Cochrane Library

Cochrane Database of Systematic Reviews

Tafenoquine for preventing relapse in people with Plasmodium vivax malaria (Review)

Rajapakse S, Rodrigo C, Fernando SD

Rajapakse S, Rodrigo C, Fernando SD.
Tafenoquine for preventing relapse in people with Plasmodium vivax malaria.
Cochrane Database of Systematic Reviews 2015, Issue 4. Art. No.: CD010458.
DOI: 10.1002/14651858.CD010458.pub2.

www.cochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Tafenoquine for preventing relapse in people with *Plasmodium vivax* malaria

Senaka Rajapakse[1], Chaturaka Rodrigo[1], Sumadhya Deepika Fernando[2]

[1]Department of Clinical Medicine, Faculty of Medicine, University of Colombo, Colombo, Sri Lanka. [2]Department of Parasitology, Faculty of Medicine, University of Colombo, Colombo, Sri Lanka

Contact address: Chaturaka Rodrigo, Department of Clinical Medicine, Faculty of Medicine, University of Colombo, 25, Kynsey Road, Colombo, Sri Lanka. chaturaka.rodrigo@gmail.com.

Editorial group: Cochrane Infectious Diseases Group.
Publication status and date: Unchanged, published in Issue 4, 2015.

Citation: Rajapakse S, Rodrigo C, Fernando SD. Tafenoquine for preventing relapse in people with *Plasmodium vivax* malaria. *Cochrane Database of Systematic Reviews* 2015, Issue 4. Art. No.: CD010458. DOI: 10.1002/14651858.CD010458.pub2.

ABSTRACT

Background

Plasmodium vivax malaria is widespread, and the persistent liver stage causes relapse of the disease which contributes to continued *P. vivax* transmission. Primaquine is currently the only drug that cures the parasite liver stage, but requires 14 days to be effective and can cause haemolysis in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency. In addition, there is some evidence of parasite resistance to the drug. Tafenoquine is a new alternative with a longer half-life.

Objectives

To assess the effects of tafenoquine in people with *P. vivax* infection.

Search methods

We searched the following databases up to 13 April 2015: the Cochrane Infectious Diseases Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL), published in The Cochrane Library; MEDLINE; EMBASE; CINAHL; SCOPUS; and LILACS. We also searched the World Health Organization (WHO) International Clinical Trial Registry Platform and the metaRegister of Controlled Trials (*m*RCT) for ongoing trials using "tafenoquine" and "malaria" as search terms up to 13 April 2015.

Selection criteria

Randomized controlled trials (RCTs) in people with *P. vivax* malaria. Adverse effects of tafenoquine are assessed in populations where people with G6PD deficiency have been excluded, and in populations without screening for G6PD deficiency.

Data collection and analysis

All review authors independently extracted data and assessed trial quality. Meta-analysis was carried out where appropriate, and estimates given as relative risk with 95% confidence intervals. We assessed the quality of the evidence using the GRADE approach.

Main results

Three RCTs met our inclusion criteria, with the asexual infection in both the tafenoquine and comparator arm treated with chloroquine, and in all trials G6PD deficiency patients were excluded.

Tafenoquine dose comparisons

Three of the included trials compared eight different dosing regimens. Tafenoquine doses of 300 mg and above resulted in fewer relapses than no hypnozoite treatment over six months follow-up in adults (300 mg single dose: RR 0.19, 95% CI 0.08 to 0.41, one trial, 110 participants, moderate quality evidence; 500 to 600 mg single dose: RR 0.14, 95%CI 0.06 to 0.34, two trials, 122 participants, moderate quality evidence; 1800 mg to 3000 mg in divided doses: RR 0.05, 95% CI 0.01 to 0.23, two trials, 63 participants, low quality evidence).

In people with normal G6PD status, there may be little or no difference in serious adverse events (three trials, 358 participants, *low quality evidence*); or any adverse event (one trial, 272 participants, *low quality evidence*).

Tafenoquine versus primaquine

Two of the included trials compared four different dosing regimens of tafenoquine against the standard primaquine regimen of 15 mg/day for 14 days. A single tafenoquine dose of 600 mg may be more effective than primaquine in relation to relapses at six months follow-up (RR 0.29, 95% CI 0.10 to 0.84, two trials, 98 participants, *low quality evidence)*

In people with normal G6PD status, there may be little or no difference for serious adverse events (two trials, 323 participants, *low quality evidence*) or any adverse event (two trials, 323 participants, *low quality evidence*) between tafenoquine and primaquine.

Authors' conclusions

Tafenoquine prevents relapses after clinically and parasitologically confirmed *P. vivax* malaria. The drug is untested in pregnancy, children and in G6PD-deficient people. The shorter treatment course is an important practical advantage in people who do not have G6PD deficiency, but the longer half-life may have more substantive consequences if given inadvertently to people with G6PD deficiency.

PLAIN LANGUAGE SUMMARY

Tafenoquine for preventing relapse in people with vivax malaria

Background

Vivax malaria is caused by the parasite *Plasmodium vivax*. The disease includes a stage of liver infection and this can cause relapse unless treated. The only drug available until recently was primaquine, but this requires a 14-day course of treatment. Alternatives have been tried, one of which is tafenoquine, which does not need such a long course of treatment. Both primaquine and tafenoquine can cause haemolysis in people with glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency, which is a common genetic defect. We conducted a Cochrane Review on the effect of the drug tafenoquine on clearing the dormant *P. vivax* parasites in infected patients to prevent a relapse.

Review findings

Researchers in the Cochrane Collaboration examined the research published up to 13 April 2015. We identified three trials conducted in Thailand, India, Peru and Brazil on adults with confirmed*P. vivax* malaria that randomized 453 participants. All adults received chloroquine (to clear the parasites in the blood) and some groups received either tafenoquine, primaquine or no further treatment. All were observed for recurrences of *P. vivax* malaria (up to six months) and all trials tested people for G6PD enzyme, and excluded patients who were deficient.

Adults receiving tafenoquine at doses greater than 300 mg had fewer relapses than adults who had no further treatment (*moderate quality evidence*). Tafenoquine 600 mg may be better in relapse prevention than standard primaquine doses (*low quality evidence*). In patients who do not have G6PD deficiency, there may be little or no difference in adverse effects (*low quality evidence*).

