Cochrane Library

Cochrane Database of Systematic Reviews

Primaquine for preventing relapse in people with *Plasmodium vivax* malaria treated with chloroquine (Review)

Galappaththy GNL, Tharyan P, Kirubakaran R

Galappaththy GNL, Tharyan P, Kirubakaran R.
Primaquine for preventing relapse in people with *Plasmodium vivax* malaria treated with chloroquine.
Cochrane Database of Systematic Reviews 2013, Issue 10. Art. No.: CD004389.
DOI: 10.1002/14651858.CD004389.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Primaquine for preventing relapse in people with *Plasmodium vivax* malaria treated with chloroquine

Gawrie NL Galappaththy[1], Prathap Tharyan[2], Richard Kirubakaran[2]

[1]National Malaria Control Programme, Ministry of Health, Dehiwala, Sri Lanka. [2]South Asian Cochrane Network & Centre, Prof. BV Moses & ICMR Advanced Centre for Research & Training in Evidence Informed Health Care, Christian Medical College, Vellore, India

Contact: Gawrie NL Galappaththy, National Malaria Control Programme, Ministry of Health, 45/2C Auburn Side, Dehiwala, Colombo, Sri Lanka. hapugalleg@gmail.com.

Editorial group: Cochrane Infectious Diseases Group.
Publication status and date: Unchanged, published in Issue 10, 2013.

Citation: Galappaththy GNL, Tharyan P, Kirubakaran R. Primaquine for preventing relapse in people with *Plasmodium vivax* malaria treated with chloroquine. *Cochrane Database of Systematic Reviews* 2013, Issue 10. Art. No.: CD004389. DOI: 10.1002/14651858.CD004389.pub3.

ABSTRACT

Background

Plasmodium vivax infections are an important contributor to the malaria burden worldwide. The World Health Organization recommends a 14-day course of primaquine (0.25 mg/kg/day, giving an adult dose of 15 mg/day) to eradicate the liver stage of the parasite and prevent relapse of the disease. Many people find a 14-day primaquine regimen difficult to complete, and there is a potential risk of haemolytic anaemia in people with glucose-6-phosphate-dehydrogenase enzyme (G6PD) deficiency. This review evaluates primaquine in *P. vivax*, particularly alternatives to the standard 14-day course.

Objectives

To compare alternative primaquine regimens to the recommended 14-day regimen for preventing relapses (radical cure) in people with *P.* vivax malaria treated for blood stage infection with chloroquine. We also summarize trials comparing primaquine to no primaquine that led to the recommendation for the 14-day regimen.

Search methods

We searched the Cochrane Infectious Diseases Group's Specialized Register, CENTRAL (*The Cochrane Library*), MEDLINE, EMBASE and LILACS up to 8 October 2013. We checked conference proceedings, trial registries and reference lists and contacted researchers and pharmaceutical companies for eligible studies.

Selection criteria

Randomized controlled trials (RCTs) and quasi-RCTs comparing various primaquine dosing regimens with the standard primaquine regimen (15 mg/day for 14 days), or with no primaquine, in people with vivax malaria treated for blood stage infection with chloroquine.

Data collection and analysis

We independently assessed trial eligibility, trial quality, and extracted data. We calculated risk ratios (RR) with 95% confidence intervals (CI) for dichotomous data, and used the random-effects model in meta-analyses if there was significant heterogeneity. We assessed the overall quality of the evidence using the GRADE approach.

Main results

We included 15 trials (two cluster-RCTs) of 4377 adult and child participants. Most trials excluded people with G6PD deficiency. Trials compared various regimens of primaquine with the standard primaquine regimen, or with placebo or no treatment. All trials treated blood stage infection with chloroquine.

Alternative primaquine regimens compared to 14-day primaquine

Relapse rates were higher over six months with the five-day primaquine regimen than the standard 14-day regimen (RR 10.05, 95% CI 2.82 to 35.86; two trials, 186 participants, *moderate quality evidence).* Similarly, relapse over six months was higher with three days of primaquine than the standard 14-day regimen (RR 3.18, 95% CI 2.1 to 4.81; two trials, 262 participants, *moderate quality evidence*; six months follow-up*)*; and with primaquine for seven days followed up over two months, compared to 14-day primaquine (RR 2.24, 95% CI 1.24 to 4.03; one trial, 126 participants, *low quality evidence*).

Relapse with once-weekly supervised primaquine for eight weeks was little different over nine months follow-up compared to 14-day self-administered primaquine in one small study (RR 2.97, 95% CI 0.34 to 25.87; one trial, 129 participants, *very low quality evidence*).

Primaquine regimens compared to no primaquine

The number of people that relapsed was similar between people given five days of primaquine or given placebo or no primaquine (four trials, 2213 participants, *high quality evidence*; follow-up six to 15 months); but lower with 14 days of primaquine (RR 0.6; 95% CI 0.48 to 0.75; ten trials, 1740 participants, *high quality evidence*; follow-up seven weeks to 15 months).

No serious adverse events were reported. Treatment-limiting adverse events were rare and non-serious adverse events were mild and transient. Trial authors reported that people tolerated the drugs.

We did not find trials comparing higher dose primaquine regimens (0.5 mg/kg/day or more) for five days or more with the 14-day regimen.

Authors' conclusions

The analysis confirms the current World Health Organization recommendation for 14-day primaquine (15 mg/day) to prevent relapse of vivax malaria. Shorter primaquine regimens at the same daily dose are associated with higher relapse rates. The comparative effects with weekly primaquine are promising, but require further trials to establish equivalence or non-inferiority compared to the 14-day regimen in high malaria transmission settings.

23 April 2019

No update planned

Review superseded

This Cochrane Review has been superseded. The research question has changed and this review has been superseded by Milligan 2017 https://doi.org/10.1002/14651858.CD012656

PLAIN LANGUAGE SUMMARY

Primaquine for preventing relapses in people with *Plasmodium vivax* malaria

Malaria due to *Plasmodium vivax* parasites is widespread. The World Health Organization (WHO) recommends that people with *P. vivax* malaria are treated with chloroquine for three days to eliminate the parasites in the blood that cause the symptoms of malaria, followed by 15 mg/day of primaquine for 14 days to treat the liver stage of the infection to prevent the disease recurring. However, many people do not complete the primaquine treatment once they feel better after chloroquine treatment. In addition, primaquine can destroy red blood cells in people with a genetic enzyme deficiency (glucose-6-phosphate-dehydrogenase enzyme (G6PD) deficiency), and clinicians avoid giving primaquine in areas where people commonly have this deficiency. Shorter courses of primaquine could potentially increase treatment completion and reduce adverse events.

The review authors included 15 trials of 4377 adults and children older than one year with vivax malaria. All were treated with chloroquine for the blood stage infection, and then randomized to the 14-day primaquine course, or to shorter primaquine courses (three, five, or seven days); or to higher doses of primaquine given once a week for eight weeks; or to a placebo or no treatment. In twelve studies, treatments were supervised. The evidence is current to 8 October 2013.

Relapse over six months to one year is probably higher with shorter regimens when compared to the standard 14-day primaquine regimen (*moderate quality evidence*). We do not know from the available evidence whether the number of relapses with weekly primaquine differs from 14 days of primaquine treatment based on one study of 126 people followed up for nine months (*very low quality evidence*). Better conducted studies on more people are needed to be sure that they are equally effective against relapse. Five days of primaquine was as ineffective against relapse as placebo or no treatment over six months to 15 months based on four studies (*high quality evidence*). The 14-

day primaquine course prevented many more people relapsing with vivax malaria over 12 months than placebo (*high quality evidence*). No serious adverse reactions to primaquine were reported.

This review update confirms that the 14-day primaquine course recommended by the WHO is more effective against relapse of vivax malaria than treatment with shorter courses of primaquine.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Primaquine five days compared to 14 days

What are the effects of five days of primaquine compared to 14 days of primaquine for preventing relapses in people with *P. vivax* malaria treated for blood stage infections with chloroquine?

Patient or population: People with *P. vivax* malaria[1]
Intervention: Chloroquine (25 mg/kg over three to five days) plus primaquine (0.25 mg/kg per day) for five days
Comparison: Chloroquine (25 mg/kg over three days) plus primaquine (0.25 mg/kg per day) for 14 days

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Primaquine 14 days	Primaquine 5 days				
***P. vivax* parasitaemia detected > 30 days after starting primaquine** Follow-up: 3 to 6 months	**21 per 1000**	**183 more per 1000** (from 49 more to 742 more)	**RR 10.05** (2.82 to 35.86)	186 (2 studies)[2]	⊕⊕⊕⊖ **moderate** [3,4,5]	
Serious adverse events	none reported	none reported	Not estimable	186 (2 studies)		
Other adverse events	none reported	none reported	Not estimable	186 (2 studies)		

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

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

[1] Gogtay 1999 was done in Mumbai, India, and Villalobos 2000 was done in Porto Velho, Brazil; treatments were supervised in both and follow-up was for three to six months. Kim 2012 was done in Kolkata, India; primaquine was not supervised; follow-up was for 15 months.

[2] Data from a third trial (Kim 2012) were not pooled due to substantial heterogeneity (I^2 = 87%). This trial was at risk of selection and detection bias, and the trial authors reported that the lack of significant difference in recurrences over 15 months (27%, 16/59 with 5-day primaquine; 38%, 16/42 with 14-day primaquine) was likely due to non-adherence to unsupervised primaquine.

[3] No serious study limitations: the trials were at low risk bias in all domains we assessed.
[4] No serious inconsistency: there was inconsistency in the magnitude of effect estimates (I^2 = 53%), though not in the direction of effect. Using random effects did not change the estimates appreciably.
[4] Serious indirectness: trials excluded children. Although other trials in this review that included children did not find five or 14 days of primaquine to differ in efficacy in children and adults, more direct evidence of the comparative effects in children are needed. Two trials in low transmission areas provided the data. We downgraded by 1.
[5] No serious imprecision: the upper and lower limits of the 95% CI of the pooled estimate indicates appreciable benefit with 14 days of primaquine, and no inconsistency in the direction of effects. The combined sample size was greater than the optimal information size given the magnitude of the relative risk reduction.

Summary of findings 2. Primaquine three days compared to 14 days

What are the effects of primaquine (3 days) compared to primaquine (14 days) for preventing relapses in people with *P. vivax* malaria treated for blood-stage infections with chloroquine?

Patient or population: People with *P. vivax* malaria[1]
Intervention: Chloroquine (1500 mg over three days) with concurrently primaquine (3.5 mg/kg over three days; 45 mg over three days)
Comparison: Chloroquine (1500 mg over three days) with concurrent primaquine (0.25 mg/kg for 14 days)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Primaquine 14 days	Primaquine three days				
***P. vivax* parasitaemia detected > 30 days after starting primaquine** Follow-up: 3 to 6 months	**167 per 1000**	**363 more per 1000** (from 183 more to 635 more)	**RR 3.18** (2.10 to 4.81)	262 (2 studies)	⊕⊕⊕⊖ **moderate** 2,3,4,5	
Serious adverse events	None reported	None reported	Not estimable	262 (2 studies)		
Other adverse events	Not reported	Not reported	Not estimable	262 (2 studies)		

*The basis for the **assumed risk** is the average of the risk in the control group in the two trials. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

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

[1] Alvarez 2006 and Carmona-Fonseca 2009 conducted the trials in the same semi-rural areas of Columbia, South America.
[2] No study limitations: both trials were free of the risk of bias.
[3] No serious inconsistency: the effect estimates in both trials were consistent (I^2 = 5%).
[4] Serious indirectness: Carmona-Fonseca 2009 included children and both trials were done in endemic settings with unstable and high malaria transmission. Trial authors confirmed parasitic clearance by day 28. The possibility of new infections being mistaken for relapses was minimized by the duration of follow-up and the lack of heterogeneity in results for follow-up before and after three months. However, the two trials were done in the same area in Columbia and more data from other regions with differing transmission intensities would add to our confidence in the comparative effects of shorter courses of primaquine. We downgraded by 1.
[5] No imprecision: the upper and lower limits of the 95% CI indicated appreciable benefit with 14 days of primaquine. Although the total number of events was < 300, the sample size of the trials exceeded the optimal information size, given the magnitude of benefit.

Summary of findings 3. Primaquine seven days compared to 14 days

What are the effects of primaquine (seven days) compared to primaquine (14 days) for preventing relapses in people with *P. vivax* malaria treated for blood stage infections with chloroquine?

Patient or population: People with *P. vivax* malaria[1]
Intervention: Chloroquine (600 mg per day over three days) with concurrent primaquine (15 mg base per day for seven days; total dose 105 mg)
Comparison: Chloroquine (600 mg per day over three days) with concurrent primaquine (15 mg base per day for 14 days; total dose 210 mg)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	14 days primaquine	7 days primaquine				
***P. vivax* parasitaemia detected > 30 days after starting primaquine** Follow-up: 2 months	**188 per 1000**	**233 more per 1000** (from 45 more to 568 more)	**RR 2.24** (1.24 to 4.03)	126 (1 study)	⊕⊕⊖⊖ **low** [2,3]	
Severe adverse events	None reported	None reported	Not estimable	126 (1 study)		
Other adverse events	Not reported	Not reported	Not estimable	126 (1 study)		

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

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

Very low quality: We are very uncertain about the estimate.

[1] Alvarez 2006 was conducted in Columbia, South America.

[2] Serious indirectness: trial authors did not include children < 15 years in this trial. However, another trial done in the same area by the same group of investigators (Carmona-Fonseca 2009) immediately after this trial included children as well, and results for three days of primaquine versus 14 days of primaquine did not differ in children from that in adults. Duration of follow-up was two months. While this ensures the detection of early relapses, it does not cover relapses after two months. The relapse rates at six months in Carmona-Fonseca 2009 also showed that most relapses occur by two months. However, the data for the effects of seven days of primaquine come from only one trial. We downgraded by 1.

[3] Serious imprecision: though the upper and lower limits of the 95% CI of the risk ratio in this trial showed statistically significant and clinically appreciable benefit with 14 days of primaquine over seven days of primaquine, the total number of events was 38 and the sample size of the trial was 104. This is lower than the optimal information size. We downgraded by 1.

Summary of findings 4. Primaquine (weekly for eight weeks) compared to daily primaquine for 14 days

What are the effects of supervised primaquine (weekly for 8 weeks) versus primaquine (daily for 14 days) for preventing relapses in people with *P. vivax* malaria treated for blood stage infections with chloroquine?

Patient or population: Children and adults with blood smear positive *P. vivax* malaria[1]
Intervention: Chloqoquine (600 mg over three days) plus primaquine (45 mg weekly for eight weeks; total dose 360 mg)[2]
Comparison: Chloroquine (600 mg per day over three days) plus primaquine (22.5 mg base daily for 14 days; total dose 315 mg)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Primaquine for 14 days	Primaquine weekly for eight weeks				
***P. vivax* parasitaemia detected > 30 days after starting primaquine** Follow-up: 6 to 11 months	**18 per 1000**	**36 more per 1000** (from 12 fewer to 452 more)	**RR 2.97** (0.34 to 25.87)	129 (1 study)	⊖⊖⊖⊖ **very low** [3,4,5]	
Serious adverse events Follow-up: 9 to 11 months	None reported	None reported	Not estimable	129 (1 study)[6]		
Adverse events Follow-up: 9 to 11 months	None reported	None reported	Not estimable	129 (1 study)		

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

GRADE Working Group grades of evidence

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

[1] Leslie 2008 was conducted in three Afghan refugee camps in North West Frontier Province in Pakistan during a period of low transmission.
[2] These were doses used in adults; doses for children were proportionately lower.
[3] Very serious study limitations: mixed randomization and allocation procedures resulted in high risk of selection bias and imbalanced numbers of participants and unequal distribution of prognostic indicators. The occurrence of selection bias was demonstrated by significant differences in outcome estimates that varied by site, and by intervention. The sample size was not powered to detect significant differences between interventions, and recruitment did not achieve the estimated sample size in the 14-day primaquine arm. We downgraded by 2.
[4] Serious indirectness: this trial included children and adults and was done in displaced persons in refugee camps. However, trial authors did not confirm parasitic clearance after chloroquine by day 28, though it is unclear if recrudescence or relapses would be differentially distributed in the intervention arms. The estimates for recurrences for periods greater than 3 to 6 months is likely to differ if applied to high transmission settings (transmission was unusually low during the period of recruitment of this trial); and the supervision options for 8 weeks of primaquine may also differ in populations that are not restricted to refugee settlements with limited geographical mobility. We downgraded by 1.
[5] Very serious imprecision: sample size was under-powered to detect important differences between interventions; the number of events were very low and the total sample size was much lower than the optimal information size. The 95% CI of the risk ratio indicates appreciable benefit for the 8-week, intermittent primaquine and for 14 daily doses of primaquine that do not rule out random error. We downgraded by 2.
[6] Trial authors allocated insufficient numbers of people with G6PD deficiency (only one in the report) to the 8-week arm to be sure that intermittent primaquine is a safer alternative than 14 days of primaquine; none given the 14-day regimen had this deficiency.

Summary of findings 5. Primaquine for five days

What are the effects of primaquine (five days) compared to no intervention or placebo for preventing relapses in people with *P. vivax* malaria treated for blood stage infections with chloroquine?

Patient or population: People with *P. vivax* malaria[1]

Intervention: Chloroquine (25 mg/kg for three days) plus primaquine (0.25 mg/kg) for five days[2]
Comparison: Chloroquine (25 mg/kg for three days)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No primaquine	5 days primaquine				
***P. vivax* parasitaemia detected > 30 days after starting primaquine** Follow-up: 6 to 15 months	**193 per 1000** [2]	**4 fewer per 1000** (from 53 fewer to 59 more)	**RR 0.98** (0.73 to 1.3)	2213 (4 studies)	⊕⊕⊕⊕ **high** [3,4,5,6]	
Serious adverse events	None reported	None reported	Not estimable	2213 (4 studies)		

Other adverse events	None reported	None reported	Not estimable	2213 (4 studies)	

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

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

[1] Trial authors performed trials in outpatients in Mumbai, India (Gogtay 1999; Rajgor 2003) and Kolkota, India (Kim 2012), and in the Adizai Afghan refugee camp in the North West Frontier Province of Pakistan (Rowland 1999b).
[2] Chloroquine and primaquine were given sequentially in the four trials.
[3] No serious study limitations: three trials were free of the risk of bias in all domains assessed. Kim 2012 was at risk of selection and detection bias, but the results were consistent with that seen in two other trials with follow-up beyond six months; and this trial contributed only 16% weight to the pooled results. Removal of Kim 2012 in sensitivity analysis did not alter the results appreciably.
[4] No serious inconsistency: the pooled effect estimates of Kim 2012; Rowland 1999b and Yadav 2002 that evaluated parasitaemia after 6 months were inconsistent in their direction of effect from Gogtay 1999 that assessed this at six months (I^2 = 50%). However, inconsistency was not evident within subgroups based on the duration of follow-up > than or < than six months, irrespective of whether treatments were supervised.
[5] No serious indirectness: Kim 2012 and Rowland 1999b included children > 1 to 3 years of age; all four trials were conducted in low income countries and the transmission patterns were representative of the patterns seen with tropical strains and seasonality in other parts of the region. Though the outcome used is a proxy measure for relapse, the absence of widely available tests using valid molecular genetic marker makes clinical diagnoses based on recurrence timings the best available outcome to asses relapses in vivax malaria.
[6] No serious imprecision: the 95% CI of the risk ratio indicates appreciable benefit with both interventions; however the total number of events was more than 300 and the total sample size exceeded the optimal information size.

Summary of findings 6. Primaquine for 14 days

What are the effects of primaquine (14 days) compared to no intervention or placebo for preventing relapses in people with *P. vivax* malaria treated for blood stage infection with chloroquine?

Patient or population: People with *P. vivax* malaria[1]
Intervention: Chloroquine (25 mg/kg for three days) plus primaquine (0.25 mg/kg) for 14 days
Comparison: Chloroquine (25 mg/kg for three days)

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	No primaquine	**Primaquine 14 days**				

***P. vivax* parasitaemia detected > 30 days after starting primaquine** Follow-up: 7 weeks to 15 months	**84 per 1000**	**34 fewer per 1000** (from 21 fewer to 44 fewer)	**RR 0.60** (0.48 to 0.75)	1740 (10 studies)	⊕⊕⊕⊕ **high** [2,3,4,5]
Serious adverse events	None reported	None reported	Not estimable	1740 (10 studies)	
Other adverse events	None reported	None reported	Not estimable	1740 (10 studies)	

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

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

[1] Trial authors conducted the studies in Ethiopia (Yeshiwondim 2010), India (Gogtay 1999; Rajgor 2003; Kim 2012; Ganguly 2013), Pakistan (Rowland 1999a; Leslie 2004; Walsh 2004; Leslie 2008) and Thailand (Pukrittayakamee 1994).
[2] No serious study limitations: Leslie 2008, Ganguly 2013, and Kim 2012 were at high risk of bias. However, these studies contributed only 15.5% weight to the pooled effect estimates and their removal from the sensitivity analysis did not alter the results appreciably.
[3] No serious inconsistency: results were consistent within subgroups of trials based on duration of follow-up < than or > than six months, and whether treatments were supervised or not; the I^2 value for the pooled effect estimates from the 10 trials was 30%.
[4] No serious indirectness: trials included children and were also done in transmission settings and countries representative of vivax malaria burden. The outcome used was the best estimate currently available in the absence of widely available validated molecular techniques to differentiate relapse from new infections.
[5] No serious imprecision: upper and lower limits of the 95% CI of the pooled relative risk indicated appreciable benefit with chloroquine plus primaquine for 14 days. The total number of events was less than 300 but the total sample size was larger than the optimal information size, given the magnitude of risk reduction.

BACKGROUND

Description of the condition

Malaria is usually caused by the parasites *Plasmodium vivax and Plasmodium falciparum.* In 2010, malaria episodes occurred in an estimated 149 million to 274 million people worldwide, approximately 81% of whom were living in Africa, and 13% in South-East Asia (WHO 2011). In 2010, malaria killed between 537,000 to 907,000 people; and 86% of these deaths were children under five years of age (WHO 2011). *P. vivax* infects an estimated 130 million to 391 million people annually (Hay 2004; Price 2007). Around 40% of the world's population living in 95 countries in Central, South East, and South Asia; Africa; and South America are at risk of *P. vivax* infection. The geographical distribution of vivax malaria is more widespread than falciparum malaria (Guerra 2010). Co-infection with *P. falciparum* is also common in many of these regions (Kumar 2007; Mueller 2009). Vivax infections during pregnancy increase neonatal, infant, and maternal morbidity and mortality (Poespoprodjo 2008; ter Kuile 2008; Poespoprodjo 2009; Price 2009). Case series studies of adults and children in endemic areas have documented severe disease in people with confirmed*P. vivax* mono-infections, similar to that produced by *P. falciparum* (Anstey 2007; Barcus 2007; Beg 2008; Genton 2008; Tjitra 2008; Mueller 2009; Price 2009; Valecha 2009; Kochar 2010; Maguire 2010; Saravu 2011; Srivastava 2011; Singh 2011; Tanwar 2011). Also, less severe forms of vivax malaria can adversely affect personal well-being, growth, and economic performance at the individual, family, community, and national level (Breman 2001; Mendis 2001).

In addition, people infected with *P. vivax* may have relapses of the disease. The infective stage of the parasite (sporozoites) is injected into a person's bloodstream through the bite of a female anopheline mosquito, enters the liver within minutes, invades liver cells, and develops into either of two stages. The asexual blood-stage infection results in the clinical symptoms of vivax malaria; while a dormant liver-stage infection (hypnozoite) that can be activated weeks to years after the initial infection, causes relapses of the blood-stage infection, and increases the potential for transmission of the sexual gametocyte forms (Krotoski 1985; Baird 2009; Doolan 2009; Mueller 2009). Relapse occurrence varies depending on the genetic makeup of the sporozoites (Cogswell 1992; Craig 1996; Rowland 2001), the number of sporozoites inoculated, and climatic conditions that favour transmission (White 2011). In general, people infected with tropical strains from Asia have high relapse rates (80% to 100%), with relapses usually occurring within six months of treatment (Fonseka 1987; Looareesuwan 1997; Luxemburger 1999; Pukrittayakamee 2004; Krudsood 2008). Relapse rates with vivax strains from India are reportedly lower, but are highly variable (8% to 40%); and although the majority occur within the first six months (Gogtay 2000) relapses can also occur within a few weeks to a year or more, in different parts of the country (White 2011). People infected with tropical strains from New Guinea (the Chesson strain) relapse within or shortly after a month and relapses occur several times over a period of a year or more (Collins 1996; Baird 2009). Relapses usually occur much later with temperate strains, such as the North Korean strain (Collins 1996; White 2011).

Re-infection is also a problem with vivax malaria. Apart from innate (or natural) immunity to malaria, a partial immunity (acquired immunity) that mitigates the clinical effects of malaria develops in individuals who live in areas where malaria is highly endemic (Doolan 2009). This clinical immunity is lost when individuals living in endemic areas move to non-endemic areas (Maguire 2010). In highly endemic areas, the risk of severe *P. vivax* disease is highest among children less than two years of age, while uncomplicated *P. vivax* illness is less common in children over five years of age, though infections occur even in adolescents and adults (Michon 2007; Genton 2008; Lin 2010). However, in many parts of the world, relapses caused by the hypnozoite represent the dominant source of recurrences of parasitaemia compared to new infections (Maguire 2010; White 2011).

Description of the intervention

People with vivax malaria require effective treatment with a combination of chloroquine to treat the blood-stage infection, and primaquine to treat hypnozoites and prevent relapses (radical cure). The recommended adult treatment with chloroquine is 25 mg/kg body weight administered daily over three days. Chloroquine is inexpensive and people usually tolerate it well. People frequently report itching from chloroquine but they do not usually discontinue treatment for this reason (Valecha 2006). The standard recommended dose of primaquine is 15 mg per day (0.25 mg/kg) for 14 days, delivering a total dose of 210 mg of primaquine. Primaquine may cause abdominal pain, nausea, and vomiting, but these adverse events are dose-dependant and are minimized if people take the drug after meals (Parfitt 1999; Vale 2008; Baird 2009).

Glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency

Primaquine also causes the destruction of red blood cells (haemolysis) in people with a hereditary enzyme deficiency known as glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency, which occurs due to mutations in the G6PD gene (q28 locus on the X chromosome) (Beutler 2007; Cappellini 2008). Over 400 million people worldwide have this enzyme deficiency; and the enzyme deficiency variant and dose of primaquine determine the severity of haemolytic anaemia (Hill 2006; Beutler 2007). G6PD deficiency that is common in Africa, and the Mahidol variant seen in Thailand and Malaysia, result in mild and self-limiting haemolysis that permits primaquine use even at high doses (Beutler 2007). In the Middle East and India, where over 60% of G6PD deficient individuals carry the Mediterranean variant, haemolysis due to primaquine can be severe and prolonged (Beutler 2007). Variations in the frequency and variants of G6PD enzyme deficiency occur within countries, and even within tribal communities in the same country (Bouma 1995; Tripathy 2007). This deficiency can be detected by various tests, but these may not always be affordable or feasible in many parts of the developing world.

Methaemoglobinaemia

Less commonly, primaquine treatment can result in methaemoglobinaemia. Methaemoglobin (MetHB) is a reduced form of haemoglobin that results from oxidative stress, which normally is kept under 1% within the red blood cells through normal enzymatic activity. When this level exceeds 2%, methaemoglobinaemia is diagnosed. Levels greater than 30% can lead to breathing difficulties, cardiovascular and neurological symptoms; and levels above 70% are invariably fatal. However, in usual practice this increase in methaemoglobin levels with primaquine is usually less than 20%, and symptoms are mild, self-

limited, and well-tolerated in otherwise healthy people, even at higher than normal doses (Hill 2006; Carmona-Fonseca 2009a).

Other drugs for radical cure of vivax malaria

Artemesinin-based combination therapy (ACT) is at least as effective as chloroquine in treating the blood stage *P. vivax* infection, but current drugs that constitute ACT are not effective against the liver stage of *P. vivax* (Douglas 2010; Sinclair 2011). Primaquine is still the only commercially available drug for widespread use to achieve radical cure. Two longer-acting synthetic analogues of primaquine undergoing evaluation and not yet available for widespread commercial use are tafenoquine (Walsh 2004; Kitchner 2007; Baird 2009) and bulaquine (also called elubaquine; CDRI 80/53) (Adak 2001; Krudsood 2006; Vale 2008).

How the intervention might work

Chloroquine acts on the blood stages of the parasite and also has schizonticidal activity (against the mature, infective stage of the malaria parasite). Chloroquine-sensitive *P. vivax* are suppressed by whole-blood concentrations of 70 to 90 ng/mL of chloroquine and its metabolite, mono-desethyl-chloroquine (WHO 2010b). Due to the persistence of therapeutic blood levels for 21 to 35 days, chloroquine also eliminates blood forms that emerge from hypnozoites within the first month (Baird 1997). Primaquine has some schizonticidal activity against the blood stages of vivax malaria, but is more effective against hypnozoites (liver stage) and gametocytes (only the mature sexual gametocytes) of *P. vivax*; it therefore has the potential to block the transmission of vivax malaria, if used with a drug active against blood forms of the parasite (Pukrittayakamee 2008; Baird 2009; Maguire 2010).

Differentiating recrudescence, relapse and re-infection

Following treatment of the blood stage of malaria, *P. vivax* parasites may be found in peripheral blood smears because of r*ecrudescence* (due to blood stage parasites that were not eliminated from the original infection due to a failure of chloroquine); *relapse* (due to new parasites emerging from hypnozoites due to failure of primaquine); or a *re-infection* due to new parasites from fresh mosquito bites (Baird 2009). The term*recurrence* is used for parasitaemia of unknown origin (unclear if a recrudescence, relapse, or re-infection) (Baird 2009). Recrudescence and relapse of vivax malaria may also be due to inadequate doses or drug levels of either drug, apart from drug resistance (Duarte 2001).

Primaquine treatment failure or relapse is 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). In endemic areas with a high risk of re-infection, microscopy cannot reliably differentiate new infections with the same or different strains of *P. vivax* from relapses of the original infecting strain due to failure of primaquine. Attempts to differentiate a new infection (re-infection) from a relapse of the initial infection using the polymerase chain reaction (PCR) technique, which compares parasite genotypes (gene types), were based on the assumption that parasites causing a relapse would be a sub-set of the parasites that caused the primary infection. A true relapse was confirmed when the genotypes of parasites collected on the first day of the infection were similar to those that re-appeared during the follow-up period, and a new infection when the genotypes were different (Craig 1996; Looareesuwan 1997).

However, due to the considerable genetic diversity seen in vivax infections, relapses (particularly in adults) may originate from reactivation of either the same parasite clone found in the primary blood-stage infection (homologous hypnozoites) or another genetically different clone (heterologous hypnozoites); or due to relapses from infections with multiple *P. vivax* strains (Chen 2007; Imwong 2007a; Karunaweera 2008; Orjuela-Sanchez 2009; Imwong 2012). Thus, mismatched primary and secondary parasite populations may represent either a new infection or a relapse, and this genetic diversity makes current methods of genotyping of recurrent infections with PCR in differentiating relapse from re-infections of limited utility in vivax malaria (Imwong 2007a). This is in contrast to the value of molecular techniques in falciparum malaria, where three-loci genotyping has proved useful in detecting recrudescence (Baird 2009). Increasing the number of genetic markers also increases the possibility of detecting multiple clones in vivax recurrence; and micro-satellite genotyping, using five to eight or more genetic loci, appears promising as a method to reliably differentiate relapses, recrudescence or re-infection with *P. vivax* (Imwong 2007b; Havryliuk 2009; Gunawardena 2010; Van den Eede 2010a; Van den Eede 2011; Imwong 2012). However, these methods have yet to be validated for widespread use.

Therefore, the demonstration of clearance of parasite within the first month after treatment with chloroquine, and the timing of recurrences after primaquine are used to determine the efficacy of radical cure in vivax malaria (Baird 2003a; Baird 2009). Recurrence of parasitaemia in the three to six months after primaquine is likely to be a relapse (Alves 2002; Carmona-Fonseca 2006). Differentiating a relapse from a re-infection beyond six months is more difficult, as the chances of re-infections (new primary infections) increases. This time frame may also differ in areas of high transmission, with the strain of parasite, due to seasonal variations, and due to unstable transmission patterns from year to year.

Why it is important to do this review

Although policies regarding radical cure of vivax malaria in India and Sri Lanka changed from five day to 14-day primaquine regimens (NIMR 2011) following the 2007 version of this review (Galappaththy 2007), five days of primaquine is still used in many parts of South Asia, South-East Asia, and Latin America for radical cure of vivax malaria (Leslie 2010). The main problems with the standard 14-day course of 15 mg/day of primaquine following chloroquine are:

1. Poor adherence, since people become rapidly asymptomatic after treatment with chloroquine and are poorly motivated to complete primaquine treatment (Grietens 2010);
2. The risk (perceived and real) of adverse events;
3. The lack of availability of cheap, rapid and practical tests for G6PD deficiency; and
4. Less than optimal prevention of relapses in spite of adherence to the regimen, due to primaquine resistance in some areas of the world.

Thus practitioners are still struggling to successfully implement the 14-day regimen. The alternatives suggested to the five and 14-day primaquine treatments include:

Using higher doses of primaquine (after chloroquine) for shorter periods to overcome problems with adherence: Case series studies have shown that higher doses of primaquine given over fewer

days are highly effective, well-tolerated, and equivalent to the standard 15 mg/day for 14 days regimen for radical cure in vivax malaria (Schmidt 1977; Baird 2003a; Krudsood 2008; Ebringer 2011). In order to overcome adherence problems, the national drug policy in Peru recommends a shortened regimen of seven days of primaquine at an increased daily dosage of 0.5 mg/kg/day combined with three days of chloroquine (Van den Eede 2010a).

Using higher doses of primaquine (after chloroquine) for 14 days or longer to overcome primaquine resistance: Primaquine resistance is particularly important in some countries in the Western Pacific, South-East Asia, South America, and parts of Africa (Charoenlarp 1973; Hill 2006; Baird 2009). The Centres for Disease Control (CDC 2005; CDC 2011) recommends a dose of 30 mg of primaquine for 14 days as standard therapy for radical cure of vivax malaria. This higher dose is also recommended for travellers with vivax malaria acquired in SE Asia and Oceania (Lalloo 2007; WHO 2010a; CDC 2011). It is also used in Thailand as second-line treatment (Looareesuwan 1997). In parts of Latin America, primaquine is given at 0.25 (15 mg/day) or 0.5 mg/kg (30 mg/day) for longer courses up to 28 days in people who relapse with the standard 14-day course (Carmona-Fonseca 2006). Resistance to chloroquine is less of a global problem (Naing 2010), except in Indonesia, the Solomon Islands, and Vanuatu, where ACTs are used due to extensive chloroquine resistance (WHO 2010b).

Ensuring an adequate total dose of primaquine: Alving 1960 attempted to reduce the incidence of haemolysis with primaquine treatment and demonstrated good efficacy against relapse with eight weekly doses of 45 mg (360 mg in total). Some guidelines recommend 30 mg/day (0.5 mg/kg) for 14 days, or even higher doses of 45 mg/day (0.75 mg/kg) due to concerns about relapses because of inadequate doses in heavier people (Duarte 2001; WHO 2010a). Goller 2007 demonstrated that the total dose of primaquine, as well as the dose per kilogram of body weight, affects relapse rates. The relapse risk decreased by 60% for a total adult dose of 75 mg (15 mg/day for five days); by 80% for a total primaquine regimen of 210 mg (15 mg/day for 14 days), and by 95% for regimens of 315 mg (22.5 mg/day for 14 days) and 420 mg (30 mg/day for 14 days), compared to no primaquine (Goller 2007).

