Standard blood schizonticidal therapy was chloroquine in Ethiopia, Afghanistan, and Vietnam and dihydroartemisinin-piperaquine in Indonesia, according to local guidelines
Outcomes	• Recurrent *P vivax* parasitaemia • Adverse events • Anaemia Follow-up: 28 days, 42 days, 3 months, 6 months, 1 year.
Notes	Location: Afghanistan (Jalalabad, Laghman), Ethiopia (Arba Minch, Metahara), Indonesia (Hanura, Tanjung Leidong), and Vietnam (Dak O & Bu Gia Map, Krong Pa). Setting: Two health-care clinics in each country. Funding: UK Department for International Development, UK Medical Research Council, UK National Institute for Health Research, and the Wellcome Trust through the Joint Global Health Trials Scheme and the Bill & Melinda Gates Foundation. Authors were contacted and provided 3-month and 6-month recurrence data presented in Appendix 3b.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Randomisation was done using STATA version 14.1.(StataCorp, College Station, TX, USA), which generated blocks of 20 for each dosing band”.
Allocation concealment (selection bias)	Low risk	Quote: “The independent statistician who generated the randomisation list and selected code letters for primaquine or placebo was not otherwise involved in the conduct of the trial and did not visit any of the study sites. Identical primaquine and placebo tablets were produced by the same manufacturer”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “Participants and all of the local study team were masked to treatment assignments.”
Blinding of outcome assessment (detection bias) All outcomes	Low risk	98.6% accuracy in expert quality control of microscopy malaria films: Quote: "Microscopists were trained in study laboratory procedures on-site and continuous quality control was implemented at all sites. Approximately 10% of slides, including all the slides from day 0, the day of recurrent parasitaemia, and the 6-month follow-up visits were assessed periodically over the course of the trial by expert malaria microscopists"

Taylor 2019 MULTI *(Continued)*

		Safety outcomes: Quote: "The Data and Safety Monitoring Board did a blinded safety review every 6 months"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Available case analysis, attrition after one year was 32% (297/935) in 7-day primaquine group and 29% (270/937) in 14-day primaquine group, reasons for leaving the study early were reported.
Selective reporting (reporting bias)	Low risk	Protocol and online trial registry were checked; all outcomes and sensitivity analyses were reported.
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.

Durand 2014 PER

Study characteristics	
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) Follow-up: 210 days

Durand 2014 PER *(Continued)*

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

Study characteristics

Methods	RCT September 2004 to July 2006
Participants	129 Afghan 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

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%).

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

Study characteristics	
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.

Pareek 2015 IND *(Continued)*

Outcomes	• Relapse • Compliance • 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	Unclear 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

Study characteristics

Rajgor 2014 IND *(Continued)*

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

Rajgor 2014 IND *(Continued)*

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.
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 events. 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

Study characteristics	
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).

Saravu 2018 IND *(Continued)*

	• 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 level in the blood at 7 days) 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

Study characteristics

Methods	RCT October 1998 to January 1999
Participants	60 participants enrolled. Inclusion criteria

Solari-Soto 2002 PER *(Continued)*

	• 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. 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.

Taylor 2019 MULTI

Study characteristics	
Methods	RCT, multicentre July 2014 to November 2018
Participants	2336 participants were randomised. 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 schizontocidal 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. Diagnosis: microscopy Patients with G6PD deficiency were excluded from the randomised trial, but were enrolled into a parallel observational group and treated with chloroquine or dihydroartemisinin-piperaquine plus supervised primaquine (0.75 mg/kg) once a week for 8 weeks. No details CYP2D6 status.
Interventions	• 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. • Standard blood schizonticidal therapy plus 14 days of supervised primaquine (7 mg/kg total dose) administered once per day (0.5 mg/kg). (Additional arm Standard blood schizonticidal therapy plus 14 days placebo was not included in the review; no primaquine was administered to participants in this arm).

Taylor 2019 MULTI *(Continued)*

	Supervised treatment. Primaquine and blood schizonticidal therapy given concurrently. Standard blood schizonticidal therapy was chloroquine in Ethiopia, Afghanistan, and Vietnam and dihydroartemisinin-piperaquine in Indonesia, according to local guidelines
Outcomes	• Recurrent *P vivax* parasitaemia • Adverse events • Anaemia Follow-up: 28 days, 42 days, 3 months, 6 months, 1 year.
Notes	Location: Afghanistan (Jalalabad, Laghman), Ethiopia (Arba Minch, Metahara), Indonesia (Hanura, Tanjung Leidong), and Vietnam (Dak O & Bu Gia Map, Krong Pa). Setting: Two health-care clinics in each country. Funding: UK Department for International Development, UK Medical Research Council, UK National Institute for Health Research, and the Wellcome Trust through the Joint Global Health Trials Scheme and the Bill & Melinda Gates Foundation. Authors were contacted and provided 3-month and 6-month recurrence data presented in Appendix 3b.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Randomisation was done using STATA version 14.1.(StataCorp, College Station, TX, USA), which generated blocks of 20 for each dosing band”.
Allocation concealment (selection bias)	Low risk	Quote: “The independent statistician who generated the randomisation list and selected code letters for primaquine or placebo was not otherwise involved in the conduct of the trial and did not visit any of the study sites. Identical primaquine and placebo tablets were produced by the same manufacturer”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “Participants and all of the local study team were masked to treatment assignments.”
Blinding of outcome assessment (detection bias) All outcomes	Low risk	98.6% accuracy in expert quality control of microscopy malaria films: Quote: "Microscopists were trained in study laboratory procedures on-site and continuous quality control was implemented at all sites. Approximately 10% of slides, including all the slides from day 0, the day of recurrent parasitaemia, and the 6-month follow-up visits were assessed periodically over the course of the trial by expert malaria microscopists" Safety outcomes: Quote: “The Data and Safety Monitoring Board did a blinded safety review every 6 months”
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Available case analysis, attrition after one year was 32% (297/935) in 7-day primaquine group and 29% (270/937) in 14-day primaquine group, reasons for leaving the study early were reported.
Selective reporting (reporting bias)	Low risk	Protocol and online trial registry were checked; all outcomes and sensitivity analyses were reported.

Taylor 2019 MULTI *(Continued)*

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.
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.
Daher 2018	Wrong comparator: same dose primaquine in all treatment arms (two tablets of 15 mg PQ for 7, 8 or 9 days, total dose between 3.0 and 4.2 mg/kg).
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).
Hamid 2018	Wrong comparator: Artesunate and Sulphadoxine/pyrimethamine + concomitant versus delayed 14-day primaquine.
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.
Ladeia-Andrade 2019	Wrong comparator: concomitant versus delayed regimen (chloroquine with primaquine 0.5 mg/kg once a day, for seven days (total dose, 3.5mg/kg) versus chloroquine with primaquine introduced on day 28
Leslie 2004	No PQ comparison group: supervised versus unsupervised therapy.

Study	Reason for exclusion
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.
Moore 2018	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.
Warrasak 2019	No primaquine comparison arm, ophthalmological outcomes.

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

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

NCT01837992

Study name	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 ("Hb < 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.

NCT01837992 *(Continued)*	• 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. • 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; Hb: haemoglobin; PCR: polymerase chain reaction; RCT: randomized controlled trial; RDT: rapid diagnostic test; WHO: World Health Organization.

DATA AND ANALYSES

Comparison 1. 0.5 mg/kg/day 7 days versus standard 0.25 mg/kg/day 14 days

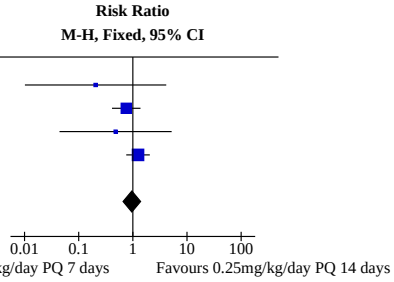
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Recurrence by 6 to 7 months' follow-up	4	1211	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.66, 1.39]
1.2 Recurrence by 6 to 7 months' follow-up (PCR-adjusted)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.3 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]
1.3.1 South America	2	397	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.39, 1.26]
1.3.2 Asia	2	814	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.73, 1.94]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 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]
1.4.1 DOT	3	1017	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.67, 1.43]
1.4.2 Non-DOT	1	194	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.04, 5.20]
1.5 Serious adverse events	5	1427	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.6 Adverse events that result in discontinuation of treatment	5	1427	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.15, 7.38]
1.7 Adverse events during chloroquine administration	1	779	Risk Ratio (M-H, Fixed, 95% CI)	9.40 [0.51, 174.01]
1.8 Adverse effects during primaquine administration	2	1019	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [0.75, 3.57]
1.9 Other adverse events	2	135	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.23, 1.36]
1.10 Anaemia or change in haemoglobin status	1	240	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.12, 72.91]

Analysis 1.1. Comparison 1: 0.5 mg/kg/day 7 days versus standard 0.25 mg/kg/day 14 days, Outcome 1: Recurrence by 6 to 7 months' follow-up