The drug is untested in children and pregnant women. The shorter treatment course is a practical advantage, but the longer half-life could may have more substantive consequences if given inadvertently to people with G6PD deficiency.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Tafenoquine vs placebo/no hypnozoite treatment in people with *Plasmodium vivax* malaria

Patient or population: Adults and children with *P. vivax* malaria
Settings: *P. vivax* endemic areas
Intervention: Tafenoquine. Both intervention and control received chloroquine treatment.
Comparison: No hypnozoite treatment.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	CQ alone	TQ plus CQ			
Recurrent *P. vivax* parasitaemia during six months of follow-up	300 mg as a single dose		RR 0.19 (0.08 to 0.41)	110 (1 trial)	⊕⊕⊕◯ moderate[1,2,3]
	57 per 100	11 per 100 (5 to 23)			
	500 mg or 600 mg as a single dose		RR 0.14 (0.06 to 0.34)	122 (2 trials)	⊕⊕⊕◯ moderate[4,5,6,7]
	57 per 100	8 per 100 (3 to 19)			
	1800 mg to 3000 mg in divided doses		RR 0.05 (0.01 to 0.23)	63 (2 trials)	⊕⊕◯◯ low[5,7,8,9]
	57 per 100	3 per 100 (1 to 13)			
Serious adverse events	6 per 100	6 per 100 (2 to 16)	RR 0.94 (0.34 to 2.59)	358 (3 trials)	⊕⊕◯◯ low[10,11]

*The basis for the **assumed risk** (for example, the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **CQ:** Chloroquine; **TQ:** Tafenoquine; **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]No serious risk of bias: This trial was at low risk of selection and reporting bias.
[2]No serious indirectness: This trial enrolled adults with *P. vivax* malaria in Peru, Thailand, India and Brazil. CQ was given in the standard adult dose to all participants.
[3]Downgraded by 1 for serious imprecision: This single trial is small and had few events during six months, as such this result is at high risk of being a chance finding or of overestimating the true effect.
[4]No serious risk of bias: One trial is at low risk of selection or detection bias. The second smaller trial is at unclear risk of selection bias.
[5]No serious inconsistency.
[6]No serious indirectness: These trials enrolled adults with *P. vivax* malaria in Peru, Thailand, India and Brazil. CQ was given in the standard adult dose to all participants.
[7]Downgraded by 1 for serious imprecision: These two trials are small with few events, as such this result is at high risk of being a chance finding or of overestimating the true effect.
[8]Downgraded by 1 for serious risk of bias: Both trials are at unclear risk of selection bias.
[9]No serious indirectness: These trials enrolled adults with *P. vivax* malaria in Thailand. CQ was given in the standard adult dose to all participants.
[10]Downgraded by 1 for serious indirectness: These trials excluded children, pregnant women and people with G6PD deficiency.
[11]Downgraded by 1 for serious imprecision.

BACKGROUND

Malaria remains an important cause of illness and death in many tropical countries. In 2011, 216 million cases of malaria were estimated to have occurred globally and in 2010 there were approximately 655,000 deaths due to malaria (WHO 2012). Global malaria eradication efforts have resulted in a decrease in mortality and morbidity, with global mortality from malaria falling by 25% since 2000 (WHO 2012). Most malaria cases are caused by the species *Plasmodium falciparum* and *Plasmodium vivax*. *P. falciparum* causes a more severe form of malaria with multi-organ involvement (Fernando 2011a). *P. vivax* is less virulent than *P. falciparum* and seldom causes death. However, it causes substantive illness-related burden in endemic areas. The incidence of *P. vivax* infection has become particularly important in countries aiming for malaria elimination. Currently, there are 32 such countries, of which, 25 are mainly targeting elimination (interruption of transmission without local cases) of*P. vivax*. Another 67 countries are working towards reducing and controlling the high burden of malaria mortality and morbidity (Feachem 2010; Fernando 2011a). *P. vivax* infection has been treated with chloroquine (CQ) but resistance to this widely available drug has been reported on all continents in which malaria caused by *P. vivax* is endemic (Rieckmann 1989; WHO 2009). Eradication of liver stages of the disease is necessary to avoid relapses. Due to the large number of infections reported, malaria caused by *P. vivax* is increasingly being identified as an important public health problem in endemic areas (WHO 2009).

Description of the condition

The life cycles of *P. falciparum* and *P. vivax* differ. *P. vivax* can have dormant forms in the hepatocytes, known as hypnozoites, which can remain dormant for weeks or even months. Thus, a single infection with *P. vivax* can be responsible for a relapse or series of relapses after an apparent cure. Therefore, eradication of the dormant hepatic forms of the *P. vivax* parasite is necessary to prevent recurrences. Treatment of people infected with *P. vivax* with blood schizonticidal agents alone will not result in complete cure as these agents are not capable of clearing the hypnozoites.

Description of the intervention

Primaquine (PQ), an 8-aminoquinoline, was first licensed for use in the 1950s by the Food and Drug Administration (FDA), United States (Hill 2006), for treatment of vivax malaria. It is the only licensed drug capable of eliminating the vivax hypnozoites. Without administration of PQ in adequate doses, complete cure of patients with *P. vivax* infection is difficult, and patients often have relapses of clinical disease (Baird 2004; Fernando 2011b). There are several potential alternatives to PQ but tafenoquine (TQ) has been the most extensively studied option over the last 15 years. TQ is an 8-aminoquinoline (Wells 2010) and is a synthetic analogue of PQ (Walsh 2004a). It has potential to be useful in regimens for prophylaxis and radical cure of *P. vivax* malaria.

PQ can precipitate haemolysis (which can be life-threatening) in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, an X-linked recessive condition (Ramos Júnior 2010). In addition, it has other undesirable side effects such as methaemoglobinaemia and gastrointestinal disturbances (Carmona-Fonseca 2009). PQ resistance has been reported as isolated cases from different areas even after it has been administered in adequate doses according to body weight (Ehrman 1944; Goller 2007; Hill 2006; Reddy 2006). PQ treatment has to be continued for 14 days, which often leads to poor compliance (Hill 2006).