Concurrent (instead of sequential) administration of chloroquine and primaquine : Since primaquine has some activity against the asexual blood stages, Alving 1955 suggested that the efficacy of primaquine in preventing relapses may be greater when chloroquine is co-administered with primaquine, than if it is administered sequentially, as is current practice. Carmona-Fonseca 2006 demonstrated the safety of giving the two drugs in combination, but more data are needed to clarify the effects of concurrent versus sequential administration of chloroquine and primaquine on recrudescence and relapse. On the other hand, others postulate that since the long half life of chloroquine suppresses early relapses of blood stage infections from activation of hypnozoites, the delayed administration of primaquine after chloroquine (administering primaquine towards the latter part of the 28 to 35 day period of chloroquine's schizonticidal activity) has a greater likelihood to effect radical cure than if used immediately after chloroquine (Baird 2009).

Chloroquine monotherapy: Some policy experts recommend the use of only chloroquine to treat blood-stage infection, in areas of low transmission; and the use of primaquine for 14 days only in those who relapse (Kshirsagar 2006). Chloroquine monotherapy is also used in some parts of the world due to fears of haemolysis with primaquine in people with G6PD deficiency (Beutler 1994).

The burden of disease caused by *P. vivax* infection and the substantial amount of money governments have to spend to treat relapses makes effective treatment a priority. With several primaquine regimens currently in use, it is important to determine the comparative effects of the different regimens.

This is an update of a Cochrane Review first published in *The Cochrane Library* in Issue 1, 2007.

OBJECTIVES

To compare alternative primaquine regimens to the recommended 14-day regimen for preventing relapses (radical cure) in people with *P.* vivax malaria treated for blood stage infection with chloroquine. We also summarize the evidence from trials comparing primaquine to no primaquine that led to the recommendation for the 14-day regimen.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) and quasi-RCTs.

Types of participants

Adults and children with microscopically confirmed asexual *P. vivax* malaria. We excluded trials that recruited people with co-infection with *P. vivax* and *P. falciparum* (mixed infections).

Types of interventions

Efficacy of alternative regimens

Intervention: primaquine (any dose or duration other than used in control group) plus chloroquine*.
Control: primaquine (15 mg/day for 14 days) plus chloroquine*.

Efficacy of regimens compared to either placebo or no treatment

Intervention: primaquine (any dose or duration) plus chloroquine*.
Control: placebo or no intervention plus chloroquine*.

*same dose in each group

Types of outcome measures

Primary outcomes

1. *P. vivax* parasitaemia detected more than 30 days after starting primaquine.
2. Serious adverse events (fatal, life threatening, or requiring hospitalization).

Secondary outcomes

1. Adverse events that result in the discontinuation of treatment.
2. Events known to occur with primaquine (cyanosis, leucopenia, methaemoglobinaemia, hypertension, cardiac arrhythmia, abdominal pain, nausea, vomiting, and haemolysis) or those due to a comparator drug used along with primaquine.
3. Other adverse events.

Search methods for identification of studies

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

Electronic searches

Databases

On 8 October 2013, Vittoria Lutje (VL), the Cochrane Infectious Diseases Review Group's Information Specialist, updated searches of the following databases: Cochrane Infectious Diseases Group Specialized Register (August 2006 to October 2013); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2013, Issue 10); MEDLINE (August 2006 to October 2013); EMBASE (August 2006 to October 2013); and LILACS (August 2006 to November 2010), using the search terms and strategies described in Table 1. PT also searched the South Asian Database of Controlled Clinical Trials (http://www.cochrane-sadcct.org/) on 4 February 2013 using the search terms "primaquine" AND "vivax", to identify trials from journals that may not be indexed in these databases,.

Conference proceedings

We have listed the details of the conference proceedings searched in Appendix 1.

Clinical Trials Registries

On 8 October 2013, VL searched the WHO International Clinical Trials Platform Search Portal (http://www.who.int/ictrp/search/en/) and the metaRegister of Controlled Trials (mRCT) (http://www.controlled-trials.com/mrct/) for ongoing trials using the terms "primaquine" AND "vivax".

Searching other resources

Researchers, organizations and pharmaceutical companies

On 18 November 2011, we contacted individual researchers working in the field, the WHO, and the pharmaceutical companies GlaxoSmithKline and Novartis for unpublished data.

Reference lists

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

Data collection and analysis

Selection of studies

We independently assessed the full reports of all potentially relevant studies for inclusion using an eligibility form based on the inclusion and exclusion criteria. We scrutinized trial reports for multiple publications from the same data set. We stated the reasons for excluding studies in the Characteristics of excluded studies table and we resolved any disagreements through discussion.

Data extraction and management

We independently extracted data using data extraction forms. We resolved any disagreements by referring to the trial report and through discussion. Where data were insufficient or missing, we contacted authors for additional information.

Where possible, we extracted data to allow an intention-to-treat analysis, in which all randomized participants should have been analyzed in the groups to which they were originally assigned. If we identified any discrepancies in the number randomized to and analyzed in each treatment group, we calculated the percentage loss to follow-up in each group and reported this information.

For dichotomous outcomes from individually randomized trials, we recorded the number of participants experiencing the event and the number analyzed in each treatment group.

For cluster-RCTs, we recorded the number of clusters in the trial, the average size of clusters and the unit of randomization (for example, household or institution), when trial authors provided this data. We also documented the statistical methods trial authors used to analyze the trial, along with details describing whether these methods adjusted for clustering or other covariates. When reported, we recorded estimates of the intra-cluster correlation (ICC) coefficient for each outcome.

Assessment of risk of bias in included studies

We independently assessed the risk of bias in the included trials on six domains: sequence generation; allocation concealment; blinding; incomplete outcome data; selective outcome reporting; and other biases. For each of these components, we assigned a judgment regarding the risk of bias as either high, low or unclear based on guidance in Higgins 2011a. We attempted to contact the trial authors if details were missing in the publications or were unclear. We resolved disagreements through consensus. We recorded our judgements and justifications in risk of bias tables for each included study and generated a risk of bias summary graph and figure. We used these judgements while grading of the overall quality of evidence for outcomes in the summary of findings tables for each comparison.

Measures of treatment effect

We compared dichotomous outcomes using the risk ratio (RR) and presented all results with their 95% confidence intervals (CIs).

Unit of analysis issues

Pooling data from cluster randomized trials (such as randomization by family or household) without accounting for intra-class correlation leads to 'unit of analysis' errors in the analysis of treatment effects, whereby P values are spuriously low and CIs are unduly narrow (Divine 1992). We extracted the adjusted point estimates and their 95% CIs from cluster randomised trials that had adjusted results for clustering. We attempted to account for clustering in trials where authors had not provided adjusted results using approximate methods described in the Cochrane Handbook, Chapter 16.3.4 and 16.3.5 (Higgins 2011b). When data were insufficient to ensure the accuracy of the assumptions used to derive the adjusted effect estimates, we extracted the data as for the individually randomized trials and compared the results in sensitivity analyses.

In order to avoid a unit of analysis error in interpreting cumulative episodes of relapses (count data) as relapse rates (Deeks 2011), we extracted data for relapse rates only (the first relapse per individual) and subgrouped them according to the duration of follow-up (more or less than six months).

Dealing with missing data

We conducted an intention-to-treat analysis in trials with no loss to follow-up and completed-case analysis for trials with incomplete follow-up. We attempted to obtain missing data from study authors. We made no assumptions about those lost to follow-up but utilised this information in assessing each study for the risk of attrition bias due to incomplete outcome data reporting; and in assessing the overall quality of evidence for each outcome in the summary of findings tables for each comparison.

Assessment of heterogeneity

We assessed heterogeneity between the trials by examining the forest plot to check for overlapping CIs, using the Chi^2 test for heterogeneity with a 10% level of significance to detect inconsistency in study results that were not due to random error (chance), and the I^2 statistic to denote the percentage of inconsistency in results due to inter-trial variability that exceeded chance. In general, we interpreted an I^2 value of 50% or greater to denote significant heterogeneity (Higgins 2003). We acknowledged that this cut-off is arbitrary. We therefore interpreted I^2 values between 0% to 40% as possibly unimportant, 30% to 60% as possibly significant, 50% to 90% as possibly substantial, and 75% to 100% as possibly considerable; depending on whether the inconsistency in results were due to differences in the direction of effects estimates between trials, rather than due to differences in the magnitude of effect estimates favouring an intervention; as well as the strength of the evidence for heterogeneity from the P value for the Chi^2 test for heterogeneity (Deeks 2011).

Assessment of reporting biases

We planned to use funnel plots to assess publication bias if we included 10 or more trials in a meta-analysis.

Data synthesis

We analyzed data using Review Manager 5.2. When data from trials using similar comparisons were available, we synthesized data using the Mantel-Haenszel method to derive pooled, weighted risk ratios in fixed-effect meta-analyses. We used the random-effects model for data synthesis when we identified heterogeneity was significant (see Assessment of heterogeneity) and we could not be explain it by subgroup analyses (see Subgroup analysis and investigation of heterogeneity).

We stratified (subgrouped) the data by length of follow-up: six months or less and greater than six months.

We combined the results of cluster-RCTs that had been adjusted for clustering with that of individually RCTs using the generic inverse variance method (Deeks 2011).

Subgroup analysis and investigation of heterogeneity

We undertook two of the planned subgroup analyses to explore potential sources of heterogeneity, for the primary outcome of *P. vivax* parasitaemia detected after day 30: based on 1) the length of follow-up: six months or less; and greater than six months, and 2) chloroquine and primaquine doses supervised versus unsupervised. We intended to explore potential sources of heterogeneity in four additional subgroup analyses (defined in Galappaththy 2007, and in the Differences between protocol and review section). We did not undertake them since heterogeneity, when noted, was explained by differences in the duration of follow-up or supervision of treatment.

Sensitivity analysis

When there were sufficient data, we undertook sensitivity analyses to investigate the robustness of the estimates for the primary outcome to the exclusion of trials at high risk of bias. We also undertook sensitivity analyses in order to explore assumptions used in cluster RCTs.

Summarising and interpreting results

We used the GRADE approach to interpret findings (Schunemann 2008). We used GRADE Profiler software (GRADE 2004), and imported data from Review Manager 5.2 to create 'Summary of findings' tables for each comparison included in this review. These tables provide information concerning the overall quality of the evidence from the trials, the magnitude of effect of the interventions examined, and the sum of available data on the primary outcome and secondary outcomes rated as important or critically important to health decision-making.

The outcomes we selected for inclusion in these tables were:

1. *P. vivax* parasitaemia detected more after than 30 days after starting primaquine;
2. Serious adverse events;
3. Adverse events leading to treatment discontinuation.

We used these summary findings to guide our conclusions and recommendations.

RESULTS

Description of studies

Results of the search

We included 15 trials described in 18 reports in quantitative synthesis (meta-analysis) in this review. No trials currently await classification (Figure 1). We identified 64 reports, of which we screened 53 abstracts for eligibility after removing duplicates and irrelevant reports. We obtained and scrutinized 24 potentially relevant full text articles. We included 10 trials from 14 reports in this review update. When we added these to the nine trials (described in eight reports) from the 2007 review, we included a total of 19 trials from 22 reports in the qualitative synthesis of this review update. Of these trials, four were on-going trials that are described in Characteristics of ongoing studies. Excluded studies are detailed in the Characteristics of excluded studies section.

Figure 1. Study flow diagram: 2013 review update

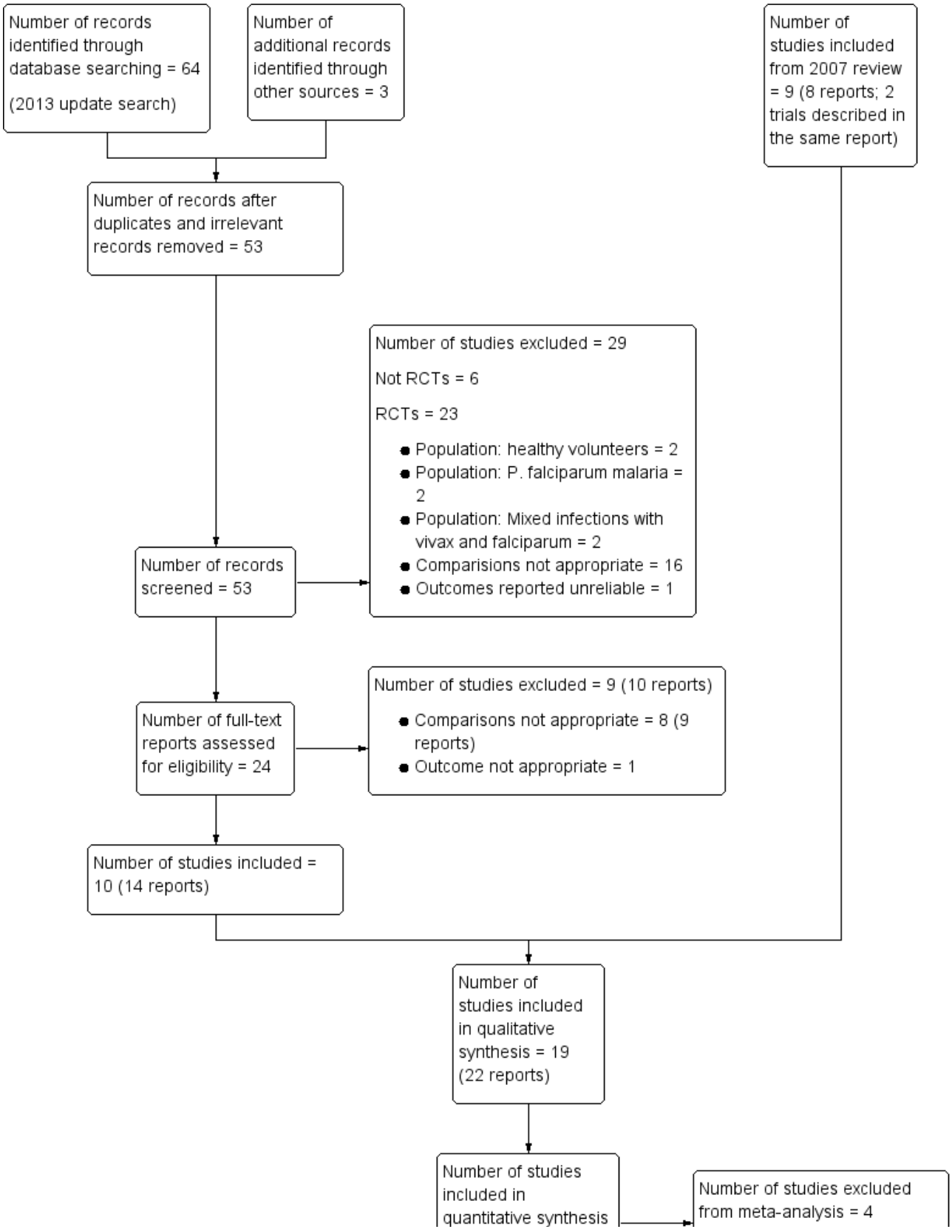
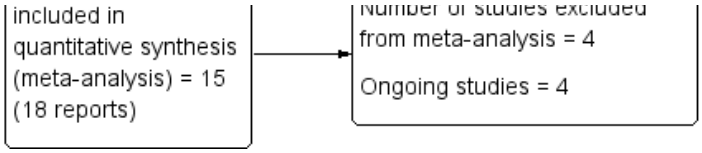


Figure 1. (Continued)



Included studies

We have described these 15 trials in more detail in the Characteristics of included studies table. Rowland 1999a and Rowland 1999b were described in the same publication.

This 2013 update has, in addition to the previous addition, six new trials, conducted between 1997 to 2012, adding 4377 adults and children (aged older than one year) from Africa (Ethiopia, one trial), Asia (India, five trials; Pakistan, four trials; Thailand, two trials), South America (Brazil, one trial; and Columbia, two trials). .

Design

Of the 15 trials, one was a cluster RCT(Leslie 2004) that randomized households, and another used mixed cluster and individual randomization (Leslie 2008). One of the other 13 trials that individually randomized was a quasi-RCT (Yeshiwondim 2010). Seven trials had multiple treatment arms, ranging from three (Pukrittayakamee 1994; Gogtay 1999; Leslie 2004; Alvarez 2006; Kim 2012), and four (Carmona-Fonseca 2009) to six (Walsh 2004) intervention arms. We did not include some of the trial arms in this review as they were not relevant.

Interventions

All the included trials treated the blood stage of the parasite with identical chloroquine courses in the treatment arms.

Primaquine (any dose or duration) versus the standard regimen of primaquine (15 mg/day for 14 days)

Six trials had treatment arms that compared different dosing schedules of primaquine versus the standard primaquine regimen:

- Two trials compared three days of primaquine to standard primaquine treatment (Alvarez 2006; Carmona-Fonseca 2009);
- Three trials compared five days of primaquine to the standard primaquine regimen (Gogtay 1999; Villalobos 2000; Kim 2012);
- One trial compared seven days of primaquine to standard primaquine treatment (Alvarez 2006);
- One trial compared primaquine (45 mg) given weekly for eight weeks, to 14 days of primaquine given at a higher dose than is standard (22.5 mg) daily(Leslie 2008).

Primaquine (any dose or duration) compared to no primaquine

Fourteen trials compared participants receiving primaquine with placebo or no anti-relapse treatment:

1. Four trials examined primaquine given for five days (Gogtay 1999; Rowland 1999b; Yadav 2002; Kim 2012);
2. Ten trials evaluated primaquine given for 14 days (Gogtay 1999; Pukrittayakamee 1994; Rowland 1999a; Rajgor 2003; Leslie 2004; Walsh 2004; Leslie 2008; Yeshiwondim 2010; Kim 2012; Ganguly 2013).

Dosing regimens and supervision

All trials used the standard primaquine 0.25 mg/kg (15 mg per day) dosing regimen, except Leslie 2008 that used a higher dose of 22.5 mg primaquine base (0.5 mg/kg) in the 14-day primaquine arm and 45 mg/week (0.75 mg/kg) in the once-weekly primaquine arm. The total dose of primaquine delivered in different arms of the trials ranged from 45 mg (Alvarez 2006; Carmona-Fonseca 2009); 75 mg (Gogtay 1999; Rowland 1999b; Villalobos 2000; Yadav 2002; Kim 2012); 105 mg (Alvarez 2006); 210 mg (Pukrittayakamee 1994; Gogtay 1999; Rowland 1999a; Rowland 1999b; Villalobos 2000; Rajgor 2003; Leslie 2004; Walsh 2004; Carmona-Fonseca 2009; Yeshiwondim 2010; Kim 2012; Ganguly 2013); to 315 mg in the 14-day daily primaquine arm; and 360 mg in the eight-week primaquine arm (Leslie 2008).

Two trials from the same region in Columbia initiated primaquine treatment concurrently with chloroquine (Alvarez 2006; Carmona-Fonseca 2009). One trial from Brazil (Villalobos 2000) compared five days of primaquine given concurrently with chloroquine versus the standard sequential administration of three days of chloroquine followed by 14 days of primaquine. In Yeshiwondim 2010 (Ethiopia), trial authors aimed to compare 14 days of primaquine versus chloroquine alone in treating acute symptoms, but they gave primaquine treatment for 14 days from day 29 in the chloroquine-only arm to prevent relapses. We thus directly studied (as suggested by Baird 2009), the effects of delayed sequential administration of primaquine following treatment of the blood-stage infection with chloroquine, compared with the control arm which was given the standard sequential regimen 14 days of primaquine immediately after three days of chloroquine treatment.

Eleven trials ensured compliance by directly supervising treatment in both arms for all participants. Leslie 2004 directly compared the effects of unsupervised and supervised 14 days of primaquine treatments (although we only used data from the unsupervised arm in meta-analysis) with a placebo arm. Ganguly 2013 supervised chloroquine and the first seven of the 14-day primaquine regimen. Three studies only supervised the administration of chloroquine and not of primaquine (Yadav 2002; Yeshiwondim 2010; Kim 2012); trial authors did not describe any methods to ascertain adherence.

Follow-up

Trials varied the duration of follow-up and used 42 days (Ganguly 2013); two months (Pukrittayakamee 1994); three months (Villalobos 2000; Walsh 2004); four months (Yeshiwondim 2010); six months (Gogtay 1999; Rajgor 2003; Alvarez 2006); nine months (Leslie 2004; Leslie 2008); 12 months (Rowland 1999a; Rowland 1999b; Yadav 2002); and 15 months (Kim 2012) follow-up. We could not ascertain from some of the trials with shorter follow-up periods whether the duration of follow-up was from initiation or end of treatment. We subgrouped the results according to duration of follow-up of six months or less, and greater than six months; this enabled us to evaluate the extent that relapses and re-infections contributed to vivax parasitaemia at follow-up.

Cluster RCTs

Leslie 2004 used cluster randomization of families but presented results for randomized individuals adjusted for clustering and also reported the number of clusters in each arm. For this update, since we chose to express results using relative risks rather than odds ratios (as in Galappaththy 2007), we calculated and combined the log of the risk ratio (adjusted for clustering) with its standard error with log risk ratios and standard errors computed for the other individually randomized trials using the generic inverse variance method in Review Manager 5.2.

Leslie 2008 also used cluster randomization by household in two of the study sites (refugee camps at Baghicha and Khagan villages) and used individual randomization in a third site (Adizai) that was added subsequently after an unscheduled interim analysis due to low rates of enrolment downsized the sample size estimate. The number of participants they randomized to each arm of this three-armed trial were unequal with the majority recruited from Adizai (50%); and with Adizai accounting for the most treatment failures. The trial authors presented odds ratios, adjusted for clustering, village, age and sex; and we could not obtain intra-cluster coefficient coefficients from the report or the authors. We calculated the log of the risk ratio with its standard error for the primary outcome assessed beyond six months, adjusted for clustering using the approximate methods described in Higgins 2011b. We also calculated and combined similar measures from the other relevant trials in meta-analysis using the generic inverse variance method. Leslie 2008 did not report the number of participants randomized in clusters (families), and the number of clusters lost to follow-up. Unequal rates of completion in the arms with cluster randomization can introduce biases due to loss of clusters (households). We, therefore, used the unadjusted relapse rates presented in the trial report in sensitivity analyses (ignoring the cluster effect, since participants from Adizai that constituted the majority of trial participants were individually randomized) to compare the robustness of the results with data that were adjusted for clustering.

Funding

One trial was partly funded by a drug company (Walsh 2004). The remainder were funded by academic institutions, local governments, international aid agencies, charitable donors, or by the UN/WHO.

Excluded studies

We excluded 65 studies (67 reports), including those excluded from the previous version of this review, and we listed the reasons for exclusion in the Characteristics of excluded studies. Of these excluded trials, 26 were not RCTs. Of the 39 that were RCTs, four randomized healthy volunteers, and five randomized people with falciparum malaria or with mixed vivax and falciparum infections. The remainder had comparisons that did not fulfil the inclusion and exclusion criteria.

Risk of bias in included studies

Most trials were at low risk of bias in many of the six domains we assessed (Figure 2). See Figure 3 for a summary of the judgements of the risk of bias for each domain in each of the included trials.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

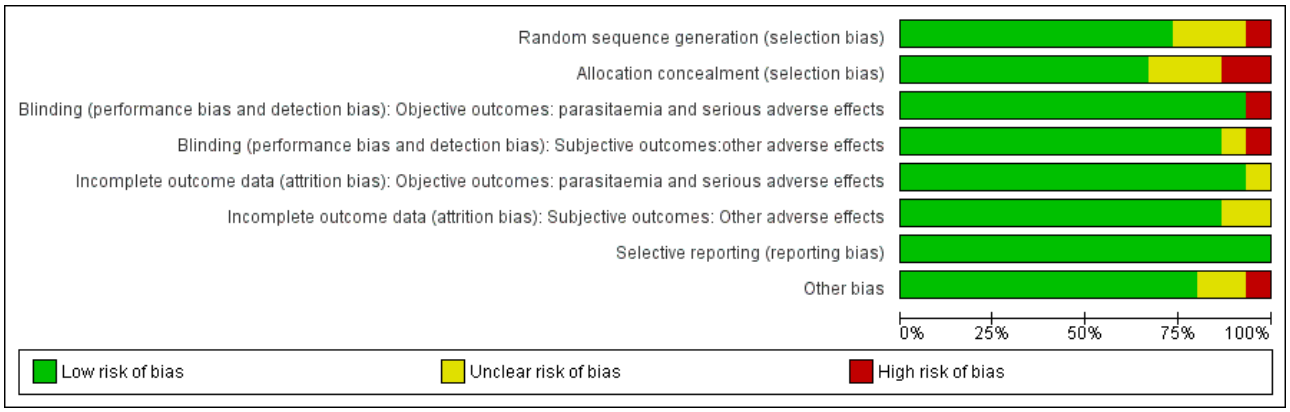


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

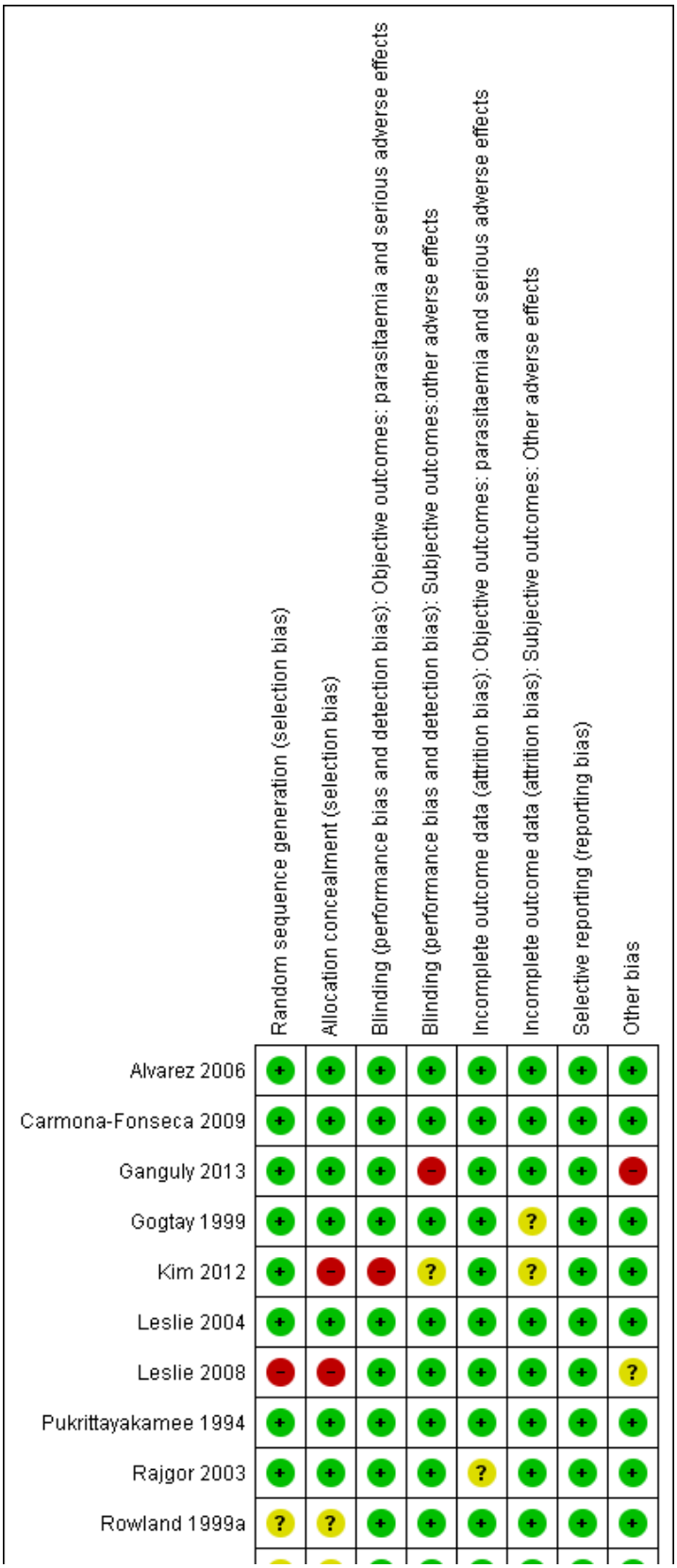
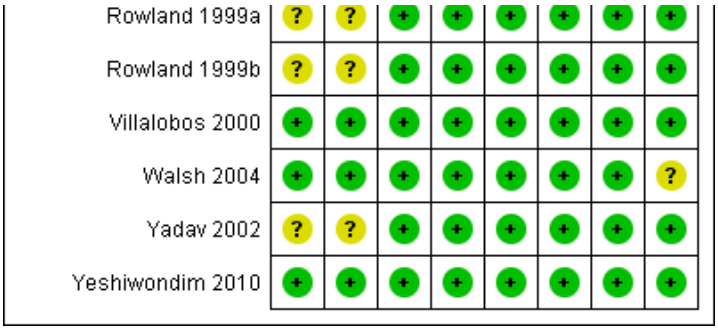


Figure 3. (Continued)



Allocation

Leslie 2008 was at high risk of selection bias due to the mixed methods trial authors used to recruiting participants, with resultant imbalances in the proportions randomized to each site, and in baseline prognostic variables; as well as site-specific higher relapse rates. Kim 2012 was at high risk of bias for allocation concealment as the unequal numbers in the two primaquine arms were not explained by the methods of random sequence generation and allocation supposedly used. This suggested that allocation according to the randomization sequence was compromised; and although the presented baseline variables did not reveal serious imbalances across treatment arms, we could not rule out the risk of bias due to residual confounding. Rowland 1999a; Rowland 1999b; Yadav 2002 were at unclear risk of selection bias since trial authors provided insufficient details in their trial reports. Although Yeshiwondim 2010 used quasi-random methods to recruit participants, an extensive list of baseline demographic, clinical, parasitological, and biochemical parameters were well-balanced between intervention arms, indicating a low risk of selection bias. Ganguly 2013 did not describe the methods used to ensure allocation concealment, but described balanced prognostic variables at baseline in the intervention arms.

Blinding

All but one of the included trials (many open-label) were at low risk of performance and detection bias for objectively determined outcomes. Kim 2012 was at high risk of outcome detection bias for efficacy outcomes and for serious adverse events because the trial authors reported that those allotted unsupervised primaquine had probably not adhered to treatment. This raises the possibility of unreliable effect estimates, even if the outcomes were objective.

Incomplete outcome data

Twelve trials included between 90% and 100% of randomized participants in the final analyses. Pukrittayakamee 1994 included 71%, and Rajgor 2003 followed up 75% of participants. Gogtay 1999 reported results for 76% of randomized participants who completed six months follow-up, from a trial that appears to have been terminated early. Walsh 2004 reported results for 22/25 participants (88%) in the two arms that we included in this review. None of the trials with less than 90% follow-up had significantly different rates of trial completion in the intervention and control arms, and hence were at low risk of attrition bias.

Selective reporting

Although only Leslie 2008 and Ganguly 2013 were prospectively registered, and only Kim 2012 (that was retrospectively registered) and Leslie 2008 had available trial protocols, all trials reported all pre-stated outcomes and we did not detect instances of selective reporting.

Other potential sources of bias

It was unclear whether the interim analysis and revised sample size estimates in Leslie 2008 introduced biases other than the high risk of selection bias. Unequal rates of completion in treatment arms of cluster randomized trials can introduce biases due to loss of clusters (households); we were unable to obtain the data needed to evaluate this from the report. Walsh 2004 was also unclear for other biases as it was partly industry-funded. Trial authors did not clarify the role of the industry sponsor in the trial report. Ganguly 2013 had a follow-up of only 42 days, and effectively 14 days where relapses that were not eliminated by chloroquine could be detected. This trial was biased and could not detect further early and late relapses after 42 days.

Effects of interventions

See: **Summary of findings for the main comparison** Primaquine five days compared to 14 days; **Summary of findings 2** Primaquine three days compared to 14 days; **Summary of findings 3** Primaquine seven days compared to 14 days; **Summary of findings 4** Primaquine (weekly for eight weeks) compared to daily primaquine for 14 days; **Summary of findings 5** Primaquine for five days; **Summary of findings 6** Primaquine for 14 days

Alternative regimens versus 14 days primaquine

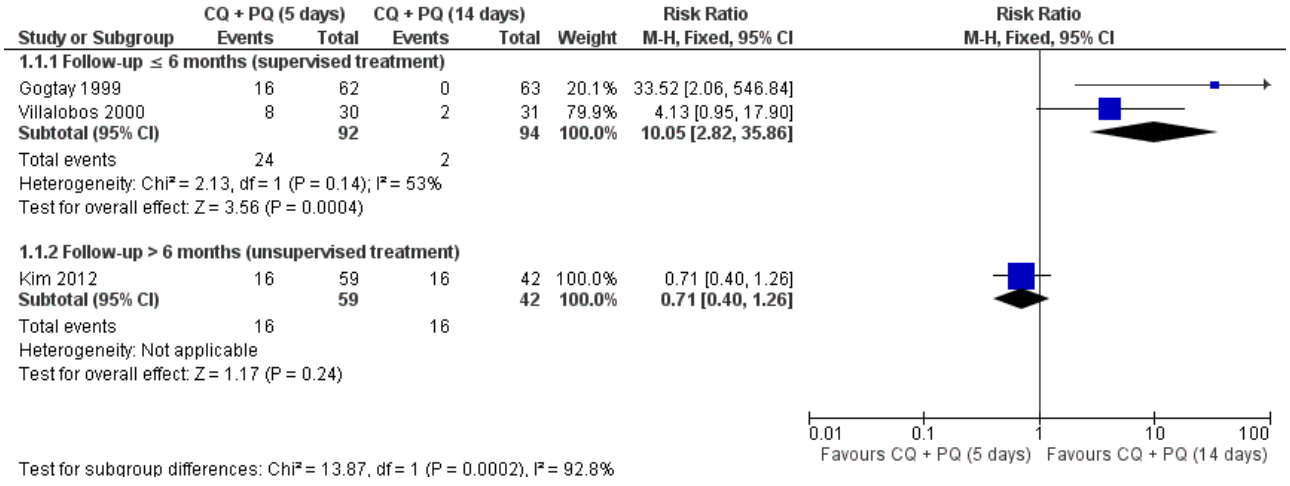
Shorter daily regimens (five trials)

We first evaluated the effects of the widely used five-day primaquine regimen (75 mg total dose) compared with the standard regimen (15 mg/day for 14 days; 210 mg in total). Three trials (Gogtay 1999; Villalobos 2000; Kim 2012) included 287 adults and children (aged older than three years). Gogtay 1999 was conducted in a hospital in Mumbai, India, where malaria transmission was stable and low, treatments were supervised, and participants were followed up for six months. Kim 2012 included outpatients attending a specialist malaria treatment centre in Kolkota, India. Chloroquine was supervised, and only the first dose of primaquine was supervised; follow-up was for fifteen months. Villalobos 2000 included outpatients in the Western Amazon region of Brazil, treatments were supervised, and participants were

followed up for three months. The trials used standard dosing (0.25 mg/kg) for primaquine; but Villalobos 2000 used five days of chloroquine given concurrently with five days of primaquine, compared with the standard regimen of three days of chloroquine followed by 14 days of primaquine.

Relapse was common over the first six months with five days of supervised primaquine: 25% (16/62) in Gogtay 1999, and 27% (8/30) in Villalobos 2000, with no failures in Gogtay 1999 and two in Villalobos 2000 in the supervised 14-day primaquine arm (RR 10.05, 95% CI 2.82 to 35.86, I^2 = 53%; two trials, 186 participants; Figure 4; Analysis 1.1). In Kim 2012, 27% (16/59) of participants given five days of unsupervised primaquine and 38% (16/42) given 14 days of unsupervised primaquine experienced a recurrence over 15 months of follow-up. This difference was not statistically significant (Figure 4; Analysis 1.1), and the trial authors surmised that the lack of benefit seen with 14-day primaquine was most likely due to poor adherence to the unsupervised 14-day primaquine regimen.

Figure 4. Forest plot of comparison: 1 Primaquine: 5 days versus 14 days, outcome: 1.1 *P. vivax* parasitaemia > 30 days after starting primaquine.