Study or Subgroup	0.5mg/kg/day PQ 7 days Events	Total	0.25mg/kg/day PQ 14 days Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abdon 2001 BRA (1)	0	39	2	40	4.8%	0.20 [0.01 , 4.14]
Durand 2014 PER (2)	16	156	22	162	42.2%	0.76 [0.41 , 1.38]
Pareek 2015 IND (3)	1	99	2	95	4.0%	0.48 [0.04 , 5.20]
Rajgor 2014 IND (4)	30	298	26	322	48.9%	1.25 [0.76 , 2.06]
Total (95% CI)		**592**		**619**	**100.0%**	**0.96 [0.66 , 1.39]**
Total events:	47		52			

Heterogeneity: Chi² = 2.99, df = 3 (P = 0.39); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)
Test for subgroup differences: Not applicable

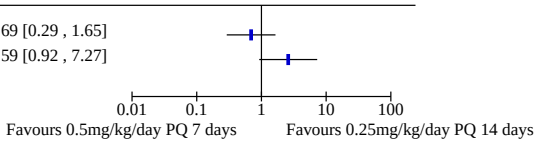


Footnotes
(1) Follow up 180 days (6 months)
(2) Follow up 210 days (7 months)
(3) Follow up 6 months. Primaquine 30mg sustained release preparation used.
(4) 6 months follow up

Analysis 1.2. Comparison 1: 0.5 mg/kg/day 7 days versus standard 0.25 mg/kg/day 14 days, Outcome 2: Recurrence by 6 to 7 months' follow-up (PCR-adjusted)

Study or Subgroup	0.5mg/kg/day PQ 7 days Events	Total	0.25mg/kg/day PQ 14 days Events	Total	Risk Ratio M-H, Fixed, 95% CI
Durand 2014 PER (1)	8	156	12	162	0.69 [0.29 , 1.65]
Rajgor 2014 IND (2)	12	298	5	322	2.59 [0.92 , 7.27]

Test for subgroup differences: Not applicable



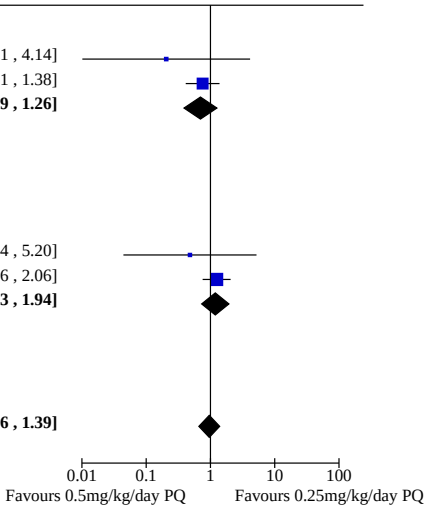
Footnotes

(1) Follow up 210 days (7 months)

(2) Follow up 6 months

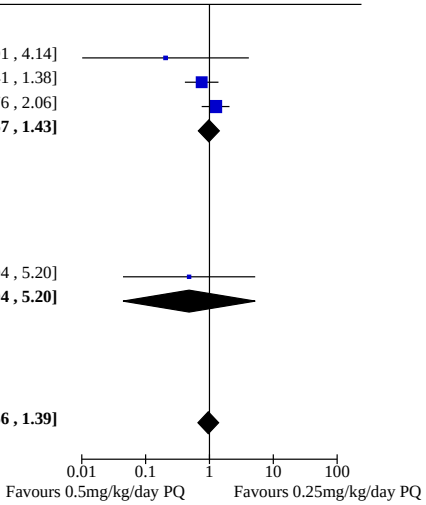
Analysis 1.3. Comparison 1: 0.5 mg/kg/day 7 days versus standard 0.25 mg/kg/day 14 days, Outcome 3: Recurrence by 6 to 7 months subgrouped by geographical region

Study or Subgroup	0.5mg/kg/day PQ 7 days Events	Total	0.25mg/kg/day PQ 14 days Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 South America						
Abdon 2001 BRA	0	39	2	40	4.8%	0.20 [0.01 , 4.14]
Durand 2014 PER	16	156	22	162	42.2%	0.76 [0.41 , 1.38]
Subtotal (95% CI)		**195**		**202**	**47.1%**	**0.70 [0.39 , 1.26]**
Total events:	16		24			
Heterogeneity: Chi² = 0.70, df = 1 (P = 0.40); I² = 0%						
Test for overall effect: Z = 1.19 (P = 0.23)						
1.3.2 Asia						
Pareek 2015 IND	1	99	2	95	4.0%	0.48 [0.04 , 5.20]
Rajgor 2014 IND	30	298	26	322	48.9%	1.25 [0.76 , 2.06]
Subtotal (95% CI)		**397**		**417**	**52.9%**	**1.19 [0.73 , 1.94]**
Total events:	31		28			
Heterogeneity: Chi² = 0.59, df = 1 (P = 0.44); I² = 0%						
Test for overall effect: Z = 0.69 (P = 0.49)						
Total (95% CI)		**592**		**619**	**100.0%**	**0.96 [0.66 , 1.39]**
Total events:	47		52			
Heterogeneity: Chi² = 2.99, df = 3 (P = 0.39); I² = 0%						
Test for overall effect: Z = 0.23 (P = 0.82)						
Test for subgroup differences: Chi² = 1.86, df = 1 (P = 0.17), I² = 46.1%						



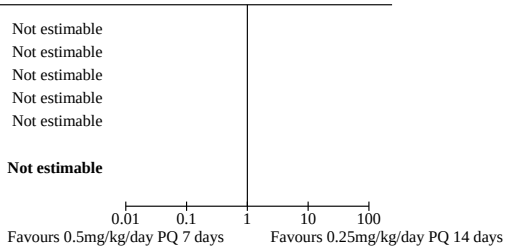
Analysis 1.4. Comparison 1: 0.5 mg/kg/day 7 days versus standard 0.25 mg/kg/day 14 days, Outcome 4: Recurrence by 6 to 7 months subgrouped by directly observed therapy (DOT) versus non-DOT

Study or Subgroup	0.5 mg/kg/day PQ 7 days Events	Total	0.25 mg/kg/day PQ 14 days Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 DOT						
Abdon 2001 BRA	0	39	2	40	4.8%	0.20 [0.01 , 4.14]
Durand 2014 PER	16	156	22	162	42.2%	0.76 [0.41 , 1.38]
Rajgor 2014 IND	30	298	26	322	48.9%	1.25 [0.76 , 2.06]
Subtotal (95% CI)		**493**		**524**	**96.0%**	**0.98 [0.67 , 1.43]**
Total events:	46		50			
Heterogeneity: Chi² = 2.64, df = 2 (P = 0.27); I² = 24%						
Test for overall effect: Z = 0.12 (P = 0.91)						
1.4.2 Non-DOT						
Pareek 2015 IND	1	99	2	95	4.0%	0.48 [0.04 , 5.20]
Subtotal (95% CI)		**99**		**95**	**4.0%**	**0.48 [0.04 , 5.20]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.60 (P = 0.55)						
Total (95% CI)		**592**		**619**	**100.0%**	**0.96 [0.66 , 1.39]**
Total events:	47		52			
Heterogeneity: Chi² = 2.99, df = 3 (P = 0.39); I² = 0%						
Test for overall effect: Z = 0.23 (P = 0.82)						
Test for subgroup differences: Chi² = 0.33, df = 1 (P = 0.56), I² = 0%						



Analysis 1.5. Comparison 1: 0.5 mg/kg/day 7 days versus standard 0.25 mg/kg/day 14 days, Outcome 5: Serious adverse events

Study or Subgroup	0.5mg/kg/day PQ 7 days Events	Total	0.25mg/kg/day PQ 14 days Events	Total	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 (1)	0	99	0	95		Not estimable
Rajgor 2014 IND (2)	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			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



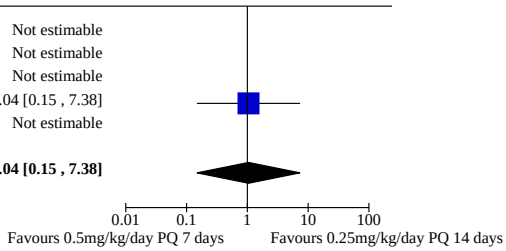
Footnotes

(1) Primaquine 30mg sustained release preparation used.
(2) 6 months follow up

Analysis 1.6. Comparison 1: 0.5 mg/kg/day 7 days versus standard 0.25 mg/kg/day 14 days, Outcome 6: Adverse events that result in discontinuation of treatment

Study or Subgroup	0.5mg/kg/day PQ 7 days Events	Total	0.25mg/kg/day PQ 14 days Events	Total	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 (1)	0	99	0	95		Not estimable
Rajgor 2014 IND	2	381	2	398	100.0%	1.04 [0.15 , 7.38]
Solari-Soto 2002 PER	0	28	0	28		Not estimable
Total (95% CI)		**704**		**723**	**100.0%**	**1.04 [0.15 , 7.38]**
Total events:	2		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.04 (P = 0.97)
Test for subgroup differences: Not applicable

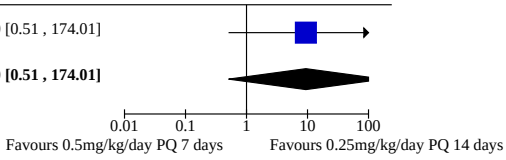


Footnotes
(1) Primaquine 30mg sustained release preparation used.