A search for a replacement drug for PQ in its curative role has been ongoing for the last few decades. The characteristics of an ideal replacement would be: a) has a shorter duration of treatment, b) has better efficacy in clearing hypnozoites, c) is free from the significant side effects of PQ such as haemolysis in individuals with G6PD deficiency and d) lower chance of the parasite developing resistance to the drug. Several options have been explored in this regard, including TQ, bulaquine, tinidazole and imidazolidinone. Bulaquine is the pro-drug of PQ and is currently not licensed for sale outside India (Wells 2010). Of other options, only TQ has been tested to show promising results for both prevention and radical cure in individual trials. Also, its shorter duration of therapy makes it an attractive option to improve adherence. It also causes haemolysis, and its longer half-life makes any haemolytic effect more prolonged and thus potentially more serious. In 2013, the FDA designated TQ as a breakthrough therapy. This Cochrane review will pool the evidence from all RCTs on use of TQ for radical cure of*P. vivax* malaria to answer key questions on its efficacy and adverse event profile as compared to no treatment or PQ.

How the intervention might work

The exact mechanism of action of TQ is not yet known. Based on early in vitro and animal studies, some believed it to be longer acting and more effective than PQ (Walsh 2004a). Preclinical studies showed better activity of TQ compared to PQ against both hepatic and erythrocytic forms of the parasite. Phase I and II trials have been conducted to evaluate its safety (Brueckner 1998a; Brueckner 1998b). It has been more than a decade since TQ has been studied for treating *P. vivax* malaria.

Why it is important to do this review

PQ is a unique drug in combating vivax malaria but has side effects, which can sometimes be serious in people with G6PD deficiency. The long duration of treatment also leads to poor adherence. TQ is a possible alternative that has shown promise in replacing PQ and it can be administered as a single dose or in much shorter treatment

regimens. Therefore, it is important to establish the effects of TQ from available data for preventing relapses of vivax malaria after an acute infection.

OBJECTIVES

To assess the effects of tafenoquine in people with *P. vivax* infection.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled clinical trials (RCTs). We excluded quasiRCTs..

Types of participants

Adults and children with confirmed (clinical and parasitological) diagnosis of *P. vivax* malaria.
We included trials where people with G6PD deficiency have been excluded, and in populations without screening for G6PD deficiency.

Types of interventions

Intervention

Tafenoquine

Control

No drug or placebo;
Primaquine in standard WHO 14-day regimen
Both intervention and control groups must have received the same treatment, either CQ or an ACT, for the blood-borne stage of the *P. vivax* infection.

Types of outcome measures

Episodes of *P. vivax* parasitaemia during follow-up
Serious adverse events:death, symptomatic haemolysis, symptomatic methaemoglobinaemia, any other potentially life threatening observation or complaint that required treatment and monitoring by further investigations.
Any adverse events: all adverse effects either reported by subjects or elicited by investigators during treatment and follow-up.

Search methods for identification of studies

We identified all relevant trials regardless of language or publication status (published, unpublished, in press and in progress). There were no time limits for the search.

Electronic searches

We searched the following databases using the search terms detailed in Appendix 1: the Cochrane Infectious Diseases Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL), published in The Cochrane Library; MEDLINE; EMBASE; CINAHL; SCOPUS; and LILACS. We also searched the World Health Organization (WHO) International Clinical Trial Registry Platform and the metaRegister of Controlled Trials (mRCT) for ongoing trials using “tafenoquine” and “malaria” as search terms. The date of the last search for all databases was 13 April 2015 and included all entries within these databases up to this date.

Searching other resources

Conference proceedings

We searched relevant proceedings of the Multilateral Initiative on Malaria (MIM) Pan-African Malaria Conference and the American Society of Tropical Medicine and Hygiene Annual Meeting from 1990 onwards for trial information. The date of the last search was 13 April 2015.

Researchers

We contacted researchers working in the field and the WHO for unpublished and ongoing trials.

Reference lists

We checked the reference lists of existing reviews and of all trials identified by the above methods.

Data collection and analysis

Selection of studies

We (SR, CR and SDF) independently screened all trials identified by the search strategy and obtained full reports of potentially relevant trials. We independently applied the inclusion criteria to the full reports using an eligibility form and scrutinized publications to ensure each trial was included in the review only once. If necessary, we contacted the trial authors for clarification. Any disagreement was resolved by consensus. We have listed the ineligible trials and the reasons for their exclusion in the ’Characteristics of excluded studies’ table.

Data extraction and management

We (SR, CR and SDF) extracted data from the selected trials and independently recorded outcomes. We developed and used a data extraction and assessment form suited for the needs of this review according to the instructions provided by The Cochrane Collaboration (Higgins 2011). We used RevMan 2014 for data analysis and storage, and created 'Summary of findings' tables with GRADEpro 2014 software. In each of the selected trials, we identified key information such as demographic characteristics of selected populations, G6PD status of the subjects, trial design and measures taken to minimize bias, treatment offered in different trial arms (with respect to dose and duration), duration of follow-up, adverse events and reported outcomes. We also noted the limitations in each of the trials.

Assessment of risk of bias in included studies

We (SR, CR and SDF) independently assessed the risk of bias for each included trial using a 'Risk of bias' assessment form. We resolved any discrepancies between the results of the 'Risk of bias' analysis through discussion and consensus. If data were unclear or not reported, we wrote to the trial authors for clarification. We did not calculate quality scores for individual trials as it is not perceived by some authors as an objective measure of risk of bias (Greenland 1994).

We assessed the risk of bias for individual trials using the Cochrane 'Risk of bias' tool. This covers six domains of bias: allocation (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other potential sources of bias. Furthermore, we summarized the risk of bias for individual trials in a 'Risk of bias' table.

Measures of treatment effect

We expressed the effect of treatment within trials as risk ratio (RR) for dichotomous outcomes (for example, relapse of vivax malaria, new infections of vivax malaria). We defined the level of significance of differences according to the Chi^2 statistic of $P < 0.05$. For all results, we calculated 95% confidence intervals (CIs) and performed meta-analyses if sufficient data were available. We split the control groups between trial arms of a single trial where appropriate for meta-analysis.

Unit of analysis issues

We did not identify any cluster-RCTs in the search. Trials used different doses of TQ in multiple-treatment arms against a control. If the doses were identical in certain trial groups, we combined them for pair-wise comparison in a meta-analysis. When comparing different TQ doses, we split the control group to avoid duplication in data entry.