We also included trials that evaluated three day regimens (two trials) and seven day regimens (one trial), both showing higher numbers of relapses in the shorter courses. For the three day regimen, we included two trials conducted in the same unstable malaria transmission area in Colombia on adults and children. Trial authors administered chloroquine and primaquine concurrently in these trials in both intervention arms. One trial (Alvarez 2006) administered a total dose of 45 mg primaquine in the three-day arm versus 210 mg in 14-day primaquine arm; and Carmona-Fonseca 2009 administered 210 mg of primaquine for three days at a dose of 3.5 mg/kg (or 1.17 mg/kg/day), compared to the 0.25 mg/kg/day used with the standard 14-day regimen in both trials. Relapse rates were significantly lower with 14-day primaquine in both trials (53% versus 17%) over 3 to 6 months of follow-up (RR 3.18, 95% CI 2.1 to 4.81; two trials, 262 participants; Analysis 2.1).

For the seven day regimen, Alvarez 2006 examined seven days of primaquine (105 mg) given concurrently with chloroquine. Relapse rates were 42% with 7-day primaquine versus 19% with 14-day primaquine at two months follow-up (RR 2.24, 95% CI 1.24 to 4.03; one trial, 126 participants; Analysis 3.1).

For adverse events, none of the included trials reported severe or treatment limiting adverse events; and none provided numerical data on non-serious adverse events. Gogtay 1999 reported that nausea and skin rash were mild and infrequent; and Villalobos 2000 reported frequent, mild, transient headache, vertigo, abdominal pain, and nausea. The other trials reported that primaquine regimens were well-tolerated.

Sensitivity analysis was not indicated, as three of the trials were at low risk of bias; and we explained the heterogeneity detected when the results of Kim 2012 (that was at high risk of bias) were pooled with the results of Gogtay 1999 and Villalobos 2000 by follow-up duration and whether treatments were supervised or not.

Weekly primaquine (one trial)

Leslie 2008 compared weekly supervised primaquine (45 mg/week; 360 mg in total) for eight weeks with self-administered primaquine (22.5 mg/kg) for 14 days (315 mg in total) among refugees in an area of unstable, seasonal, low malaria transmission near the Pakistan-Afganistan border. Relapses were infrequent over 11 months follow-up: 4/74 (5.4%) in the weekly regimen, and 1/55 (1.8%) in the self-treated regime; Analysis 4.1).

Trial authors did not report any adverse effects, except one person with G6PD directly allocated to the 8-week primaquine arm who experienced a transient and mild drop in hematocrit but otherwise tolerated treatment well.

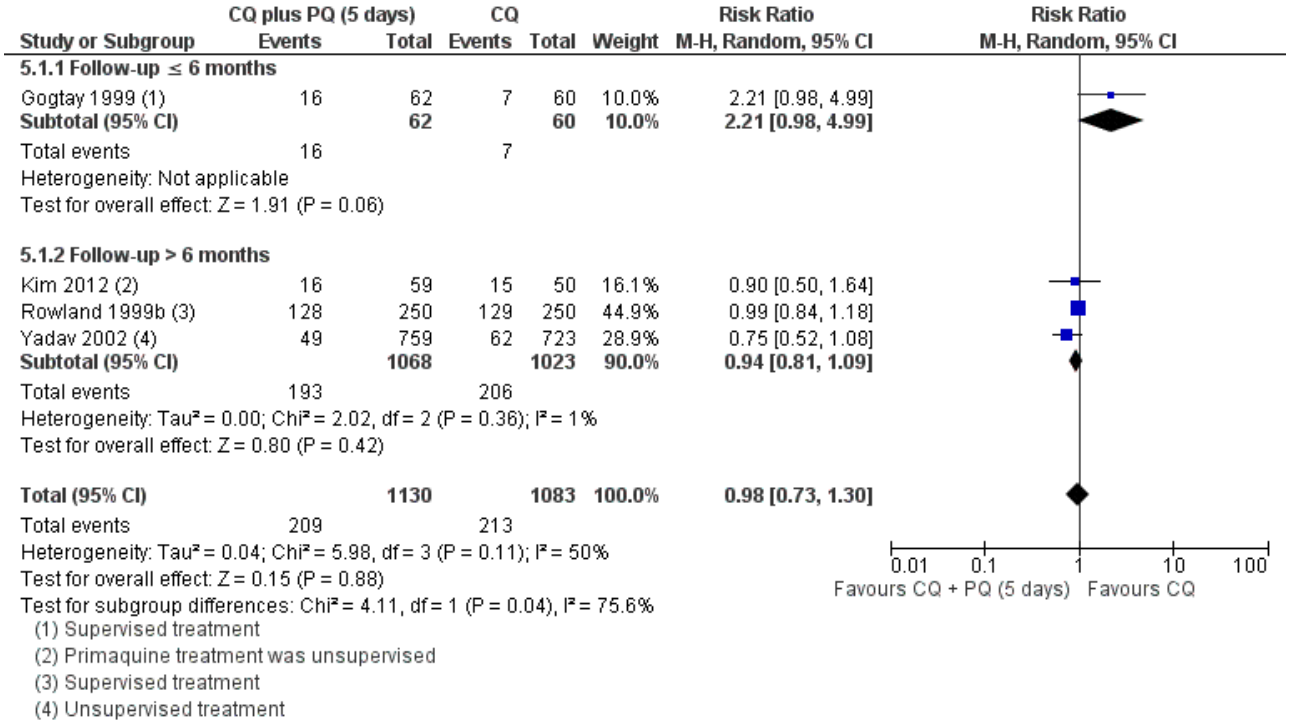
Any primaquine regimens compared to no intervention or placebo

Five days primaquine (four trials)

Four trials compared 5-day primaquine (75 mg primaquine) versus placebo and included 2213 adults and children. Relapse was more frequent with five days of primaquine compared to placebo over six months in one small trial conducted in a hospital in Mumbai (Gogtay 1999) with follow-up for six months (25% versus 12%, 122 participants; Analysis 5.1), but this difference was not statistically significant. Relapse was little different in the two arms in three trials followed up over 12 to 15 months (18% versus 20%; 2091 participants; Analysis 5.1), one of which was conducted in a mostly

urban population in Kolkata, India (Kim 2012), the other in a refugee camp in Afghanistan (Rowland 1999b), and the third in tribal villages in Orissa, India (Yadav 2002). The pooled results for relapse from the three trials did not significantly differ for 5-day primaquine or no primaquine (18% versus 19%; I^2 = 50%; 2213 participants; Figure 5, Analysis 5.1).

Figure 5. Primaquine (5 days) plus chloroquine versus chloroquine: *P. vivax* parasitaemia detected > 30 days after starting primaquine.

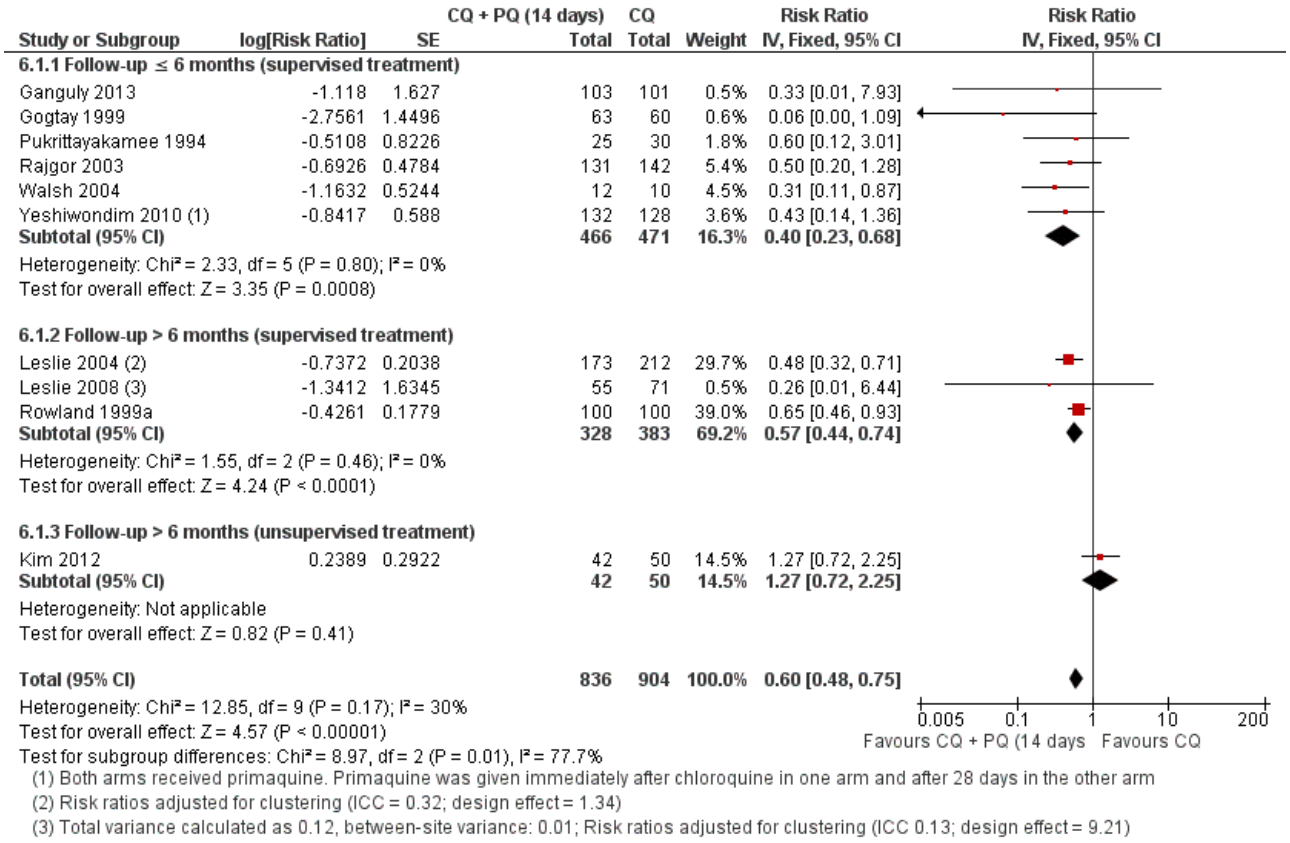


Fourteen days primaquine (ten trials)

Ten trials evaluated primaquine given for 14 days versus placebo and randomized 1740 adults and children. Four were conducted in India: two in the same hospital in Mumbai (Gogtay 1999; Rajgor 2003) with six months of follow-up and the other two included outpatients from the same centre in Kolkota (Kim 2012; Ganguly 2013), and followed up participants for 42 days from treatment initiation (Ganguly 2013), to 15 months after primaquine (Kim 2012). Two trials were in refugee camps in Pakistan in an area with unstable malaria transmission, one (Leslie 2004) during a period of high transmission, and the other (Leslie 2008) when transmission was low; follow-up was for nine months. Two trials were conducted in Bangkok, Thailand (Pukrittayakamee 1994; Walsh 2004), where there is no local transmission of malaria; follow-up was for two months. One trial was in an area of seasonal, unstable malaria transmission in Ethiopia (Yeshiwondim 2010), with four months follow-up. Eight trials used standard 15 mg/day primaquine dosing with a total dose of 210 mg, but in Leslie 2008, the total dose in adults was (22.5 mg/day) 315 mg in the 14-day primaquine arm. In Yeshiwondim 2010, trial authors gave primaquine treatment for 14 days from day 29 in the chloroquine arm, compared to the standard sequential dosing in the chloroquine and primaquine arm. Kim 2012 was the only trial where trial authors did not supervise primaquine treatments and did not monitor adherence. Two trials (Gogtay 1999; Rajgor 2003) supervised the first seven days of primaquine treatment and checked adherence for the remaining seven days of primaquine. The remaining trials supervised the 14 days of primaquine treatment.

With 14-day primaquine, fewer people relapsed than with placebo over six weeks to 15 months of follow-up (9% versus 18%; RR 0.60; 95% CI 0.48 to 0.75; 10 trials, 1740 participants; Figure 6, Analysis 6.1). We consistently observed this benefit for 14-day primaquine in the subgroup of trials of supervised primaquine with follow-up from seven weeks to six months (six trials, 937 participants), and beyond six months to one year (three trials, 711 participants; Analysis 6.1). The one trial of unsupervised primaquine (Kim 2012) failed to show any benefit for 14-day primaquine over placebo (92 participants; Analysis 6.1), which the trial authors presumed was due to non-adherence to primaquine.

Figure 6. Forest plot of comparison: 6 Chloroquine plus primaquine (14 days) versus chloroquine, outcome: 6.1 *P. vivax* parasitaemia detected > 30 days after starting primaquine.



Sensitivity analysis using data unadjusted for clustering in Leslie 2008, since the majority of participants were individually randomized, did not alter these estimates (RR 0.53, 0.42, 0.67). Three trials at risk of bias (Leslie 2008; Kim 2012; Ganguly 2013) contributed 15.5% weight to the pooled effect estimates, and their removal from further sensitivity analysis also did not alter the results appreciably (RR 0.53, 95% CI 0.42 to 0.68; seven trials, 1318 participants).

For adverse effects, no serious adverse events were reported in any of the trials. Only one trial withdrew one person because of adverse events (Yeshiwondim 2010) but did not provide any details. Two trials (Walsh 2004; Ganguly 2013) reported headache, nausea, vomiting, abdominal pain, diarrhoea, and itching in both treatment arms which were mild and transient. Walsh 2004 measured methaemoglobin levels, and rises were mild and also transient. The few patients in Rowland 1999a and Leslie 2008 with G6PD deficiency reportedly tolerated the 14 days of primaquine treatment well.

DISCUSSION

Summary of main results

Efficacy

In evaluating alternative regimens of primaquine for people with vivax malaria treated with chloroquine: 14 days of primaquine (0.25 mg/kg/day; 210 mg total dose) is probably more effective than shorter primaquine-containing regimens (total dose 45 mg to 105 mg) (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3)

Weekly primaquine for eight supervised doses (45 mg; 360 mg in total) and 14 days of primaquine (22.5 mg/kg; 315 mg in total) were effective in reducing relapse but the weekly regimen needs further evaluation to show it is at least as good as 14-day primaquine (Summary of findings 4).

In trials of people with vivax malaria treated with chloroquine, and randomized to primaquine or placebo or no primaquine, five days of primaquine (0.25 mg/kg/day; 75 mg total dose) was associated with high relapse rates similar to relapse rates in those not given primaquine (Summary of findings 5). Relapse rates were lower in people given 14 days of primaquine (0.25 mg/kg/day; 210 mg in total) compared to those given no primaquine (Summary of findings 6).

Safety

Most trials excluded people with G6PD deficiency and none of the primaquine dosing regimens (45 mg to 325 mg over three to 14 days and 360 mg given weekly over eight weeks) in the 15 included trials that treated 4377 adults and children were reported to cause serious or treatment limiting adverse events. The few people with G6PD deficiency included in some of the trials, and exposed to primaquine, did not experience serious or non-serious adverse events. Other adverse events were reportedly mild and

transient. Elevated methaemoglobin levels, where measured, were not associated with symptoms of methaemoglobinaemia.

Overall completeness and applicability of evidence

Completeness

We identified six additional trials including one (Alvarez 2006) published before the updated 2007 review, but after the date of our last search in August 2006. None of the included trials compared higher doses of primaquine (0.5 mg/kg or 30 mg/day; 0.75 mg/kg or 45 mg per day) given for seven or 14 days; or the standard 0.25 mg/kg (15 mg/day) dose of primaquine given for periods longer than 14 days; with the standard 14-day primaquine dosing regimen. None of the included trials reported infection with temperate strains of *P. vivax.*

The review did not specifically address the issues of treating mixed vivax and falciparum infections; preventing transmissibility of vivax infections to mosquitoes by the gametocidal activity of interventions, or directly evaluating the safety of different primaquine regimens in people with and without G6PD deficiency. We did not find any trials comparing alternative primaquine dosing regimens in people from regions with widespread resistance to the standard 0.25 mg per kg body weight of primaquine, and where other regimens are standard practice.

Applicability

The trials in this review included children and adults with confirmed vivax mono-infections and evaluated a variety of primaquine dosing schedules that provide data to inform policy and practice. Most trials excluded people with G6PD deficiency.

Intermittent primaquine treatment requires further evaluation

Intermittent dosing of primaquine at higher doses given at weekly intervals for eight weeks, after three days of chloroquine treatment, may be an effective alternative to the standard 14-day primaquine regimen in reducing relapses, but this needs evaluation in additional trials, powered to demonstrate equivalence or non-inferiority, compared to the standard 14-day primaquine regimen. Intermittent dosing is postulated to be safer in people with G6PD deficiency, but this also needs further evaluation in larger numbers of people with this deficiency.

The total dose of primaquine is important

The observations of Alving 1960 and Goller 2007 (see: Why it is important to do this review), and more recent observational data (John 2012) that total doses of primaquine of 210 mg or more result in greater reductions in relapse than with lower total doses of primaquine, were also evident in the randomized comparisons in this review. Significantly lower relapse occurred with primaquine doses of 210 mg or more, compared to primaquine given at lower doses. We presented relapse in the treatment arms of the trials in this review, grouped by the total dose and duration of primaquine, in Table 2. The comparisons of relapse are confounded by variable rates of vivax transmission between trials; but on average relapse was less common in the treatment arms where primaquine was given at a total dose of 210 mg or more, compared to the treatment arms where the total dose of primaquine was lower.

The duration over which the total dose of primaquine was delivered also appeared to influence relapse (Table 2). Carmona-Fonseca 2009 directly compared the efficacy of the same total dose of primaquine in people randomized to shorter versus longer courses of treatment. Relapse was higher in those randomized to 210 mg of primaquine administered over three days, compared to those randomized to 210 mg of primaquine over 14 days (57% versus 14%, RR 3.9, 95% CI 2.1 to 7.1; one trial, 133 participants). Trial authors administered primaquine and chloroquine concurrently in the shorter three-day treatment arm and sequentially in the longer treatment arm of this trial (see next section below).

Concurrent versus sequential administration of chloroquine and primaquine

Primaquine usually follows on from chloroquine treatment. As discussed in the background section "Why it is important to do this review", in some parts of the world (primarily in Latin America), primaquine is co-administered with chloroquine rather than sequentially after chloroquine. This is based on the premise that primaquine has some activity against the asexual blood stages, and the efficacy of primaquine in preventing relapses may be greater with the concurrent, rather than sequential, administration of chloroquine and primaquine.

Three trials in this review used concurrent chloroquine and primaquine in one or all their intervention arms. Villalobos 2000 (Brazil) directly compared the concurrent administration of chloroquine and primaquine, with each given for five days, versus the standard sequential administration of chloroquine for three days followed by primaquine for 14 days. Relapse was less frequent in the arm given sequential treatment of chloroquine and primaquine (3% versus 26%), but this result was confounded by the lower total dose of primaquine in the shorter concurrent treatment arm (105 mg) compared to the 210 total dose of primaquine in the longer sequential treatment arm.

Two trials conducted in Columbia (Alvarez 2006; Carmona-Fonseca 2009) used concurrent chloroquine and primaquine in all intervention arms. However Alvarez 2006 used different total doses of primaquine in the three arms (210 mg, 105 mg, and 45 mg), again preventing unconfounded inferences of the efficacy of concurrent administration of the two drugs. As discussed previously, Carmona-Fonseca 2009 compared a total dose of 210 mg of primaquine co-administered with chloroquine over three days versus primaquine 210 mg co-administered with chloroquine for the first three days, and continued until day 14. Relapse was significantly less frequent with 210 mg of primaquine given for 14 days, providing limited direct evidence to suggest that the co-administration of primaquine with chloroquine may be less important than an adequate total dose of primaquine, given for a longer period after chloroquine, to eliminate emerging hypnozoites.

Another suggestion discussed in the background section to improve the efficacy of primaquine in preventing relapses is to delay the sequential administration of primaquine towards the latter part of the 28 to 35 day period of chloroquine's schizonticidal activity in order to increase the likelihood of radical cure, than if used immediately after chloroquine (Baird 2009). In Yeshiwondim 2010 (Ethiopia), relapse was more common in the treatment arm that delayed the sequential administration of 14-day primaquine (210 mg total dose) after chloroquine to commence at day 28, than in the comparator arm, where 14-day primaquine (210 mg total dose) was given sequentially but immediately after chloroquine (7% versus 3%). However, this difference was not

statistically significant, possibly because this trial was primarily powered to demonstrate the efficacy of chloroquine against blood stage infections, and not the relative benefits of the delayed versus standard sequential administration of chloroquine and primaquine.

This review found evidence only to support the standard sequential administration of chloroquine followed by primaquine given for at least 14 days at a total dose of 210 mg or more of primaquine, or weekly treatment delivering 360 mg of primaquine.

Differentiating relapses from re-infections may not be critical for reducing transmission of vivax malaria

It is not possible to reliably differentiate vivax relapses from re-infections in endemic areas with currently available molecular techniques, and though newer techniques show promise, they are not available for routine use. However, the data in this review show that the 14-day and weekly primaquine regimens are effective in the first six months of follow-up in people living in endemic areas, as well as in trials with follow-up at nine months to one year. Since hypnozoites form the major source of recurrent malaria episodes in many parts of the world where vivax malaria is a burden, widespread use of 14 days of primaquine has the potential to effectively reduce the hypnozoite pool and reduce transmission, and the burden of vivax malaria; provided concerns about poor compliance and safety in people with G6PD deficiency can be addressed.

Ensuring adherence to 14-day primaquine regimens is important

Assessing adherence to primaquine was not a primary objective of this review, but is an important issue to consider if governments and national programmes are to continue to endorse, or be encouraged to switch to, the 14-day regimen. All trials, apart from Kim 2012, Yadav 2002 and Yeshiwondim 2010, provided supervised primaquine, and the efficacy of 14 days of primaquine was seemingly not influenced in Yadav 2002, and Yeshiwondim 2010 by the provision of supervision. The authors of Kim 2012 believe that people given 14-day primaquine were likely to have not been adherent, although they did not report the methods to monitor adherence, the proportions non-adherent, or the extent of non-adherence. Only Leslie 2004 formally evaluated the effects of supervised treatments, where in two of the three arms, 346 participants given chloroquine plus 14-days of primaquine were randomized equally to supervised therapy or unsupervised therapy. Efficacy did not significantly differ between supervised and non-supervised primaquine arms.

Although poor adherence with primaquine is reported as a major cause of relapse (Baird 2004; Hill 2006), recommending 14 days of primaquine should not be dismissed on grounds of adherence alone. Equally important are concerns expressed by some malaria experts that shorter courses of ineffective regimens could accelerate the selection of primaquine-resistant strains (Collins 1996; Price 2011). Leslie 2004 demonstrated that, at least in the context of an RCT, simple measures such as health education messages were sufficient to improve adherence. If these measures were routinely employed in malaria control programmes, the effective life of this unique anti-malarial drug could be prolonged. Ensuring adherence for 14-day primaquine may not be as difficult as with long-term interventions, since improving short-term adherence is relatively successful with a variety of simple interventions (Haynes 2008). The evidence specific to improving adherence in malaria, such as unit-dose packaging supported by educational interventions, though promising in general (Qingjun 1998), requires further evaluation (Orton 2005).

In contrast to the conclusions of Leslie 2004, two trials done along the Thai-Myanmar border demonstrated superior efficacy with the 14-day primaquine regimen following chloroquine in people randomized to receive primaquine by directly observed treatment (DOT) versus self-administered treatment (Takeuchi 2010; Manneeboonyang 2011). Leslie 2004 conducted the trial in the relatively structured confines of a refugee camp where geographical mobility is likely to have been less than in the Thai-Myanmar trials, and where health services were provided by a single agency. These conditions differ from the usual situations where vivax malaria is treated.

Primaquine and G6PD deficiency

Most of the trials had G6PD deficiency as a criterion for exclusion, so it is not surprising that treatment limiting adverse events were uncommon in the 1209 people given the 14-day regimen. Leslie 2008 included people with G6PD deficiency in a safety arm given eight weekly doses of 45 mg primaquine base, but reported that only one person with the deficiency was in this safety arm. This trial was conducted in an area of Pakistan where primaquine was not used routinely due to fears of haemolysis given the estimated 15% to 17% prevalence of G6PD deficiency (Beutler 1994). The data from Leslie 2008 suggest that these fears are based on overestimates of the prevalence and the relevance of G6PD deficiency to relapse prevention with primaquine. Observational data suggest that haemolytic anaemia due to G6PD deficiency following exposure to primaquine among people infected with *P. vivax* might be lower than previously assumed; leading to inferences that G6PD deficiency (at least certain types) may confer protection against *P. vivax* infection, and may thus be less common among *P. vivax*-infected patients than among the general population (Louicharoen 2009; Leslie 2010). These observations of the protection against *P. vivax* infection conferred by G6PD deficiency need replication in other settings, particularly where the Mediterranean variant is common and haemolysis due to primaquine can be severe and prolonged.

G6PD deficiency can be detected with either a quantitative determination of the enzyme level or a qualitative screening test; the latter is less expensive and is sufficient to identify individuals with a G6PD deficiency in most instances (Beutler 1994). However, many low-income countries have limited facilities to detect this condition before administering primaquine. While eight weekly doses of primaquine may be safe in this population, data from the one person in the trial with this deficiency do not provide sufficient assurance to advocate the wider use of this regimen in people with this deficiency, without carefully monitoring their safety.

Primaquine in vulnerable populations

The trials in this review excluded very young children (younger than one year), pregnant and nursing mothers, people with severe malnutrition, and severe anaemia; and this review does not provide evidence of the safety of the 14-day or the 8-weekly dose primaquine regimens in these vulnerable populations.The data from Leslie 2004 and Leslie 2008, done during periods of high and low seasonal transmission respectively, indicate that very young children living in areas of high transmission are likely to have higher recurrence rates than older children and adults. The

trial participants had lived in refugee camps for several years and hence differences in acquired immunity and re-infections probably explain the age-related recurrence rates, rather than differential efficacy of anti-relapse regimens. Hence, the pooled effect estimates for the 14-day and 8-week primaquine regimens in Leslie 2008, particularly in very young children, may differ when applied elsewhere according to local transmission intensities and population migration patterns.

Quality of the evidence

We assessed the overall quality of the evidence using the GRADE approach (Schunemann 2008).

Alternative primaquine dosing regimens compared to the standard 14-day primaquine regimen (blood stage infections treated with chloroquine)

The overall quality of evidence for relapse over six months of follow-up with shorter courses of primaquine versus 14-day primaquine was of "*moderate quality*" for the commonly used 5-day primaquine regimen (Summary of findings for the main comparison). This indicates that it is possible that further trials with follow-up beyond six months, and in settings with different transmission intensities, may alter these estimates. However, considering the magnitude of the estimates favouring 14 days of primaquine, it is unlikely that these will be altered significantly in favour of a 5-day primaquine regimen, unless primaquine doses higher than 0.25 mg/kg/day are used. The overall quality of the evidence of efficacy of the shorter 3-day primaquine regimen was also "*moderate quality*" (Summary of findings 2). Further research is likely to change these estimates; but unless higher doses given for five days or seven days are first shown effective, compared to 14-day primaquine, research evaluating 3-day regimens appear unwarranted. Data from the one trial evaluating the effects of seven days of primaquine were of "*low quality*" (Summary of findings 3). It seems likely that the efficacy estimates will be significantly altered by further research, especially if higher primaquine doses (0.5 mg/kg or 0.75 mg/kg per day) are used.

Weekly primaquine versus 14-day primaquine (blood stage infections treated with chloroquine)

The "*very low quality*" evidence from a single multicentre, multicountry trial of weekly primaquine means that we do not know if eight weekly doses of primaquine is as effective, or even non-inferior to 14 days of primaquine in preventing recurrences over 11 months after an episode of vivax malaria (Summary of findings 4). This uncertainty stems from very serious study limitations, serious indirectness, and very serious imprecision in the effect estimates of this trial.

Primaquine regimens versus no treatment or placebo (blood stage infections treated with chloroquine)

Primaquine (five days)

We graded the pooled effect estimates for relapse prevention with 5-day primaquine versus placebo as "*high quality*" (Summary of findings 5). Three of the four trials were free of the risk of bias, all four were consistent in their estimates in showing no significant difference, and were done in the usual situations and populations where vivax malaria is a burden. In spite of imprecision in the effect estimates, the trials had sufficient power (422 events in 2212 participants) to detect appreciable differences, had there been any. Additionally, the high estimated recurrence rates with five days of primaquine (mean 28%; 95% CI 27% to 30%) and with chloroquine alone (mean 22%; 95% CI 19% to 26%) in the treatment arms of the trials (Table 2) provide sufficient evidence to refute any suggestions of its efficacy as an anti-relapse treatment for people with vivax malaria.

Primaquine (14 days)

We assessed the pooled effect estimates for relapse prevention with chloroquine plus primaquine (14 days) versus placebo as "*high quality*" for follow-up periods ranging from one month to a year after interventions (Summary of findings 6). Further research to compare 14 days of treatment versus no anti-relapse treatment is unlikely to change this estimate, unless complemented by the use of multi-locus molecular genetic tests that have been pre-validated for the region, in order to correct for re-infections, in people whose adherence to treatments are supervised, and followed up for at least one year. The corrected estimates could differentiate between true relapses and re-infections (both early and late), but it is uncertain if this would significantly alter the estimates of the relative efficacy of the 14-day primaquine regimen. Considering the magnitude of benefit favouring 14-day primaquine, whatever contributions early and late new-infections may add to this estimate, appreciable clinical benefits are likely to accrue for people with vivax malaria with 14 days of primaquine.

Potential biases in the review process

We stated that included trials should have used the same dose of chloroquine in all intervention arms, but in the 2007 version of this review we included Villalobos 2000 that used five days of chloroquine in one arm and three days in the other. We chose to retain this trial among the included trials because the trial ensured parasitic clearance in both arms by day 28 and they evaluated the anti-relapse potential of primaquine. We also reviewed all other excluded trials to ensure that none were excluded on the basis of different doses of chloroquine used in the interventions.

We identified and included Yeshiwondim 2010 in this update, which gave primaquine, not immediately following chloroquine as is usually done, but after day 28 for 14 days in one intervention arm. We also included two trials where trial authors gave primaquine and chloroquine concurrently (Alvarez 2006; Carmona-Fonseca 2009). We chose these departures from our approach in the 2007 review in order to address issues highlighted in the Why it is important to do this review section regarding the relative merits of concurrent and delayed sequential administration. We also ensured that none of the trials that we had previously excluded were due to concurrent administration of the two interventions or because of delayed sequential administration.

We also included the sole trial that used intermittent primaquine dosing compared to the 14-day primaquine arm that used a dose was higher (22.5 mg/day) than the standard 15 mg/day dose recommended by the WHO. However, the WHO recommend 30 mg/day and even 45 mg/day for daily dosing (WHO 2010a).

Agreements and disagreements with other studies or reviews

The updated WHO malaria treatment guidelines (WHO 2010a) recommend the standard oral regimen of chloroquine (25 mg base/kg body weight) given over three days plus primaquine at either

a low dose (0.25 mg base/kg body weight per day) for 14 days; or high dose (0.5 to 0.75 mg base/kg body weight per day) for 14 days, as effective and safe for the radical cure of chloroquine-sensitive vivax malaria in patients with no G6PD deficiency. This review update provides direct and indirect evidence to support the efficacy and safety of 14 days of primaquine in reducing relapses due to vivax malaria. Only one of the included trials (Leslie 2008) used 0.5 to 0.75 mg base/kg body weight in the daily and intermittent dosing regimens; hence the recommendation for a higher daily dose requires further evaluation in head-to-head comparisons and in areas where there is a reported reduced efficacy of standard primaquine doses.

The strong recommendation of WHO 2010a endorsing 14 days of primaquine over five days of primaquine graded the overall evidence as "*low quality*" for the PCR-uncorrected efficacy estimates from the two contributory trials directly comparing the two regimens, and as "*very low quality*" for the PCR-corrected estimates from one of them. We did not include PCR-corrected estimates as an outcome in this review update due to the unavailability for routine use of validated methods of molecular differentiation of relapses from re-infections. Our judgements differ from the quality assessments for PCR-uncorrected estimates of the WHO recommendation. We graded the overall quality for the PCR-uncorrected efficacy estimates as of "*moderate quality*". Additional unpublished information from the first author of one of the trials (Gogtay 1999) permitted a more accurate estimation of the risk of bias in this study,

WHO 2010a also recommended a primaquine regimen of 0.75 mg base/kg body weight once per week for eight weeks as anti-relapse therapy for *P. vivax* and *P. ovale* malaria in patients with mild G6PD deficiency, based on data from Leslie 2008. However they did not report the quality of the evidence supporting this recommendation. Our assessments of the same data suggest the WHO 2010a recommendation is based on "*very low quality evidence*".

AUTHORS' CONCLUSIONS

Implications for practice

The standard 15 mg/day, 14-day primaquine regimen (210 mg primaquine) to prevent relapses, following chloroquine treatment of the blood stage infection is more effective than shorter primaquine regimens at the same dose. It was well-tolerated in people without G6PD deficiency. It also appears to be well-tolerated in people with mild forms of this deficiency, although adverse events and hematocrit should be monitored if primaquine is used in people with all forms of G6PD deficiency.

National programmes that use the 14-day primaquine, or do not recommend primaquine at all, should change such policies since the burden of vivax malaria is considerable, and the use of no primaquine, or shorter, ineffective primaquine regimens, is a waste of resources. They are likely to increase the risk of primaquine failure, and may result in primaquine resistance.

Even countries where relapse rates are low, and where anti-relapse prophylaxis may not be considered worthwhile (Kshirsagar 2006), should use the standard 14-day regimen in order to reduce the risk of transmission from the hypnozoite pool in infected people, and to prevent the development of resistance due to selective drug pressure and higher transmission intensities in the future due to relapses and re-infections.

Malaria control programmes that decide to change to the 14-day regimen should routinely screen for G6PD deficiency in populations with this deficiency and enhance health education activities routinely to improve adherence.

Patients and the communities they come from should implement general measures to reduce the risk of infection through insecticide treated bed-nets, mosquito source management and other methods to prevent being bitten (Lengeler 2004; Gamble 2006; Tusting 2013).

Implications for research

Further trials comparing the standard 14-day primaquine regimen (0.25 mg/kg body weight per day) with no primaquine, or with primaquine given for less than seven days at 15 mg/day, appear unwarranted as the perceived advantage for adherence and adverse events of these shorter courses are unlikely to be matched by the efficacy against relapse of the 14-day regimen.

However, research is needed on the efficacy and safety of higher doses of primaquine given for periods between seven and 14 days, conforming to international standards (Moher 2010). Trials using 0.5 mg/kg body weight per day (30 mg/day) of primaquine for seven to 10 days need to be evaluated against the standard 14-day primaquine regimen given at 0.25 mg/kg per day, and even 0.5 mg/kg per day. The recommendation of 30 mg/day of primaquine for 14 days (and even higher doses of 0.75 mg/kg body weight per day; 45 mg/day) (CDC 2005; WHO 2010a) needs to be evaluated in the context of trials done in areas with different transmission intensities. The efficacy and safety of weekly primaquine at doses of 45 mg/week (0.75 mg/kg/day) given for eight weeks, needs to be re-evaluated against the standard 14-day primaquine regimen at doses of 22.5 mg/day and even 30 mg/day in adults and children with vivax malaria, stratified by the presence or absence of G6PD deficiency.

Such trials should ideally use equivalence or non-inferiority designs to estimate sample sizes and should also follow the CONSORT extension for reporting equivalence and non-inferiority trials (Piaggio 2006). If cluster randomized designs are used, then the number of clusters in each arm and the number of individuals randomized to each intervention should both be routinely reported, along with the ICC (if adjusted analyses are reported), so that the data from these trials can be properly analyzed in meta-analyses along with the results of parallel group randomized trials. The risk of bias in cluster RCTs differ from those in parallel group trials and the use of the appropriate CONSORT extension for cluster-RCTs (Campbell 2004) will help improve transparency in reporting, and in their interpretation.

Trials should ensure parasitic clearance through serial blood smears until day 28, or even day 35, to confirm the efficacy of chloroquine in eradicating blood stage infections, and follow-up should be for at least one year after treatment with primaquine in order to detect late recurrences. . The adherence of people given longer or intermittent courses of primaquine, as well as methods to improve adherence also need to be systematically assessed. The results of two studies (Takeuchi 2010; Manneeboonyang 2011) indicate that DOT may increase the efficacy of the 14-day regimen;

however, studies estimating resource use and costs, and the incremental cost efficacy or cost-savings of 14 days of primaquine, with and without DOT, would be required to inform health policy.