Analysis 1.7. Comparison 1: 0.5 mg/kg/day 7 days versus standard 0.25 mg/kg/day 14 days, Outcome 7: Adverse events during chloroquine administration

Study or Subgroup	0.5mg/kg/day PQ 7 days Events	Total	0.25mg/kg/day PQ 14 days Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rajgor 2014 IND	4	381	0	398	100.0%	9.40 [0.51 , 174.01]
Total (95% CI)		**381**		**398**	**100.0%**	**9.40 [0.51 , 174.01]**
Total events:	4		0			

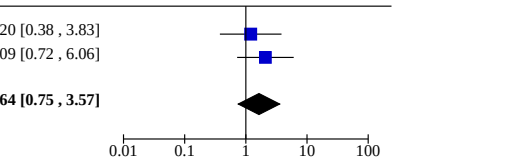
Heterogeneity: Not applicable
Test for overall effect: Z = 1.50 (P = 0.13)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: 0.5 mg/kg/day 7 days versus standard 0.25 mg/kg/day 14 days, Outcome 8: Adverse effects during primaquine administration

Study or Subgroup	0.5mg/kg/day PQ 7 days Events	Total	0.25mg/kg/day PQ 14 days Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pareek 2015 IND (1)	6	120	5	120	50.6%	1.20 [0.38 , 3.83]
Rajgor 2014 IND	10	381	5	398	49.4%	2.09 [0.72 , 6.06]
Total (95% CI)		**501**		**518**	**100.0%**	**1.64 [0.75 , 3.57]**
Total events:	16		10			

Heterogeneity: $Chi^2 = 0.48$, df = 1 (P = 0.49); $I^2 = 0\%$
Test for overall effect: Z = 1.25 (P = 0.21)
Test for subgroup differences: Not applicable

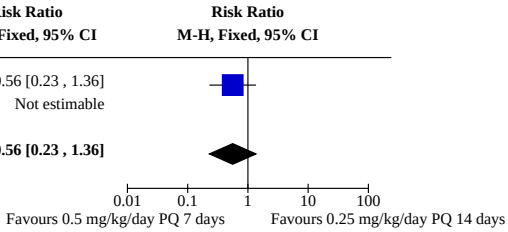


Footnotes
(1) Primaquine 30mg sustained release preparation used.

Analysis 1.9. Comparison 1: 0.5 mg/kg/day 7 days versus standard 0.25 mg/kg/day 14 days, Outcome 9: Other adverse events

Study or Subgroup	0.5 mg/kg/day PQ 7 days Events	Total	0.25 mg/kg/day PQ 14 days Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abdon 2001 BRA	6	39	11	40	100.0%	0.56 [0.23 , 1.36]
Solari-Soto 2002 PER	0	28	0	28		Not estimable
Total (95% CI)		**67**		**68**	**100.0%**	**0.56 [0.23 , 1.36]**
Total events:	6		11			

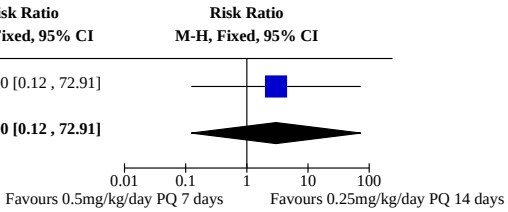
Heterogeneity: Not applicable
Test for overall effect: Z = 1.28 (P = 0.20)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: 0.5 mg/kg/day 7 days versus standard 0.25 mg/kg/day 14 days, Outcome 10: Anaemia or change in haemoglobin status

Study or Subgroup	0.5mg/kg/day PQ 7 days Events	Total	0.25mg/kg/day PQ 14 days Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pareek 2015 IND (1)	1	120	0	120	100.0%	3.00 [0.12 , 72.91]
Total (95% CI)		**120**		**120**	**100.0%**	**3.00 [0.12 , 72.91]**
Total events:	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)
Test for subgroup differences: Not applicable



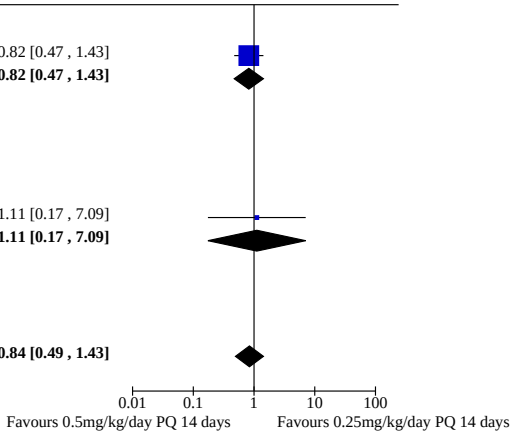
Footnotes
(1) Primaquine 30mg sustained release preparation used.

Comparison 2. High-standard 0.5 mg/kg/day 14 days versus standard 0.25 mg/kg/day 14 days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Recurrence by 6 months' follow-up	2	677	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.49, 1.43]
2.1.1 6 months (chloroquine blood-stage treatment)	1	639	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.47, 1.43]
2.1.2 6 months (chloroquine or ACT blood-stage treatment)	1	38	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.17, 7.09]
2.2 Recurrence by 6 months' follow-up (PCR-adjusted)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.3 Serious adverse events	1	778	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.4 Adverse events that result in discontinuation of treatment	1	778	Risk Ratio (M-H, Fixed, 95% CI)	4.19 [0.90, 19.60]
2.5 Other adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.5.1 AEs during chloroquine treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.5.2 AEs during primaquine treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: High-standard 0.5 mg/kg/day 14 days versus standard 0.25 mg/kg/day 14 days, Outcome 1: Recurrence by 6 months' follow-up

Study or Subgroup	0.5mg/kg/day PQ 14 days Events	Total	0.25mg/kg/day PQ 14 days Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 6 months (chloroquine blood-stage treatment)						
Rajgor 2014 IND (1)	21	317	26	322	93.2%	0.82 [0.47 , 1.43]
Subtotal (95% CI)		**317**		**322**	**93.2%**	**0.82 [0.47 , 1.43]**
Total events:	21		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.48)						
2.1.2 6 months (chloroquine or ACT blood-stage treatment)						
Saravu 2018 IND (2)	2	18	2	20	6.8%	1.11 [0.17 , 7.09]
Subtotal (95% CI)		**18**		**20**	**6.8%**	**1.11 [0.17 , 7.09]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.11 (P = 0.91)						
Total (95% CI)		**335**		**342**	**100.0%**	**0.84 [0.49 , 1.43]**
Total events:	23		28			
Heterogeneity: Chi^2 = 0.09, df = 1 (P = 0.76); I^2 = 0%						
Test for overall effect: Z = 0.64 (P = 0.52)						
Test for subgroup differences: Chi^2 = 0.09, df = 1 (P = 0.76), I^2 = 0%						



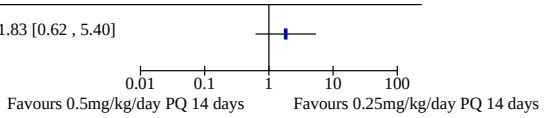
Footnotes

(1) Chloroquine used for blood stage treatment, treatment supervised

(2) Blood stage treatment is either chloroquine or an ACT, treatment unsupervised

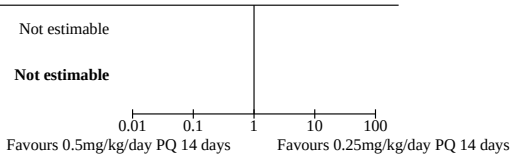
Analysis 2.2. Comparison 2: High-standard 0.5 mg/kg/day 14 days versus standard 0.25 mg/kg/day 14 days, Outcome 2: Recurrence by 6 months' follow-up (PCR-adjusted)

Study or Subgroup	0.5mg/kg/day PQ 14 days Events	Total	0.25mg/kg/day PQ 14 days Events	Total	Risk Ratio M-H, Fixed, 95% CI
Rajgor 2014 IND	9	317	5	322	1.83 [0.62 , 5.40]
Test for subgroup differences: Not applicable					



Analysis 2.3. Comparison 2: High-standard 0.5 mg/kg/day 14 days versus standard 0.25 mg/kg/day 14 days, Outcome 3: Serious adverse events