Dealing with missing data

We contacted the corresponding author of one trial (Llanos-Cuentas 2014) regarding data not reported in the paper and we obtained relevant data. No trials were excluded due to missing data.

Assessment of heterogeneity

We assessed heterogeneity using the I^2 statistic (Higgins 2003), which examines the percentage of total variation across studies that are due to heterogeneity rather than chance. An I^2 statistic value > 70% indicates a high level of heterogeneity.

Assessment of reporting biases

Since an insufficient number of RCTs met our inclusion criteria (< 10 trials) for each primary objective, we could not construct funnel plots to look for evidence of publication bias.

Data synthesis

We analysed data using RevMan 2014. CR conducted the initial analysis, and SR and SDF independently double checked and performed recalculations. We compared relapses following treatment between groups treated with TQ-containing drug regimens against CQ alone or CQ plus PQ. Also, we compared the reported adverse events between TQ and controls. We used a fixed-effect model for analysis (and rechecked for any differences of results in a random-effects model).

Subgroup analysis and investigation of heterogeneity

When several trials were combined in a meta-analysis, we calculated heterogeneity to express the treatment effect of TQ and CQ versus CQ alone or CQ plus PQ. We presented data in subgroups depending on the different doses of TQ used and whether single doses or split doses were used.

Sensitivity analysis

We did not perform a sensitivity analysis as only three trials were eligible for a valid comparison in a meta-analysis.

RESULTS

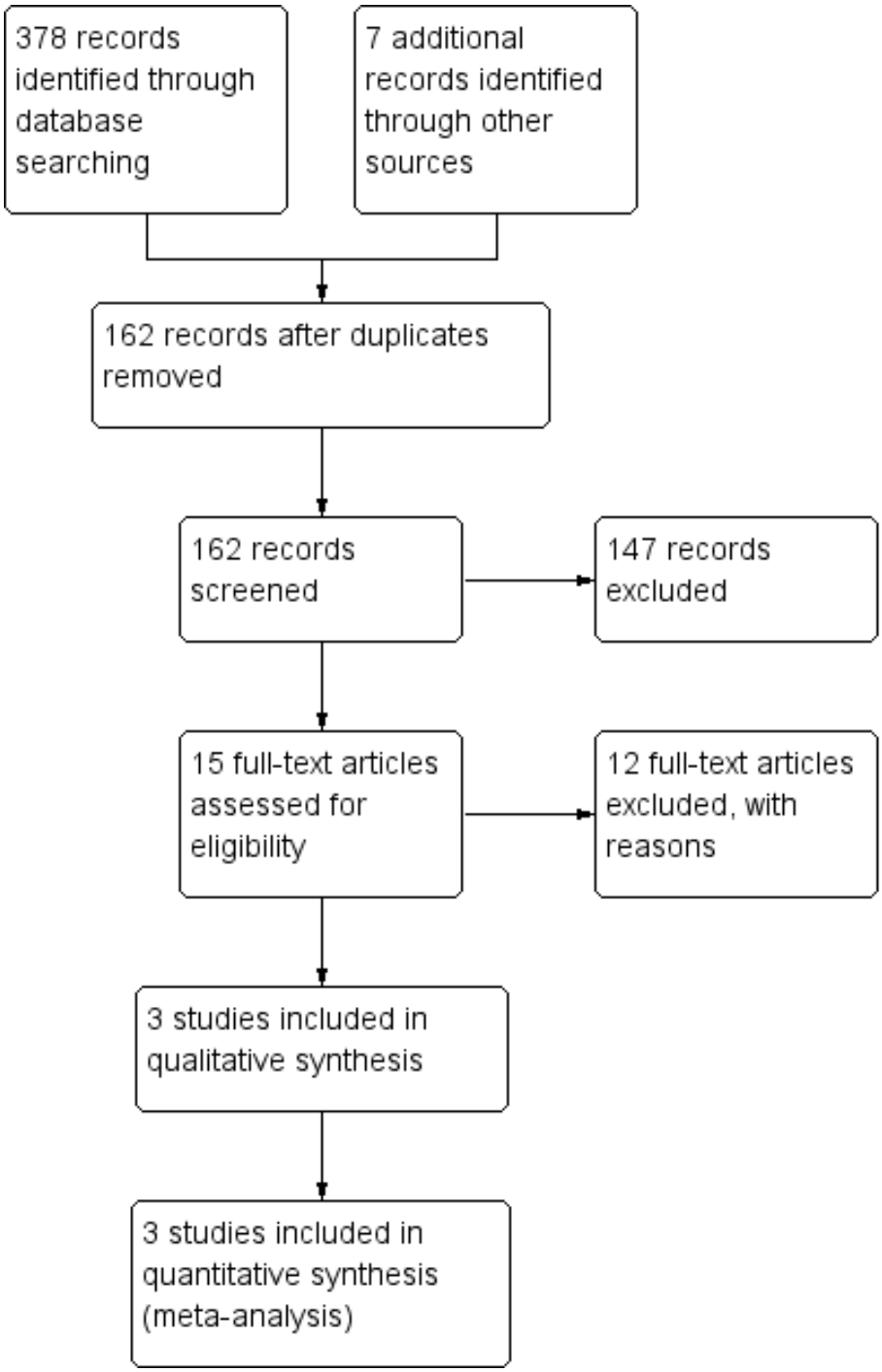
Description of studies

See: Characteristics of included studies, Characteristics of excluded studies and Characteristics of ongoing studies. We have given a summary of drug doses used in each trial arm of all included trials for ease of comparison (Table 1).

Results of the search

The results of the search, after excluding duplicate and irrelevant articles, yielded 15 papers that we deemed potentially useful for this Cochrane review (Figure 1). However, only three trials met the inclusion criteria.

Figure 1. PRISMA flow diagram indicating the process of inclusion and exclusion of studies.



Included studies

Three individually RCTs met the inclusion criteria (Llanos-Cuentas 2014; Walsh 1999; Walsh 2004a). All patients received a full course of CQ to treat their *P. vivax* infection (1500 mg over three days). Comparisons included TQ + CQ versus CQ only (all three trials) and TQ + CQ versus CQ + PQ (two trials). No trials were conducted with ACTs as the background treatment.