ACKNOWLEDGEMENTS

2013 review update:

We acknowledge the contributions of Aika Omari who was a co-author of the 2007 review. We are grateful for editorial support from the Cochrane Infectious Diseases Group (Anne-Marie Stephani; and Vittoria Lutje-for searching and locating trials). We are grateful to Patricia Graves for constructive editorial comments. We also acknowledge the suggestions provided by Paul Garner and Dave Sinclair. This review update is an output from the Effective Health Care Research Consortium; a project funded by UKaid, the UK Department for International Development (DFID) for the benefit of developing countries. The views expressed are not necessarily those of DFID.

2007, Issue 1 review:

Gawrie Galappaththy developed the protocol in July 2002 and the initial version of this review in July 2004 and July 2005 while visiting the Cochrane Infectious Diseases Group at the Liverpool School of Tropical Medicine. This fellowship was provided by the Effective Healthcare Research Alliance Programme (EHCAP), which was supported by the DFID. Prathap Tharyan helped re-write and complete the review while visiting Colombo, Sri Lanka as a funded partner of the Effective Health Care Research Programme Consortium (previously know as EHCAP) in June 2006. We are also grateful to Georgia Salanti for statistical advice for the initial version of the review.

REFERENCES

References to studies included in this review

Alvarez 2006 *{published data only}*

Alvarez G, Pineros JG, Tobon A, Rios A, Maestre A, Blair S, et al. Efficacy of three chloroquine-primaquine regimens for treatment of *Plasmodium vivax* malaria in Colombia. *American Journal of Tropical Medicine and Hygiene* 2006;**75**(4):605-9.

Carmona-Fonseca 2009 *{published data only}*

Carmona-Fonseca J, Maestre A. Prevention of *Plasmodium vivax* malaria recurrence: efficacy of the standard total dose of primaquine administered over 3 days. *Acta Tropica* 2009;**112**(2):188-92.

Ganguly 2013 *{published data only}*

Ganguly S. Studies on *P. vivax* malaria in urban population of Kolkata with special reference to chloroquine sensitivity and relapse pattern. Clinical Trials Registry India. [Registration Number: CTRI/2011/09/002031]

* Ganguly S, Saha P, Guha SK, Das S, Bera DK, Biswas A, et al. In vivo therapeutic efficacy of chloroquine alone or in combination with primaquine against vivax malaria in Kolkata, West Bengal, India, and polymorphism in pvmdr1 and pvcrt-0 genes. *Antimicrobial Agents and Chemotherapy* 2013;**57**(3):1246-51.

Gogtay 1999 *{published and unpublished data}*

Gogtay NJ, Deshai S, Kamtekar KD, Kadam VS, Dalvi SS, Kshirsagar NA. Efficacies of 5 and 14 day primaquine regimens in the prevention of relapses in *Plasmodium vivax* infections. *Annals of Tropical Medicine and Parasitology* 1999;**93**(8):809-12.

Kim 2012 *{published data only (unpublished sought but not used)}*

ISRCTN14027467. Open label comparison of chloroquine (CQ) alone versus CQ plus 5 days unobserved primaquine or CQ plus 14 days unobserved primaquine. http://www.controlled-trials.com/ISRCTN14027467/ Vol. (accessed 22 July 2013).

Kim J-R, Nandy A, Pukrittayakamee S, White NJ, Imwong M. A randomised trial to assess the effectiveness of different primaquine regimens for the radical treatment of vivax malaria in Kolkota. PLoS ONE 2012; Vol. 7, issue 7:S1.

* Kim JR, Nandy A, Maji AK, Addy M, Dondorp AM, Day NPJ, et al. Genotyping of *Plasmodium vivax* reveals both short and long latency relapse patterns in Kolkata. *PLoS ONE* 2012;**7**(7):e39645.

Leslie 2004 *{published data only}*

Leslie T, Rab MA, Ahmadzai H, Durrani N, Fayaz M, Kolaczinski J, et al. Compliance with 14-day primaquine therapy for radical cure of vivax malaria - a randomized placebo-controlled trial comparing unsupervised with supervised treatment. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2004;**98**(3):168-73.

Leslie 2008 *{published data only (unpublished sought but not used)}*

* Leslie T, Mayan I, Mohammed N, Erasmus P, Kolaczinski J, Whitty CJ, et al. A randomised trial of an eight-week, once weekly primaquine regimen to prevent relapse of *Plasmodium vivax* in Northwest Frontier Province, Pakistan. *PLoS ONE* 2008;**3**(8):e2861.

Leslie T, Mayan I, Mohammed N, Erasmus P, Kolaczinski J, Whitty CJ, et al. Abstract 337: A randomised trial of an eight-week, once weekly primaquine regimen to prevent relapse of *Plasmodium vivax* in Pakistan. *American Journal of Tropical Medicine and Hygiene* 2008;**79**(Suppl 6):120.

Pukrittayakamee 1994 *{published data only}*

Pukrittayakamee S, Vanijanonta S, Chantra A, Clemens R, White NJ. Blood stage antimalarial efficacy of primaquine in *Plasmodium vivax* malaria. *Journal of Infectious Diseases* 1994;**169**(4):932-5.

Rajgor 2003 *{published and unpublished data}*

Rajgor DD, Gogtay NJ, Kadam VS, Kamtekar KD, Dalvi SS, Chogle AR, et al. Efficacy of a 14-day primaquine regimen in preventing relapses in patients with *Plasmodium vivax* malaria in Mumbai, India. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2003;**97**(4):438-40.

Rowland 1999a *{published data only}*

Rowland M, Durrani N. Randomized controlled trials of 5- and 14-days primaquine therapy against relapses of vivax malaria in an Afghan refugee settlement in Pakistan. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1999;**93**(6):641-3.

Rowland 1999b *{published data only}*

Rowland M, Durrani N. Randomized controlled trials of 5- and 14-days primaquine therapy against relapses of vivax malaria in an Afghan refugee settlement in Pakistan. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1999;**93**(6):641-3.

Villalobos 2000 *{published data only}*

Villalobos-Salcedo JM, Tada MS, Kimura E, Menezes MJ, Pereira da Silva LH. In-vivo sensitivity of *Plasmodium vivax* isolates from Rondonia (western Amazon region, Brazil) to regimens including chloroquine and primaquine. *Annals of Tropical Medicine and Parasitology* 2000;**94**(8):749-58.

Walsh 2004 *{published data only}*

Walsh DS, Wilairatana P, Tang DB, Heppner DG Jr, Brewer TG, Krudsood S, et al. Randomized trial of 3-dose regimens of tafenoquine (WR238605) versus low-dose primaquine for preventing *Plasmodium vivax* malaria relapse. *Clinical Infectious Diseases* 2004;**39**(8):1095-103.

Yadav 2002 *{published data only}*

Yadav RS, Ghosh SK. Radical curative efficacy of five-day regimen of primaquine for treatment of *Plasmodium vivax* malaria in India. *Journal of Parasitology* 2002;**88**(5):1042-4.

Yeshiwondim 2010 *{published data only}*

Yeshiwondim AK, Tekle A, Dengela DO, Yohannes AM, Teklehaimanot A. Therapuetic efficacy of chloroquine and chloroquine plus primaquine for the treatment of *Plasmodium vivax* in Ethiopia. *Acta Tropica* 2010;**113**(2):105-13.

References to studies excluded from this review

Abdon 2001 *{published data only}*

Abdon NP, Pinto AY, das Silva Rdo S, de Souza JM. Assessment of the response to reduced treatment schemes for vivax malaria. *Revista da Sociedade Brasileira de Medicina Tropical* 2001;**34**(4):343-8.

ACTRN1261000055406 *{unpublished data only}*

Congpuong K. Efficacy and safety of chloroquine for the treatment of uncomplicated *Plasmodium vivax* malaria in Mae Hong Son and Kanchanaburi provinces in Thailand. http://www.anzctr.org.au/ACTRN12610000554066.aspx (accessed November 28, 2010).

ACTRN12613000003774 *{unpublished data only}*

Sim K. Assessing the safety of weekly administered primaquine in vivax malaria infected Cambodians. http://www.anzctr.org.au/ACTRN12613000003774.aspx (accessed 8 October 2013).

Appavoo 1984 *{published data only}*

Appavoo NC, Roy RG, Kapali V. Results of 3-day radical treatment of *Plasmodium vivax* in North Arcot and South Arcot Districts of Tamil Nadu. *Indian Journal of Malariology* 1984;**21**(1):21-4.

Arango 2012 *{published data only}*

Arango EM, Upegui YA, Carmona-Fonseca J. Efficacy of different primaquine-based antimalarial regimens against *Plasmodium falciparum* gametocytemia. *Acta Tropica* 2012;**122**(2):177-82.

Baird 1995 *{published data only}*

Baird JK, Fryauff DJ, Basri H, Bangs MJ, Subianto B, Wiady I, et al. Primaquine for prophylaxis against malaria among nonimmune transmigrants in Irian Jaya, Indonesia. *American Journal of Tropical Medicine and Hygiene* 1995;**52**(6):479-84.

Baird 2001 *{published data only}*

Baird JK, Lacy MD, Basri H, Barcus MJ, Maguire JD, Bangs MJ, et al. Randomized, parallel placebo-controlled trial of primaquine for malaria prophylaxis in Papua, Indonesia. *Clinical Infectious Diseases* 2001;**33**(12):1990-7.

Baird 2003b *{published data only}*

Baird JK, Fryauff DJ, Hoffman SL. Primaquine for prevention of malaria in travellers. *Clinical Infectious Diseases* 2003;**37**(12):1659-67.

Basavaraj 1960 *{published data only}*

Basavaraj HR. Observations on the treatment of 678 malaria cases with primaquine in an area free from malaria transmission in Mysore State, India. *Indian Journal of Malariology* 1960;**14**:269-81.

Betuela 2012a *{published data only}*

Betuela I, Bassat Q, Kiniboro B, Robinson LJ, Rosanas-Urgell A, Stanisic D, et al. Tolerability and safety of primaquine in Papua New Guinean children 1 to 10 years of age. *Antimicrobial Agents and Chemotherapy* 2012;**56**(4):2146-9.

Betuela 2012b *{published data only}*

Betuela I, Rosanas A, Kiniboro B, Stanisic D, Samol L, Lazzari E, et al. Relapses are contributing significantly to risk of P. vivax infection and disease in Papua New Guinean children 1-5 years of age. Tropical Medicine and International Health. 7th European Congress on Tropical Medicine and International Health; 2011 October 03-06; Barcelona. Barcelona: Tropical Medicine and International Health, 2011; Vol. 16:60-61.

* Betuela I, Rosanas-Urgell A, Kiniboro B, Stanisic DI, Samol L, de Lazzari E, et al. Relapses contribute significantly to the risk of *Plasmodium vivax* infection and disease in Papua New Guinean children 1-5 years of age. *Journal of Infectious Diseases* 2012;**206**(11):1771-80.

Buchachart 2001 *{published data only}*

Buchachart K, Krudsood S, Singhasivanon P, Treeprasertsuk S, Phophak N, Srivilairit S, et al. Effect of primaquine standard dose (15 mg/day for 14 days) in the treatment of vivax malaria patients in Thailand. *Southeast Asian Journal of Tropical Medicine and Public Health* 2001;**32**(4):720-6.

Bunnag 1994 *{published data only}*

Bunnag D, Karbwang J, Thanavibul A, Chittamas S, Ratanapongse Y, Chalermrut K, et al. High dose of primaquine in primaquine resistant vivax malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1994;**88**(2):218-9.

Carmona-Fonseca 2003 *{published data only}*

Carmona-Fonseca J, Alvarez G. *Plasmodium vivax* malaria: treatment of primary attacks with primaquine, in three different doses, and a fixed dose of chloroquine, Antioquia, Colombia, 2003-2004. *Biomedica* 2006;**26**(3):353-65.

Carmona-Fonseca 2006 *{published data only}*

Carmona-Fonseca J, Alvarez G. *Plasmodium vivax* malaria: treatment of primary attacks with primaquine, in three different doses, and a fixed dose of chloroquine, Antioquia, Colombia, 2003-2004. *Biomedica* 2006;**26**(3):353-65.

Carmona-Fonseca 2009a *{published data only}*

Carmona-Fonseca J, Álvarez G, Maestre A. Methemoglobinemia and adverse events in *Plasmodium vivax* malaria patients associated with high doses of primaquine treatment. *American Journal of Tropical Medicine and Hygiene* 2009;**80**(2):188-93.

Carmona-Fonseca 2010 *{published data only}*

Carmona-Fonseca J. Vivax malaria in children: recurrences with standard total dose of primaquine administered in 3 versus 7 days [Malaria vivax en ninos: recurrencias con dosis total estandar de primaquina administrada durante 3 frente a 7 dias]. *Iatreia* 2010;**23**(1):10-20.

Cedillos 1978 *{published data only}*

Cedillos RA, Warren M, Jeffery GM. Field evaluation of primaquine in the control of *Plasmodium vivax*. *American Journal of Tropical Medicine and Hygiene* 1978;**27**(3):466-72.

Clyde 1977 *{published data only}*

Clyde DF, McCarthy VC. Radical cure of Chesson strain vivax malaria in man by 7, not 14, days of treatment with

primaquine. *American Journal of Tropical Medicine and Hygiene* 1977;**26**(3):562-3.

Contacos 1974 *{published data only}*

Contacos PG, Collins WE, Chin W, Jeter MH, Briesch PE. Combined chloroquine-primaquine therapy against vivax malaria. *American Journal of Tropical Medicine and Hygiene* 1974;**23**(2):310-2.

CTRI/2011/09/002031 *{unpublished data only}*

Maji A. A study to determine the effectiveness of two drugs chloroquine and primaquine in *P. vivax* malaria in Kolkata. http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=3592 (accessed April 10, 2012). [CTRI/2011/09/002031]

CTRI/2012/03/002511 *{unpublished data only}*

Joglekar S, Jalal, J. TAF112582- A multi-centre, double-blind, randomised, parallel-group, active-controlled study to evaluate the efficacy, safety and tolerability of tafenoquine (SB-252263,WR238605) in subjects with *Plasmodium vivax* malaria. http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=4295 (accessed 13 April 2012).

Dao 2007 *{published data only}*

Dao NV, Cuong BT, Ngoa ND, Thuy le TT, The ND, Duy DN, et al. Vivax malaria: preliminary observations following a shorter course of treatment with artesunate plus primaquine. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2007;**101**(6):534-9.

da Silva 2003 *{published data only}*

da Silva Rdo S, Pinto AY, Calvosa VS, de Souza JM. Short course schemes for vivax malaria treatment [Esquemas terapeuticos encurtados para o tratamento de malaria por *Plasmodium vivax*]. *Revista da Sociedade Brasileira de Medicina Tropical* 2003;**36**(2):235-9.

Dua 2001 *{published data only}*

Dua VK, Sharma VP. *Plasmodium vivax* relapses after 5 days of primaquine treatment, in some industrial complexes of India. *Annals of Tropical Medicine and Parasitology* 2001;**95**(7):655-9.

Elmes 2008 *{published data only}*

Elmes NJ, Nasveld PE, Kitchener SJ, Kocisko D A, Edstein MD. The efficacy and tolerability of three different regimens of tafenoquine versus primaquine for post-exposure prophylaxis of *Plasmodium vivax* malaria in the Southwest Pacific. *Transactions of the Royal Society of Tropical Medicine and Hygiene.* 2008;**102**(11):1095-101.

Fryauff 1997 *{published data only}*

Fryauff DJ, Baird JK, Purnomo, Awalludin M, Jones T, Subianto B, et al. Malaria in a nonimmune population after extended chloroquine or primaquine prophylaxis. *American Journal of Tropical Medicine and Hygiene* 1997;**56**(2):137-40.

Gogtay 1998 *{published data only}*

Gogtay N, Garg M, Kadam V, Kamtekar K, Kshirsagar NA. A 5 days primaquine regimen as anti-relapse therapy for *Plasmodium vivax*. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1998;**92**(3):341.

Hamedi 2004 *{published data only}*

Hamedi Y, Safa O, Zare S, Tan-ariya P, Kojima S, Looareesuwan S. Therapeutic efficacy of artesunate in *Plasmodium vivax* malaria in Thailand. *Southeast Asian Journal of Tropical Medicine and Public Health* 2004;**35**(3):570-4.

Herrera 2011 *{published data only}*

Herrera S, Solarte Y, Jordán-Villegas A, Echavarría JF, Rocha L, Palacios R, et al. Consistent safety and infectivity in sporozoite challenge model of *Plasmodium vivax* in malaria-naive human volunteers. *American Journal of Tropical Medicine and Hygiene* 2011;**2 Suppl**:4-11.

ISRCTN82366390 *{unpublished data only}*

Nelwn EJ. Randomized, open-label trial of the safety, tolerability and efficacy of primaquine against relapse when combined with pyronaridine tetraphosphate-artesunate or dihydroartemisinin-piperquine phosphate for radical cure of acute *Plasmodium vivax* malaria in soldiers. http://isrctn.org/ISRCTN82366390 (accessed 8 October 2013).

Kolaczinski 2012 *{published data only}*

Kolaczinski K, Leslie T, Ali I, Durrani N, Lee S, Barends M, et al. Defining *Plasmodium falciparum* treatment in South West Asia: a randomized trial comparing artesunate or primaquine combined with chloroquine or SP. *PLoS One* 2012;**7**(1):e28957.

Looareesuwan 1999 *{published data only}*

Looareesuwan S, Wilairatana P, Krudsood S, Treeprasertsuk S, Singhasivanon P, Bussaratid V, et al. Chloroquine sensitivity of *Plasmodium vivax* in Thailand. *Annals of Tropical Medicine and Parasitology* 1999;**93**(3):225-30.

Luxemburger 1999 *{published data only}*

Luxemburger C, van Vugt M, Jonathan S, McGready R, Looareesuwan S, White NJ, et al. Treatment of vivax malaria on the western border of Thailand. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1999;**93**(4):433-8.

Manneeboonyang 2011 *{published data only}*

Maneeboonyang W, Lawpoolsri S, Puangsa-Art S, Yimsamran S, Thanyavanich N, Wuthisen P, et al. Directly observed therapy with primaquine to reduce the recurrence rate of *Plasmodium vivax* infection along the Thai-Myanmar border. *Southeast Asian Journal of Tropical Medicine and Public Health* 2011;**42**(1):9-18.

Nasveld 2010 *{published data only}*

Nasveld PE, Edstein MD, Reid M, Brennan L, Harris IE, Kitchener SJ, et al. Randomized, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. *Antimicrobial Agents and Chemotherapy* 2010;**54**(2):792-8.

NCT01074905 *{unpublished data only}*

Chu C, Chia PY. A randomised open label study comparing the efficacy of chloroquine/primaquine, chloroquine and artesunate in the treatment of vivax malaria along the Thai-Burmese border. http://clinicaltrials.gov/show/NCT01074905 (accessed 13 April 2012). [SMRU0908]

Nosten F, Cheah PY. Study on the treatment of vivax malaria (VHX). http://clinicaltrials.gov/ct2/show/record/NCT01074905 (accessed November 28, 2010). [CTG: NCT01074905; Secondary ID: SMRU0908]

NCT01288820 *{unpublished data only}*

Pasaribu AP. Comparison of the efficacy and safety of two ACTs plus primaquine for uncomplicated *Plasmodium vivax* malaria in North Sumatera, Indonesia: 1 year follow up. http://clinicaltrials.gov/show/NCT01288820 (accessed 13 April 2012).

NCT01290601 *{unpublished data only}*

Looareesuwan S, Miller RE. Study to evaluate the efficacy and safety of tafenoquine for the treatment of *Plasmodium vivax* in adults. http://clinicaltrials.gov/show/NCT01290601 (accessed 13 April 2012).

NCT01716260 *{unpublished data only}*

Dorjey Y. Parasitic clearance and recurrence rates among patients with vivax malaria on chloroquine and primaquine therapy. http://clinicaltrials.gov/show/NCT01716260 (accessed 8 October 2013).

NCT01780753 *{unpublished data only}*

McGready R. A study of the pharmacokinetics of primaquine in lactating women and breastfed infants for the radical treatment of uncomplicated maternal P. vivax. http://clinicaltrials.gov/show/NCT01780753 (accessed 8 October 2013).

NCT01814683 *{unpublished data only}*

Price R. Improving the radical cure of vivax malaria: A multicentre randomised comparison of short and long course primaquine regimens. http://clinicaltrials.gov/show/NCT01814683 (accessed 8 October 2013).

NCT01837992 *{unpublished data only}*

Mueller I. Evaluation of Safety and Efficacy of Two Primaquine Dosing Regimens for the Radical Treatment of Plasmodium Vivax Malaria in Vanuatu and Solomon Islands. http://clinicaltrials.gov/show/NCT01837992 (accessed 8 October 2013).

Pasaribu 2013 *{published data only}*

Pasaribu AP, Chokejindachai W, Sirivichayakul C, Tanomsing N, Chavez I, Tjitra E, et al. A randomized comparison of dihydroartemisinin-piperaquine and artesunate-amodiaquine combined With primaquine for radical treatment of vivax malaria in Sumatera, Indonesia. *Journal of Infectious Diseases* 2013;**Aug 28**:[Epub ahead of print].

Pinto 1998 *{published data only}*

Pinto AY, Ventura AM, Calvosa VS, Silva Filho MG, Santos MA, Silva RS, et al. Clinical efficacy of four schemes for vivax malaria treatment in children. *Jornal de Pediatria* 1998;**74**(3):222-7.

Prasad 1991 *{published data only}*

Prasad RN, Virk KJ, Sharma VP. Relapse/reinfection patterns of *Plasmodium vivax* infection: a four year study. *Southeast Asian Journal of Tropical Medicine and Public Health* 1991;**22**(4):499-503.

Pukrittayakamee 2010 *{published data only}*

Pukrittayakamee S, Imwong M, Chotivanich K, Singhasivanon P, Day NP, White NJ. A comparison of two short-course primaquine regimens for the treatment and radical cure of *Plasmodium vivax* malaria in Thailand. *American Journal of Tropical Medicine and Hygiene* 2010;**82**(4):542-7.

RBR-77q7t3 *{unpublished data only}*

Pereira D. Study of efficacy and safety of a new co-blister packs of chloroquine and primaquine for malaria treatment of uncomplicated *Plasmodium vivax* in Brasil. http://www.ensaiosclinicos.gov.br/rg/RBR-77q7t3/v1/ (accessed 13 April 2012).

Roy 1977 *{published data only}*

Roy RG, Chakrapani KP, Dhinagaran D, Sitaraman NL, Ghosh RB. Efficacy of 5-day radical treatment of *P. vivax* infection in Tamil Nadu. *Indian Journal of Medical Research* 1977;**65**(5):652-6.

Saint-Yves 1977 *{published data only}*

Saint-Yves IF. Comparison of treatment schedules for *Plasmodium vivax* infections in the Solomon Islands. *Papua New Guinea Medical Journal* 1977;**20**(2):62-5.

Schwartz 2000 *{published data only}*

Schwartz E, Regev-Yochay G, Kurnik D. Short report: a consideration of primaquine dose adjustment for radical cure of *Plasmodium vivax* malaria. *American Journal of Tropical Medicine and Hygiene* 2000;**62**(3):393-5.

Sharma 1973 *{published data only}*

Sharma MID, Sehgal PN, Vaid BK, Dubey RC, Nagendra S, Paithne PK, et al. Effectiveness of drug schedule being followed under the National Malaria Eradication Programme, India, for radical cure of vivax malaria cases. *Journal of Communicable Diseases* 1973;**5**:167-74.

Shekalaghe 2010 *{published data only}*

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

Shekalaghe 2011 *{published data only}*

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

Shin 2011 *{published data only}*

Shin CS, Kwak YG, Lee KD, Borghini-Fuhrer I, Miller RM, Duparc S. Treatment of Korean vivax malaria patients with the fixed-dose combination of pyronaridine/artesunate. Tropical Medicine and International Health. 7th European Congress on Tropical Medicine and International Health; January 3 to 6, 2011; Barcelona. Barcelona: Tropical Medicine and International Health, 2011; Vol. 16, issue 1:149.

Singh 1990 *{published data only}*

Singh N, Mishra AK, Sharma VP. Radical treatment of vivax malaria in Madhya Pradesh, India. *Indian Journal of Malariology* 1990;**27**(1):55-6.

Sinha 1989 *{published data only}*

Sinha S, Dua VK, Sharma VP. Efficacy of 5 day radical treatment of primaquine in *Plasmodium vivax* cases at the BHEL industrial complex, Hardwar (U.P.). *Indian Journal of Malariology* 1989;**26**(2):83-6.

Smithuis 2010 *{published data only}*

Smithuis F, Kyaw MK, Phe O, Win T, Aung PP, Oo AP, et al. Effectiveness of five artemisinin combination regimens with or without primaquine in uncomplicated falciparum malaria: an open-label randomised trial. *Lancet Infectious Diseases* 2010;**10**(10):673-81.

Soto 1998 *{published data only}*

Soto J, Toledo J, Rodriquez M, Sanchez J, Herrera R, Padilla J, et al. Primaquine prophylaxis against malaria in nonimmune Colombian soldiers: efficacy and toxicity. A randomized, double-blind, placebo-controlled trial. *Annals of Internal Medicine* 1998;**129**(3):241-4.

Soto 1999 *{published data only}*

Soto J, Toledo J, Rodriquez M, Sanchez J, Herrera R, Padilla J, et al. Double-blind, randomized, placebo-controlled assessment of chloroquine/primaquine prophylaxis for malaria in nonimmune Colombian soldiers. *Clinical Infectious Diseases* 1999;**29**(1):199-201.

Sutanto 2012 *{published data only}*

Sutanto I, Tjahjono B, Basri H, Taylor WR, Putri FA, Meilia RA, et al. Randomized, open label trial of primaquine against vivax malaria relapse in Indonesia. *Antimicrobial Agents and Chemotherapy* 2012;**57**(3):1128-35.

Takeuchi 2010 *{published data only}*

Takeuchi R, Lawpoolsri S, Imwong M, Kobayashi J, Kaewkungwal J, Pukrittayakamee S, et al. Directly-observed therapy (DOT) for the radical 14-day primaquine treatment of *Plasmodium vivax* malaria on the Thai-Myanmar border. *Malaria Journal* 2010;**9**:308.

Valibayov 2003 *{published data only}*

Valibayov A, Abdullayev F, Mammadov S, Gasimov E, Sabatinelli G, Kondrachine AV, et al. Clinical efficacy of chloroquine followed by primaquine for *Plasmodium vivax* treatment in Azerbaijan. *Acta Tropica* 2003;**88**(1):99-102.

Vásquez 2009 *{published data only}*

Vásquez AM, Sanín F, Álvarez LG, Tobón A, Ríos A, Blair S. Therapeutic efficacy of a regimen of artesunate-mefloquine-primaquine treatment for *Plasmodium falciparum* malaria and treatment effects on gametocytic development [Estudio piloto de la eficacia y de los efectos sobre los gametocitos del esquema artesunato-mefloquina-primaquina para la malaria por *Plasmodium falciparum*]. *Biomédica* 2009;**29**(2):307-19.

Wilairatana 1999 *{published data only}*

Wilairatana P, Silachamroon U, Krudsood S, Singhasivanon P, Treeprasertsuk S, Bussaratid V, et al. Efficacy of primaquine regimens for primaquine-resistant *Plasmodium vivax* malaria in Thailand. *American Journal of Tropical Medical Hygiene* 1999;**61**(6):973-7.

References to ongoing studies

NCT01178021 *{unpublished data only}*

Awab GR, Cheah YP, Woodrow C. Estimating the risk of *Plasmodium vivax* relapses in Afghanistan (VRA). http://clinicaltrials.gov/ct2/show/study/NCT01178021 (accessed November 28, 2010). [CTG: NCT01178021 ; Secondary ID: BAKMAL0903]

NCT01376167 *{unpublished data only}*

Hudson C. Ph 2B/3 tafenoquine (TFQ) study in prevention of vivax relapse. http://clinicaltrials.gov/show/NCT01376167 (accessed 13 April 2012).

NCT01640574 *{unpublished data only}*

Chu C. Randomised parallel open label comparison between 7 and 14 day primaquine combined with 3-day dihydroartemisinin-piperaquine or 3-day chloroquine regimens for radical cure of plasmodium vivax. http://clinicaltrials.gov/show/NCT01640574 (accessed 8 October 2013).

NCT01680406 *{unpublished data only}*

Centers for Disease Control and Prevention. Ethiopia antimalarial in vivo efficacy study 2012: Evaluating the efficacy of artemether-lumefantrine alone compared to artemether-lumefantrine plus primaquine and chloroquine alone compared to chloroquine plus primaquine for *Plasmodium vivax* infection. http://clinicaltrials.gov/ct2/show/record/NCT01680406 (accessed 21 July 2013).

Additional references

Adak 2001

Adak T, Valecha N, Sharma VP. *Plasmodium vivax* polymorphism in a clinical drug trial. *Clinical and Diagnostic Laboratory Immunology* 2001;**8**(5):891-4.

Alves 2002

Alves FP, Durlacher RR, Menezes MJ, Krieger H, Silva LH, Camargo EP. High prevalence of asymptomatic *Plasmodium vivax* and *Plasmodium falciparum* infections in native Amazonian populations. *American Journal of Tropical Medicine and Hygiene* 2002;**66**(6):641-8.

Alving 1955

Alving AS, Arnold J, Hockwald RS, Clayman CB, Dern RJ, Beutler E, et al. Potentiation of the curative action of primaquine in vivax malaria by quinine and chloroquine. *Journal of Laboratory and Clinical Medicine* 1955;**46**(2):301-6.

Alving 1960

Alving AS, Johnson CF, Tarlov AR, Brewer GJ, Kellermeyer RW, Carson PE. Mitigation of the haemolytic effect of primaquine

and enhancement of its action against exoerythrocytic forms of the Chesson strain of *Plasmodium vivax* by intermittent regimens of drug administration: a preliminary report. *Bulletin of the World Health Organization* 1960;**22**:621-31.

Anstey 2007

Anstey NM, Handojo T, Pain MC, Kenangalem E, Tjitra E, Price RN, et al. Lung injury in vivax malaria: pathophysiological evidence for pulmonary vascular sequestration and posttreatment alveolar-capillary inflammation. *Journal of Infectious Diseases* 2007;**195**(4):589-96.

Baird 1997

Baird JK, Leksana B, Masbar S, Fryauff DJ, Sutanihardja MA, Suradi, et al. Diagnosis of resistance to chloroquine by *Plasmodium vivax*: Timing of recurrence and whole blood chloroquine levels. *American Journal of Tropical Medicine and Hygiene* 1997;**56**(6):621-6.

Baird 2003a

Baird JK, Rieckmann KH. Can primaquine therapy for vivax malaria be improved?. *Trends in Parasitology* 2003;**19**(3):115-20.

Baird 2004

Baird JK, Hoffman SL. Primaquine therapy for malaria. *Clinical Infectious Diseases* 2004;**39**(9):1336-45.

Baird 2009

Baird JK. Resistance to therapies for infection by *Plasmodium vivax*. *Clinical Microbiology Reviews* 2009;**22**(3):508-34.

Barcus 2007

Barcus MJ, Basri H, Picarima H, Manyakori C, Sekartuti, Elyazar I, et al. Demographic risk factors for severe and fatal vivax and falciparum malaria among hospital admissions in northeastern Indonesian Papua. *American Journal of Tropical Medicine and Hygiene.* 2007;**77**(5):984-91.

Beg 2008

Beg MA, Sani N, Mehraj V, Jafri W, Khan MA, Malik A, et al. Comparative features and outcomes of malaria at a tertiary care hospital in Karachi, Pakistan. *International Journal of Infectious Diseases* 2008;**12**(1):37-42.

Beutler 1994

Beutler E. G6PD deficiency. *Blood* 1994;**84**(11):3613-36.

Beutler 2007

Beutler E, Duparc S, G6PD Deficiency Working Group. Glucose-6-phosphate dehydrogenase deficiency and antimalarial drug development. *American Journal of Tropical Medicine and Hygiene* 2007;**77**(4):779-89.

Bouma 1995

Bouma MJ, Goris M, Akhtar T, Khan N, Khan N, Kita E. Prevalence and clinical presentation of glucose-6-phosphate dehydrogenase deficiency in Pakistani Pathan and Afghan refugee communities in Pakistan; implications for the use of primaquine in regional malaria control programmes. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1995;**89**(1):62-4.

Breman 2001

Breman JG. The ears of the hippopotamus: manifestations, determinants, and estimates of the malaria burden. *American Journal of Medicine and Hygiene* 2001;**64**(Suppl 1-2):1-11.

Campbell 2004

Campbell MK, Elbourne DR, Altman DG, CONSORT group. CONSORT statement: extension to cluster randomised trials. *BMJ* 2004;**328**(7441):702-8.

Cappellini 2008

Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. *Lancet* 2008;**371**(9606):64-74.

CDC 2005

Centers for Disease Control and Prevention, Kozarsky PE, Arguin PM, Navin AW. Health information for international travel 2005–2006. Philadelphia: Elsevier, 2005.

CDC 2011

Centres for Disease Control and Prevention. Treatment of malaria (guidelines for clinicians). Available at: www.cdc.gov/malaria/pdf/treatmenttable.pdf, 2011.

Charoenlarp 1973

Charoenlarp P, Harinasuta T. Relapses of vivax malaria after a conventional course of primaquine and chloroquine: report of 2 cases. *Southeast Asian Journal of Tropical Medicine and Public Health* 1973;**4**(1):135-7.

Chen 2007

Chen N, Auliff A, Rieckmann K, Gatton M, Cheng Q. Relapses of *Plasmodium vivax* infection result from clonal hypnozoites activated at predetermined intervals. *Journal of Infectious Diseases* 2007;**195**(7):934-41.

Cogswell 1992

Cogswell FB. The hypnozoite and relapse in primate malaria. *Clinical Microbiology Review* 1992;**5**(1):26-35.

Collins 1996

Collins WE, Jeffery GM. Primaquine resistance in P. vivax. *American Journal of Tropical Medicine and Hygiene* 1996;**55**(3):243-9.

Craig 1996

Craig AA, Kain KC. Molecular analysis of strains of *Plasmodium vivax* from paired primary and relapse infections. *Journal of Infectious Diseases* 1996;**174**(2):373-9.

Deeks 2011

Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. Available from www.cochrane-handbook.org. Chichester: John Wiley & Sons.

Divine 1992

Divine GW, Brown JT, Frazier LM. The unit of analysis error in studies about physicians' patient care behavior. *Journal of General Internal Medicine* 1992;**7**(6):623-9.

Doolan 2009

Doolan DL, Dobano C, Baird JK. Acquired immunity to malaria. *Clinical Microbiology Reviews* 2009;**22**(1):13-36.

Douglas 2010

Douglas NM, Anstey NM, Angus BJ, Nosten F, Price RN. Artemisinin combination therapy for vivax malaria. *Lancet Infectious Diseases* 2010;**10**(6):405-16.

Duarte 2001

Duarte EC, Pang LW, Ribeiro LC, Fontes CJ. Association of subtherapeutic dosages of a standard drug regimen with failures in preventing relapses of vivax malaria. *American Journal of Tropical Medicine and Hygiene* 2001;**65**(5):417-6.

Ebringer 2011

Ebringer A, Heathcote G, Baker J, Waller M, Shanks GD, Edstein MD. Evaluation of the safety and tolerability of a short higher-dose primaquine regimen for presumptive anti-relapse therapy in healthy subjects. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2011;**105**(10):568-73.

Fonseka 1987

Fonseka J, Mendis KN. A metropolitan hospital in a non-endemic area provides a sampling pool for epidemiological studies on vivax malaria in Sri Lanka. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1987;**81**(3):360-4.