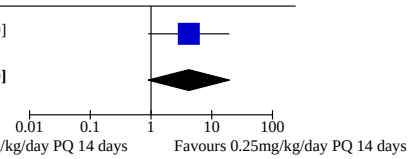
Study or Subgroup	0.5mg/kg/day PQ 14 days Events	Total	0.25mg/kg/day PQ 14 days Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rajgor 2014 IND	0	380	0	398		Not estimable
Total (95% CI)		**380**		**398**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



Analysis 2.4. Comparison 2: High-standard 0.5 mg/kg/day 14 days versus standard 0.25 mg/kg/day 14 days, Outcome 4: Adverse events that result in discontinuation of treatment

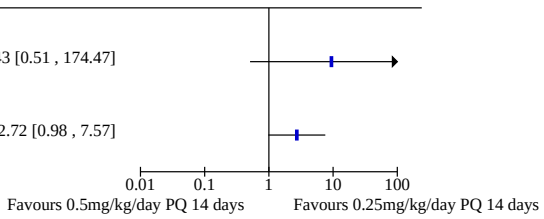
Study or Subgroup	0.5mg/kg/day PQ 14 days Events	Total	0.25mg/kg/day PQ 14 days Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rajgor 2014 IND	8	380	2	398	100.0%	4.19 [0.90 , 19.60]
Total (95% CI)		**380**		**398**	**100.0%**	**4.19 [0.90 , 19.60]**
Total events:	8		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.82 (P = 0.07)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: High-standard 0.5 mg/kg/day 14 days versus standard 0.25 mg/kg/day 14 days, Outcome 5: Other adverse events

Study or Subgroup	0.5mg/kg/day PQ 14 days Events	Total	0.25mg/kg/day PQ 14 days Events	Total	Risk Ratio M-H, Fixed, 95% CI
2.5.1 AEs during chloroquine treatment					
Rajgor 2014 IND	4	380	0	398	9.43 [0.51 , 174.47]
2.5.2 AEs during primaquine treatment					
Rajgor 2014 IND	13	380	5	398	2.72 [0.98 , 7.57]

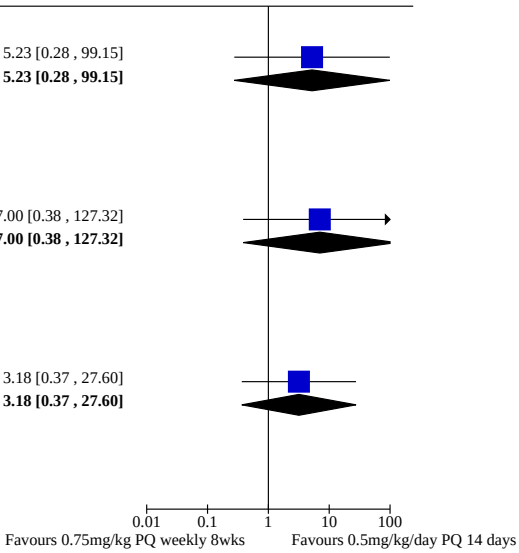


Comparison 3. 0.75 mg/kg/week 8 weeks versus high-standard 0.5 mg/kg/day 14 days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Recurrence	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1.1 5 months	1	129	Risk Ratio (M-H, Fixed, 95% CI)	5.23 [0.28, 99.15]
3.1.2 8 months	1	126	Risk Ratio (M-H, Fixed, 95% CI)	7.00 [0.38, 127.32]
3.1.3 11 months	1	122	Risk Ratio (M-H, Fixed, 95% CI)	3.18 [0.37, 27.60]
3.2 Serious adverse events	1	129	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.3 Anaemia (haemoglobin < 7 g/dL)	1	129	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.4 Other adverse events	1	129	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

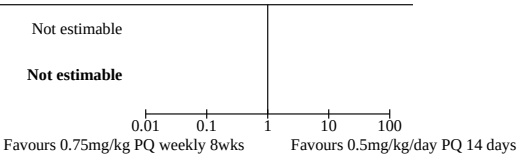
Analysis 3.1. Comparison 3: 0.75 mg/kg/week 8 weeks versus high-standard 0.5 mg/kg/day 14 days, Outcome 1: Recurrence

Study or Subgroup	0.75mg/kg PQ weekly 8wks Events	Total	0.5mg/kg/day PQ 14 days Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 5 months						
Leslie 2008 PAK	3	74	0	55	100.0%	5.23 [0.28 , 99.15]
Subtotal (95% CI)		**74**		**55**	**100.0%**	**5.23 [0.28 , 99.15]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.10 (P = 0.27)						
3.1.2 8 months						
Leslie 2008 PAK	4	71	0	55	100.0%	7.00 [0.38 , 127.32]
Subtotal (95% CI)		**71**		**55**	**100.0%**	**7.00 [0.38 , 127.32]**
Total events:	4		0			
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	100.0%	3.18 [0.37 , 27.60]
Subtotal (95% CI)		**68**		**54**	**100.0%**	**3.18 [0.37 , 27.60]**
Total events:	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.29)						
Test for subgroup differences: $Chi^2 = 0.20$, df = 2 (P = 0.91), $I^2 = 0\%$						



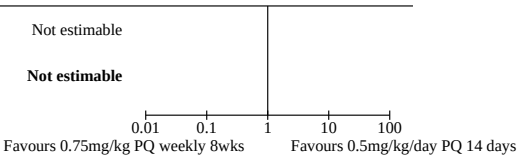
Analysis 3.2. Comparison 3: 0.75 mg/kg/week 8 weeks versus high-standard 0.5 mg/kg/day 14 days, Outcome 2: Serious adverse events

Study or Subgroup	0.75mg/kg PQ weekly 8wks Events	Total	0.5mg/kg/day PQ 14 days Events	Total	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			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



Analysis 3.3. Comparison 3: 0.75 mg/kg/week 8 weeks versus high-standard 0.5 mg/kg/day 14 days, Outcome 3: Anaemia (haemoglobin < 7 g/dL)

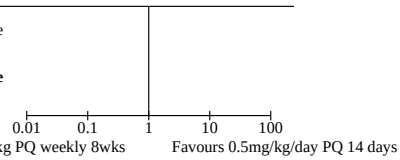
Study or Subgroup	0.75mg/kg PQ weekly 8wks Events	Total	0.5mg/kg/day PQ 14 days Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Leslie 2008 PAK	0	74	0	55		Not estimable
Total (95% CI)		**74**		**55**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: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



Analysis 3.4. Comparison 3: 0.75 mg/kg/week 8 weeks versus high-standard 0.5 mg/kg/day 14 days, Outcome 4: Other adverse events

Study or Subgroup	0.75mg/kg PQ weekly 8wks Events	Total	0.5mg/kg/day PQ 14 days Events	Total	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			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



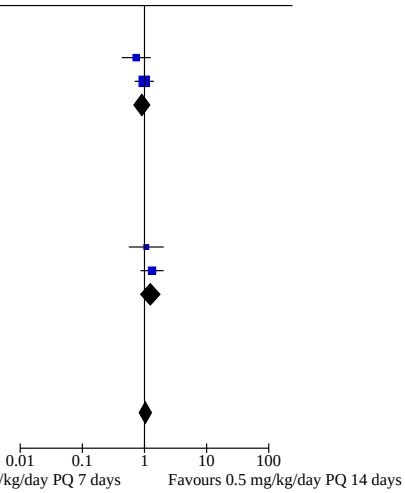
Comparison 4. 1.0 mg/kg/day primaquine 7 days versus high-standard 0.5 mg/kg/day 14 days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Recurrence by 12 months' follow-up	2	2526	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.82, 1.30]
4.1.1 Chloroquine blood-stage treatment	2	1404	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.67, 1.22]
4.1.2 DHA-PPQ blood-stage treatment	2	1122	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.87, 1.77]
4.2 Recurrence by 12 months' follow-up subgrouped by geographical region	2	2526	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.82, 1.29]
4.2.1 Afghanistan	1	348	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.44, 1.28]
4.2.2 Ethiopia	1	466	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.74, 2.30]
4.2.3 Indonesia	1	797	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.86, 2.03]
4.2.4 Thailand	1	654	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.57, 1.30]
4.2.5 Vietnam	1	261	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.43, 2.53]
4.3 Recurrence by 6 months' follow-up	1	474	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.61, 1.97]
4.3.1 Chloroquine blood-stage treatment	1	256	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.42, 1.86]
4.3.2 DHA-PPQ blood-stage treatment	1	218	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [0.60, 4.05]
4.4 Recurrence by 3 months' follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.4.1 Chloroquine blood-stage treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.4.2 DHA-PPQ blood-stage treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.5 *P vivax* parasitaemia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.5.1 Day 28	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.5.2 Day 42	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.6 Serious adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.6.1 Up to 42 days follow-up	1	1872	Risk Ratio (M-H, Fixed, 95% CI)	12.03 [1.57, 92.30]
4.6.2 Up to 1 year follow-up	1	1872	Risk Ratio (M-H, Fixed, 95% CI)	3.61 [1.35, 9.68]
4.7 Adverse events that resulted in discontinuation of treatment	2	2526	Risk Ratio (M-H, Fixed, 95% CI)	2.50 [0.49, 12.87]
4.8 Other adverse events	2		Other data	No numeric data
4.8.1 Up to day 14	1		Other data	No numeric data
4.8.2 Chloroquine group, up to day 42	1		Other data	No numeric data
4.8.3 DHA-PPQ group, up to day 42	1		Other data	No numeric data
4.9 Anaemia	2	2440	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.62, 1.41]
4.9.1 Up to 3 days	1	1786	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.38, 2.66]
4.9.2 Up to 42 days follow-up	1	654	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.58, 1.44]