All trials were in symptomatic patients with uncomplicated vivax malaria, and all trials excluded patients with G6PD deficiency, pregnant females and children.

Two trials were conducted in Bangkok, Thailand (Walsh 1999; Walsh 2004a) and the latest trial was a multicentre trial in Thailand, India, Peru and Brazil (Llanos-Cuentas 2014). The earlier two trials examined comparatively high doses of TQ starting from 500 mg (Walsh 1999) or 600 mg (Walsh 2004a) administered as single doses and 1800 to 3000 mg administered as split doses over three to seven days. Llanos-Cuentas 2014 tested single doses of TQ at strengths of 50, 100, 300 and 600 mg. The main outcomes assessed were: a) recurrences of vivax malaria up to six months follow-up and b) adverse events. We contacted the authors of Llanos-Cuentas 2014 for details not published in the paper (exact number of relapses during follow-up) and we included the data in this analysis.

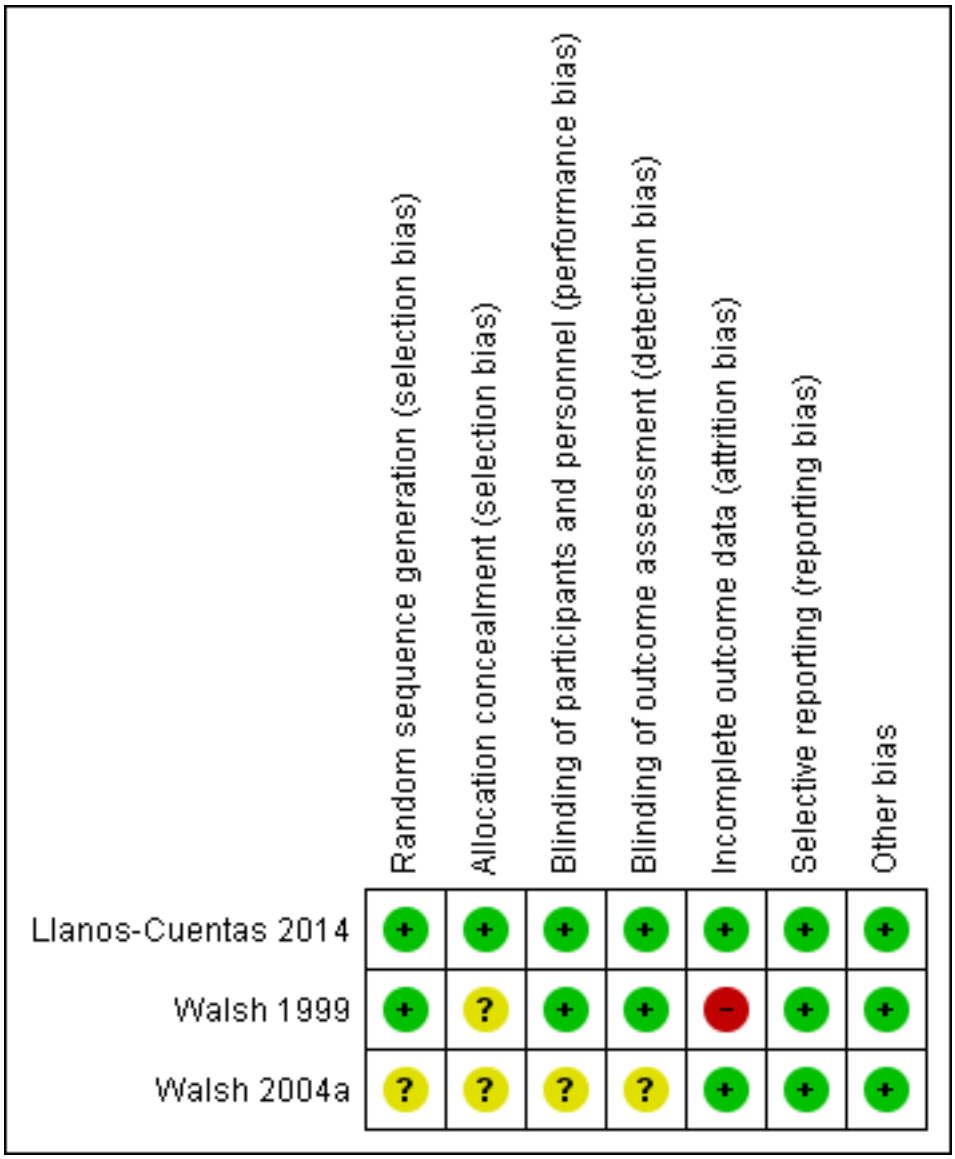
Excluded studies

We excluded randomized trials on prophylaxis, non-controlled trials, case reports and pharmacokinetic studies (see Characteristics of excluded studies).

Risk of bias in included studies

For a summary of risk of bias please see the 'Characteristics of included studies' table and Figure 2.

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



All three included trials were described as randomized with computer generated sequence allocation. However in Walsh 2004a, some randomizations were eliminated and a few others were shifted between groups to balance the number of participants recruited in each group. Therefore we were unclear regarding the selection bias.

Both Walsh 1999 and Walsh 2004a were open label studies. However, the primary outcome of vivax parasitaemia was unlikely to be influenced by this fact as long as the microscopists were blinded. Walsh 1999 mentions that the microscopists were blinded but Walsh 2004a does not. So we judged that Walsh 1999 was at low risk of bias and Walsh 2004a was at unclear risk of bias. Llanos-Cuentas 2014 was a double blind trial at low risk of bias. Walsh 1999 had a high attrition rate (27% of total sample during the first two months). It was lower but significant in Walsh 2004a (15% of total sample were lost to follow-up during the first two months). The attrition rates were less than 6% for any of the trial arms in Llanos-Cuentas 2014 which had a low risk of attrition bias.

All missing patients were accounted for and there was no reporting bias in all trials.