Gamble 2006

Gamble CL, Ekwaru JP, ter Kuile FO. Insecticide-treated nets for preventing malaria in pregnancy. *Cochrane Database of Systematic Reviews* 2006, Issue 2. [DOI: 10.1002/14651858.CD003755]

Genton 2008

Genton B, D'Acremont V, Rare L, Baea K, Reeder JC, Alpers MP, et al. *Plasmodium vivax* and mixed infections are associated with severe malaria in children: a prospective cohort study from Papua New Guinea. *PLoS Med* 2008;**5**(6):e127.

Gogtay 2000

Gogtay NJ, Desai S, Kadam VS, Kamtekar KD, Dalvi SS, Kshirsagar NA. Relapse pattern of *Plasmodium vivax* in Mumbai: a study of 283 cases of vivax malaria. *Journal of the Association of Physicians of India* 2000;**48**(11):1085-6.

Goller 2007

Goller JL, Jolley D, Ringwald P, Biggs BA. Rerional differences in the response of *Plasmodium vivax* malaria to primaquine as anti-relapse therapy. *American Jourrnal of Tropical Medicine and Hygiene* 2007;**76**(2):203-7.

GRADE 2004 [Computer program]

Brozek J, Oxman A, Schunemann H. GRADEpro. Version 3.6 for Windows. 2012.

Grietens 2010

Grietens KP, Soto V, Erhart A, Ribera JM, Toomer E, Tenorio A, et al. Adherence to 7-day primaquine treatment for the radical cure of *P. vivax* in the Peruvian Amazon. *American Journal of Tropical Medicine and Hygiene* 2010;**82**(6):1017-23.

Guerra 2010

Guerra CA, Howes RE, Patil AP, Gething PW, Van Boeckel TP, Temperley WH, et al. The International limits and population at risk of *Plasmodium vivax* transmission in 2009. *PLoS Neglected Tropical Diseases* 2010;**4**(8):e774.

Gunawardena 2010

Gunawardena S, Karunaweera ND, Ferreira MU, Phone-Kyaw M, Pollack RJ, Alifrangis M, et al. Geographic structure of *Plasmodium vivax*: microsatellite analysis of parasite populations from Sri Lanka, Myanmar, and Ethiopia. *American Journal of Tropical Medicine and Hygiene* 2010;**82**(2):235-42.

Havryliuk 2009

Havryliuk T, Ferreira MU. A closer look at multiple-clone *Plasmodium vivax* infections: detection methods, prevalence and consequences. *Memórias do Instituto Oswaldo Cruz* 2009;**104**(1):67-73.

Hay 2004

Hay SI, Guerra CA, Tatem AJ, Noor AM, Snow RW. The global distribution and population at risk of malaria: past, present, and future. *Lancet Infectious Diseases* 2004;**4**(6):327-36.

Haynes 2008

Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. *Cochrane Database of Systematic Reviews* 2008, Issue 2. [DOI: 10.1002/14651858.CD000011]

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60.

Higgins 2005

Higgins JPT, Green S, editors. Highly sensitive search strategies for identifying reports of randomized controlled trials in MEDLINE. Cochrane Handbook for Systematic Reviews of Interventions [4.2.5] updated [May 2005]; Appendix 5b. Available from www.cochrane-handbook.org.

Higgins 2011a

Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Higgins 2011b

Higgins JPT, Deeks JJ, Altman DG (editors). Chapter 16: Special topics in statistics. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hill 2006

Hill DR, Baird JK, Parise ME, Lewis LS, Ryan ET, Magill AJ. Primaquine: Report from CDC expert meeting on malaria chemoprophylaxis I. *American Journal of Tropical Medicine and Hygiene* 2006;**75**(3):402-15.

Imwong 2007a

Imwong M, Snounou G, Pukrittayakamee S, Tanomsing N, Kim JR, Nandy A. Relapses of *Plasmodium vivax* infection usually result from activation of heterologous hypnozoites. *Journal of Infectious Diseases* 2007;**195**(7):927-33.

Imwong 2007b

Imwong M, Nair S, Pukrittayakamee S, Sudimack D, Williams JT, Mayxay M, et al. Contrasting genetic structure in *Plasmodium vivax* populations from Asia and South America. *International Journal of Parasitology* 2007;**37**(8-9):1013-22.

Imwong 2012

Imwong M, Boel ME, Pagornrat W, Pimanpanarak M, McGready R, Day NP, et al. The first *Plasmodium vivax* relapses of life are usually genetically homologous. *Journal of Infectious Diseases* 2012;**205**(4):680-3.

John 2012

John GK, Douglas NM, von Seidlein L, Nosten F, Baird JK, White NJ, et al. Primaquine radical cure of Plasmodium vivax: a critical review of the literature. *Malaria Journal* 2012;**11**:280.

Karunaweera 2008

Karunaweera ND, Ferreira MU, Munasinghe A, Barnwell JW, Collins WE, King CL, et al. Extensive microsatellite diversity in the human malaria parasite *Plasmodium vivax*. *Gene* 2008;**410**(1):105-12.

Kitchner 2007

Kitchener S, Nasveld P, Edstein MD. Tafenoquine for the treatment of recurrent *Plasmodium vivax* malaria. *American Journal of Tropical Medicine and Hygiene* 2007;**76**(3):494-6.

Kochar 2010

Kochar DK, Tanwar GS, Khatri PC, Kochar SK, Sengar GS, Gupta A, et al. Clinical features of children hospitalized with Malaria - a study from Bikaner, northwest India. *American Journal of Tropical Medicine and Hygiene* 2010;**83**(5):981-9.

Krotoski 1985

Krotoski WA. Discovery of the hypnozoite and a new theory of malarial relapse. *Transactions of the Royal Society of Medicine* 1985;**79**(1):1-11.

Krudsood 2006

Krudsood S, Wilairatana P, Tangpukdee N, Chalermrut K, Srivilairit S, Thanachartwet V, et al. Safety and tolerability of elubaquine (bulaquine, CDRI 80/53) for treatment of *Plasmodium vivax* malaria in Thailand. *Korean Journal of Parasitology* 2006;**44**(3):221-8.

Krudsood 2008

Krudsood S, Tangpukdee N, Wilairatana P, Phophak N, Baird JK, Brittenham GM, et al. High-dose primaquine regimens against relapse of *Plasmodium vivax* malaria. *American Journal of Tropical Medicine and Hygiene* 2008;**78**(5):736-40.

Kshirsagar 2006

Kshirsagar NA. Malaria: anti malarial resistance and policy ramifications and challenges. *Journal of Postgraduate Medicine* 2006;**52**(4):291-3.

Kumar 2007

Kumar A, Valecha N, Jain T, Dash AP. Burden of malaria in India: retrospective and prospective view. *American Journal of Tropical. Medicine and Hygiene* 2007;**77**(Suppl 6):69-78.

Lalloo 2007

Lalloo DG, Shingadia D, Pasvol G, Chiodini PL, Whitty CJ, Beeching NJ, et al. UK malaria treatment guidelines. *Journal of Infection* 2007;**54**(2):111-21.

Lengeler 2004

Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. *Cochrane Database of Systematic Reviews* 2004, Issue 2. [DOI: 10.1002/14651858.CD000363]

Leslie 2010

Leslie T, Briceño M, Mayan I, Mohammed N, Klinkenberg E, Sibley CH, et al. The impact of phenotypic and genotypic G6PD deficiency on risk of *Plasmodium vivax* infection: a case-control study amongst Afghan refugees in Pakistan. *PLoS Med* 2010;**7**(5):e1000283.

Lin 2010

Lin E, Kiniboro B, Gray L, Dobbie S, Robinson L, Laumaea A, et al. Differential patterns of infection and disease with *P. falciparum* and *P. vivax* in young Papua New Guinean children. *PLoS ONE* 2010;**5**(2):e9047.

Looareesuwan 1997

Looareesuwan S, Buchachart K, Wilairatana P, Chalermrut K, Rattanapong Y, Amradee S, et al. Primaquine-tolerant vivax malaria in Thailand. *Annals of Tropical Medicine and Hygiene* 1997;**91**(8):939-43.

Louicharoen 2009

Louicharoen C, Patin E, Paul R, Nuchprayoon I, Witoonpanich B, Peerapittayamongkol C, et al. Positively selected G6PD-Mahidol mutation reduces *Plasmodium vivax* density in Southeast Asians. *Science* 2009;**326**(5959):1546-9.

Maguire 2010

Maguire JD, Baird JK. The 'non-falciparum' malarias: the roles of epidemiology, parasite biology, clinical syndromes, complications and diagnostic rigour in guiding therapeutic strategies. *Annals of Tropical Medicine and Parasitology* 2010;**104**(4):283-301.

Mendis 2001

Mendis K, Sina JB, Marchesini P, Carter R. The neglected burden of *P. vivax* malaria. *American Journal of Medicine and Hygiene* 2001;**64**(Suppl 1-2):97-106.

Michon 2007

Michon P, Cole-Tobian JL, Dabod E, Schoepflin S, Igu J, Susapu M, et al. The risk of malarial infections and disease in Papua New Guinean children. *American Journal of Tropical Medicine and Hygiene* 2007;**76**(6):997-1008.

Moher 2010

Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *Journal of Clinical Epidemiology* 2010;**63**(8):e-1-37.

Mueller 2009

Mueller I, Galinski MR, Baird JK, Carlton JM, Kochar DK, Alonso PL, et al. Key gaps in the knowledge of *Plasmodium vivax*, a neglected human malaria parasite. *Lancet Infectious Diseases* 2009;**9**(9):555-66.

Naing 2010

Naing C, Aung K, Win DK, Wah MJ. Efficacy and safety of chloroquine for treatment in patients with uncomplicated *Plasmodium vivax* infections in endemic countries. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2010;**104**(11):695-705.

NIMR 2011

National Institute of Malaria Research, Indian Council of Medical Research. Diagnosis and treatment of Malaria in India. 2nd Edition. New Delhi: National Insitute of Malaria Research, 2011.

Orjuela-Sanchez 2009

Orjuela-Sanchez P, da Silva NS, da Silva-Nunes M, Ferreira MU. Recurrent parasitemias and population dynamics of *Plasmodium vivax* polymorphisms in rural Amazonia. *American Journal of Topical Medicine and Hygiene* 2009;**81**(6):961-8.

Orton 2005

Orton L, Barnish G. Unit-dose packaged drugs for treating malaria. *Cochrane Database of Systematic Reviews* 2005, Issue 2. [DOI: 10.1002/14651858.CD004614.pub2]

Parfitt 1999

Parfitt K, editor. Martindale: the complete drug reference. 2nd Edition. London: Pharmaceutical Press, 1999.

Piaggio 2006

Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ, CONSORT group. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. *JAMA* 2006;**295**(10):1152-60.

Poespoprodjo 2008

Poespoprodjo JR, Fobia W, Kenangalem E, Lampah DA, Warikar N, Seal A, et al. Adverse pregnancy outcomes in an area where multidrug-resistant *Plasmodium vivax* and *Plasmodium falciparum* infections are endemic. *Clinical Infectious Diseases* 2008;**46**(9):1374-81.

Poespoprodjo 2009

Poespoprodjo JR, Fobia W, Kenangalem E, Lampah DA, Hasanuddin A, Warikar N, et al. Vivax malaria: a major cause of morbidity in early infancy. *Clinical Infectious Diseases* 2009;**48**(12):1704-12.

Price 2007

Price RN, Tjitra E, Guerra CA, Yeung S, White N, Anstey NM. Vivax malaria: neglected and not benign. *American Journal of Tropical Medicine and Hygiene* 2007;**77**(Suppl 6):79-87.

Price 2009

Price RN, Douglas NM, Anstey NM. New developments in *Plasmodium vivax* malaria: severe disease and the rise of chloroquine resistance. *Current Opinion in Infectious Diseases* 2009;**22**(5):430-35.

Price 2011

Price RN, Douglas NM, Anstey NM, von Seidlein L. *Plasmodium vivax* treatments: what are we looking for?. *Current Opinion in Infectious Diseases* 2011;**24**(6):578-85.

Pukrittayakamee 2004

Pukrittayakamee S, Chantra A, Simpson JA, Vanijanonta S, Clemens R, Looareesuwan S, et al. Therapeutic responses to different antimalarial drugs in vivax malaria. *Antimicrobial Agents and Chemotherapy* 2000;**44**(6):1680-5.

Pukrittayakamee 2008

Pukrittayakamee S, Imwong M, Singhasivanon P, Stepniewska K, Day NJ, White NJ. Effects of different antimalarial drugs on gametocyte carriage in *P. vivax* malaria. *American Journal of Tropical Medicine and Hygiene* 2008;**79**(3):378-84.

Qingjun 1998

Qingjun L, Jihui D, Laiyi T, Xiangjun Z, Jun L, Hay A, et al. The effect of drug packaging on patients' compliance with treatment for *Plasmodium vivax* malaria in China. *Bulletin of the World Health Organization* 1998;**76**(Suppl 1):21-7.

Review Manager 5.2 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

Rowland 2001

Rowland M, Nosten F. Malaria epidemiology and control in refugee camps and complex emergencies. *Annals of Tropical Medicine and Parasitology* 2001;**95**(8):741-54.

Saravu 2011

Saravu K, Docherla M, Vasudev A, Shastry BA. Thrombocytopenia in vivax and falciparum malaria: an observational study of 131 patients in Karnataka, India. *Annals of Tropical Medicine and Parasitology* 2011;**105**(8):593-8.

Schmidt 1977

Schmidt LH, Fradkin R, Vaughan D, Rasco J. Radical cure of infections with *Plasmodium cynomolgi*: a function of total 8-

aminoquinoline dose. *American Journal of Tropical Medicine and Hygiene* 1977;**26**(6 Pt 1):1116-28.

Schunemann 2008

Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, Guyatt GH. Chapter 12: Interpreting results drawing conclusions. In: Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Review of Intervention Version 5.0.1 [updated September 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

Sinclair 2011

Sinclair D, Gogtay N, Brand F, Olliaro PL. Artemisinin-based combination therapy for treating uncomplicated Plasmodium vivax malaria. *Cochrane Database of Systematic Reviews* 2011, Issue 7. [DOI: 10.1002/14651858.CD008492]

Singh 2011

Singh H, Parakh A, Basu S, Rath B. *Plasmodium vivax* malaria: is it actually benign?. *Journal of Infection and Public Health.* 2011;**4**(2):91-5.

Srivastava 2011

Srivastava S, Ahmad S, Shirazi N, Kumar Verma S, Puri P. Retrospective analysis of vivax malaria patients presenting to tertiary referral centre of Uttarakhand. *Acta Tropica* 2011;**117**(2):82-5.

Tanwar 2011

Tanwar GS, Khatri PC, Sengar GS, Kochar A, Kochar SK, Middha S, et al. Clinical profiles of 13 children with *Plasmodium vivax* cerebral malaria. *Annals of Tropical Paediatrics* 2011;**31**(4):351-6.

ter Kuile 2008

ter Kuile FO, Rogerson SJ. *Plasmodium vivax* infection during pregnancy: an important problem in need of new solutions. *Clinical Infectious Diseases* 2008;**46**(9):1382-84.

Tjitra 2008

Tjitra E, Anstey NM, Sugiarto P, Warikar N, Kenangalem E, Karyana M, et al. Multidrug-resistant *Plasmodium vivax* associated with severe and fatal malaria: a prospective study in Papua, Indonesia. *PLoS Med* 2008;**5**(6):e128.

Tripathy 2007

Tripathy V, Reddy BM. Present status of understanding on the G6PD deficiency and natural selection. *Journal of Postgraduate Medicine* 2007;**53**(3):193-202.

Tusting 2013

Tusting LS, Thwing J, Sinclair D, Fillinger U, Gimnig J, Bonner KE, Bottomley C, Lindsay SW. Mosquito larval source management for controlling malaria. *Cochrane Database of Systematic Reviews* 2013, Issue 8. [DOI: 10.1002/14651858.CD008923.pub2]

Vale 2008

Vale N, Moreira R, Gomes P. Primaquine revisited six decades after its discovery. *European Journal of Medicinal Chemistry* 2008;**44**(3):937-53.

Valecha 2006

Valecha N, Joshi H, Eapen A, Ravinderan J, Kumar A, Prajapati SK, et al. Therapeutic efficacy of chloroquine in *Plasmodium vivax* from areas with different epidemiological patterns in India and their Pvdhfr gene mutation pattern. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2006;**100**(9):831-7.

Valecha 2009

Valecha N, Pinto RG, Turner GD, Kumar A, Rodrigues S, Dubhashi NG, et al. Histopathology of fatal respiratory distress caused by *Plasmodium vivax* malaria. *American Journal of Tropical Medicine and Hygiene* 2009;**81**(5):758-62.

Van den Eede 2010a

Van den Eede P, Van der Auwera G, Delgado C, Huyse T, Soto-Calle VE, Gamboa D, et al. Multilocus genotyping reveals high heterogeneity and strong local population structure of the *Plasmodium vivax* population in the Peruvian Amazon. *Malaria Journal* 2010;**9**:151.

Van den Eede 2011

Van den Eede P, Soto-Calle VE, Delgado C, Gamboa D, Grande T, Rodriguez H, et al. *Plasmodium vivax* sub-patent infections after radical treatment are common in Peruvian patients: results of a 1-year prospective cohort study. *PLoS ONE* 2011;**6**(1):e16257.

White 2011

White NJ. Determinants of relapse periodicity in *Plasmodium vivax* malaria. *Malaria Journal* 2011;**10**:297.

WHO 2000

World Health Organization. Severe falciparum malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2000;**94**(Suppl 1):1-90.

WHO 2006

World Health Organization. Guidelines for the treatment of malaria. Geneva: World Health Organization, 2006.

WHO 2009

World Health Organization. Methods for surveillance of antimalarial drug efficacy. Geneva: World Health Organization, 2009.

WHO 2010a

World Health Organization. Guidelines for the treatment of malaria -- 2nd edition. Geneva: World Health Organization, 2010.

WHO 2010b

World Health Organization. Global report on antimalarial drug efficacy and drug resistance: 2000-2010. Geneva: World Health Organization, 2010.

WHO 2011

World Health Organization. World Malaria Report 2011. Geneva: World Health Organization, 2011.

References to other published versions of this review

Galappaththy 2007

Galappaththy GN, Omari AA, Tharyan P. Primaquine for preventing relapses in people with *Plasmodium vivax* malaria. *Cochrane Database of Systematic Reviews* 2007, Issue 1. [DOI: 10.1002/14651858.CD004389]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Alvarez 2006

Methods	Randomized, parallel-group, open-label, three armed, active controlled trial **Period of study:** September 2003 to September 2004
Participants	**Participants:** 210 Patients that attended the local malaria clinics with acute symptomatic vivax malaria and a positive thick blood smear during period of study were eligible. **Inclusion criteria:** 1. Age 15 years or older 2. *P. vivax* parasitaemia of 1,000 asexual forms/L 3. Permanent residency in the municipalities of the study 4. Willingness to give informed consent and agreement to attend follow-up for six months 5. Normal G6PD screening test result **Exclusion criteria:** 1. Pregnant women 2. Co-infection with associated infectious diseases 3. History of anti-malarial intake during the previous two weeks 4. Diarrhoea or vomiting (> 5 episodes in 24 hours) 5. Hypersensitivity to anti-malarials 6. Intake of any anti-malarial different from those provided by the researchers 7. Travel to a different municipality 8. Severe undernourishment 9. Symptoms or signs of severe malaria (according to WHO 2000) 10. Consent withdrawal
Interventions	**Intervention:** 1. CQ plus PQ 45 mg over three days (N = 71) 2. CQ plus PQ 105 mg over seven days) (N = 71) **Control:** CQ * plus PQ 210 mg over for fourteen days (N = 68) CQ (600 mg): 250-mg tablets with 150 mg of CQ base, on day 0 and 450 mg on days 1 and 2 (total dose 1,500 mg) PQ: 26.3 mg tablets with 15 mg base/day
Outcomes	Recurrence (defined as any *P. vivax* parasitaemia observed (in 200 oil-immersion fields on microscopy) after day 28 in patients with adequate treatment response)
Notes	**Setting:** Local malaria clinics in two malaria endemic (El Bagre: gold-mining and Turbo: banana plantations) municipalities; malaria transmission perennial and unstable; tropical strains of *P. vivax* (from

Alvarez 2006 *(Continued)*

report); chloroquine-sensitive *P. vivax* accounted for 75% of the cases of malaria in the country (> 100,000 per year).

Country: Colombia

Funding: Universidad de Antioquia and Dirección Seccional de Salud de Antioquia, Medellin, Colombia

Comments:

- Sample size estimated to detect a minimum 15% difference in therapeutic efficacy and corrected for 20 drop-outs per arm
- Parasite clearance by day 28: confirmed in 97% by day 3 and in 100% by day 28
- Primaquine was administered concurrently with chloroquine (mentioned in this report and stated in another report from the same study group (Carmona-Fonseca 2009))
- No children were included in this trial
- Chloroquine and primaquine treatments were supervised
- Duration of follow-up: six months
- Patients were followed-up by active surveillance at the clinic or their homes for six months to identify relapses; microscopy of thick blood smears taken at 60, 120, and 180 days
- Recurrences confirmed by microscopy were given the same course of treatment (for up to two more times) as at enrolment. If parasitaemia reappeared a third time, PQ (plus a standard dose of CQ), 15 mg/day for 28 days, was given
- Trial not prospectively registered

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"We conducted a non-blind random clinical and controlled trial without placebo. A total of 210 patients with vivax malaria were recruited and allocated a treatment using an Excel (Microsoft, Redmond, WA) function". Computer generated randomization sequence.
Allocation concealment (selection bias)	Low risk	"patients were randomly assigned, in an open fashion, to one of the three treatment groups." Trial authors did not conceal allocation; however, there were no baseline imbalances between the three treatment groups with regards to age, sex, parasitaemia, weight, duration of symptoms, history of malaria, number of previous episodes, or ethnicity. Selection bias appears unlikely to have occurred.
Blinding (performance bias and detection bias) Objective outcomes: parasitaemia and serious adverse effects	Low risk	The study was not blinded and trial authors actively followed up patients at home; the microscopist was probably aware of treatment allocation, but the definition of recurrence used was any parasitaemia detected during specified follow-up examinations during six months. We feel this was unlikely to have biased outcome reporting. No serious adverse events were presented in the trial report.
Blinding (performance bias and detection bias) Subjective outcomes:other adverse effects	Low risk	No adverse events or subjective outcomes were reported.
Incomplete outcome data (attrition bias) Objective outcomes: parasitaemia and serious adverse effects	Low risk	"Between days 28 and 180 of the follow-up period, 19 patients were lost; these were equally distributed among the three groups of study and had no effect on the results observed." The total loss to follow-up was 9%, (9%, 13%, 6%).

Alvarez 2006 *(Continued)*

		"All patients were included in analysis of efficacy (to time of recurrence or loss to follow-up) and all outcomes were included for analysis, regardless of compliance with dosing regimens (intent-to-treat)." "The number of lost patients during the follow-up period had no effect on the final results, as confirmed after per protocol, intend-to-treat, and worst-case scenario analysis." Sensitivity analyses did not differ in direction of effect estimates.
Incomplete outcome data (attrition bias) Subjective outcomes: Other adverse effects	Low risk	Not applicable as trial authors did not report any subjective outcomes or other adverse events.
Selective reporting (reporting bias)	Low risk	Trial authors only pre-stated the outcome of recurrence in the methods and adequately reported this. They did not report any safety outcomes specifically.
Other bias	Low risk	We did not detect any other potential sources of bias.

Carmona-Fonseca 2009

Methods	Randomized, parallel-group, open-label, four-armed, active controlled trial **Period of study:** September 2003 to September 2006
Participants	**Participants:** 188 Patients that attended the local health clinics with acute symptomatic vivax malaria and a positive thick blood smear during the period of the study were eligible. **Inclusion criteria:** 1. Age > 2 years 2. *P. vivax* parasitaemia of >1000 asexual forms/L 3. Wllingness to participate 4. A normal quantitative G6PD screening test **Exclusion criteria:** 1. Pregnant women 2. Associated acute infectious diseases 3. History of antimalarials intake during the previous two weeks 4. Presence of diarrhoea or vomiting (> 5 episodes in 24 hours) 5. Symptoms or signs of severe malaria (according to WHO 2006), 6. Hypersensitivity to antimalarials 7. Severe under-nutrition 8. Intake of any antimalarial different from those provided by the researchers 9. Failure to attend follow-up appointments 10. Treatment failure during the primary episode (28 days of follow-up) 11. Consent withdrawal
Interventions	**Intervention:** 1. CQ + PQ STD 3 days (equivalent of standard total dose of 3.5 mg/kg but administered over 3 days; 1.17 mg/kg day for 3 days) (N = 65)

Carmona-Fonseca 2009 *(Continued)*

	Control: 1. CQ + PQ 14 days (standard total dose of 3.5 mg/kg administered over 14 days; 0.25 mg/kg day for 14 days) (N = 68) All participants received chloroquine as recommended by the Colombian health authorities (10mg/kg day on day 1 and 7.5mg/kg day on days 2 and 3) **Not used for quantitative synthesis in the review*:** 1. CQ + PQ 71% STD 3 days (2.5 mg/kg, which is lower than the total standard dose and given over 3 days, (i.e. 0.83 mg/kg day for 3 days) (N = 28) 2. CQ + PQ 50% STD 3 days (1.75 mg/kg, which is lower than the standard total dose and administered over 3 days; i.e. 0.58 mg/kg day for 3 days) (N = 27) * Trial authors stopped recruitment to these arms early, after recruiting only around half the estimated sample, due to lack of efficacy.
Outcomes	Recurrence (defined as any *P. vivax* parasitaemia (in 200 oil-immersion fields on microscopy) observed after day 28 on patients with adequate treatment response) and during follow-up
Notes	**Setting:** Local malaria clinics in two malaria endemic (El Bagre; gold-mining and Turbo: banana plantations) municipalities; malaria transmission perennial and unstable; tropical strains of *P. vivax* (from report); chloroquine-sensitive *P. vivax* accounted for 70% to 80 % of the malaria cases in the country **Country:** Colombia **Funding:** Universidad de Antioquia and Dirección Seccional de Salud de Antioquia, Medellin, Colombia **Comments:** • Sample size estimated to detect a minimum 15% difference in therapeutic efficacy and increased by 30% to correct for drop-outs per arm • Parasite clearance by day 28: confirmed in 100% by day 28 • Primaquine was administered concurrently with chloroquine • Children > 2 years old were included in this trial • Chloroquine and primaquine treatments were supervised • Duration of follow-up: four months • Patients were followed up by active surveillance at the clinic or their homes for six months to identify relapses; microscopy of thick blood smears taken at 60 and 120 days • Recurrences confirmed by microscopy were given the same course of treatment (for up to two more times) as at enrolment. If parasitaemia reappeared a third time, PQ (plus a standard dose of CQ), 15 mg/day for 28 days, was given • Recruitments into the two low dose three days of primaquine arms were stopped after recruiting half the estimated sample (28 and 27 patients respectively), due to the high number of recurrences observed (we did not use data from these arms for meta-analysis) • Trial not prospectively registered

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"After clinical evaluation and examination of thick and thin blood smears to establish the diagnosis, patients were randomly assigned, in an open fashion, to one of four treatment groups." Method not mentioned, but trial due during the same period by the same group (Alvarez 2006) used computer generated sequences.

Carmona-Fonseca 2009 *(Continued)*

Allocation concealment (selection bias)	Low risk	"...patients were randomly assigned, in an open fashion, to one of four treatment groups." Trial authors did not conceal allocation, but as in Alvarez 2006, there were no baseline imbalances in age, weight, duration of symptoms, and malaria history; and parasite density or G6PD activity. Unlikely to be at risk of selection bias.
Blinding (performance bias and detection bias) Objective outcomes: parasitaemia and serious adverse effects	Low risk	"We confirmed the absence of severe complications or adverse effects and therefore recommend the simultaneous administration of chloroquine and primaquine." As with Alvarez 2006, the study was not-blinded and patients were actively followed up at home; the microscopist was probably aware of treatment allocation, but the definition of recurrence used was any parasitaemia detected during specified follow-up examinations during six months. We felt it unlikely that the open-label design would bias outcome reporting of parasitaemia. No serious adverse events were observed in the trial.
Blinding (performance bias and detection bias) Subjective outcomes:other adverse effects	Low risk	No participants reported adverse events; no subjective outcomes were reported.
Incomplete outcome data (attrition bias) Objective outcomes: parasitaemia and serious adverse effects	Low risk	"Patients lost during the follow-up period represented < 5% in all groups." Trial authors did not report actual proportions in each arm, but at these rates of dropout, we thought differential effects were unlikely.
Incomplete outcome data (attrition bias) Subjective outcomes: Other adverse effects	Low risk	Trial authors did not report any subjective outcomes or other adverse events.
Selective reporting (reporting bias)	Low risk	The stated outcome was recurrence only and trial authors adequately reported this. Trial authors did not report any safety outcomes specifically other than lack of severe adverse events.
Other bias	Low risk	We did not detect any other biases.

Ganguly 2013

Methods	Randomized, parallel-group, open-label, two-armed trial **Period of study:** December 2011 to August 2012
Participants	**Participants:** 250 All patients attending the clinic who were screened for malaria parasite presence, by examining thick and thin smears of peripheral blood followed by Giemsa staining, were eligible. **Inclusion criteria:** 1. Age > 6 months 2. Axillary temperature > 37.5 °C, or history of fever during 48 hours before recruitment 3. *P. vivax* mono-infection, confirmed by presence of negative HRP-II test, with parasitaemia of 1000–100000 parasites/µL blood

Ganguly 2013 *(Continued)*

4. No anti-malarial treatment during the preceding four weeks
5. Absence of severe malaria
6. Able to swallow oral medicine
7. No history of hepatic or kidney diseases
8. Ability and willingness to comply with study protocol and visit schedule
9. Written informed consent provided by patient or guardian

Exclusion criteria:

1. Patients who repeatedly vomited their study medicines
2. Severe malnutrition by WHO standards
3. Contraindication to study medication
4. Pregnancy
5. Other febrile conditions

Interventions	**Intervention:** CQ (25 mg/kg base) over 3 days + PQ (0.25 mg/kg) for 14 days (N = 125) **Control:** CQ (25 mg/kg base) over 3 days (N = 125)
Outcomes	**Outcomes used in this review:** 1. Adequate clinical and parasitological response (APCR) at day 42 (WHO 2009) 2. Adverse events **Outcomes not used in quantitative synthesis in this review:** 1. Early treatment failure (ETF) 2. Late clinical failure (LCF) 3. Late parasitological failure (LPF) 4. PCR-corrected APCR at day 42 5. Genus and species specific PCR for polymorphisms of pvmdr1 and 58 pvcrt-0 genes by DNA sequencing
Notes	**Setting:** Malaria clinic attached to the protozoology unit, Calcutta School of Tropical Medicine. *P. falciparum* and *P. vivax* infection are equally predominant; *P. vivax* is perennial; *P. falciparum* is seasonal with an annual peak from August to December **Country:** India **Funding:** Department of Health and Family Welfare, Government of West Bengal **Comments:** • This trial primarily aimed to evaluate the sensitivity of chloroquine in eliminating blood stage vivax infection • Sample size estimation not reported • Mixed infections were ruled out by*P. vivax* specific pLDH 169 and HRP-II (SD Bio Standard Diagnostics Pvt. Ltd., Gurgaon, India) • G6PD level of all recruited patients were determined qualitatively using G6PDH Hemopak kit; no G6PD deficiency identified • Parasite clearance by day 28: confirmed in 100% by day 28 • Primaquine and chloroquine were administered sequentially • Children > 6 months old were eligible, but age of included participants ranged from 5 years to 65%; approximately 20% were aged 5 to 15 years • Chloroquine treatments were supervised in all and primaquine was supervised for first 7 days and by checking empty blister packs till day 14

Ganguly 2013 *(Continued)*

- Duration of follow-up: 42 days
- Patients were followed up by active surveillance at the clinic or their homes 1, 2, 3, 7, 14, 21, 28, 35 and 42 days after initiation of treatment and were examined both clinically and parasitologically
- PCR-corrected APCR not used as an outcome for this update, due to doubtful validity of the PCR method used to reliably differentiate relapse and re-infection
- Trial was prospectively registered in the Clinical Trials Registry- India: Registration No. CTRI/2011/09/002031

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from trials registration record, "Computer generated randomisation."
Allocation concealment (selection bias)	Low risk	Quote from trials registration record, "An open list of random numbers." Allocation can be predicted with the use of an open list, but participants had to have vivax mono-infection by smear and a rapid diagnostic test; and there were no baseline imbalances between treatment groups for age, sex, temperature, and baseline parasite count, making selection bias less likely.
Blinding (performance bias and detection bias) Objective outcomes: parasitaemia and serious adverse effects	Low risk	The trial was open label and trial authors did not conceal allocation; but two microscopists independently read blood smears. We don't think this would be have biased detection of parasitaemia or serious adverse events.
Blinding (performance bias and detection bias) Subjective outcomes:other adverse effects	High risk	The open label nature of the trial, lack of allocation concealment, and lack of placebo in the CQ only arm could have biased reporting of subjective outcomes.
Incomplete outcome data (attrition bias) Objective outcomes: parasitaemia and serious adverse effects	Low risk	In the CQ arm 24/125 were lost to follow-up compared to 21/124 in the CQ plus 14-day PQ arm (plus one exclusion after randomization due to detection of mixed *P. vivax* and *P. falciparum* infection). There were 101/125 evaluable participants in the CQ arm and 103/125 in those randomized to CQ + 14-day PQ arm. Overall 18% were not included in the per-protocol analysis, but no differential drop-out rates were seen.
Incomplete outcome data (attrition bias) Subjective outcomes: Other adverse effects	Low risk	Trial authors actively followed up all participants with clinical assessments at regular intervals up to day 42.
Selective reporting (reporting bias)	Low risk	Trial authors prospectively registered the trial and we did not detect any evidence of selective reporting.
Other bias	High risk	Follow-up was for only 42 days (two weeks after the 28 day period where CQ alone would be effective against relapses). This is inadequate to detect future relapses over the next four to five months.