Analysis 4.1. Comparison 4: 1.0 mg/kg/day primaquine 7 days versus high-standard 0.5 mg/kg/day 14 days, Outcome 1: Recurrence by 12 months' follow-up

Study or Subgroup	1 mg/kg/day PQ 7 days Events	Total	0.5 mg/kg/day PQ 14 days Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 Chloroquine blood-stage treatment						
Chu 2019 THA (1)	20	165	27	164	20.7%	0.74 [0.43 , 1.26]
Taylor 2019 MULTI (2)	54	535	55	540	41.8%	0.99 [0.69 , 1.41]
Subtotal (95% CI)		**700**		**704**	**62.5%**	**0.91 [0.67 , 1.22]**
Total events:	74		82			
Heterogeneity: Chi² = 0.82, df = 1 (P = 0.37); I² = 0%						
Test for overall effect: Z = 0.65 (P = 0.52)						
4.1.2 DHA-PPQ blood-stage treatment						
Chu 2019 THA (1)	17	162	16	163	12.2%	1.07 [0.56 , 2.04]
Taylor 2019 MULTI (3)	44	400	33	397	25.3%	1.32 [0.86 , 2.03]
Subtotal (95% CI)		**562**		**560**	**37.5%**	**1.24 [0.87 , 1.77]**
Total events:	61		49			
Heterogeneity: Chi² = 0.29, df = 1 (P = 0.59); I² = 0%						
Test for overall effect: Z = 1.18 (P = 0.24)						
Total (95% CI)		**1262**		**1264**	**100.0%**	**1.03 [0.82 , 1.30]**
Total events:	135		131			
Heterogeneity: Chi² = 2.87, df = 3 (P = 0.41); I² = 0%						
Test for overall effect: Z = 0.27 (P = 0.79)						
Test for subgroup differences: Chi² = 1.75, df = 1 (P = 0.19), I² = 43.0%						

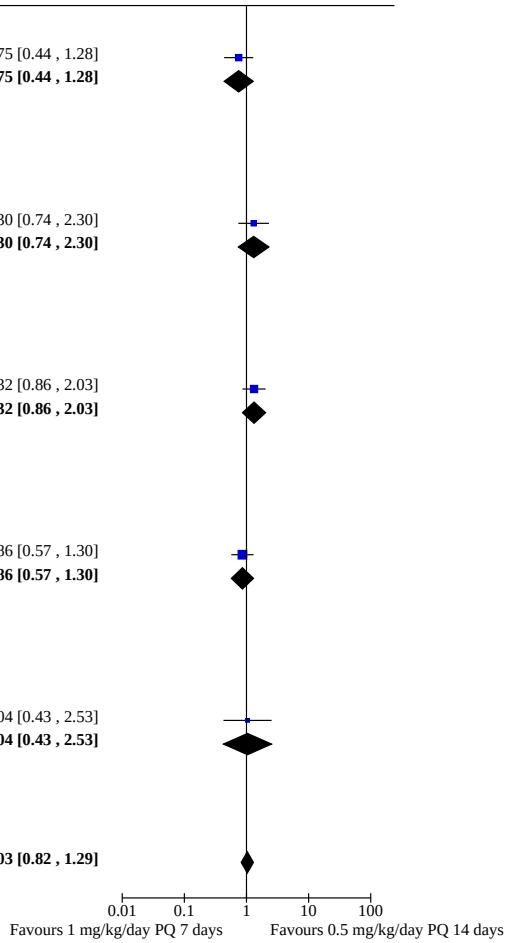


Footnotes

(1) first *P. vivax* infection within 1 year
(2) first *P. vivax* recurrence, Afghanistan, Ethiopia, and Vietnam cohorts
(3) first *P. vivax* recurrence, Indonesia cohort

Analysis 4.2. Comparison 4: 1.0 mg/kg/day primaquine 7 days versus high-standard 0.5 mg/kg/day 14 days, Outcome 2: Recurrence by 12 months' follow-up subgrouped by geographical region

Study or Subgroup	1 mg/kg/day PQ 7 days Events	Total	0.5 mg/kg/day PQ 14 days Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.1 Afghanistan						
Taylor 2019 MULTI (1)	20	173	27	175	20.5%	0.75 [0.44 , 1.28]
Subtotal (95% CI)		**173**		**175**	**20.5%**	**0.75 [0.44 , 1.28]**
Total events:	20		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.29)						
4.2.2 Ethiopia						
Taylor 2019 MULTI (2)	25	234	19	232	14.6%	1.30 [0.74 , 2.30]
Subtotal (95% CI)		**234**		**232**	**14.6%**	**1.30 [0.74 , 2.30]**
Total events:	25		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.92 (P = 0.36)						
4.2.3 Indonesia						
Taylor 2019 MULTI (3)	44	400	33	397	25.3%	1.32 [0.86 , 2.03]
Subtotal (95% CI)		**400**		**397**	**25.3%**	**1.32 [0.86 , 2.03]**
Total events:	44		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.28 (P = 0.20)						
4.2.4 Thailand						
Chu 2019 THA (4)	37	327	43	327	32.9%	0.86 [0.57 , 1.30]
Subtotal (95% CI)		**327**		**327**	**32.9%**	**0.86 [0.57 , 1.30]**
Total events:	37		43			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
4.2.5 Vietnam						
Taylor 2019 MULTI (5)	9	128	9	133	6.7%	1.04 [0.43 , 2.53]
Subtotal (95% CI)		**128**		**133**	**6.7%**	**1.04 [0.43 , 2.53]**
Total events:	9		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.08 (P = 0.93)						
Total (95% CI)		**1262**		**1264**	**100.0%**	**1.03 [0.82 , 1.29]**
Total events:	135		131			
Heterogeneity: Chi² = 4.05, df = 4 (P = 0.40); I² = 1%						
Test for overall effect: Z = 0.27 (P = 0.79)						
Test for subgroup differences: Chi² = 4.04, df = 4 (P = 0.40), I² = 1.1%						

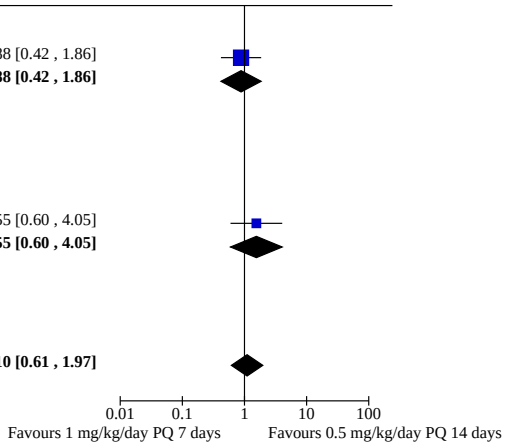


Footnotes

(1) first recurrent *P. vivax* parasitaemia, Afghanistan
(2) first recurrent *P. vivax* parasitaemia, Ethiopia
(3) first recurrent *P. vivax* parasitaemia, Indonesia
(4) first *P. vivax* infection within 1 year
(5) first recurrent *P. vivax* parasitaemia, Vietnam

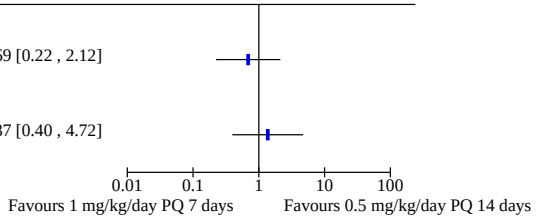
Analysis 4.3. Comparison 4: 1.0 mg/kg/day primaquine 7 days versus high-standard 0.5 mg/kg/day 14 days, Outcome 3: Recurrence by 6 months' follow-up

Study or Subgroup	1 mg/kg/day PQ 7 days Events	Total	0.5 mg/kg/day PQ 14 days Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.1 Chloroquine blood-stage treatment						
Chu 2019 THA	12	131	13	125	67.2%	0.88 [0.42 , 1.86]
Subtotal (95% CI)		**131**		**125**	**67.2%**	**0.88 [0.42 , 1.86]**
Total events:	12		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						
4.3.2 DHA-PPQ blood-stage treatment						
Chu 2019 THA	11	118	6	100	32.8%	1.55 [0.60 , 4.05]
Subtotal (95% CI)		**118**		**100**	**32.8%**	**1.55 [0.60 , 4.05]**
Total events:	11		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.90 (P = 0.37)						
Total (95% CI)		**249**		**225**	**100.0%**	**1.10 [0.61 , 1.97]**
Total events:	23		19			
Heterogeneity: Chi² = 0.84, df = 1 (P = 0.36); I² = 0%						
Test for overall effect: Z = 0.33 (P = 0.75)						
Test for subgroup differences: Chi² = 0.84, df = 1 (P = 0.36), I² = 0%						