Effects of interventions

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

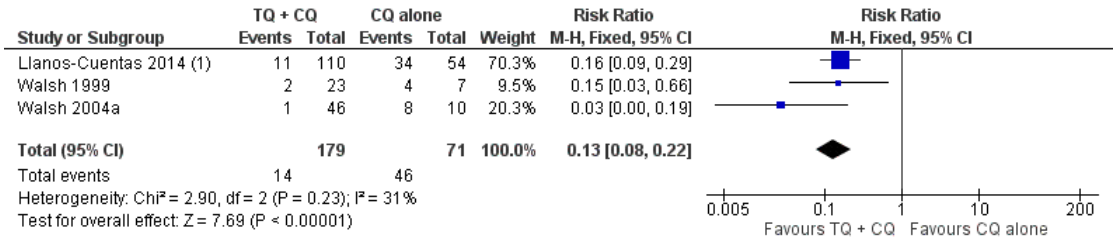
1. Tafenoquine versus no hypnozoite treatment

All three trials included arms that evaluated TQ against no specific anti-hypnozoite drug. The TQ doses varied from 50 to 600 mg in single doses and from 1800 to 3000 mg in spilt doses over three to seven days. All patients in all included arms received CQ 1500 mg for three days.

Recurrent *P. vivax* parasitaemia during six months follow-up

We first analysed the data for this outcome for four groups based on the total dose of TQ used in the trials; 50 to 100 mg, 300 mg, 500 to 600 mg and 1800 to 3000 mg. The analysis indicate that low doses (50 to 100 mg) had outcomes comparable to no treatment (one trial, 162 participants, Analysis 1.1) and hence we did not use these groups for further analysis. A repeat analysis of all trials after excluding the low dose groups showed that TQ reduced the *P. vivax* recurrences compared to no treatment during a six month follow-up (RR 0.13, 95% CI 0.08 to 0.22, three trials, 250 participants, *moderate quality evidence*; Analysis 1.2; Figure 3).

Figure 3. Forest plot of comparison: 1 TQ and CQ versus CQ alone, outcome: 1.2 Recurrent *P. vivax* parasitaemia by six months (excluding TQ doses < 300 mg).



Footnotes

(1) The trial groups that used low doses of tafenoquine (50 and 100 mg) were excluded from the analysis

Adverse events

Serious adverse events: We included the low dose TQ groups in the adverse event analysis.There was no difference between TQ groups and controls regarding serious adverse events (three trials, 358 participants, Analysis 1.3). No deaths were reported in any of the trials during treatment or follow-up.

Any adverse events: There was no difference for any reported adverse events between the two groups (one trial, 272 participants, Analysis 1.4).

We also carried out a dose-wise comparison (TQ 300 mg and 600 mg) for each type of adverse event reported and found no difference between TQ groups and controls except for a fewer number of chills in the TQ group (Analysis 1.5; Analysis 1.6).

There was also a dose-dependent rise in methaemoglobin (MHb) levels in TQ treated groups, which was asymptomatic. In Walsh 1999 peak levels of MHb were 13.5%, 14.7% and 6.4% in treatment groups with total doses of 2100 mg, 3000 mg and 500 mg, respectively (normal value: 1 to 3%). Similarly, in Walsh 2004a the highest mean MHb level (12.1%) was reported from the trial arm which had the highest total TQ dose (2100 mg).

All trials screened and excluded patients with G6PD deficiency prior to randomization. Therefore, data on safety of TQ in G6PD-deficient individuals are currently not available. The longer half-life of TQ can potentially make it more harmful for patients with G6PD deficiency.

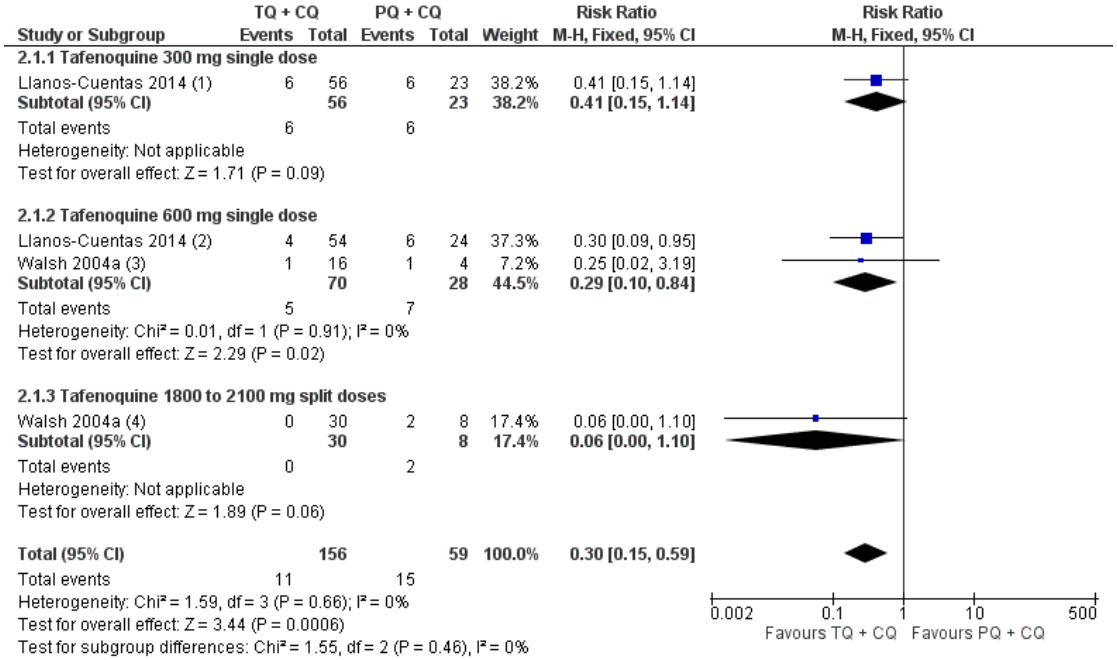
2. Tafenoquine versus primaquine

Two trials included this comparison (Llanos-Cuentas 2014; Walsh 2004a). Both trials used the same dose of PQ (15 mg/day for 14 days). All patients received CQ 1500 mg for three days. Walsh 1999 did not have a PQ arm.