Gogtay 1999

Methods	Parallel group, randomized, open-label, active controlled, observer-blinded, trial with three intervention arms

Gogtay 1999 *(Continued)*

	Period of study: October 1997 to September 1998
Participants	**Participants:** 244 Patients residing within 12 km of the hospital and referred for suspected malaria were eligible. **Inclusion criteria:** 1. Smear positive for *P. vivax* 2. Willing to be hospitalized, followed up and comply with study instructions **Exclusion criteria:** 1. Mixed infections 2. G6PD deficiency participants
Interventions	**Interventions:** 1. CQ 25 mg/kg for 3 days (N = 83) 2. CQ 25 mg/kg for 3 days plus PQ 0.25 mg/kg for 14 days (N = 81) **Control:** 1. CQ 25 mg/kg for 3 days plus PQ 0.25 mg/kg for 5 days (N = 80) CQ 10mg/kg on day and 5 mg/kg on day 2 and day 3
Outcomes	**Outcomes** 1. Number of participants relapsing during the 6-month follow-up period 2. Adverse events **Outcomes not available in report:** Parasitemia between 6 months and one year follow-up (specified in methods)
Notes	**Setitng:** K.E.M. Hospital in Mumbai; Malaria endemicity: 80% of infections in Mumbai were due to vivax malaria at the time of the report. Tropical strains; low transmission setting. Chloroquine-sensitive parasite at the time of the report. **Country:** India **Funding:** Not stated. Drugs provided free of cost by municipal authorities **Comments:** • No sample size estimation reported • Parasite clearance by day 28: Confirmed in 100% by day 4 and remained smear negative till day 29 • Primaquine was administered after chloroquine on day 4 • No children < 16 years were included in this trial • Chloroquine and primaquine treatments were supervised • Duration of follow-up: Six months; 60/83 (72%) in CQ only arm, 62/80 (78%) in the CQ + PQ 5 days arm, and 63/81 (78%) in the CQ + PQ 14-day arm completed six months of follow-up; data from period 6 months to one year not available in the report. • Patients were followed-up at the hospital monthly for a year or when they had fever; in some instances the smear technician visited their homes for six months to identify relapses; microscopy of thick blood smears taken monthly from all participants at monthly clinic visits • Recurrences confirmed by microscopy were given CQ + PQ for 14 days • Trial protocol not available
Risk of bias	

Gogtay 1999 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were "randomly assigned". The first author clarified that randomization codes were generated from a list of random numbers by personnel not otherwise involved in the study.
Allocation concealment (selection bias)	Low risk	Trial authors did not state the method used for allocation concealment; however, the first author clarified that coded containers with the interventions were prepared by the pharmacists; person recruiting subjects did not have access to the code.
Blinding (performance bias and detection bias) Objective outcomes: parasitaemia and serious adverse effects	Low risk	The trial was unblinded with supervised treatment of 5 or 14 days of primaquine, and the third group receiving no treatment after CQ. The first author clarified that microscopist had no knowledge of treatment assignment. We judged this was unlikely to introduce bias for ascertainment of objective outcomes.
Blinding (performance bias and detection bias) Subjective outcomes:other adverse effects	Low risk	The trial was unblinded with supervised treatment of 5 or 14 days of primaquine, with the third group receiving no treatment. This raised the possibility of bias, but as trial authors reported that no participants developed adverse effects, hence the risk of bias is unlikely.
Incomplete outcome data (attrition bias) Objective outcomes: parasitaemia and serious adverse effects	Low risk	"One patient in Group A (CQ only) who came back with *P. vivax* parasitaemia on Day 14 (indicative of RI resistance to chloroquine) was excluded from analysis" Unlikely to introduce bias in the intention to treat analysis used in this review. Follow-up completed only by 72% to 77% of participants randomized but nearly equal numbers in each group completed follow-up at six months; follow-up data from 6 months to one year not reported but this was because the trial was terminated due to lack of efficacy in the 5 day PQ arm. Relapse in India behave like temperate strains with few early relapses with most occurring between six months to a year. Unlikely to introduce bias in relative efficacy reported at 6 month follow-up. Adverse events appear not to have been systematically ascertained nor reported; however, trial authors state that all participants tolerated drugs and none reported adverse events other than mild nausea and itching.
Incomplete outcome data (attrition bias) Subjective outcomes: Other adverse effects	Unclear risk	Trial authors did not systematically report adverse events or numerical data on adverse events by treatment arm.
Selective reporting (reporting bias)	Low risk	Apart from incomplete outcome reporting between 6 months to one year, trial authors reported all pre-stated outcomes.
Other bias	Low risk	"No attempt was made to distinguish relapses and re-infections in the present study" Trial authors do not believe that re-infections were likely based on local epidemiology; and parasitic clearance was confirmed by day 28. We did not detect any other sources of bias.

Kim 2012

Methods	Randomized, parallel group, open-label, three arm trial **Period of study:** April 2003 to September 2004 (recruitment)
Participants	**Participants:** 151 **Inclusion criteria:** 1. Acute uncomplicated vivax malaria, confirmed by positive blood smear with asexual forms of *P. vivax* 2. Male or female, aged from 36 months to 65 years old, inclusive 3. Fever defined as ≥ 37.5°C tympanic temperature or a history of fever within the last 24 hours 4. Written informed consent (by legally acceptable representative in case of children) 5. Willingness and ability of the patients/guardians to comply with the study protocol for the duration of the study **Exclusion criteria:** 1. Signs of severe/complicated malaria (WHO 2000) 2. Haematocrit < 25% or haemoglobin (Hb) < 8 g/dL at enrolment 3. Acute illness other than malaria requiring treatment 4. For females: pregnancy, breast feeding 5. Patients who have received anti-malarial treatment within the previous 7 days 6. History of allergy or known contraindication to study drugs 7. G6PD deficiency: patients who are deficient on spot testing were not allocated to the two primaquine groups
Interventions	**Interventions:** 1. Chloroquine (25 mg base/kg total) only; 10 mg/kg on day 1, 10 mg/kg on day 2 then 5 mg/kg on day 3 (N = 50) 2. Chloroquine (25 mg base/kg total as above) followed by primaquine 0.25 mg base/kg/day for 5 days - total dose 1.25 mg base/kg (75 mg in an adult) (doses were unsupervised) (N = 59) **Control:** 3. Chloroquine (25mg base/kg total) followed by primaquine 0.25mg base/kg/day for 14 days - total dose 3.5 mg base/kg (210 mg in an adult) (doses were unsupervised) (N = 42)
Outcomes	**Outcomes used in quantitative synthesis** 1. Recurrence rate of vivax malaria over 15 months 2. Serious adverse events **Outcomes reported but not used in quantitative synthesis** 1. Parasite clearance time assessed by microscopy 2. Fever clearance time (the time taken for the tympanic temperature to fall below 37˚C and remain there for at least 24 hours) 3. Genotype assessments
Notes	**Setting:** Calcutta School of Tropical Medicine. Of around 6,000 malaria cases seen annually, approximately 65% are caused by *P. vivax.* Patients were mainly from urban, and a few were from peri-urban Kolkata. **Country:** India **Source of funding:**

Kim 2012 *(Continued)*

- Wellcome Trust-Mahidol University, Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain- Wellcome Trust (UK) (reference No. 066439/2/01/2);
- National Science and Technology Development Agency, the office of the Higher Education Commission and Mahidol University under the National Research Universities Initiative, and Wellcome Trust Intermediate Fellow [grant 080867/Z/06/Z] to Mallika Imwong.

Comments:

- Trial authors based sample size estimation on an assumption that relapse rates would be 30% in the chloroquine only group and 4% in the 14-day primaquine group, and allowed for 20% loss to follow-up or incomplete data; trial authors aimed for a total of 150 participants with 50 in each arm.
- Trial authors generated computer generated randomization sequences in the ratio 1:1:1 and allocation was through sequentially numbered opaque envelopes containing the randomization codes; this does not explain the unequal numbers allocated (CQ n = 50; CQ plus PQ 5 days n = 59; CQ plus PQ 14 days n = 42)
- Parasite clearance by day 28: confirmed in 100%
- Primaquine was administered after chloroquine on day 4
- Children < 16 years were included in this trial
- Although G6PD deficiency was an exclusion criterion, two people in the CQ only arm were reported to have this deficiency
- Chloroquine treatment was supervised. Primaquine was supervised for the first dose only
- Duration of follow-up: 15 months
- Patients were seen daily until afebrile then weekly for one month and thereafter every one to two months for 15 months.
- If vivax malaria recurred blood was taken for parasite genotyping and comparison with the original infection, and patients were treated with chloroquine followed by primaquine 0.25 mg base/kg daily for 21 days.
- Study used eight microsatellite and three antigenic markers were initially genotyped in 90 samples and three polymorphic microsatellite and antigenic molecular markers found sensitive to PCR amplification at low parasite densities were used for subsequent analyses for 39 of 47 recurrences. Only three markers were used in the remaining eight recurrences due to insufficient DNA to use all six markers.
- Trial protocol available as supplementary file with published report
- Contact author named in trial registration document and in the trial report were contacted for additional information- no reply was obtained till submission of this review update.

Registration Number: ISRCTN14027467

This trial was registered retrospectively: date applied: 12/11/2011; date registered: 16/11/2011

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quotes from trial protocol: "Subjects who fulfil all the inclusion criteria and have none of the exclusion criteria will be randomized 1:1;1 to one of the three treatment arms." "The subjects will be assigned a study arm through a computer-generated randomisation schedule."
Allocation concealment (selection bias)	High risk	Quotes from trial protocol: "Allocation will be done by drawing the next sequential numbered opaque envelope, which contains the study number of the patient referring to the study treatment" "..., the randomisation procedure allows for adequate drug allocation concealment before envelopes are opened." The unequal numbers in the three arms (CQ alone n = 50; 5-day PQ n= 59, 14-day PQ n = 42) is unexplained for a planned total sample of 150 participants with 50 each in each arm (1:1:1 computer-generated randomization), and the stated method of allocation concealment. The estimated sample size was achieved, so even if simple, and not block randomization was used, unequal

Kim 2012 *(Continued)*

		numbers, particularly the 59 in the 5-day PQ arm. is unlikely; unless method of allocation concealment was compromised during execution of the study.
Blinding (performance bias and detection bias) Objective outcomes: parasitaemia and serious adverse effects	High risk	Quotes from study protocol: "This is an open-label study so the blinding of investigators and patients is not applicable." "All laboratory investigations will be performed without knowledge of the treatment allocation.." Quote from report: "All patients tolerated their medication well and recovered following antimalarial treatment. The treatments were generally well tolerated and (*there*) were no serious adverse effects." Quote from report: "In this open randomised comparison neither primaquine regimen reduced the incidence of *P. vivax* recurrence. The most likely explanation for this lack of effectiveness is poor adherence to the 14-day primaquine regimen, and lack of efficacy of the shorter course regimen". The method used (if any) to monitor adherence was not mentioned in the trial report and was not available from the authors. In this trial of unsupervised primaquine treatment, the expected benefit with 14-day primaquine (4% relapse was used for sample size estimations) was not seen, but without data to confirm the explanation offered by the authors, and to adjust for non-adherence, the results for efficacy and safety are unreliable.
Blinding (performance bias and detection bias) Subjective outcomes:other adverse effects	Unclear risk	The trial authors did not report any other adverse effects; we do not know if the trial authors systematically ascertained these. Evaluation of risk of bias is also confounded by possibility (raised by trial authors) that participants given primaquine did not take their drugs.
Incomplete outcome data (attrition bias) Objective outcomes: parasitaemia and serious adverse effects	Low risk	The trial authors did not report any other adverse events.
Incomplete outcome data (attrition bias) Subjective outcomes: Other adverse effects	Unclear risk	All randomized participants completed the trial and trial authors reported data for all participants.
Selective reporting (reporting bias)	Low risk	The trial was retrospectively registered, but from the trial protocol made available in a supplementary online file, no selective reporting was evident.
Other bias	Low risk	We did not detect any other biases.

Leslie 2004

Methods	Cluster-randomized, placebo and active controlled, three armed trial: unit of allocation = family; unit of analysis = individuals **Period of study:** June 2000 to August 2001
Participants	**Participants:** 595 **Inclusion criteria:** 1. Clinical malaria cases with blood smear positive for *P. vivax* 2. Temperature > 37.5 ºC or recent history of fever **Exclusion criteria:**

Leslie 2004 *(Continued)*

1. G6PD deficiency
2. Age < 3 years
3. Pregnancy
4. Severe anaemia
5. Mixed infections

Interventions	**Interventions** 1. CQ (3 days) plus PQ (14 days): unsupervised (N = 173; 87 families) **Control:** 1. CQ (3 days) and placebo: (N = 212; 98 families) **Not used in quantitative synthesis in this review** 1. CQ* (3 days) plus PQ# (14 days); supervised (N = 210; 105 families) CQ dose: 25 mg/kg PQ dose: 0.25 mg/kg *data from unsupervised primaquine and placebo arms used as they were considered comparable since the placebo arm was not supervised; and since estimates did not differ significantly between supervised and unsupervised arms
Outcomes	1. Number of participants relapsing (confirmed by microscopy) during the 9-month follow-up period 2. Adverse events
Notes	**Setting:** Adizai (Afghan) refugee camp, North-West Frontier Province. Malaria endemicity: highly endemic for *P. vivax* and *P. falciparum* malaria with active transmission from June to November **Country:** Pakistan **Funding:** European Commission (DG1), UNHCR, and WHO/UNDP/World Bank Special Programme for Research and Training in Tropical Diseases; Department for International Development (DFID); Gates Foundation **Comments:** • Trial authors did not report any sample size estimation • They did not confirm parasitic clearance after intervention • Included children > 3 years and 38% of sample were aged 3 to 5 years, and 55% below the age of 10 years • G6PD deficiency was an exclusion criterion but 10/474 individuals tested (2.1%) were G6PD deficient • Chloroquinne and primaquine were given sequentially • The trial compared outcomes in two arms CQ + PQ for 14 days given unsupervised treatment by direct observation, and one arm of PQ 14 days that was supervised. Unsupervised group and those on placebo may have been blinded; supervised group was not blinded • Duration of follow-up: nine months. Patients were followed up by passive case detection, but all healthcare was provided in-camp, and was free. Follow-up completed by > 90% of 595 participants enrolled from 290 families • Data analyzed in report by random-effects logistic regression: unit of analysis was the participant and adjusted for clustering • Data used in meta-analysis were adjusted odds ratios and 95% CIs for relapse at 9 months for unsupervised primaquine group (n = 34/210; 19.7%) and in placebo group (n = 86/212; 40.6%). Data for supervised primaquine groups not used; results not notably different from unsupervised group compared to placebo • Trial protocol not available

Leslie 2004 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomised by family". Cluster randomization: method used for generating sequence not stated but likely to be adequate as baseline characteristics balanced across groups.
Allocation concealment (selection bias)	Low risk	Trial authors did not state the method they used, but there were no baseline imbalances for known confounders.
Blinding (performance bias and detection bias) Objective outcomes: parasitaemia and serious adverse effects	Low risk	Trial authors did not state whether they performed blinding in report but the risk of bias for objective outcomes is unlikely.
Blinding (performance bias and detection bias) Subjective outcomes:other adverse effects	Low risk	Trial authors did not state whether they performed blinding in report and the risk of bias for subjective outcomes is possible, though unlikely, as trial authors did not report adverse effects as different in treatment groups.
Incomplete outcome data (attrition bias) Objective outcomes: parasitaemia and serious adverse effects	Low risk	"All families were still residing in the camp after 9 months of follow up". There appear to have been no drop outs or withdrawals and trial authors fully reported outcome data for primary outcomes, which were presented stratified by age group.
Incomplete outcome data (attrition bias) Subjective outcomes: Other adverse effects	Low risk	Trial authors did not report numerical data for adverse events by treatment group but stated that PQ was well-tolerated throughout.
Selective reporting (reporting bias)	Low risk	The trial was not prospectively registered but trial authors reported all prestated outcomes.
Other bias	Low risk	Trial authors did not differentiate relapses from re-infections and conducted the trial in an endemic area during a period of intense transmission; males had higher rates of infection at follow-up and trial authors surmised that this could be due to re-infection. However, it is unlikely that this would introduce bias for relative efficacy of treatments.

Leslie 2008

Methods	Parallel-group, placebo and active controlled, cluster and individually randomized, open-label, clinical trial **Period of study:** 13 July 2006 to 17th June 2007
Participants	**Participants:** 200 **Inclusion criteria** 1. Patients diagnosed with *P. vivax* parasitaemia at study BHUs 2. Patients over 3 years of age 3. Patients with G6PD deficiency to a sub-study, safety trial

Leslie 2008 *(Continued)*

4. Patients without G6PD deficiency to all other groups.

Exclusion criteria

1. Children under the age of three
2. Pregnant / breast feeding women
3. Patients with severe clinical anaemia (<7 g/dL)
4. Patients with *P. falciparum* or mixed infections
5. Patients unavailable for the duration of follow-up
6. Patients who have taken any antimalarial drugs in the 2 weeks prior to consultation
7. Patients with concomitant infections or whose general health is considered too poor

Interventions	**Intervention:** 1. CQ 3 days followed by supervised 8 week PQ treatment (45 mg / week) (N = 74) **Controls:** 1. CQ 3 days with supervised weekly placebo for 8 weeks (-ve control group) (N = 71) 2. CQ 3 days followed by supervised 14-day primaquine treatment (+ ve control group) – excluding G6PD deficient patients (N = 55) CQ (600 mg) total dose in adults was 1200 mg over three days in adults PQ total dose in adults was (22.5 mg base) 325 mg for 14-day PQ group; and (45 mg for 8 doses) 360 for 8-week PQ Additional intervention: health education messages and strong advice to complete the course. **Safety arm:** Quote from study protocol: "In addition a safety arm will be used for G6PD deficient patients; this will be used to compare HB with group 3 (above). This will be an 8 week regimen, administered by direct observation, and will receive close monitoring for signs of haemolysis".
Outcomes	**Primary outcome:** 1. Treatment failure (defined as the occurrence of any episode of microscopically-confirmed vivax malaria over the 11 months) **Secondary outcomes:** 1. Any notable adverse events **Outcomes not used for quantitative synthesis in this review:** 1. Number of subsequent episodes during and up to 2 weeks post-treatment 2. Anaemia rates during and up to 2 weeks post-treatment
Notes	**Setting:** Afghan refugee settlements in Adizai, Baghicha and Khagan villages, close to Peshawar, North-west Frontier Province. Seasonal malaria transmission, predominantly vivax. Chloroquine and primaquine sensitive parasites; study conducted in a period with low transmission intensities (75% reduction compared to studies in the same camps five years previously). Relapse patterns are as with tropical strains, early, frequent relapses, mostly in the early months (but also later) **Country:** Pakistan **Funding:** UNDP/World Bank/WHO Special Program for Research in Tropical Diseases; Gates Malaria Partnership **Comments:** • Trial authors revised the sample size estimation before the start of the trial following an unscheduled interim analysis conducted in June/July 2006 due to low transmission and slow recruitment. They reduced sample size from 212 to 66 per treatment arm and aimed for a 25% difference between treated

Leslie 2008 *(Continued)*

and non-treated arms. The trial was not powered to show equivalence or non-inferiority between the 14-day or 8 weekly-dose primaquine arms.

- Parasitic clearance after intervention was not confirmed
- Included children > 3 years of age
- All treatments were supervised according to the regimen
- Chloroquine and primaquine were given sequentially
- Duration of follow-up nine months after the 8 week treatments (11 months from start): follow-up was by active surveillance (being visited in their homes every two weeks) and passively on presentation at the basic health centre.
- Only people with fever suggestive of malaria had blood smears taken
- Blood smears were read by two independent microscopists blind to other results (not clear if blind to allocation)
- For practical reasons, trial authors used two randomization methods. In Baghicha and Khagan villages, they randomized patients by household, whereas in Adizai randomization was at the individual (since this site was added later, and was not in the protocol). In addition, those with G6PD deficiency were not randomized, but assigned to the 8-week PQ group in order to follow closely to assess safety.
- Numbers enrolled to 8-week placebo and 8-week PQ were similar (N = 71 and N = 74) but were less in 14-day PQ (N = 55), due to exclusion of G6PD deficient persons from this arm
- The numbers randomized to each arm of this three-armed trial were unequal with the majority recruited from Adizai (Adizai 100 (50.0%), Baghicha 79 (39.5%), and Khagan 21 (10.5%)
- The numbers recruited to each of the three arms also differed by trial site with Adizai contributing 38% of those given 8 week placebo, 54.5% of those given 14-day primaquine, and 58% of those given 8 weeks of primaquine; and Khagan contributing the least to the three arms (14%, 3.6% and 10.8%, respectively).
- The percentage of people who were anaemic at enrolment (haemoglobin <10 g/dL) were also unequally distributed (14.1% of those on 8-week placebo; 3.6% of those given 14 days of primaquine and 9.5% of those treated with 8 weekly doses of primaquine).
- People from Adizai village also had the largest proportion of treatment failures over 11 months of follow-up, particularly in those on placebo (67%, versus 3.3% on 14 days primaquine, and 9.3% on 8 weeks of primaquine). Baghicha also experienced treatment failures on 8-week placebo following chloroquine (12.1%), while none of the people in the other treatment arms relapsed. There were no treatment failures in Khagan for those on any of the three interventions.
- Loss to follow-up and withdrawals were 5% of those enrolled and occurred by 8 weeks (3 with 8-week placebo (4.2%), 1 with 14-day PQ (1.8%), and 6 with 8-week PQ (8.1%)); no losses over nine months of follow-up
- Results reported were odds ratios adjusted for clustering and for sites, age and sex
- Trial registration number: ClinicalTrials.gov NCT00158587
- Numbers enrolled to 8-week placebo and 8-week PQ were similar (N = 71 and 74) but were less in 14-day PQ (N = 55), due to exclusion of G6PD deficient persons from this arm
- The numbers randomized to each arm of this three-armed trial were unequal with the majority recruited from Adizai (Adizai 100 (50.0%), Baghicha 79 (39.5%), and Khagan 21 (10.5%).
- The numbers recruited to each of the three arms also differed by trial site with Adizai contributing 38% of those given 8 week placebo, 54.5% of those given 14-day primaquine, and 58% of those given 8 weeks of primaquine; and Khagan contributing the least to the three arms (14%, 3.6% and 10.8%, respectively).
- The percentage of people who were anaemic at enrolment (haemoglobin <10 g/dL) were also unequally distributed (14.1% of those on 8-week placebo; 3.6% of those given 14 days of primaquine and 9.5% of those treated with 8 weekly doses of primaquine).
- People from Adizai village also had the largest proportion of treatment failures over 11 months follow-up, particularly in those on placebo (67%, versus 3.3% on 14 days primaquine, and 9.3% on 8 weeks of primaquine). Baghicha also experienced treatment failures on 8-week placebo following chloroquine (12.1%), while none of the people in the other treatment arms relapsed. There were no treatment failures in Khagan for those on any of the three interventions
- Loss to follow-up and withdrawals were 5% of those enrolled and occurred by 8 weeks (3 with 8-week placebo (4.2%), 1 with 14-day PQ (1.8%), and 6 with 8-week PQ (8.1%)); no losses over nine months follow-up

Leslie 2008 *(Continued)*

- Results reported were odds ratios adjusted for clustering and for sites, age and sex
- Trial registration number: ClinicalTrials.gov NCT00158587

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote from report: "Randomisation lists for each village were generated using a random number list (MS Excel, Microsoft Corp., Seattle, USA) by staff not involved in patient recruitment." Quote from report: "Those with G6PD deficiency were not randomised, but assigned to the 8-week PQ group in order to follow closely to assess safety." Quote from study protocol: "All patients will be randomly allocated into three groups using randomisation blocks of different sizes." While the procedure to generate random sequences is adequate, the application of the random sequences appear to have been compromised by the exclusion of G6PD deficient persons from the 14-day primaquine arm leading to a 22% lower enrolment rate in this arm (55), compared to the CQ + placebo arm (71) and the 8-week supervised PQ arm (74). The 55 in the 14-day PQ arm is below the estimated 66 per treatment arm estimated in the unscheduled revised sample size calculation. Also see below under allocation concealment.
Allocation concealment (selection bias)	High risk	Quote from report: "In Baghicha and Khagan villages, patients 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. Patients were randomized on enrolment by study staff in the BHUs based on house number or sequential patient numbers, depending on the study site." This appears to be a quasi-random allocation method where allocation was not unpredictable. The study protocol available from the online PLoS One publication does not list Adizai village; this village appears to have been added after the unscheduled interim analysis (that also resulted in a revised sample size estimate from 212 per treatment arm to 66 per treatment arm) due to low recruitment rates caused by lower than expected malaria transmission during the study period. The mixed randomization design and, in particular, the sequential allocation of participants to the Adizai site, which had the highest enrolment (50%) and was also associated in multivariate analysis to have the highest treatment failure rates in the placebo arm, indicates that there was a high risk of selection bias. In addition, the trial report states that only one G6PD deficiency participant was enrolled (see quote below under blinding for objective outcomes). This does not then explain the difference in enrolment in the three arms, considering that block-randomization was to have been used.
Blinding (performance bias and detection bias) Objective outcomes: parasitaemia and serious adverse effects	Low risk	Quotes from report, "Patients were monitored during the eight weeks of treatment and for nine additional months by active surveillance (being visited in their homes every two weeks) and passively on presentation at the basic health centre. Patients presenting at the basic health unit with suspected treatment failure (febrile illness) were assessed by thick and thin "blood smear". "Blood slides were double read by two independent microscopists, blinded to the others result." Although this was an open label study, the independent confirmation adds credibility to the results, but since study staff allocated participants (using quasi-random techniques), and home visits were made, detection bias is possible. However, the detection of parasitaemia is an objective outcome measure, and unlikely to introduce detection bias.

Leslie 2008 *(Continued)*

		Quote from study protocol: "An adverse event is defined as any noxious, pathological or unintended change in anatomical, physiological or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes occurring in any phase of the clinical study whether associated with the study drug or placebo and whether or not considered drug related. Adverse events will be classified as follows: ...Severe adverse event: For example, an adverse experience which prevents normal everyday activities e.g. haemolysis". Quote from report: "The sole G6PD deficient patient showed a slight drop in haemoglobin which was not clinically significant. " Trial authors monitored serious adverse events and none were reported.
Blinding (performance bias and detection bias) Subjective outcomes:other adverse effects	Low risk	No other adverse events were reported.
Incomplete outcome data (attrition bias) Objective outcomes: parasitaemia and serious adverse effects	Low risk	Attrition was 5% of those enrolled and occurred by 8 weeks; the difference in attrition between groups was not statistically significant. There were no serious adverse events reported.
Incomplete outcome data (attrition bias) Subjective outcomes: Other adverse effects	Low risk	No other adverse events were reported.
Selective reporting (reporting bias)	Low risk	Trial authors reported all pre-stated outcomes in the protocol and the registration document in the published report.
Other bias	Unclear risk	The interim analysis was unscheduled. The sample size estimation initially was powered to detect differences between the 14-day PQ arm and the placebo arm but later changed to detect differences between the 8-week PQ (assuming a failure rate of 5%) and the placebo arm (assumed failure rate of 30%). However, it is unclear if this unscheduled interim analysis and downward revision introduced biases other than what was commented on under selection bias.

Pukrittayakamee 1994

Methods	Parallel group, randomized controlled, open-label trial with three intervention arms **Period of study:** 1992 to 1993
Participants	**Number randomized:** 85 males **Inclusion criteria:** 1. Confirmed*P. vivax* infection **Exclusion criteria:** 1. History of taking any antimalarials within the past 48 h; 2. Urine positive for sulphonamides or 4-aminoquinoline; 3. G6PD deficiency
Interventions	**Intervention:**

Pukrittayakamee 1994 *(Continued)*

	1. CQ (3 days): N = 30 **Control:** 1. CQ (3 days) plus PQ (14 days): N = 25 **Not included in quantitative synthesis in this review** 1. PQ only (not included in review): N = 30 CQ dose: 25 mg/kg PQ dose: 0.25 mg/kg **Co-interventions:** Oral acetaminophen for fever
Outcomes	1. Number of participants relapsing during the 2-month follow-up period
Notes	**Location:** Bangkok Hospital for Tropical Diseases; Malaria endemicity: very high endemicity with multiple-drug resistant *P. falciparum* malaria; no local transmission in Bangkok **Country:** Thailand **Funding:** Welcome-Mahidol University-Oxford Tropical Medicine Research programme, via the Wellcome Trust, UK **Comments:** • Sample size estimation not reported • All participants were hospitalised during treatment; 71/85 participants were hospitalised > 30 days • Age range: 15 to 50 years • Parasitic clearance by day 28 was confirmed • Chloroquine and primaquine were given sequentially • Duration of follow-up: 2 months. Patients were asked to return for weekly check- up or if they developed fever. • Inclusion of all randomized participants in final analysis: 61 of the 85 (71%) enrolled participants returned for follow-up after 2 months (no significant difference between groups) • Trial protocol not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were allocated at random". Unclear if trial authors used adequate methods for sequence generation but there were no baseline imbalances for important prognostic variables.
Allocation concealment (selection bias)	Low risk	Trial authors did not state methods, but there were no baseline imbalances in age, parasitaemia on admission, haematological or biochemical tests.
Blinding (performance bias and detection bias) Objective outcomes: parasitaemia and serious adverse effects	Low risk	Not stated but likely to be unblinded as groups were treated for differing durations with no mention of dummy tablets used; however, the risk of bias for objective outcomes is unlikely.
Blinding (performance bias and detection bias)	Low risk	" All treatments were well tolerated. No patient developed serious adverse effects or had evidence of significant haemolysis."

Pukrittayakamee 1994 *(Continued)*

Subjective outcomes:other adverse effects		Since all groups tolerated treatments well, the risk of bias appears low.
Incomplete outcome data (attrition bias) Objective outcomes: parasitaemia and serious adverse effects	Low risk	Only 71% of participants completed follow-up but the proportion of drop outs in each group were similar.
Incomplete outcome data (attrition bias) Subjective outcomes: Other adverse effects	Low risk	Numerical data for other adverse events were not reported but trial authors state there were none.
Selective reporting (reporting bias)	Low risk	Trial authors reported all pre-stated outcomes.
Other bias	Low risk	Relapses were not differentiated from re-infections; though Bangkok is not known to have a high rate of re-infections due to low transmission, participants returned home after treatment to malaria endemic areas but this is unlikely to have affected outcomes differentially in the intervention arms.

Rajgor 2003

Methods	Randomized, parallel group, single-blinded, trial **Period of study:** July 1998 to April 2000
Participants	**Participants:** 273 Eligible were 690 people smear positive for vivax malaria **Inclusion criteria:** 1. Age > 16 years 2. Smear-positive for asexual forms of *P. vivax* 3. Normal G6PD status 4. Consented to trial and follow-up 5. Haemoglobin > 10 g/dL **Exclusion criteria:** 1. < 16 years 2. G6PD deficiency 3. Pregnant and lactating women 4. Mixed infections
Interventions	**Intervention:** 1. CQ (3 days): N = 142 **Control:** 2. CQ (3 days) plus PQ (14 days): N =131 CQ dose: 25 mg/kg PQ dose: 15 mg/day
Outcomes	**Outcome used in this review**

Rajgor 2003 *(Continued)*

1. Number of participants relapsing during the 6-month follow-up period

Outcome reported but not used in this review

1. Number of participants relapsing corrected for new infections with PCR (in people given PQ)

Notes

Setting: Seth GS Medical College & KEM Hospital, Mumbai, Malaria endemicity: 80% of infections are due to *P. vivax;* low transmission intensity

Country: India

Funding: Not stated

Comments:

- Sample size estimation not reported
- No children < 16 were recruited
- Interventions were supervised
- Chloroquine and primaquine were given sequentially
- Parasitic clearance after intervention was not confirmed
- Duration if follow-up: six months. Participants were asked to return for follow-up every month or if they developed fever
- PCR (single strand conformational polymorphism) data were not used as an outcome for this review update due to doubtful validity in differentiating relapse from re-infection
- Inclusion of all randomized participants in final analysis: 41/142 (28.8%) in chloroquine group and 28/131 (21.4 %) in the chloroquine plus 14-day primaquine group dropped out before 6 months (not statistically significant)
- Trial protocol not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were then allocated to the 2 groups using a simple, computer generated randomisation scheme".
Allocation concealment (selection bias)	Low risk	Not stated; however a similar trial done earlier by the same group in the same hospital was allocation concealed (Gogtay 1999).
Blinding (performance bias and detection bias) Objective outcomes: parasitaemia and serious adverse effects	Low risk	"The study was assessor blinded as the medical officer looking after the day to day care of patients and the technician analysing the peripheral smear were unaware of the study group to which the patient belonged".
Blinding (performance bias and detection bias) Subjective outcomes:other adverse effects	Low risk	Participants were not blind to treatment but trial authors reported there were no adverse effects.
Incomplete outcome data (attrition bias) Objective outcomes: parasitaemia and serious adverse effects	Unclear risk	Dropouts were greater in the CQ only arm (28.8%) than in the CQ + PQ 14 days arm (21.4%) and reasons for dropout are not available in the report; though difference in dropout rates were not significant.
Incomplete outcome data (attrition bias)	Low risk	Unclear whether trial authors systematically ascertained other adverse effects but since none were reported, the lack of participant blinding is unlikely to have introduced detection bias.

Rajgor 2003 *(Continued)*
Subjective outcomes:
Other adverse effects

Selective reporting (reporting bias)	Low risk	Trial authors appear to have reported all pre-stated outcomes.
Other bias	Low risk	We did not detect any other biases.

Rowland 1999a

Methods	Randomized, parallel group, placebo-controlled, assessor-blinded, trial **Period of study:** August 1997 to June 1998
Participants	**Participants:** 200 **Inclusion criteria:** 1. Positive for *P. vivax* with temperature > 37.5 °C **Exclusion criteria:** 1. Mixed infections 2. Pregnant women 3. G6PD deficiency 4. Severe anaemia 5. < 3 years 6. Very elderly 7. Recent antimalarial intake
Interventions	**Intervention:** CQ (3 days) plus placebo: N = 100 **Control:** CQ (3 days) plus PQ (14 days): N = 100 CQ dose: 25 mg/kg PQ dose: 0.25 mg/kg
Outcomes	1. Number of participants relapsing during 12-month follow-up period 2. Adverse events **Outcomes not used in quantitative synthesis in this review:** 1. Parasitaemic episodes during the 12-month follow-up period 2. 28-day *in-vivo* test on *P. vivax* infection
Notes	**Setting:** Adizai refugee camp; Malaria endemicity: predominant species is *P. vivax*; Tropical strains, seasonal with high transmission intensity **Country:** Afghanistan **Funding:** European Commission (DGI); UNHCR; Department for International Development, UK; (DFID); HealthNet International **Comments:** • Sample size estimation not reported

Rowland 1999a *(Continued)*

- Children > three years included: average age 11 years to 12 years
- G6PD deficiency was an exclusion criterion, but the report states that G6PD deficient persons tolerated the 14-day treatment well
- Parasitic clearance by day 28 was confirmed
- Medications were supervised
- Chloroquine and primaquine were administered sequentially
- Follow-up: 12 months; data analyzed were number of participants relapsing over 12 months; inclusion of all randomized participants in final analysis: no losses (100%)
- Relpases treated with same intervention as randomized
- Trial protocol not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote from report: "..year-long randomised trials were conducted". Trial authors did not state methods.
Allocation concealment (selection bias)	Unclear risk	Not mentioned. Trial authors matched baseline variables for age and sex but did not provide any other details.
Blinding (performance bias and detection bias) Objective outcomes: parasitaemia and serious adverse effects	Low risk	Quote from report: "Blood smears were taken at I to 3-day intervals for 28 days: 200 fields were examined before any blood film was classified as malaria-negative. The number of parasites were counted against 200 leucocytes". Trial authors did not mention how they identified relapses, but the likelihood of risk of bias in detecting parasitaemia during follow-up is low. No serious adverse events were reported.
Blinding (performance bias and detection bias) Subjective outcomes:other adverse effects	Low risk	No adverse events were reported; they did not perform systematic screening but the report states G6PD patients tolerated treatments well.
Incomplete outcome data (attrition bias) Objective outcomes: parasitaemia and serious adverse effects	Low risk	Trial authors reported no attrition.
Incomplete outcome data (attrition bias) Subjective outcomes: Other adverse effects	Low risk	Trial authors reported no attrition.
Selective reporting (reporting bias)	Low risk	Trial authors reported all pre-stated outcomes.
Other bias	Low risk	We did not detect any other potential sources of bias.

Rowland 1999b

Methods	Randomized, parallel group, placebo-controlled, assessor-blinded, trial **Period of study:** 1996 to 1997

Rowland 1999b *(Continued)*

Participants	**Participants:** 500 **Inclusion criteria:** 1. Positive for *P. vivax* with temperature > 37.5 °C **Exclusion criteria:** 1. Mixed infections 2. Pregnant women 3. G6PD deficiency 4. Severe anaemia 5. < 3 years 6. Very elderly 7. Recent antimalarial intake
Interventions	**Intervention:** CQ (3 days) plus placebo: N = 250 **Control:** CQ (3 days) plus PQ (5 days): N = 250 CQ dose: 25 mg/kg PQ dose: 0.25 mg/kg
Outcomes	1. Number of participants relapsing during 12-month follow-up period 2. Adverse events **Outcomes not used in quantitative synthesis in this review:** 1. Parasitaemic episodes during the 12-month follow-up period 2. 28-day *in-vivo* test on *P. vivax* infection
Notes	**Setting:** Adizai refugee camp; Malaria endemicity: predominant species is *P. vivax* **Country:** Afghanistan **Funding:** European Commission (DGI); UNHCR; Depratment for International Development, UK; (DFID); HealthNet International **Comments:** • Sample size estimation not reported • Children aged > 3 years included: average age 10 years to 10.4 years • G6PD deficiency was an exclusion criterion, but the report states that G6PD deficient persons tolerated the five day treatment well. • Parasitic clearance by day 28 was confirmed • Medications were supervised • Chloroquine and primaquine were administered sequentially • Follow-up: 12 months; data analyzed were number of participants relapsing over 12 months; Inclusion of all randomized participants in final analysis: no losses (100%) • Relapses treated with same intervention as randomized • Trial protocol not available

Risk of bias

Bias	Authors' judgement	Support for judgement

Rowland 1999b *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"..year-long randomised trials were conducted". Trial authors did not state the methods they used.
Allocation concealment (selection bias)	Unclear risk	Trial authors did not mention this. Baseline variables were matched for age and sex but they did not provide any other details.
Blinding (performance bias and detection bias) Objective outcomes: parasitaemia and serious adverse effects	Low risk	"Blood smears were taken at I to 3-day intervals for 28 days: 200 fields were examined before any blood film was classified as malaria-negative. The number of parasites were counted against 200 leucocytes". The trial authors did not mention how relapses were identified, but the likelihood of risk of bias in detecting parasitaemia during follow-up is low. No serious adverse events were reported.
Blinding (performance bias and detection bias) Subjective outcomes:other adverse effects	Low risk	No adverse events were reported; trial authors did not perform systematic screening but the report states G6PD patients tolerated treatments well.
Incomplete outcome data (attrition bias) Objective outcomes: parasitaemia and serious adverse effects	Low risk	Trial authors did not report any attrition.
Incomplete outcome data (attrition bias) Subjective outcomes: Other adverse effects	Low risk	Trial authors did not report any attrition.
Selective reporting (reporting bias)	Low risk	The trial was not prospectively registered, but trial authors reported all prestated outcomes.
Other bias	Low risk	We did not detect any other potential sources of bias.