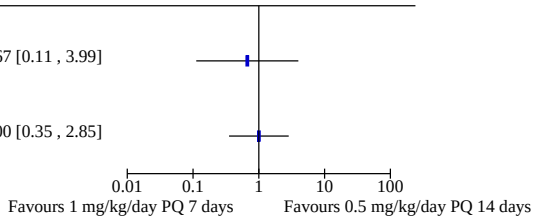
Analysis 4.4. Comparison 4: 1.0 mg/kg/day primaquine 7 days versus high-standard 0.5 mg/kg/day 14 days, Outcome 4: Recurrence by 3 months' follow-up

Study or Subgroup	1 mg/kg/day PQ 7 days Events	Total	0.5 mg/kg/day PQ 14 days Events	Total	Risk Ratio M-H, Fixed, 95% CI
4.4.1 Chloroquine blood-stage treatment					
Chu 2019 THA	5	144	7	139	0.69 [0.22 , 2.12]
4.4.2 DHA-PPQ blood-stage treatment					
Chu 2019 THA	6	125	4	114	1.37 [0.40 , 4.72]



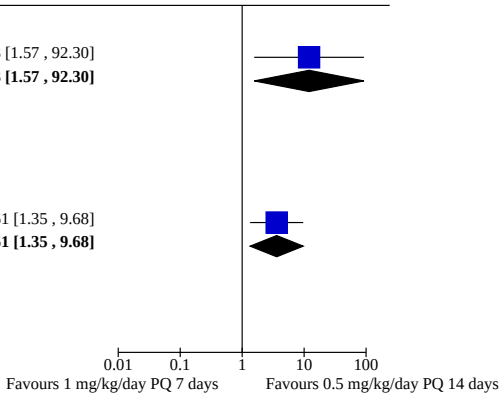
Analysis 4.5. Comparison 4: 1.0 mg/kg/day primaquine 7 days versus high-standard 0.5 mg/kg/day 14 days, Outcome 5: *P vivax* parasitaemia

Study or Subgroup	1 mg/kg/day PQ 7 days Events	Total	0.5 mg/kg/day PQ 14 days Events	Total	Risk Ratio M-H, Fixed, 95% CI
4.5.1 Day 28					
Taylor 2019 MULTI	2	935	3	937	0.67 [0.11 , 3.99]
4.5.2 Day 42					
Taylor 2019 MULTI	7	935	7	937	1.00 [0.35 , 2.85]



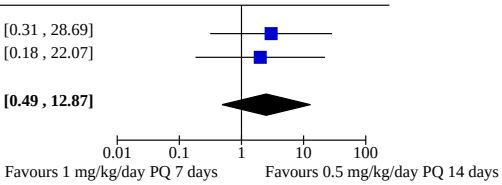
Analysis 4.6. Comparison 4: 1.0 mg/kg/day primaquine 7 days versus high-standard 0.5 mg/kg/day 14 days, Outcome 6: Serious adverse events

Study or Subgroup	1 mg/kg/day PQ 7 days Events	Total	0.5 mg/kg/day PQ 14 days Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.6.1 Up to 42 days follow-up						
Taylor 2019 MULTI	12	935	1	937	100.0%	12.03 [1.57 , 92.30]
Subtotal (95% CI)		**935**		**937**	**100.0%**	**12.03 [1.57 , 92.30]**
Total events:	12		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.39 (P = 0.02)						
4.6.2 Up to 1 year follow-up						
Taylor 2019 MULTI	18	935	5	937	100.0%	3.61 [1.35 , 9.68]
Subtotal (95% CI)		**935**		**937**	**100.0%**	**3.61 [1.35 , 9.68]**
Total events:	18		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.55 (P = 0.01)						



Analysis 4.7. Comparison 4: 1.0 mg/kg/day primaquine 7 days versus high-standard 0.5 mg/kg/day 14 days, Outcome 7: Adverse events that resulted in discontinuation of treatment

Study or Subgroup	1 mg/kg/day PQ 7 days Events	Total	0.5 mg/kg/day PQ 14 days Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chu 2019 THA (1)	3	327	1	327	50.0%	3.00 [0.31 , 28.69]
Taylor 2019 MULTI	2	935	1	937	50.0%	2.00 [0.18 , 22.07]
Total (95% CI)		**1262**		**1264**	**100.0%**	**2.50 [0.49 , 12.87]**
Total events:	5		2			
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%						
Test for overall effect: Z = 1.10 (P = 0.27)						
Test for subgroup differences: Not applicable						



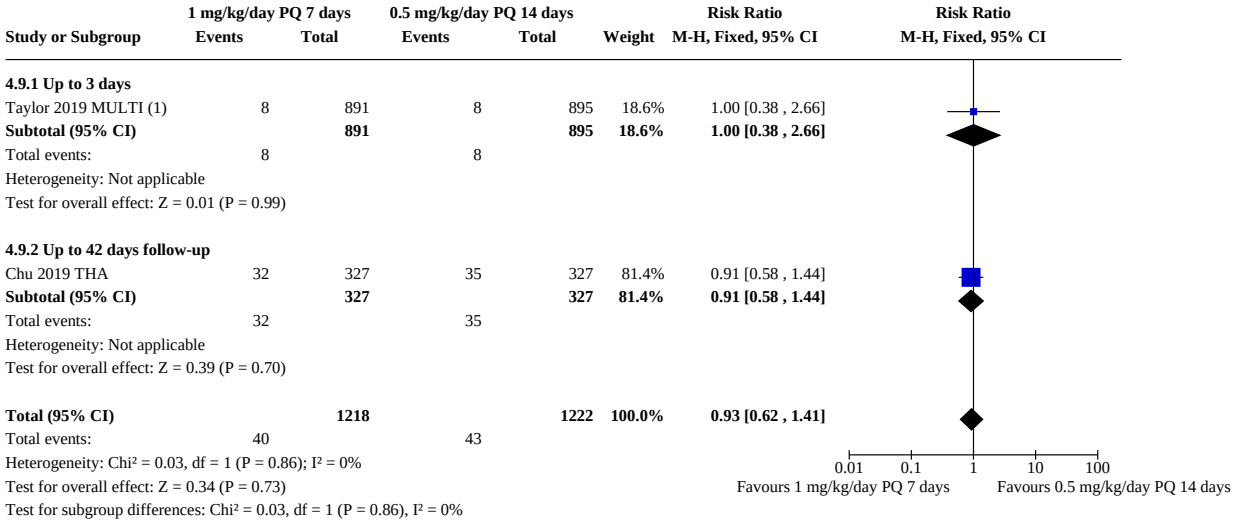
Footnotes

(1) [table S7; note table S8 reports slightly different data]

Analysis 4.8. Comparison 4: 1.0 mg/kg/day primaquine 7 days versus high-standard 0.5 mg/kg/day 14 days, Outcome 8: Other adverse events

Other adverse events		
Study	**1.0 mg/kg/day for 7 days**	**High-standard 0.5 mg/kg/day for 14 days**
Up to day 14		
Taylor 2019 MULTI	1819 events in 935 participants	1732 events in 937 participants
Chloroquine group, up to day 42		
Chu 2019 THA	97 events in 165 participants	91 events in 164 participants
DHA-PPQ group, up to day 42		
Chu 2019 THA	72 events in 162 participants	82 events in 163 participants

Analysis 4.9. Comparison 4: 1.0 mg/kg/day primaquine 7 days versus high-standard 0.5 mg/kg/day 14 days, Outcome 9: Anaemia