Recurrent *P. vivax* parasitaemia at six months

For purposes of analysis we divided the TQ groups to three subgroups based on the dose (300 mg single dose, 600 mg single dose, and 1800 to 2100 mg in split doses). A single TQ dose of 600 mg may be more effective than PQ in reducing relapses over six months follow-up (RR 0.29, 95% CI 0.1 to 0.84, two trials, 98 participants, *low quality evidence*; Analysis 2.1; Summary of findings 2). The number of events in the higher dose category was too few to draw a firm conclusion. Overall, TQ may be better than PQ (15 mg/day over 14 days) in preventing relapses of vivax malaria during a six month follow-up (RR 0.3, 95% CI 0.15 to 0.59, two trials, 215 participants, *moderate quality evidence*; Analysis 2.1; Figure 4).

Figure 4. Forest plot of comparison: 2 TQ versus PQ (both received CQ), outcome: 2.1 Recurrent *P. vivax* parasitaemia by six months (excluding TQ doses < 300 mg).



Footnotes

(1) Llanos-Cuentas 2013; TQ 300 mg group

(2) Llanos-Cuentas 2013; TQ 600 mg group

(3) Walsh 2004; TQ 600 mg group

(4) Walsh 2004; two groups combined: TQ total dose 1800 mg (600 mg daily for 3 days), TQ total dose 2100 mg (300 mg daily for 7 days)

Adverse events

Serious adverse events: the low dose TQ groups were included in the adverse event analysis. There was no difference between TQ and PQ groups with regard to serious adverse events (two trials, 323 participants, *low quality evidence*; Analysis 2.2).

Any adverse events: There was also no difference detected between the two groups with regard to any reported adverse events (two trials, 323 participants, *low quality evidence*; Analysis 2.3). We carried out a dose wise comparison (TQ 300, 600, 1800, 3000 mg) for each type of adverse event reported and still found no difference between TQ and PQ groups (two trials, 323 participants, Analysis 2.4; Analysis 2.5; Analysis 2.6).

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Tafenoquine vs primaquine in people with *Plasmodium vivax* malaria

Patient or population: Adults and children with *P. vivax* malaria
Settings: *P. vivax* endemic areas
Intervention: Tafenoquine. Both intervention and control received chloroquine treatment.
Comparison: primaquine (standard 14 day regimen)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	PQ and CQ	TQ and CQ			
Recurrent *P. vivax* parasitaemia during six months of follow-up	300 mg as a single dose		RR 0.41 (0.15 to 1.14)	79 (1 trial)	⊕⊕◯◯ low[1,2,3]
	26 per 100	11 per 100 (4 to 30)			
	600 mg as a single dose		RR 0.29 (0.1 to 0.84)	98 (2 trials)	⊕⊕◯◯ low[4,5]
	25 per 100	7 per 100 (3 to 21)			
	1800 mg to 2100 mg in divided doses		RR 0.06 (0.00 to 1.1)	38 (1 trial)	⊕⊕◯◯ low[3,5]
	25 per 100	2 per 100 (0 to 27)			
Serious adverse events	12 per 100	5.5 per 100 (2 to 13)	RR 0.47 (0.2 to 1.08)	323 (2 trials)	⊕⊕◯◯ low[6,7]

*The basis for the **assumed risk** (for example, the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **CQ:** Chloroquine; **PQ:** Primquine; **TQ:** Tafenoquine; **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]No serious risk of bias: This trial was at low risk of selection and reporting bias.
[2]No serious indirectness: This trial enrolled adults with *P. vivax* malaria in Peru, Thailand, India and Brazil. CQ was given in the standard adult dose to all participants.
[3]Downgraded by 1 for serious imprecision: This single trial is small and had few events during six months, as such this result is at high risk of being a chance finding or of overestimating the true effect. Larger trials are needed to confirm this effect.
[4]Downgraded by 1 for serious imprecision: Both trials are small and had only a few events during six months, as such this result is at high risk of being a chance finding or of overestimating the true effect. Larger trials are needed to confirm this effect.
[5]Downgraded by 1 for serious risk of selection and detection bias in one trial.
[6]Downgraded by 1 for serious indirectness: These trials excluded children, pregnant women and people with G6PD deficiency.
[7]Downgraded by 1 for serious imprecision.

DISCUSSION

Summary of main results

Please see Summary of findings for the main comparison and Summary of findings 2.

TQ reduced recurrence of vivax malaria (up to six months of observation) when combined with a standard dose of CQ compared to controls who received CQ only (*moderate quality evidence*; further research is likely to have an important impact on our confidence in the estimate of effect). TQ and CQ combination may be superior to PQ and CQ combination at a TQ dose of 600 mg or greater (*low quality evidence*; further research is very likely to have an important impact on this effect and confidence estimates). There was no difference of adverse events (serious or any event) between TQ groups and the controls. The trials that assessed comparable outcomes were consistent in their findings.

Overall completeness and applicability of evidence

Llanos-Cuentas 2014 is a multicentre, double blind RCT with a larger sample size than other included trials and gives moderate quality evidence to arrive at dosing recommendations of TQ for relapse prevention in patients with vivax parasitaemia. Llanos-Cuentas 2014 showed that TQ in single low doses (50 and 100 mg) is ineffective in relapse prevention compared to CQ monotherapy and hence should not be used. When the data for higher doses in this trial is pooled with the other two trials (which are open label trials), a benefit is seen for relapse prevention by addition of TQ compared to CQ monotherapy. All trials are consistent in this regard.

The pooled results of the two trials comparing TQ with PQ indicate that TQ may be more effective, but numbers are small.

The dose of PQ used in the control arm in both trials was 15 mg/day for 14 days. More data from further clinical trials are needed to confirm the superiority (if any) of TQ over PQ at this PQ dosage. Current recommendations in some guidelines are for higher doses of PQ (for example, 30 mg/day for 14 days) (Hill 2006) and efficacy of TQ is untested against such doses of PQ. Similarly, G6PD deficient and pregnant individuals were excluded prior to enrolment in all trials and therefore safety of TQ under these circumstances is not explored. Therefore the major disadvantages with PQ, such as haemolysis with G6PD deficiency and methaemoglobinaemia, are still a risk with the structurally similar TQ and same cautions apply for its administration.