Villalobos 2000

Methods	Randomized, parallel-group, active-controlled trial **Period of study:** April to December 1998
Participants	**Participants:** 79 **Inclusion criteria:** 1. *P. vivax* uncomplicated malaria; 2. > 12 years; 3. No history of antimalarials for the last 15 days; 4. No history of haemolytic anaemia **Exclusion criteria:** 1. Pregnant women 2. Negroid
Interventions	**Intervention:**

Villalobos 2000 *(Continued)*

	CQ* (5 days) plus PQ (5 days): N = 40 **Control:** CQ* (3 days) plus PQ (14 days): N = 39 CQ total dose: 25 mg/kg PQ dose: 0.25 mg/kg *Used different duration of CQ treatment. However, people in both arms had cleared parasites by day 28 and hence were comparable in terms of relapse-prevention evaluating primarily the effects of primaquine, after eradicating blood-stage infections.
Outcomes	**Outcomes used in this review** 1. Number of participants with parasitaemia between days 30 and 90 2. Adverse effects **Outcomes not used in this review** 1. Genotyping of *P. vivax* infection with PCR to differentiate new infections from relapses (single locus PCR)
Notes	**Setting**: People presenting to the Centreo de Pesquisa em Medicine Tropical, city of Porto Velho area of Rondonia, Western Amazon; malaria transmission is low and seasonal, and sporadic. **Country:** Brazil **Funding:** Ministry of Science and Technology and Public Health **Comments:** • Sample size calculation not reported. • Children excluded: Mean age: 30.7 years for PQ 14 days and 32.7 years for PQ 5 days • Chloroquine and primaquine were given simultaneously in the five-day regimen and sequentially in the 14-day regimen • Treatments were supervised. • Parasitic clearance confirmed in 100% within 72 hours and by 28 and 35 days • Follow-up duration: two months (90 days after initiation of interventions). Inclusion of all randomized participants in final analysis: treatment outcome was investigated for 73 of the 79 enrolled participants (92%); of the 73 participants, 61 (84%) were followed up for 90 days, while 12 were followed up for 35 days. 31/39 (80%) in the 14 -day PQ arm and 30/40 (75%) in the five-day PQ arm completed two months of follow-up. • Recurrrences (evaluated using single locus PCR) not used as an outcome in this review update. • Trial protocol not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomly assigned". No further details; however, baseline details well-matched (see below).
Allocation concealment (selection bias)	Low risk	Trial authors did not state methods used but people in both arms did not differ significantly in age, sex, previous malaria history, parasitic density, duration of local residence, clinical signs and symptoms and biochemical tests; hence selection bias with respect to prognostic indicators appears unlikely.
Blinding (performance bias and detection bias)	Low risk	Two independent microscopists detected parasitaemia on 200 microscopic fields. No serious adverse events were reported. PCR used only a single locus

Villalobos 2000 *(Continued)*

Objective outcomes: parasitaemia and serious adverse effects		and may not have accurately differentiated relapses from recurrences but this may not have affect the differential detection of this outcome.
Blinding (performance bias and detection bias) Subjective outcomes:other adverse effects	Low risk	No other adverse events were reported, and though it is unclear if they were ascertained systematically, differential effects may be unlikely.
Incomplete outcome data (attrition bias) Objective outcomes: parasitaemia and serious adverse effects	Low risk	In the 14-day PQ arm , 80%, and 75% in the five-day PQ arm completed two months of follow-up (not statistically significant).
Incomplete outcome data (attrition bias) Subjective outcomes: Other adverse effects	Low risk	Trial authors did not report any other adverse events.
Selective reporting (reporting bias)	Low risk	Trial authors reported all pre-stated outcomes.
Other bias	Low risk	We did not detect any other potential biases.

Walsh 2004

Methods	Randomized controlled, open-label, active controlled, six-armed, trial **Period of study:** August 1998 to June 1999
Participants	**Participants**: 25 included (from two arms of a 6-arm trial that randomized 80 people) **Inclusion criteria:** 1. Smear positive for *P. vivax* 2. Weight within 20% of population standards 3. Normal G6PD screening 4. No antimalarials in previous 14 days 5. Negative pregnancy test 6. Consent to participate 7. Ability to take oral medication **Exclusion criteria:** 1. Mixed infection with *P. vivax* and *P. falciparum* 2. Hematocrit < 25% 3. Protracted vomiting 4. Oliguria 5. Systolic blood pressure < 90 mm mercury 6. Lactation 7. Concomitant systemic disease
Interventions	**Intervention** 1. CQ (1500 mg over 3 days): N = 13

Walsh 2004 *(Continued)*

	Control: 2. CQ (1500 mg over 3 days) + PQ 15 mg/day for 14 days: N = 12 Not used in this review: Different doses of tafenoquine N = 55
Outcomes	1. Number of participants with parasitaemia between 8 to 24 weeks 2. Adverse effects **Outcomes not used for quantitative synthesis in review** 1. Incidence (per person-year) of relapse 2. Cumulative risk of relapse
Notes	**Setting:** Bangkok Hospital for Tropical Diseases; Tropical strains; no local transmission of vivax malaria **Country:** Thailand **Funding**: US Army Medical and Materiel Development Activity; GlaxoSmithKline **Comments:** • Sample size calculation • Children were not included • Interventions were supervised • Clearance of parasites after treatment with chloroquine was confirmed by 2 consecutive negative blood smears by day 28 • Chloroquine and primaquine were given sequentially • Follow-up: two months; patients were admitted for treatment and remained in Bangkok for 90 days after treatment initiation • 10/13 (77%) in CQ only arm and 13/13 in CQ + 14-day PQ arm completed treatment (not statistically significant) • Trial protocol not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computer-generated blocked randomisation list (block size, 5) was used to assign patients sequentially to treatment groups."
Allocation concealment (selection bias)	Low risk	"The randomisation list was kept by an off-site investigator (D.S.W.) who was not directly involved with patient enrolment." "To achieve these target sample sizes, some assignments were eliminated (6 group D, 4 group E) as the trial progressed (non-randomly). In each case, the patient was assigned the next treatment on the randomisation schedule. For 2 enrolled subjects, treatment substitutions were made (one subject was moved from group E to group B to replace a patient in group B who dropped out of the study on the day that prophylaxis began, and the other was moved from group E to group D because of an inability to remain hospitalised for 14 days). In all cases, elimination of a group D or E assignment or substitution was made without the knowledge of the next treatment assignment or the identity of the next patient to be randomised". Since allocation was concealed, the risk of selection bias is low: Groups were similar at baseline for age, sex (mostly male), mean weight, and parasite load.

Walsh 2004 *(Continued)*

Blinding (performance bias and detection bias) Objective outcomes: parasitaemia and serious adverse effects	Low risk	"Microscopic examination of blood smears was conducted by a standard operating procedure whereby 200 oil-immersion eels (magnification, 1000) were read on Giemsa-stained thick blood smears by 2 independent readers who were blinded to the patient's group assignment. The identification of 1 asexual *P. vivax* parasite was recorded as a positive smear result. For positive smear results, speciation was determined by examination of thin smears. Any discrepancies were resolved by a third senior study microscopist." (also see quote from report below for adverse events). The trial was open-label but efficacy outcomes would not be at risk of detection bias according to the procedures adopted.
Blinding (performance bias and detection bias) Subjective outcomes:other adverse effects	Low risk	"evaluations were conducted at least every 2 weeks to week 8, and then every 2–4 weeks for up to 24 weeks. A complete blood cell count was determined and standard hepatic and renal function tests were conducted approximately every other day during treatment, and then every 2–4 weeks for up to 24 weeks. Methemoglobin levels were measured on a similar schedule using an OSM-3 Hemoximeter (Radiometer)". Trial authors systematically ascertained adverse events. No significant differences were detected in subjectively reported adverse events.
Incomplete outcome data (attrition bias) Objective outcomes: parasitaemia and serious adverse effects	Low risk	77% in CQ only arm and 100% CQ + 14-day PQ arm completed treatment (not significantly different).
Incomplete outcome data (attrition bias) Subjective outcomes: Other adverse effects	Low risk	As above; treatment arms did not differ in other adverse events.
Selective reporting (reporting bias)	Low risk	The trial was not prospectively registered, but trial authors reported all prestated outcomes in the methods.
Other bias	Unclear risk	Partly industry funded; trial authors did not report the role of funding agency in the conduct and reporting of study.

Yadav 2002

Methods	Randomized, parallel-group, active-controlled trial **Period of study**: 1998 to 1999
Participants	**Participants:** 1482 **Inclusion criteria:** 1. Smear positive for *P. vivax* **Exclusion criteria:** 1. Mixed infections; 2. Pregnant women 3. Infants
Interventions	**Intervention:**

Yadav 2002 *(Continued)*

	1. CQ (single dose of 600 mg): N = 723 **Control:** 2. CQ (single dose of 600 mg) plus PQ (5 days) plus : N = 759 CQ dose: single dose of 600 mg (1500 mg base) PQ dose: 0.25 mg/kg (45 mg total dose)
Outcomes	1. Number of participants relapsing during the 1-year follow-up **Outcomes not used in quantitative synthesis:** 1. Episodes of clinical- parasitaemia during the 1-year follow-up period
Notes	**Setting**: Tribal villages in Bisra Block near the Sundarbhans, a hilly and forested area in eastern Orissa State; Predominatly *P. falciparum* malaria (77%); vivax malaria (19%); *P.malariae* (1%); mixed infections (3%); malaria meso-endemic and seasonal **Country:** India **Funding:** Not reported • Sample size estimation not reported • Children included: Age range- equal numbers in both groups from age 1 year to > 49 years • Primaquine dose unsupervised • Chloroquine and primaquine given sequentially • Parasitic clearance after treatment not confirmed • Follow-up: one year: by field worker visiting homes: none lost to follow-up • Trial protocol not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stratified randomization by decades of age from 1 to 10 years, until > 49 years; method not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated; baseline variables not reported.
Blinding (performance bias and detection bias) Objective outcomes: parasitaemia and serious adverse effects	Low risk	Blood smears were read centrally of all participants who were febrile on weekly home visits. Adverse events were not reported.
Blinding (performance bias and detection bias) Subjective outcomes:other adverse effects	Low risk	Trial authors reported no adverse events in either intervention arm.
Incomplete outcome data (attrition bias) Objective outcomes: parasitaemia and serious adverse effects	Low risk	Trial authors reported there was no attrition.
Incomplete outcome data (attrition bias)	Low risk	Trial authors reported there was no attrition.

Yadav 2002 *(Continued)*

Subjective outcomes:
Other adverse effects

Selective reporting (reporting bias)	Low risk	The only outcome the trial authors reported was efficacy. We did not think the lack of reporting of adverse events was due to selective reporting.
Other bias	Low risk	We did not detect any other biases.

Yeshiwondim 2010

Methods	Randomized (quasi-randomized), open-label, controlled trial **Period of study:** January to August 2003
Participants	**Participants:** 290 **Inclusion criteria:** 1. Aged one year and above 2. Positive for *P. vivax* mono-infection with asexual parasite density of ≥ 250/L of blood 3. Fever or history of fever 48 h prior to the time of recruitment 4. Ability and willingness to participate for the stipulated follow-up visits, 5. Informed consent in adults or of guardian in children **Exclusion criteria:** 1. Clinical conditions requiring hospitalisation 2. Evidence of severe malnutrition 3. Pregnancy-based on history of last menstrual period 4. Significant concomitant febrile illness which would interfere with follow-up 5. Chronic infectious diseases other than malaria (for example, tuberculosis, HIV/AIDS) 6. Known allergy, or intolerance to the drug being tested, or both
Interventions	**Intervention:** CQ 3 days followed by PQ 14 days (from day 29 to day 41) (N = 145) **Control:** CQ 3 days followed by PQ 14 days (from day 3 to day 16) (N = 145) CQ was given at a dose of 25 mg base/kg; 10 mg base/kg on day 0 and day 1 and 5 mg base/kg on day 2 PQ was given at a dose of 0.25 mg base/kg daily
Outcomes	1. Relapse (defined as recurrent parasitaemia with or without fever between day 29 and 157 after clearing their primary infection during the 28-day follow-up period) **Outcomes not used for quantitative synthesis in this review:** 1. Therapeutic efficacy at day 28 (primary outcome in study) 2. Cumulative risk of treatment failure in the 28 day period 3. Cumulative risk of relapse 4. Fever clearance time 5. Parasite clearance time 6. Gametocyte clearance time 7. Proportions with parasitaemia and gametocytaemia in the 28 day period

Yeshiwondim 2010 *(Continued)*

8. PCR adjusted failure rates at day 28

Notes

Setting: outpatient settings of the Malaria Diagnosis and Treatment Centers in Debre Zeit and Nazareth East Shoa;Malaria transmission is seasonal and unstable; *P. vivax* accounts for 50% of malaria transmission

Country: Ethiopia (central)

Funding: Global Malaria Program, WHO, Geneva, Switzerland

Comments:

- Trial authors performed sample size estimation based on an estimated 15% difference between arms but results showed only a 11 % difference between arms for the primary outcome of efficacy at day 28.
- Children included: 68 (24%) were aged 5 to 14 years, and 3 (1%) were between 1 to 3 years old
- G6PD deficiency screening not done as people in Ethiopia tolerate primaquine well
- Trial used sequential administration of primaquine following chloroquine in both arms but at different dosing intervals
- All CQ treatments were directly supervised; PQ treatments were not supervised
- Follow-up: 157 days (four months follow-up after primaquine treatment ended). Parasitological and clinical assessments were performed at day 42 and at any day of reappearance until day 157. Only patients who cleared parasites by day 28 or were not protocol violators or had mixed infections were followed up to day 157 (136/145 in CQ + PQ arm and 141/145 in the CQ only plus late PQ arm (overall 96% follow-up)
- Relapses differentiated from recurrences by PCR during the 28 day period, not used as this was not an outcome for this review update
- Trial protocol not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"After enrolment, patients were randomly assigned to receive either CQ or CQ + PQ treatment, using even or odd code numbers. First, the test drugs were coded either in even or odd number using a lottery method prior to the study. Then, patients registered in odd number at the outpatient settings of the two malaria laboratory and treatment enters were assigned into the CQ treatment group prior to pre-screening and recruitment while those patients registered in even number were assigned into CQ+ PQ treatment group in serial order. The same procedures were followed throughout the study period." This suggests quasi-randomization with odd and even number registrations being predictably allocated to treatment arms; however baseline prognostic variables were equal in both intervention arms.
Allocation concealment (selection bias)	Low risk	"Baseline characteristics were similar in all treatment groups" Comment: Allocation not concealed but both groups were similar with regard to sex, age, weight, previous medication, fever, vomiting, parasitaemia and gametocytaemia.
Blinding (performance bias and detection bias) Objective outcomes: parasitaemia and serious adverse effects	Low risk	"All the collected blood films were forwarded and cross-checked by an independent observer at the central level, Addis Ababa. Any discordant readings between the two observers were further cross-checked by a third independent laboratory technician. Mean parasite density was used if the parasite count between the two observers show greater than 20%" The study was open label but the determination of parasitaemia was objectively ascertained.

Yeshiwondim 2010 *(Continued)*

Blinding (performance bias and detection bias) Subjective outcomes:other adverse effects	Low risk	No patient is reported to have had other adverse effects though it is unclear if they were systematically ascertained.
Incomplete outcome data (attrition bias) Objective outcomes: parasitaemia and serious adverse effects	Low risk	Attrition was low and similar in both arms.
Incomplete outcome data (attrition bias) Subjective outcomes: Other adverse effects	Low risk	Attrition was low and similar in both arms; trial authors did not report any other adverse events.
Selective reporting (reporting bias)	Low risk	Trial authors reported all pre-stated outcomes.
Other bias	Low risk	We did not detect any other biases.

CQ: chloroquine; G6PD deficiency: glucose-6-phosphate dehydrogenase enzyme deficiency; *P. vivax*: *Plasmodium vivax*; PCR: polymerase chain reaction; PQ: primaquine.

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

Study	Reason for exclusion
Abdon 2001	RCT. Different doses of chloroquine were given to control and experimental groups and the outcome was parasitic clearance. No follow-up to detect relapses.
ACTRN1261000055406	Non-RCT: ongoing single arm trial of chloroquine followed by primaquine.
ACTRN12613000003774	Ongoing RCT. People with mixed vivax and falciparum infection are eligible for inclusion. Comparisons are oral primaquine at a dose of 0.75 mg/kg given once per week for 8 weeks versus oral dihydroartemisinin-piperaquine given once per day for 3 days.
Appavoo 1984	Non-RCT: participants were not randomly assigned.
Arango 2012	Non-RCT: case series.
Baird 1995	Non-RCT: compared primaquine with chloroquine in healthy people.
Baird 2001	RCT. Healthy participants randomized to 30 mg primaquine or placebo.
Baird 2003b	Non-RCT.
Basavaraj 1960	Non-RCT: case series.
Betuela 2012a	Non-RCT: case series.
Betuela 2012b	RCT: No chloroquine or chloroquine plus primaquine arms.

Study	Reason for exclusion
	Compared artesunate (seven days) plus primaquine (14 days), artesunate alone or no treatment.
Buchachart 2001	Non-RCT: case series.
Bunnag 1994	RCT. Compared chloroquine + primaquine (15 mg/day for 14 days) with chloroquine + primaquine (22.5 mg/day for 14 days). Only 33/81 (40%) in 15 mg/day primaquine arm and 40/86 (47%) in 22.5 mg/day primaquine arm completed 6 months follow-up; only 19 in each arm completed 18 months follow up; no usable data.
Carmona-Fonseca 2003	RCT. Comparisons: CQ (1500 mg, in 48 hours), followed by PQ 45, 105 and 210 mg. Outcomes: Effect of CQ with different doses of PQ on blood stage parasites. No follow-up beyond 28 days.
Carmona-Fonseca 2006	RCT. Comparisons: CQ (1500 mg in 48 hours) followed by total dose of PQ: 45, 105 and 210 mg. Outcome: assessed only at 28 days.
Carmona-Fonseca 2009a	RCT. Comparisons and outcomes: MetHB levels in three different dosing regimens of primaquine (twice, three-fold daily and five-fold daily standard dose over three days) following chloroquine. No arm with standard 14 days of primaquine.
Carmona-Fonseca 2010	RCT. Comparisons: children with vivax malaria given primaquine 0.50 mg/kg/day for 7 days versus 1.17 mg/kg/day for 3 days; no 14 day primaquine arm.
Cedillos 1978	RCT. Compared two regimens of primaquine with amodiaquine versus amodiaquine.
Clyde 1977	Non-RCT: No comparison group.
Contacos 1974	Non-RCT: No comparison group.
CTRI/2011/09/002031	On-going RCT. Compared chloroquine versus chloroquine plus primaquine for 14 days. Outcomes: will be assessed only up to 28 days.
CTRI/2012/03/002511	On-going RCT. Comparing tafenoquine versus chlorquine plus primaquine.
da Silva 2003	RCT. Compared artemesinin and primaquine with chloroquine and primaquine.
Dao 2007	Non-RCT: No comparison group.
Dua 2001	Non-RCT. Controlled clinical trial

Study	Reason for exclusion
Elmes 2008	Unclear if RCT; compared three doses of tafenoquine versus primaquine for post-exposure prophylaxis.
Fryauff 1997	RCT. Compared one year of weekly chloroquine, daily primaquine, or placebo.
Gogtay 1998	Non-RCT.
Hamedi 2004	RCT. Compared three doses of artesunate followed by primaquine.
Herrera 2011	RCT. Randomized Duffy + and Duffy -ve human volunteers.
ISRCTN82366390	Ongoing RCT. Comparisons of artesunate and artesunate plus primaquine ; no chloroquine in either arm.
Kolaczinski 2012	RCT. Falciparum malaria: compared artesunate or primaquine combined with chloroquine or SP.
Looareesuwan 1999	RCT. Randomized participants to chloroquine + primaquine for 14 days or chloroquine alone. Followed participants for 28 days to assess failure of initial therapy. Further follow-up beyond 28 days only for four participants with reappearance of parasitaemia in first 28 days who were retreated with chloroquine.
Luxemburger 1999	Non-RCT.
Manneeboonyang 2011	RCT. Compared DOT or self-administered therapy (SAT) in two groups given chloroquine plus primaquine for 14 days.
Nasveld 2010	RCT. Compared tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects.
NCT01074905	On-going RCT. Compared chloroquine plus primaquine 14 days versus ACT.
NCT01288820	On-going RCT. Comparing two ACTs plus primaquine. No chloroquine treatment in either arm.
NCT01290601	RCT. Compared tafenoquine versus chloroquine and primaquine.
NCT01716260	Non-RCT: Cohort study
NCT01780753	Non-RCT: Single arm study

Study	Reason for exclusion
NCT01814683	RCT. People with mixed infections with *P. vivax* and *P. falciparum* are eligible for recruitment in countries which use an artemisinin combination therapy for treating blood-stage infection.
NCT01837992	Ongoing RCT. Comparisons: No chloroquine treatment arms; randomised primaquine (0.25mg/kg or 0. 5 mg/kg for 14 days) following three days of artemether-lumefantrine.
Pasaribu 2013	RCT. Compared dihydroartemisinin-piperaquine and artesunate-amodiaquine combined with primaquine.
Pinto 1998	RCT. Low dose of chloroquine and primaquine was given for two groups for five days and seven days respectively.
Prasad 1991	Non-RCT: no comparison group.
Pukrittayakamee 2010	RCT. Compared 30 mg or 60 mg primaquine daily for seven days; no 14 day primaquine arm.
RBR-77q7t3	Non-RCT: on-going single arm trial.
Roy 1977	Non-RCT: no comparison group.
Saint-Yves 1977	RCT. Presumptive treatment of 45 mg primaquine given to all participants before randomization.
Schwartz 2000	Non-RCT: retrospective study.
Sharma 1973	Non-RCT.
Shekalaghe 2010	RCT. Children were randomized to receive SP plus AS plus PQ or placebo; those with a haemoglobin (Hb) level below 8 g/dL were excluded from receiving PQ and received SP plus AS.
Shekalaghe 2011	Cluster RCT. Compared mass drug treatment with SP plus AS plus PQ versus placebo.
Shin 2011	RCT. Compared fixed dose formulation of pyronaridine: artesunate versus chloroquine.
Singh 1990	Non-RCT.
Sinha 1989	Non-RCT.
Smithuis 2010	RCT. Falciparum malaria.

Study	Reason for exclusion
Soto 1998	RCT. Compared 30 mg primaquine for 16 weeks against placebo in healthy people.
Soto 1999	RCT. Compared 30 mg primaquine for 16 weeks against placebo in healthy people.
Sutanto 2012	RCT. Compared artesunate followed by quinine and primaquine versus dihydroartemisinin plus piperaquine followed by primaquine.
Takeuchi 2010	RCT. Compared DOT versus SAT in two groups given chloroquine plus primaquine 14 days.
Valibayov 2003	Non-RCT: no comparison group.
Vásquez 2009	RCT. Falciparum malaria.
Wilairatana 1999	Non- RCT: sequential allocation. No chloroquine.

ACT = artemesinin combination therapy; CQ = chloroquine; PQ = primaquine; DOT = directly observed treatment; RCT= randomized controlled trial; SAT = self-administered treatment.

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

NCT01178021

Trial name or title	"Estimating the risk of *Plasmodium vivax* relapses in Afghanistan (VRA)"
Methods	Phase 4 randomized, parallel-group, open label trial
Participants	**Estimated enrolment:** 600 **Inclusion criteria:** 1. Adults and children > 6 months of age 2. Negative pregnancy test in women at risk of pregnancy 3. Microscopic diagnosis of *P. vivax* mono-infection (> 200/µL asexual forms) 4. Axillary temperature ≥ 37.5°C, or an oral or rectal temperature ≥ 38°C, or history of fever within the last 24 hours 5. Ability to swallow oral medication 6. Participant (or parent or guardian if < 18 years old) is willing and able to give written informed consent 7. Ability (in the investigator's opinion) and willingness of patient, parent or guardian to comply with all study requirements **Exclusion criteria:** 1. Severe malaria (see WHO definition) 2. Patients with microscopic diagnosis of co-infection with *P. falciparum*

NCT01178021 *(Continued)*

	3. Haemoglobin concentration <8 g/dL 4. Presence of any condition which in the judgement of the investigator would place the subject at undue risk or interfere with the results of the study, for example, other acute febrile conditions or chronic disease 5. Pregnancy or lactation 6. History or phenotypic test compatible with severe G6PD deficiency 7. History of hypersensitivity to any of the drugs being tested
Interventions	**Intervention:** 1. Chloroquine/primaquine (chloroquine 10 mg/kg on day 0 and 1 and 5 mg/kg on day 2 primaquine (if given) 0.25 mg/kg/day for 14 days) **Control:** 1. Chloroquine 10 mg/kg on day 0 and 1 and 5 mg/kg on day 2
Outcomes	**Primary outcome:** 1. Secondary *P. vivax* attack (completion of the one year (± one month) follow-up period without secondary *P. vivax* attack) **Secondary outcomes:** 1. Secondary vivax attack (completion of six months (± one month) follow-up without secondary vivax attack) 2. G6PD prevalence at time of enrolment 3. Time to first recurrence (one year) 4. Median time between episodes of vivax infections 5. Total number of episodes in the follow-up period (one year) 6. Overall days of illness (one year) 7. Haematocrit below 30% over one year) 8. Chloroquine levels at Day 7; and any day of recurrence of *P. vivax* malaria 9. Adverse event profiles of chloroquine and primaquine
Starting date	January 2010
Contact information	Principal Investigator: Ghulam Rahim Awab, MD; E-mail: awabgr@yahoo.com Mahidol Tropical Medicine Research Unit; Mahidol University, Bangkok, Thailand
Notes	**Setting:** Provincial Malaria Control Centers (MRC) **Country:** Afganistan **Funding:** University of Oxford; National Malaria and Leishmaniasis Control Program, Afghanistan; Mahidol University **Comments: Estimated Study Completion Date:** December 2014 **Status:** Recruiting (last verified:August 2013; last checked 17 October 2013) **Registration Number:** Clinicaltrials.gov: NCT01178021

NCT01376167

Trial name or title	"Ph 2B/3 Tafenoquine (TFQ) study in prevention of vivax relapse"

NCT01376167 *(Continued)*

Methods	Randomized, parallel-group, double blind (subject, caregiver, investigator, outcomes assessor), double-dummy, active-controlled, multi-centre, trial
Participants	**Estimated enrolment:** 924 **Inclusion criteria**: 1. Positive Giemsa smear for *P. vivax* 2. Parasite density > 100 and < 200,000/µL 3. ≥ 16 years 4. Non-pregnant, non-lactating females of non-child bearing potential, or has a negative serum pregnancy test at screening, and uses measures to prevent pregnancy (as defined in protocol) 5. A signed and dated informed consent is obtained from the subject or the subject's legal representative prior to screening (NB assent is obtained from subjects < 18 years, where applicable and written or oral witnessed consent has been obtained from parent or guardian). 6. The subject is able to understand and comply with protocol requirements, instructions and protocol-stated restrictions and is likely to complete the study as planned. 7. Willing to be hospitalized for 3 days and return to clinic for all follow-up visits including Day 180. **Exclusion criteria:** 1. QTc < 450 msec at screening, based on a single QTcF value at screening or as an average of triplicate electrocardiogram obtained over a brief recording period by machine or manual over-read if first is > 450 msec. Exclusion criteria: mixed malaria infections (for example, identified by Giemsa-stained smear or rapid diagnostic test) 2. Severe vivax malaria as defined by WHO criteria. 3. Severe vomiting (no food or inability to take food during previous 8 hours). 4. Screening haemoglobin concentration < 7 g/dL. 5. G6PD deficiency, assessed by a quantitative spectrophotometric phenotype assay. 6. Males: any subject with an enzyme level < 70% of the site median value for G6PD normals will be excluded. 7. Females: screening Hb ≥ 10 g/dL will only be excluded if their enzyme level is < 70% of the site median value for G6PD normals. Females with Hb ≥ 7 but < 10 g/dL will be excluded if an enzyme level is not > 90% of the site median value for G6PD normals. 8. Liver function test alanine transaminase > 2x upper limit of normal. 9. Any clinically significant concurrent illness (for example, pneumonia, septicaemia), pre-existing conditions (for example, renal disease, malignancy), conditions that may affect absorption of study medication (for example, vomiting or severe diarrhoea) or clinical signs and symptoms of severe cardiovascular disease (for example, uncontrolled congestive heart failure or severe coronary artery disease). These abnormalities may be identified on the screening history and physical or laboratory examination. 10. Subject has taken antimalarials (for example, ACT, mefloquine, primaquine, chloroquine) or drugs with anti-malarial activity within the past 30 days by history. 11. History of allergy to chloroquine, mefloquine, tafenoquine, primaquine or to any other 4- or 8-aminoquinolines. 12. Any contraindications to chloroquine or primaquine administration including a history of porphyria, psoriasis or epilepsy (please refer to chloroquine and primaquine locally approved prescribing information). 13. Subject who has previously received study medication for this protocol (all parts) or has received treatment with any other investigational drug within 30 days or 5 half-lives (whichever is longer) preceding the first dose of study medication. 14. History of illicit drug abuse or heavy alcohol intake within 6 months of the study. 15. Subjects who have taken or will likely require the use of medications from the prohibited medication list which include the following classes: histamine-2 blockers and antacids. 16. Drugs with haemolytic potential. 17. Drugs known to prolong the QTc interval

NCT01376167 *(Continued)*

Interventions	**Interventions** (not relevant to this review)**:** 1. Tafenoquine 50mg (on Day 1 and Day 2 600 mg chloroquine will be administered, on Day 3 300 mg chloroquine will be administered. 50 mg tafenoquine will be administered on either Day 1 or Day 2 depending on when eligibility is confirmed). 2. Tafenoquine 100mg (on Day 1 and Day 2 600 mg chloroquine will be administered, on Day 3 300 mg chloroquine will be administered. 100 mg tafenoquine will be administered on either Day 1 or Day 2 depending on when eligibility is confirmed). 3. Tafenoquine 300mg (on Day 1 and Day 2 600 mg chloroquine will be administered, on Day 3 300 mg chloroquine will be administered. 300 mg tafenoquine will be administered on either Day 1 or Day 2 depending on when eligibility is confirmed). 4. Tafenoquine 600 mg (on Day 1 and Day 2 600 mg chloroquine will be administered, on Day 3 300 mg chloroquine will be administered. 600 mg tafenoquine will be administered on either Day 1 or Day 2 depending on when eligibility is confirmed). **Controls** (to be included in quantitative synthesis in this review): 1. Active comparator: primaquine 15 mg (on Day 1 and Day 2 600 mg chloroquine will be administered, on Day 3 300 mg chloroquine will be administered. 15 mg primaquine once daily Days 2 to 15) 2. Placebo comparator: chloroquine only (on Day 1 and Day 2 600 mg chloroquine will be administered, on Day 3 300mg chloroquine will be administered.
Outcomes	**Primary outcome measures:** 1. Relapse efficacy (180 days). Subjects for whom initial clearance of parasitaemia is confirmed (parasite numbers fall below the limit of detection in thick blood smear and remain undetectable at the second smear collected 6 to 12 hours later) and who do not present with *P. vivax* asexual stage parasites within six months will be considered treatment successes. **Secondary outcome measures:** 1. Relapse efficacy (4 months post dosing). First confirmed presence of *P. vivax* asexual stage parasites after clearance of initial parasitaemia following treatment. 2. Time to relapse (80 days post dosing). Time from initial parasite clearance to time of relapse. 3. Parasite clearance time (from first dose until Day 180). Time needed to clear asexual parasites from blood, parasites fall below limit of detection in thick blood smear and remains undetectable for at least 48 hours. 4. Fever clearance time (from first dose until Day 180). Time from first dose of treatment to time when body temperature falls to normal and remains normal for at least 48 hours.
Starting date	September 2011
Contact information	US GSK Clinical Call Center; 877-379-3718; GSKClinicalSupportHD@gsk.com; Cheri Hudson; Clinical Disclosure Advisor; GlaxoSmithKline
Notes	**Setting:** Not reported **Country:** Not reported **Funding:** GlaxoSmithKline; Medicines for Malaria Venture **Comments: Estimated study completion date**: September 2015 **Status:** Not yet recruiting (last updated on September 25, 2013; last checked 17 October 2013) **Registration number:** NCT01376167

NCT01640574

Trial name or title	"Comparison between 7 and 14 day primaquine combined with dihydroartemisinin-piperaquine or 3 day chloroquine radical cure of P. Vivax (BPD)"
Methods	Randomized, parallel group, open label, four-arm trial
Participants	**Estimated enrolment:** 900 **Inclusion criteria:** 1. ≥ 6 months old 2. Microscopic diagnosis of *P. vivax* malaria mono-infection 3. Participant or parent/guardian is willing and able to give informed consent for participation in the study 4. Able (in the Investigators opinion) and willing to comply with all study requirements. **Exclusion criteria:** 1. Severe malariaHistory of allergy or adverse reaction to artesunate, piperaquine, chloroquine, or primaquine 2. Blood transfusion in the past 3 months 3. G6PD deficiency by rapid test 4. Hematocrit ≤ 25% 5. Pregnancy at the time of screening 6. Breastfeeding an infant < 6 months old 7. Presence of any condition which in the judgement of the investigator would place the subject at undue risk or interfere with the results of the study
Interventions	**Interventions** (not relevant to this review)**:** 1. Dihydroartemisinin-piperaquine plus primaquine daily for 3 days and primaquine 1 mg/kg once daily for 7 days 2. Dihydroartemisinin-piperaquine plus primaquine daily for 3 days and primaquine 0.5 mg/kg daily for 14 days **Controls** (to be included in quantitative synthesis in this review): 1. Chloroquine (10 mg, 10 mg, 5 mg) over 3 days and primaquine 1 mg/kg once daily for 7 days 2. Chloroquine (10 mg, 10 mg, 5 mg) over 3 days and primaquine 0.5 mg/kg daily for 14 days
Outcomes	**Primary outcome measure:** 1. Recurrence with *P.vivax* malaria within 52 weeks of first treatment dose **Secondary outcome measures:** 1. Number of adverse events within 28 days of study medication 2. Recurrence with *P. vivax* malaria within 6 months of first treatment dose 3. Chloroquine, piperaquine and primaquine drug levels (not relevant to this review)
Starting date	July 2012
Contact information	Cindy Chu: +66 55 545021; cindy@shoklo-unit.com Francois Nosten:+66 55 545021; francois@tropmedres.ac
Notes	**Setting:** Shoklo Malaria Research Unit **Country:** Thailand

NCT01640574 *(Continued)*

Funding: University of Oxford

Comments: Estimated study completion date: December 2014 **Status:** recruiting (last updated on 28 August 2013; last checked 17 October 2013)

Registration Number: NCT01640574

NCT01680406

Trial name or title	"Ethiopia antimalarial in vivo efficacy study 2012: evaluating the efficacy of artemether-lumefantrine alone compared to artemether-lumefantrine plus primaquine and chloroquine alone compared to chloroquine plus primaquine for *Plasmodium Vivax* infection"
Methods	Randomized, parallel group, open label, four-arm trial
Participants	**Estimated enrolment:** 480 **Inclusion criteria:** 1. Slide-confirmed infection with *P. vivax* 2. Age > 1 year 3. Lives within 20 km of the enrolling health facility 4. Weight ≥ 5.0 kg 5. Axillary temperature ≥ 37.5° C or history of fever during the previous 48 hours 6. Patient or caregiver agrees to all finger pricks and return visits **Exclusion criteria:** 1. General danger signs or symptoms of severe malaria 2. Signs or symptoms of severe malnutrition, defined as weight-for-age ≤ 3 standard deviations below the mean (NCHS/WHO normalized reference values) 3. Slide confirmed infection with any other *Plasmodium* species. besides *P. vivax* mono-infection 4. Acute anaemia, defined as Hg < 8 g/dL 5. Known hypersensitivity to any of the drugs being evaluated 6. Presence of febrile conditions caused by diseases other than malaria 7. Serious or chronic medical condition by history (cardiac, renal, hepatic diseases, sickle cell disease, HIV/AIDS) 8. Pregnant or breastfeeding women 9. History or haemolysis or severe anaemia 10. Regular medication, which may interfere with antimalarial pharmacokinetics
Interventions	**Interventions** (not relevant to this review)**:** 1. Artemether-lumefantrine and primaquine: artemether-lumefantrine will be given in a weight-based dose to be administered as fixed-dose combination twice daily for three days. Primaquine will be given beginning on day 2 of artemether-lumefantrine to patients with a normal G6PD test; dose is weight-based to be administered once daily for 14 days. 2. Artemether-lumefantrine: weight-based dose to be administered as fixed-dose combination twice daily for three days. **Controls** (to be included in quantitative synthesis in this review): 1. Chloroquine given in a weight-based dose to be administered once daily for three days. 2. Chloroquine and primaquine: chloroquine will be given in a weight-based dose to be administered once daily for three days. Primaquine will be given beginning on day 2 of chloroquine to patients with a normal G6PD test; dose is weight-based to be administered once daily for 14 days.