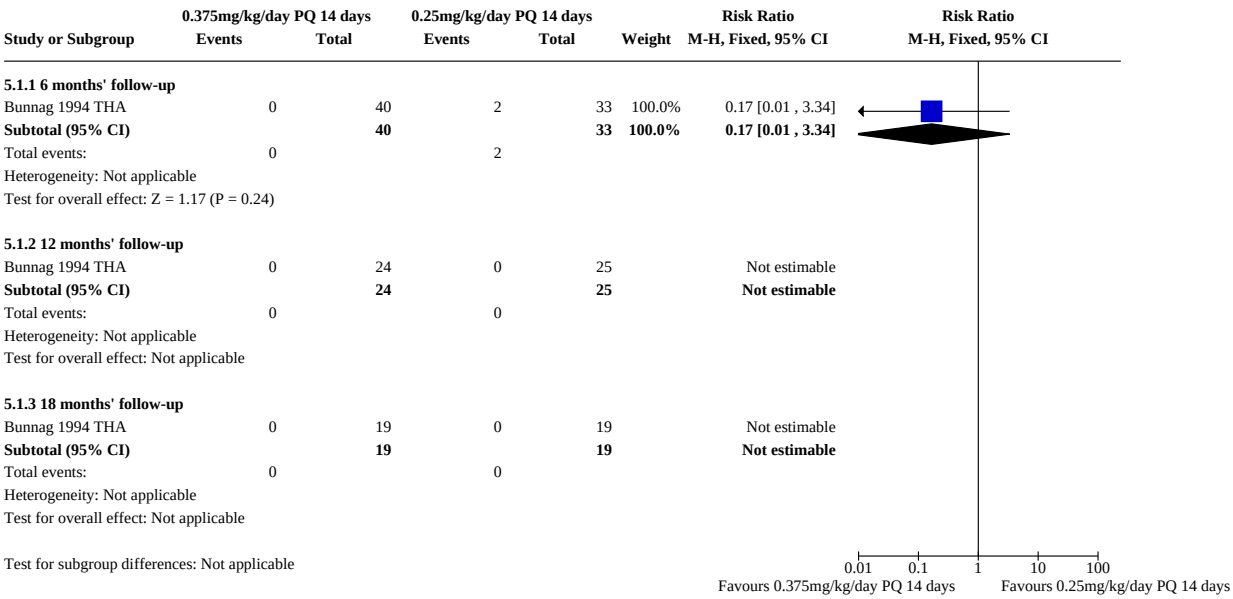
Footnotes

(1) percentage decrease in haemoglobin of more than 25% between enrolment and day 3

Comparison 5. 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
5.1 Recurrence by 6 months' follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1.1 6 months' follow-up	1	73	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.01, 3.34]
5.1.2 12 months' follow-up	1	49	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.1.3 18 months' follow-up	1	38	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

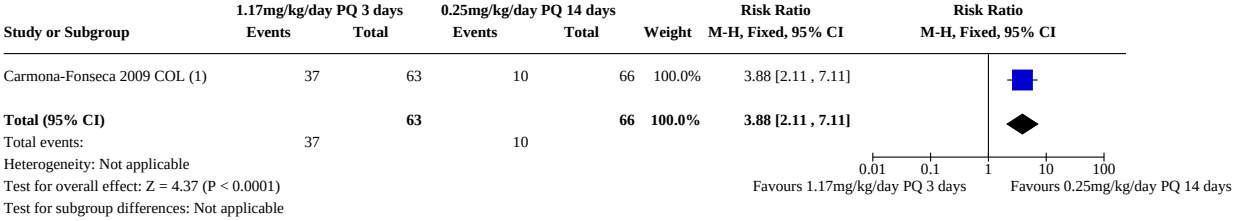
Analysis 5.1. Comparison 5: 0.375 mg/kg/day primaquine for 14 days versus standard 14-day regimen, Outcome 1: Recurrence by 6 months' follow-up



Comparison 6. 1.17 mg/kg/day primaquine for 3 days versus standard 14-day regimen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Recurrence by 4 months' follow-up	1	129	Risk Ratio (M-H, Fixed, 95% CI)	3.88 [2.11, 7.11]

Analysis 6.1. Comparison 6: 1.17 mg/kg/day primaquine for 3 days versus standard 14-day regimen, Outcome 1: Recurrence by 4 months' follow-up



Footnotes
(1) Follow up 120 days (4 months)

ADDITIONAL TABLES

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

Objective	Intervention	Control

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

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 rather than the length of treatment the important factor)?	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). 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) 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.
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

(Continued)

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

Cochrane Library

Issue 9 2019

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

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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

Appendix 2. Safety additional data

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

Study	High-standard 14-day regimen	Standard 14-day regimen
Rajgor 2014 IND	Total population = 1556 (including patients from excluded arm). Adverse events (AEs) of chloroquine (CQ) were defined as AEs reported during the chloroquine treatment. The AEs seen were: • itching (5), • burning of palms (1), • abdominal pain (1), • loose motion (1), • heat boils (1). Of these 9 AEs, 1 AE of itching and mucous membrane on lips lead to discontinuation of CQ on D3. AEs of primaquine (PQ) were defined as AEs that occurred after chloroquine treatment was completed. The AEs seen were: • nausea (1), • acidity (02), • weakness (1), • itching (09), • acidity plus itching (01), • abdominal pain (04), • acidity plus abdominal pain (01), • epigastric pain (02), • epigastric burning (01), • weakness plus abdominal pain (01), • vomiting (01), • mucocutaneous lesions on left leg and gluteal region (01), • boils on forehead and back with pus (01), • boils rash-maculopapular-all over body (01), • swelling of upper lips, legs, and palms with itching (01), • severe pruritus (01), • morbilliform rash in fingers (01), • boils inside the mouth and tongue (01).	

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

Study	0.5 mg/kg/day for 7 days	Standard 14-day regimen

(Continued)

Abdon 2001 BRA	Total population = 23 patients (including participants from excluded arm); 19.2% experienced AEs, these included: • diarrhoea (5.8%) • nausea (5%) • itching (5%) • vomiting (1.7%) • epigastric pain (1.7%) • dizziness (0.8%) • tinnitus (0.8%)	
Pareek 2015 IND	AEs during PQ administration and subsequent follow-up • Total events: 11/120 • Total N of patients with AEs: 6/120 • Malaise: 1 • Headache: 2 • Nausea: 1 • Decreased appetite: 0 • Pyrexia: 1 • Vomiting: 1 • Dizziness: 1 • Myalgia: 0 • Asthenia: 1 • Arthralgia: 0 • Pruritus: 1 • Haemoglobin decreased: 1 • Muscle spasms: 0 • Dyspnoea exertional: 0 • Dyspepsia: 1 • Diarrhoea: 0 • Diarrhoea: 0 • Cough: 0 None of the patients from primaquine SR 30mg group showed intolerance or dose-related side effects.	AEs during PQ administration and subsequent follow-up • Total events: 10/120 • Total N of patients with AEs: 5/120 • Malaise: 3 • Headache: 1 • Nausea: 2 • Decreased appetite: 0 • Pyrexia: 1 • Vomiting:1 • Dizziness: 0 • Myalgia: 2 • Asthenia: 0 • Arthralgia: 0 • Pruritus: 0 • Haemoglobin decreased: 0 • Muscle spasms: 0 • Dyspnoea exertional: 0 • Dyspepsia: 0 • Diarrhoea: 0 • Diarrhoea: 0 • Cough: 0
Rajgor 2014 IND	Total population = 1556 (including patients from excluded arm). AEs of chloroquine were defined as AEs reported during the chloroquine treatment. The AEs seen were: • itching (5), • burning of palms (1), • abdominal pain (1), • loose motion (1), • heat boils (1). Of these 9 AEs, 1 AE of itching and mucous membrane on lips lead to discontinuation of CQ on D3. AEs of primaquine were defined as AEs that occurred after chloroquine treatment was completed. The AEs seen were: • nausea (1),	

(Continued)

- acidity (02),
- weakness (1),
- itching (09),
- acidity plus itching (01),
- abdominal pain (04),
- acidity plus abdominal pain (01),
- epigastric pain (02),
- epigastric burning (01),
- weakness plus abdominal pain (01),
- vomiting (01),
- mucocutaneous lesions on left leg and gluteal region (01),
- boils on forehead and back with pus (01),
- boils rash-maculopapular-all over body (01),
- swelling of upper lips, legs, and palms with itching (01),
- severe pruritus (01),
- morbilliform rash in fingers (01),
- boils inside the mouth and tongue (01)

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

Study	1 mg/kg/day for 7 days	high-standard 14-day regimen
Chu 2019 THA	AEs leading to discontinuation of treatment by blood-stage antimalarial treatment: • chloroquine group: 1/165 • DHA-PPQ group: 2/162	AEs leading to discontinuation of treatment by blood-stage antimalarial treatment: • chloroquine group: 0/164 • DHA-PPQ: 1/163
	Anaemia or change in haemoglobin status • chloroquine group: 12/165 • DHA-PPQ group: 20/162	Anaemia or change in haemoglobin status • chloroquine group: 17/165 • DHA-PPQ group: 18/162

	Other adverse events
	• Abdominal pain
	  * chloroquine group: 44/165
	  * DHA-PPQ group: 25/162
	• Nausea or vomiting
	  * chloroquine group: 12/165
	  * DHA-PPQ group: 5/162
	• Dizziness
	  * chloroquine group: 15/165
	  * DHA-PPQ group: 18/162
	• Headache
	  * chloroquine group: 15/165
	  * DHA-PPQ group: 18/162
	• Fatigue
	  * chloroquine group: 11/165
	  * DHA-PPQ group: 6/162
		Other adverse events
		• Abdominal pain
		  * chloroquine group: 35/164
		  * DHA-PPQ group: 13/163
		• Nausea or vomiting
		  * chloroquine group: 10/164
		  * DHA-PPQ group: 9/163
		• Dizziness
		  * chloroquine group: 22/164
		  * DHA-PPQ group: 29/163
		• Headache
		  * chloroquine group: 15/164
		  * DHA-PPQ group: 21/163
		• Fatigue
		  * chloroquine group: 9/164
		  * DHA-PPQ group: 10/163