NCT01680406 *(Continued)*

Outcomes	**Primary outcome measures:** 1. *P. vivax* treatment failures in the 4 weeks following treatment with AL compared to AL+PQ (time frame: day 28). 2. *P. vivax* treatment failures in the 4 weeks following treatment with CQ compared to CQ+PQ (time frame: day 28). **Secondary outcome measures:** 1. Number of episodes of *P. vivax* parasitaemia over one year following initial effective therapy against *P. vivax* (i.e. parasite clearance) (time frame: 1 year after day 0 of enrolment). 2. *P. vivax* treatment failures in the 6 weeks following treatment (time frame: Day 42). **Other outcome measures:** 1. Safety endpoint (time frame: baseline (day 0) and day 28). 2. Change in haemoglobin concentration.
Starting date	October 2012
Contact information	Keren Z Landman, MD, fea8@cdc.gov Jimee Hwang, MD, MPH, jhwang@cdc.gov
Notes	**Setting:** Bishoftu Malaria Center, Debre Zeit; Bulbula Health Center, Zeway **Country:** Ethiopia **Funding:** Centers for Disease Control and Prevention; Ethiopia Health and Nutrition Research InstituteFederal Ministry of Health, Ethiopia Columbia University Oromia Regional Health Bureau, Ethiopia United States Agency for International Development (USAID), Menzies School of Health Research **Comments: Estimated study completion date**: October 2013 **Status:** Not yet recruiting (last updated on 6 September 2012; last checked 17 October 2013) **Registration Number:** NCT01680406

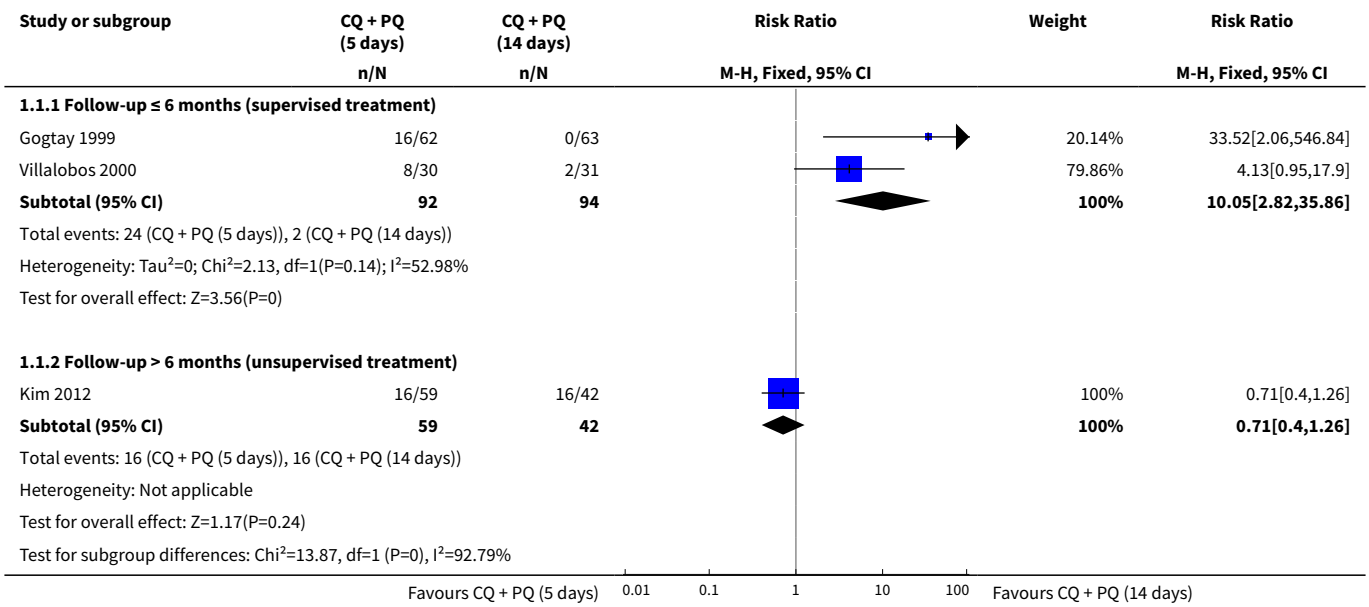
G6PD: glucose-6-phosphate dehydrogenase

DATA AND ANALYSES

Comparison 1. Primaquine: 5 days versus 14 days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 *P. vivax* parasitaemia > 30 days after starting primaquine	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Follow-up ≤ 6 months (supervised treatment)	2	186	Risk Ratio (M-H, Fixed, 95% CI)	10.05 [2.82, 35.86]
1.2 Follow-up > 6 months (unsupervised treatment)	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.40, 1.26]

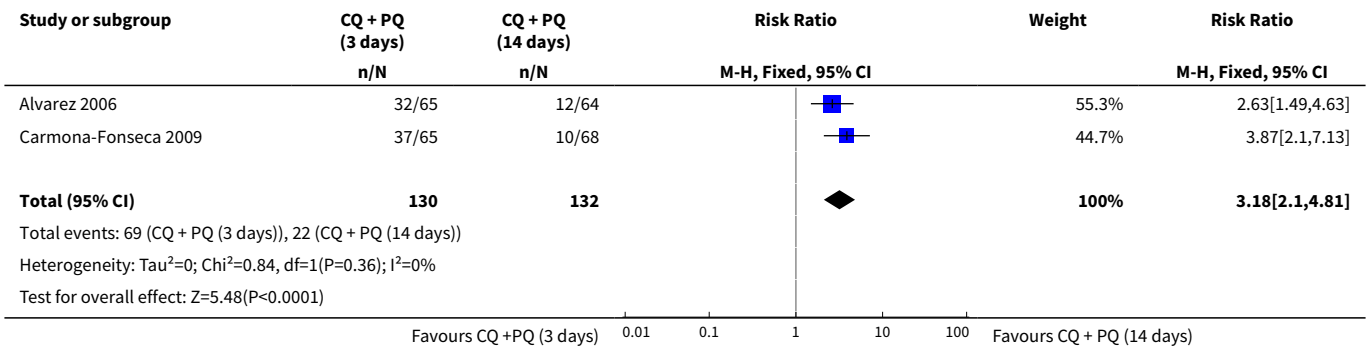
Analysis 1.1. Comparison 1 Primaquine: 5 days versus 14 days, Outcome 1 *P. vivax* parasitaemia > 30 days after starting primaquine.



Comparison 2. Primaquine: 3 days versus 14 days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 *P. vivax* parasitaemia > 30 days after starting primaquine	2	262	Risk Ratio (M-H, Fixed, 95% CI)	3.18 [2.10, 4.81]

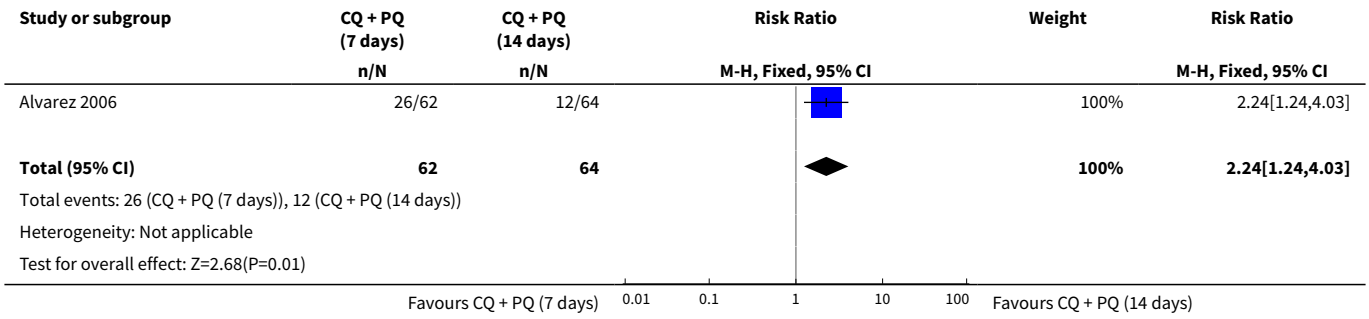
Analysis 2.1. Comparison 2 Primaquine: 3 days versus 14 days, Outcome 1 *P. vivax* parasitaemia > 30 days after starting primaquine.



Comparison 3. Primaquine: 7 days versus 14 days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 *P. vivax* parasitaemia > 30 days after starting primaquine	1	126	Risk Ratio (M-H, Fixed, 95% CI)	2.24 [1.24, 4.03]

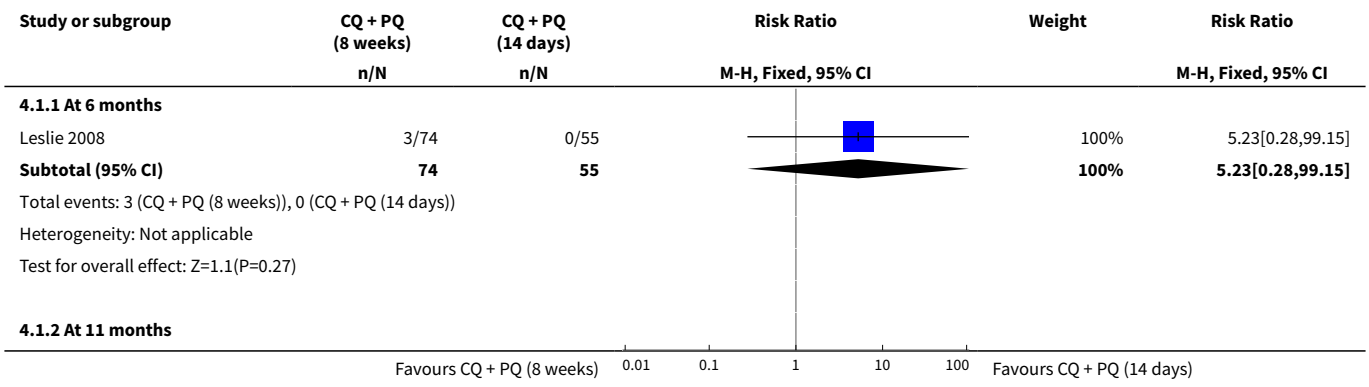
Analysis 3.1. Comparison 3 Primaquine: 7 days versus 14 days, Outcome 1 *P. vivax* parasitaemia > 30 days after starting primaquine.

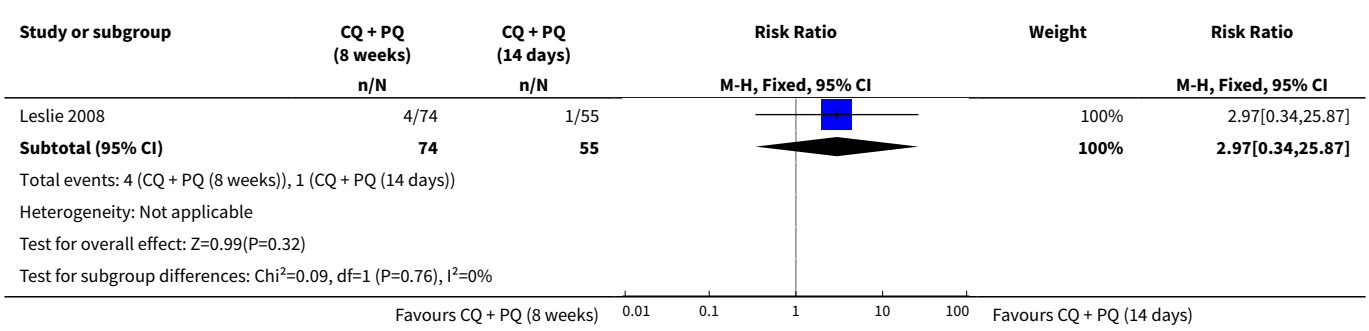


Comparison 4. Primaquine: weekly for 8 weeks versus daily for 14 days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 *P. vivax* parasitaemia > 30 days after starting primaquine	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 At 6 months	1	129	Risk Ratio (M-H, Fixed, 95% CI)	5.23 [0.28, 99.15]
1.2 At 11 months	1	129	Risk Ratio (M-H, Fixed, 95% CI)	2.97 [0.34, 25.87]

Analysis 4.1. Comparison 4 Primaquine: weekly for 8 weeks versus daily for 14 days, Outcome 1 *P. vivax* parasitaemia > 30 days after starting primaquine.

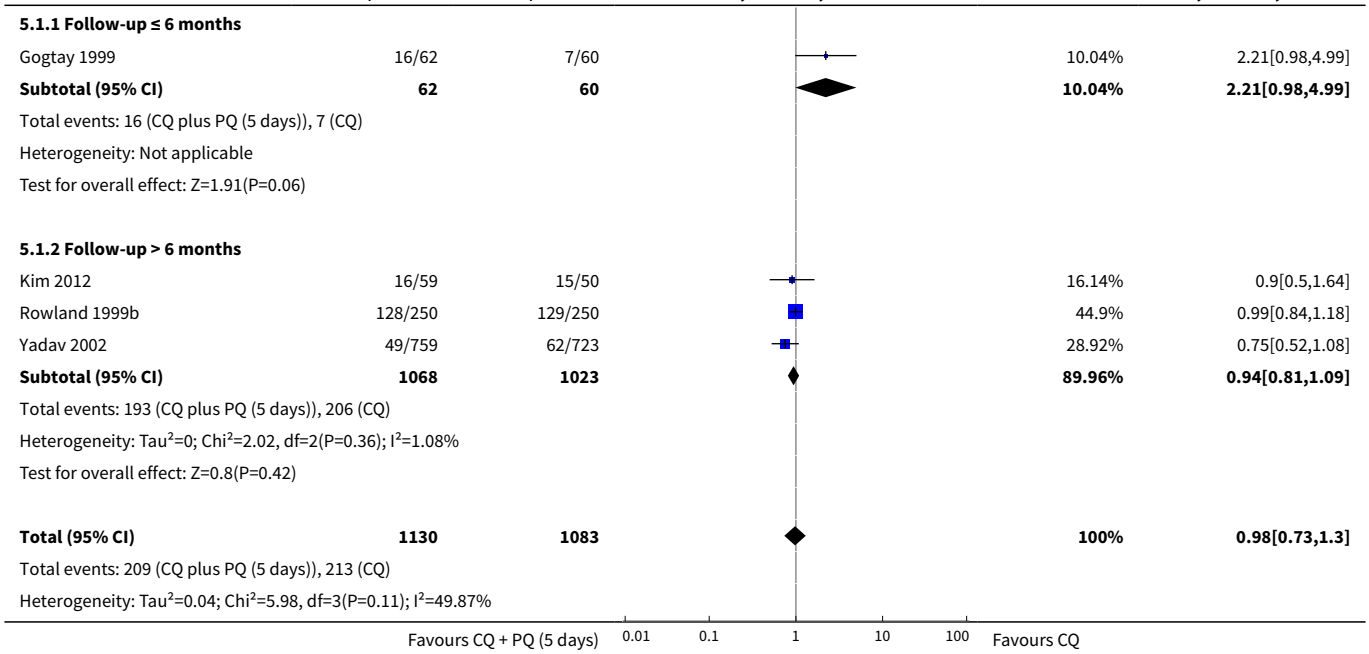


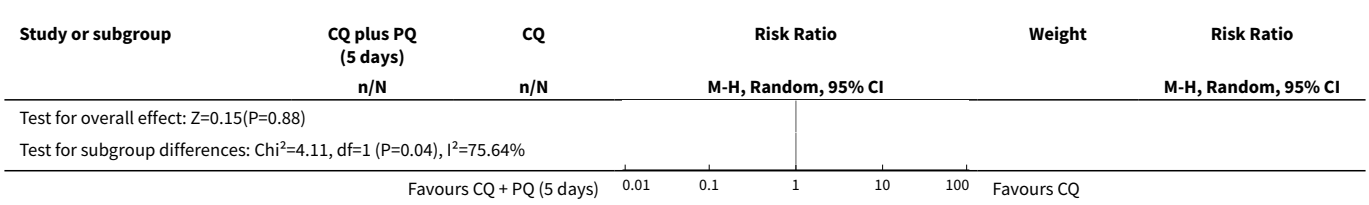


Comparison 5. Primaquine 5 days versus no primaquine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 *P. vivax* parasitaemia > 30 days after starting primaquine	4	2213	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.73, 1.30]
1.1 Follow-up ≤ 6 months	1	122	Risk Ratio (M-H, Random, 95% CI)	2.21 [0.98, 4.99]
1.2 Follow-up > 6 months	3	2091	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.81, 1.09]

Analysis 5.1. Comparison 5 Primaquine 5 days versus no primaquine, Outcome 1 *P. vivax* parasitaemia > 30 days after starting primaquine.

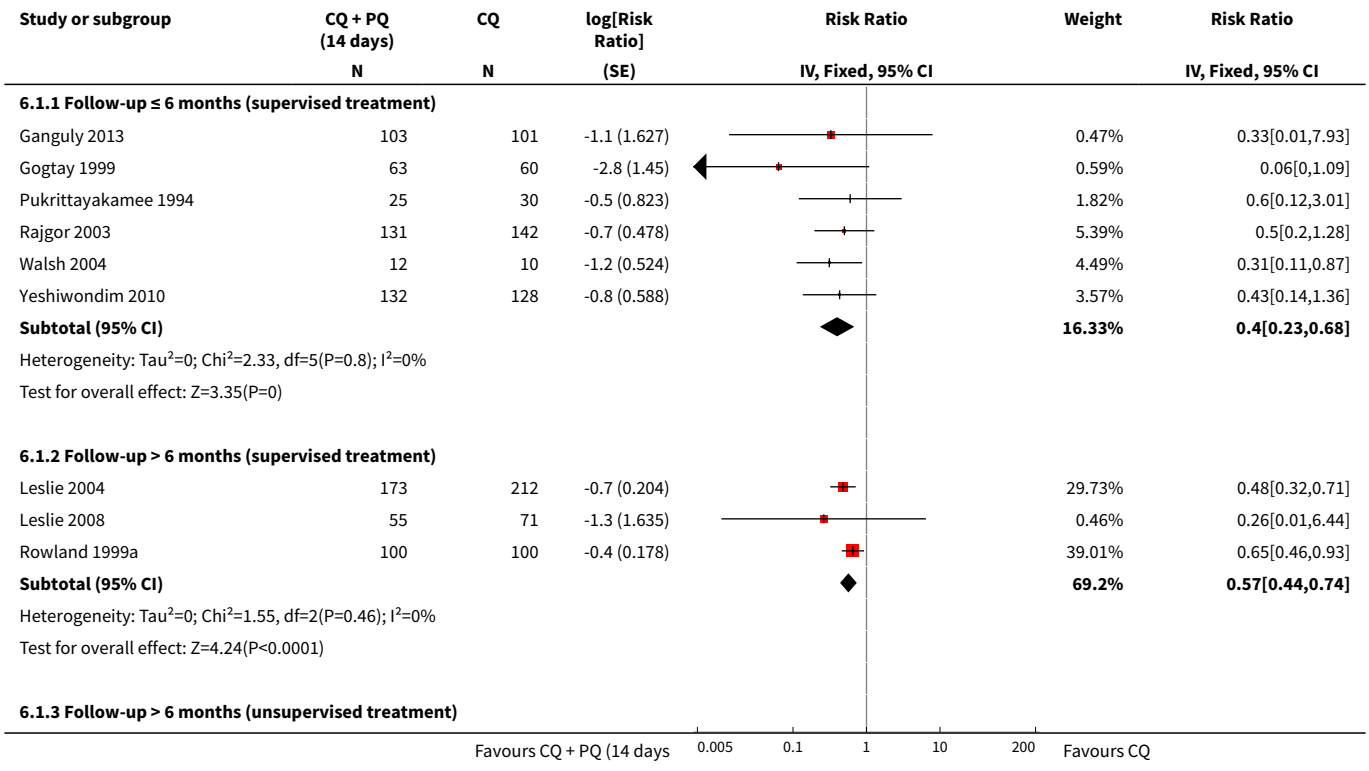


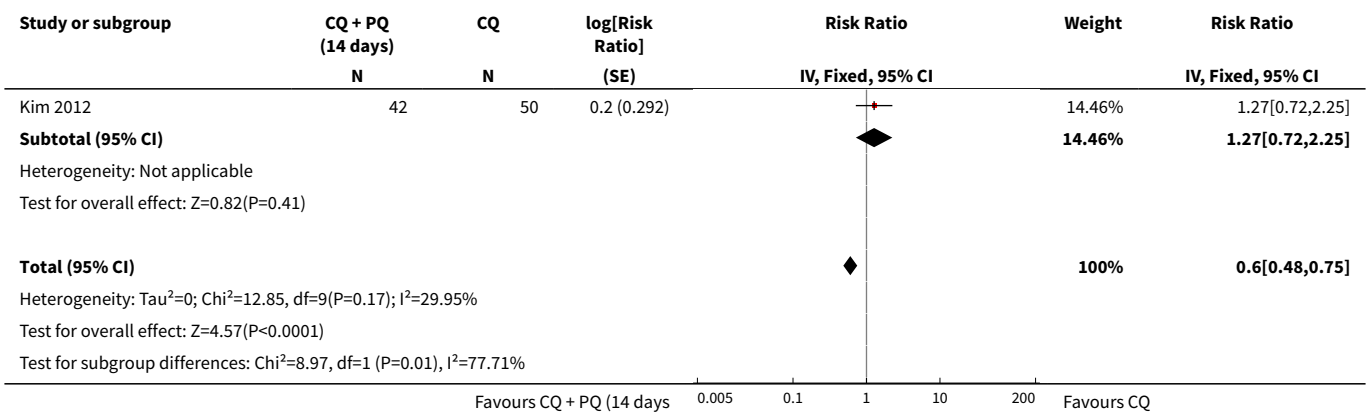


Comparison 6. Primaquine 14 days versus no primaquine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 *P. vivax* parasitaemia detected > 30 days after starting primaquine	10	1740	Risk Ratio (Fixed, 95% CI)	0.60 [0.48, 0.75]
1.1 Follow-up ≤ 6 months (supervised treatment)	6	937	Risk Ratio (Fixed, 95% CI)	0.40 [0.23, 0.68]
1.2 Follow-up > 6 months (supervised treatment)	3	711	Risk Ratio (Fixed, 95% CI)	0.57 [0.44, 0.74]
1.3 Follow-up > 6 months (unsupervised treatment)	1	92	Risk Ratio (Fixed, 95% CI)	1.27 [0.72, 2.25]

Analysis 6.1. Comparison 6 Primaquine 14 days versus no primaquine, Outcome 1 *P. vivax* parasitaemia detected > 30 days after starting primaquine.





ADDITIONAL TABLES

Table 1. Detailed search strategies

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]
1	Plasmodium vivax	primaquine		primaquine	primaquine
2	vivax malaria	PRIMAQUINE	PRIMAQUINE	PRIMAQUINE	malaria
3	primaquine	1 or 2	1 or 2	1 or 2	Plasmodium vivax
4	—	Plasmodium vivax	MALARIA, VIVAX	malaria vivax	—
5	—	vivax malaria	Plasmodium vivax	PLASMODIUM VIVAX	—
6	—	4 or 5	4 or 5	4 or 5	—
7	—	3 and 6	3 and 6	3 and 6	—

[a]Cochrane Infectious Diseases Group Specialized Register.
[b]Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Higgins 2005); upper case: MeSH or EMTREE heading; lower case: free text term.

Table 2. Relapse rates and total dose of primaquine used in the intervention arms

Total dose of primaquine in intervention arms	Study	Duration of primaquine treatment	Relapse (%)	Mean relapse rate (95% CI); Median relapse rate
No primaquine	Pukrittayakamee 1994	Nil	4/30 (13)	22% (19% to 26%); 12%
	Gogtay 1999		7/60 (12)	
	Rowland 1999a		49/100 (49)	

Table 2. Relapse rates and total dose of primaquine used in the intervention arms *(Continued)*

	Rowland 1999b		129/250 (5)	
	Yadav 2002		62/723 (9)	
	Rajgor 2003		13/142 (9)	
	Leslie 2004		88/212 (42)	
	Walsh 2004		8/10 (80)	
	Leslie 2008		2/71 (3)	
	Yeshiwondim 2010**		9/128 (7)	
	Ganguly 2013		1/100 (1)	
	Kim 2012		5/50 (15)	
45 mg	Alvarez 2006*	3 days	32/65 (49)	49% (38% to 61%)
75 mg*	Gogtay 1999	5 days	16/62 (26)	28% (27% to 30%); 27%
	Rowland 1999a		128/250 (51)	
	Villalobos 2000*		8/30 (27)	
	Yadav 2002		49/759 (7)	
105 mg	Alvarez 2006	7 days	26/62 (42)	42% (31% to 54%)
210 mg*	Carmona-Fonseca 2009*	3 days	37/65 (57)	57% (45% to 68%)
	Pukrittayakamee 1994	14 days	2/25 (8)	12% (11% to 13%); 8%
	Gogtay 1999		0/63 (0)	
	Rowland 1999a		32/100 (32)	
	Villalobos 2000		2/31 (7)	
	Rajgor 2003		6/131 (5)	
	Leslie 2004		27/173 (16)	
	Walsh 2004		3/12 (25)	
	Alvarez 2006*		12/64 (19)	
	Carmona-Fonseca 2009		10/68 (15)	
	Yeshiwondim 2010		4/132 (3)	
	Ganguly 2013		1/103 (1)	

Table 2. Relapse rates and total dose of primaquine used in the intervention arms *(Continued)*

315 mg	Leslie 2008	14 days	0/55 (0)	0%
360 mg	Leslie 2008	Weekly over 8 weeks	3/74 (4)	4% (1% to 11%)

* We did not show data for 5 days primaquine (75 mg) and 14 days primaquine (210 mg) from Kim 2012 due to high risk of selection and detection bias. Also, the trial authors expressed doubts regarding patient adherence to primaquine in this unsupervised trial, raising concerns about the reliability of relapse estimates with primaquine.

APPENDICES

Appendix 1. Conference proceedings searched

First edition of the review (2007)

- Vivax Malaria Research: 2002 and Beyond, Bangkok, Thailand, 3 to 8 February 2002;
- The Third Multilateral Initiative on Malaria (MIM) Pan-African Malaria Conference, Arusha, Tanzania, 19 to 22 November 2002;
- International Symposium on Malaria Control in the Mekong Region, Siem Reap, Cambodia, 10 to 13 December 2002;
- The American Society of Tropical Medicine and Hygiene, 51st Annual Meeting, Denver, USA, 10 to 14 November 2002;
- The Fourth Multilateral Initiative on Malaria (MIM) Pan-African Malaria Conference, Yaoundé, Cameroon, 13 to 18 November 2005.

Second edition of the review (2013)

- American Society of Tropical Medicine and Hygiene 61st Annual Meeting, Atlanta, Georgia, USA: November 11 to 15, 2012;
- American Society of Tropical Medicine and Hygiene 60th Annual Meeting Philadelphia, USA: December 4 to 8, 2011;
- American Society of Tropical Medicine and Hygiene 59th Annual Meeting Atlanta, Georgia, USA: November 3 to 7, 2010;
- American Society of Tropical Medicine and Hygiene 58th Annual Meeting Washington DC, USA: November 18 to 22, 2009;
- American Society of Tropical Medicine and Hygiene 57th Annual Meeting, New Orlens, Louisiana, USA: December 7 to 11, 2008;
- American Society of Tropical Medicine and Hygiene 56th Annual Meeting, Philadelphia, Pennsylvania, USA: November 4 to 8, 2007;
- The Third ASEAN Congress of Tropical Medicine and Parasitology (ACTMP3), Bangkok, Thailand: May 22 to 23, 2008;
- 5th MIM Pan-African Malaria Conference, Nairobi, Kenya: 2 to 6 November 2009;
- 14th International Congress on Infectious Diseases (ICID) Miami, Florida, USA: March 9 to 12, 2010;
- 13th International Congress on Infectious Diseases (ICID) Kuala Lumpur, Malaysia: June 19 to 22, 2008;
- 11th International Congress on Infectious Diseases (ICID), Cancun, Mexico: March 4 to 7, 2004;
- 10th International Congress on Infectious Diseases (ICID), Singapore: March 11 to 14, 2002;
- International Conference on Malaria: 125 years of Malaria research, New Delhi, India: November 4 to 6, 2005;
- Keystone Symposia Global Health Series: Malaria (Immunology, pathogenesis and perspectives), Alpbach, Austria: June 8 to 13, 2008;
- Gordon Research Conference, Malaria: The Science Behind Malaria Control and Eradication, Lucca (Barga), Italy: July 31 to August 5, 2011.

WHAT'S NEW

Date	Event	Description
17 October 2013	New search has been performed	We included six additional trials in this update: Alvarez 2006; Leslie 2008; Carmona-Fonseca 2009; Yeshiwondim 2010; Kim 2012; Ganguly 2013, One new author (Richard Kirubakaran) contributed to this review update and replaced an author (Aika Omari) of the 2007 review.
17 October 2013	New citation required and conclusions have changed	We updated the conclusions of this review from the 2007 review:

Date	Event	Description
		New comparisons demonstrate the relative inefficacy of three shorter primaquine regimens versus the standard 14-days of primaquine; and uncertain benefits with weekly primaquine dosing for eight weeks over the standard 14-day primaquine regimen in preventing relapses of vivax malaria.

HISTORY

Protocol first published: Issue 3, 2003
Review first published: Issue 1, 2007

Date	Event	Description
24 March 2008	Amended	We correct ed d osage figures.

CONTRIBUTIONS OF AUTHORS

For the 2012 update, Gawrie Galappaththy contributed to the revised protocol, selected trials, assessed trial quality, checked extracted data, helped to interpret results, helped address editorial revisions and approved the final review version.

Prathap Tharyan re-wrote the protocol in the new format, updated the background and methods sections, selected trials, assessed risk of bias, extracted and entered data, synthesized data, performed sensitivity analyses, summarized findings using the GRADE approach, interpreted results, incorporated editorial revisions, and wrote the final version of the review update.

Richard Kirubakaran joined the author team in place of Aika Omari; helped re-draft the protocol of this update, selected trials, assessed quality, extracted data, checked data entry, calculated intra-cluster correlations and the design effect used in sensitivity analyses, synthesized data, checked GRADE assessments, helped interpret results, helped write the review, and approved the final version of this review update.

DECLARATIONS OF INTEREST

GG, PT and RK have no known conflicts of interest to declare.

SOURCES OF SUPPORT

Internal sources

- National Malaria Control Programme, Sri Lanka.

  Salary support for Dr. Gawrie
- Christian Medical College, Vellore, India.

  Salary and logistic support for Dr. Tharyan

External sources

- Indian Council of Medical Research, India.

  Funding for Prof. BV Moses & ICMR Centre for Advanced Research in Evidence-Informed Healthcare; salary support for Richard Kirubakaran during the initial period of the review update
- Department for International Development (DFID), UK.

  Project funding for the Effective Healthcare Research Consortium; salary for Richard Kirubakaran during the latter part of this review update
- Liverpool School of Tropical Medicine, UK.

  Support for Dr. Gawrie to develop the protocol for the initial version of the review via funds from DFID (UK)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2013 review update:

We changed the effect measure from odds ratios to relative risks to aid interpretability.

We updated the background to incorporate recent findings and issues relevant to this review. We also updated the methods section to incorporate changes in Review Manager 5.2 such as 'Risk of bias' tables and 'Summary of findings' tables. We generated both of these for the included trials. For 'Summary of findings' tables, we used GRADE profiler (GRADE 2004) and interpreted the evidence for each important and critically important outcome for the comparisons in the included trials using the GRADE approach (Schunemann 2008).

For this update, we did not include the secondary outcome *P. vivax* parasitaemia detected > 30 days after starting primaquine corrected for new infections, since no valid tests are currently available for widespread use to assess this.

The subgroup analyses that we planned in the 2007 version protocol included: 1. Parasitic clearance before day 28 confirmed by microscopy *versus* not confirmed; 2. Tropical versus temperate strains; 3. Areas of high malaria transmission versus low or moderate transmission; 4. In children below 12 years versus older people. We had also hoped to expand the list of subgroup analyses to incorporate recent findings regarding potential confounders of primaquine efficacy such as chloroquine and primaquine given sequentially versus concurrently. (We defined concurrently primaquine started on any of the days of chloroquine administration; sequentially included primaquine administered from the day after chloroquine treatment to any time within or after the 28 days of initiating chloroquine and within 60 days). We did not undertake these subgroup analyses since the results were consistent within subgroups followed up for less than six months and more than six months, reflecting the contributions made by relapses and re-infections to the recurrence rates during these periods, and when subgrouped according to whether treatments were supervised or not. We have discussed the effect of sequential versus concurrent administration in the Overall completeness and applicability of evidence section.

We rechecked all extracted data and used the calculator function in Review Manager 5.2, instead of the manual calculations used for estimating log odds ratios and standard errors used in previous generic inverse variance meta-analysis. We rectified minor errors in extracted data for Walsh 2004 and Villalobos 2000 in the 2007 review.

2007, Issue 1 (review):

We stated in the protocol that we intended to stratify the results by length of follow-up: 40 days, 90 days, 120 days, six months, nine months, one year, and greater than one year. We could not do this because only nine trials met the inclusion criteria; so instead we analyzed the length of follow-up as less than or equal to six months and greater than six months. Prathap Tharyan joined the team as a co-author of this review after publication of the protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

Antimalarials [*administration & dosage]; Chloroquine [administration & dosage]; Drug Administration Schedule; Malaria, Vivax [*prevention & control]; Plasmodium vivax; Primaquine [*administration & dosage]; Randomized Controlled Trials as Topic; Secondary Prevention

MeSH check words

Adult; Child; Humans