Taylor 2019 MULTI	Serious adverse events	Serious adverse events

(Continued)

• Primaquine-related, up to 42 days follow-up: 9/935 • Primaquine-unrelated, up to 42 days follow-up: 3/935 • Primaquine-related, up to 1 year follow-up: 9/935 • Primaquine-unrelated, up to 1 year follow-up: 9/935 Related events include those that are possibly, probably or definitely related	• Primaquine-related, up to 42 days follow-up: 1/937 • Primaquine-unrelated, up to 42 days follow-up: 0/937 • Primaquine-related, up to 1 year follow-up: 1/937 • Primaquine-unrelated, up to 1 year follow-up: 4/937 Related events include those that are possibly, probably or definitely related
SAE details Up to 42 days • Persistent vomiting – 2 days after treatment (possibly related) • Acute haemolysis (Hb drop from 13.7 to 9.5 g/dL) – 3 days after treatment (definitely related) • Haemolysis (Hb drop from 11.6 to 6.9 g/dL) – 3 days after treatment (possibly related) • Epigastric pain – 4 days after treatment (possibly related) • Persistent vomiting – 4 days after treatment (probably related) • Acute haemolysis (Hb drop from 15.3 to 6.4 g/dL) – 5 days after treatment (definitely related) • Diarrhoea – 7 days after treatment (definitely related) • Fever, abdominal pain, dyspnoea – 9 days after treatment (possibly related) • Symptomatic methaemoglobinaemia and bronchopneumonia – 10 days after treatment (definitely related) • Severe malaria (*P falciparum* + *P vivax*) – 2 days after treatment (not related) • Abdominal pain, fever of unexplained origin – 6 days after treatment (not related) • Persistent vomiting – 10 days after treatment (not related) 42 days to 1 year • Severe *P falciparum* malaria – 46 days after treatment (not related) • Unilateral periorbital ecchymosis – 54 days after treatment (not related) • Severe *P falciparum* malaria – 57 days after treatment (not related) • Sudden unexpected death due to myocardial infarction – 151 days after treatment (not related) • Acute appendicitis – 170 days after treatment • Severe *P falciparum* malaria – 221 days after treatment (not related)	SAE details Up to 42 days • Haemolysis (Hb drop from 10.2 to 6.8/dL) – 3 days after treatment (probably related) 42 days to 1 year • Acute exacerbation of bronchial asthma precipitated by pneumonia – 91 days after treatment (not related) • Generalized peritonitis – 92 days after treatment (not related) • Complicated puncture wound – 129 days after treatment (not related) • Undifferentiated carcinoma in nasopharynx – 147 days after treatment (not related)
• Mean (SD) absolute decrease in haemoglobin at day 3, g/dL = 0.52 (1.19) • Mean (SD) absolute decrease in haemoglobin at day 7, g/dL = 0.01 (1.23)	• Mean (SD) absolute decrease in haemoglobin at day 3, g/dL = 0.62 (1.09) • Mean (SD) absolute decrease in haemoglobin at day 7, g/dL = 0.12 (1.09)

(Continued)

	Symptoms elicited from daily questionnaires, 1–14 days after starting antimalarial treatment • Headache: 480/935 • Diarrhoea: 95/935 • Skin rash: 22/935 • Poor appetite: 407/935 • Myalgia or arthralgia: 243/935 • Fever: 294/935 • Passing dark urine: 55/935 • Dizziness: 166/935 • Shortness of breath: 33/935 • Itching: 24/935	Symptoms elicited from daily questionnaires, 1–14 days after starting antimalarial treatment • Headache: 465/937 • Diarrhoea: 52/937 • Skin rash: 26/937 • Poor appetite: 374/937 • Myalgia or arthralgia: 236/937 • Fever: 319/937 • Passing dark urine: 48/937 • Dizziness: 157/937 • Shortness of breath: 29/937 • Itching: 26/937

Appendix 3. Primary outcomes additional analyses

3a. Rate ratios and hazard ratios for the outcome 'Recurrence' at 12 months follow-up of the comparison '1.0 mg/kg/day primaquine for 7 days versus high-standard 14-day regimen'

Subgroup	Study	Events/person-years[a]	Rate ratio (95% CI)	Pooled rate ratio (95% CI)[b]	HR (95% CI)[c]
Blood-stage drug: chloroquine	Chu 2019 THA	PQ7: 20/128 PQ14: 26/125	0.72 (0.28 to 1.90)	Subtotal: 0.99 (0.70 to 1.40)	-
	Taylor 2019 MULTI	PQ7: 54/286 PQ14: 55/303	1.04 (0.71 to 1.51)		-
Blood-stage drug: DHA-PPQ	Chu 2019 THA	PQ7: 17/114 PQ14: 16/122	1.14 (0.57 to 2.25)	Subtotal: 1.27 (0.87 to 1.85)	-
	Taylor 2019 MULTI	PQ7: 44/311 PQ14: 33/312	1.34 (0.85 to 2.10)		-
See Analysis 4.1 for risk ratio.				Total: 1.11 (0.86 to 1.44)	Total HR reported in Taylor 2019 MULTI: 1.17 (0.88 to 1.55)
Geographical region: Afghanistan	Taylor 2019 MULTI	PQ7: 20/74 PQ14: 27/78	0.78 (0.44 to 1.40)		Jalalabad: 0.74 (0.30 to 1.84) Laghman: 0.90 (0.44 to 1.83)
Geographical region: Ethiopia	Taylor 2019 MULTI	PQ7: 25/124 PQ14: 19/135	1.42 (0.78 to 2.58)		Arba Minch: 1.54 (0.79 to 2.98) Metahara: 1.08 (0.35 to 3.34)
Geographical region: Indonesia	Taylor 2019 MULTI	PQ7: 44/311 PQ14: 33/312	1.34 (0.85 to 2.10)		Hanura: 1.16 (0.71 to 1.90)

(Continued)

					Tanjung Leidong: 2.36 (0.83 to 6.69)
Geographical region: Thailand	Chu 2019 THA	PQ7: 37/242 PQ14:42/247	0.90 (0.58 to 1.40)		-
Geographical region: Vietnam	Taylor 2019 MULTI	PQ7: 9/89 PQ14:9/91	1.03 (0.41 to 2.58)		Dak O & Bu Gia Map: 1.21 (0.49 to 2.97) Krong Pa: 0.47 (0.04 to 5.18)
See Analysis 4.2 for risk ratio.				Total: 1.07 (0.84 to 1.37)	Total HR: 1.17 (0.88 to 1.55)

[a]Events/person-years (or per person-days converted to person-years) reported in study reports for estimation of rate ratios.
[b]Pooled rate ratios were calculated in RevMan 5 (analyses not shown) based on log rate ratios and their SEs using the generic inverse variance method.
[c]Hazard ratios reported by study site in Taylor 2019 MULTI.

3b. Rate ratios for the outcome 'Recurrence' at 3 and 6 months follow-up of the comparison '1.0 mg/kg/day primaquine for 7 days versus high-standard 14-day regimen'

Study	Follow-up	Subgroup	Events / person-years	Rate ratio (95% CI)
Taylor 2019 MULTI	3 months	Blood-stage drug: chloroquine	PQ7: 35/122 PQ14: 27/128	1.36 (0.82 to 2.25)
		Blood-stage drug: DHA-PPQ	PQ7: 7/98 PQ14: 5/96	1.37 (0.44 to 4.32)
See Analysis 4.3 and Analysis 4.4 for risk ratios				Total: 1.36 (0.86 to 2.16)
Taylor 2019 MULTI	6 months	Blood-stage drug: chloroquine	PQ7: 53/231 PQ14: 51/245	1.10 (0.75 to 1.62)
		Blood-stage drug: DHA-PPQ	PQ7: 32/193 PQ14: 19/189	1.65 (0.94 to 2.91)
See Analysis 4.3 and Analysis 4.4 for risk ratios				Total 1.25 (0.91 to 1.72)

WHAT'S NEW

Date	Event	Description
7 July 2020	New citation required and conclusions have changed	We included two new large important trials using higher dose for 7 days compared to high standard 14-day course, following a search update to 2 September 2019.

Date	Event	Description
7 July 2020	New search has been performed	We updated the date of search to 2 September 2019.

HISTORY

Protocol first published: Issue 5, 2017
Review first published: Issue 7, 2019

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.

Gemma Villanueva (GV): data collection and management, analysis and interpretation of results, review writing.

Hanna Bergman (HB): data collection and management, analysis and interpretation of results, review writing.

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

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.
GV works for Cochrane Response, an evidence services unit operated by the Cochrane Collaboration, and has no known conflicts of interest. Cochrane Response was contracted by the CIDG to update this review.
HB works for Cochrane Response, an evidence services unit operated by the Cochrane Collaboration, and has no known conflicts of interest. Cochrane Response was contracted by the CIDG to update this review.
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

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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