Quality of the evidence

Recurrent P. vivax parasitaemia at six months

All included trials were randomized prospective well designed clinical trials. However, two were open label trials (Walsh 1999; Walsh 2004a). Still, given the fact that the primary outcome was objectively defined (microscopically defined*P. vivax* parasitaemia), it would have offset any performance or detection bias as long as the microscopists were blinded. Only Walsh 1999 mentioned that microscopists were blinded. As mentioned previously, the sample size in individual trials was small and specially when the recruits were categorized into four or five treatment arms, the numbers in each arm were even fewer. Several of these arms had high attrition rates at two months. Considering the overall picture, we conclude that further evidence is needed to confirm these findings in larger clinical trials for the TQ versus PQ comparison . Furthermore, the maximum follow-up was six months in both trials. Relapses of vivax malaria can occur even later, probably up to one year.

Adverse events

Two trials were open label trials (Walsh 1999; Walsh 2004a) which might have caused bias in reporting adverse events. There is no foolproof method of differentiating whether an adverse reaction is actually related to the trial drug. This decision was at the discretion of the investigator and was subjective. The definition of seriousness of an adverse event is also subjective and one trial (Llanos-Cuentas 2014) had clearly reported more serious adverse events than the other two trials (Walsh 1999; Walsh 2004a) which had used much higher doses of TQ. Therefore, we have downgraded the quality of evidence to "low" with regard to this outcome. The safety of TQ in pregnancy, children and in G6PD deficient patients is untested.

Potential biases in the review process

The trial registries mentioned above were searched with specific search strategies to uncover any unpublished trials with negative results. None were identified.

Agreements and disagreements with other studies or reviews

There were no other reviews to compare with this Cochrane review on the efficacy of TQ in preventing relapses of vivax malaria. On adverse events we agree with the conclusion of individual trial investigators and other reviewers (Prashar 2009) that TQ is a well-tolerated drug in non-pregnant, non-G6PD deficient individuals in the dose ranges tested.

AUTHORS' CONCLUSIONS

Implications for practice

TQ has good efficacy in preventing relapses up to six months by clearing vivax hypnozoites when used at a total dose of 300 mg

or more (*moderate quality evidence*). Evidence from two studies also suggest that it may be better than PQ (15 mg/day for 14 days) for hypnozoite clearance (*low quality evidence*). The ability to administer TQ as single doses or a shorter course of split doses is a significant advantage.

People with G6PD deficiency were excluded from the studies so recommendations for its use derived from trials to date can only be in people in whom G6PD deficiency has been excluded.

Implications for research

Further randomized controlled clinical trials will help establish whether TQ is better in relapse prevention compared to PQ. Such trials should test TQ at doses $\geq$ 300 mg compared to PQ in standard doses(15 mg/day for 14 days). Preferably patients should have a longer follow-up period (extending to one year).

There is a greater potential risk of haemolysis with TQ than with PQ because of the longer half-life. This is important to consider researching further before deployment of the drug widely in primary care.

ACKNOWLEDGEMENTS

CR was supported from a fellowship from the Effective Health Care Research Consortium, which receives funding from UKaid in a grant from UK Government for the benefit of developing countries. We acknowledge Dr. Dulika Sumatipala for her assistance in preparing the protocol. The editorial base for the Cochrane Infectious Diseases Group is supported by UKaid from the UK Government for the benefit of developing countries.

REFERENCES

References to studies included in this review

Llanos-Cuentas 2014 *{published and unpublished data}*
Llanos-Cuentas A, Lacerda MV, Rueangweerayut R, Krudsood S, Gupta SK, Kochar SK, et al. Tafenoquine plus chloroquine for the treatment and relapse prevention of Plasmodium vivax malaria (DETECTIVE): a multicentre, double-blind, randomised, phase 2b dose-selection study. *Lancet* 2014;**383**(9922):1049–58.

Walsh 1999 *{published data only}*
Walsh DS, Looareesuwan S, Wilairatana P, Heppner DG Jr, Tang DB, Brewer TG, et al. Randomized dose-ranging study of the safety and efficacy of WR 238605 (Tafenoquine) in the prevention of relapse of Plasmodium vivax malaria in Thailand. *Journal of Infectious Diseases* 1999;**180**(4):1282–7.

Walsh 2004a *{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.

References to studies excluded from this review

Dow 2014 *{published data only}*
Dow GS, McCarthy WF, Reid M, Smith B, Tang D, Shanks GD. A retrospective analysis of the protective efficacy of tafenoquine and mefloquine as prophylactic anti-malarials in non-immune individuals during deployment to a malaria-endemic area. *Malaria Journal* 2014;**13**:49.

Edstein 2003 *{published data only}*
Edstein MD, Kocisko DA, Walsh DS, Eamsila C, Charles BG, Rieckmann KH. Plasma concentrations of tafenoquine, a new long-acting antimalarial agent, in Thai soldiers receiving monthly prophylaxis. *Clinical Infectious Diseases* 2003;**37**(12):1654–8.

Elmes 2008 *{published data only}*
Elmes NJ, Nasveld PE, Kitchener SJ, Kocisko DA, 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 Royal Society of Tropical Medicine and Hygiene* 2008;**102**(11):1095–101.

Green 2014 *{published data only}*
Green JA, Patel AK, Patel BR, Hussaini A, Harrell EJ, McDonald MJ, et al. Tafenoquine at therapeutic concentrations does not prolong Fridericia-corrected QT interval in healthy subjects. *Journal of Clinical Pharmacology* 2014;**54**(9):995–1005.

Hale 2003 *{published data only}*
Hale BR, Owusu-Agyei S, Fryauff DJ, Koram KA, Adjuik M, Oduro AR, et al. A randomized, double-blind, placebo-controlled, dose-ranging trial of tafenoquine for weekly prophylaxis against *Plasmodium falciparum*. *Clinical Infectious Diseases* 2003;**36**(5):541–9.

Kitchener 2007 *{published data only}*
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.

Lacerda 2013 *{published data only}*
Lacerda M, Ugwuegbulam C, Green J, Kellam L. Dose-ranging efficacy results from the tafenoquine 'detective' trial: A randomized, double-blind, multi-centre, parallel-group study for the radical cure of subjects with *Plasmodium vivax* malaria. American Journal of Tropical Medicine and Hygiene. Washington DC, 2013; Vol. 89 (5 Suppl 1):14.

Lell 2000 *{published data only}*
Lell B, Faucher JF, Missinou MA, Borrmann S, Dangelmaier O, Horton J, et al. Malaria chemoprophylaxis with tafenoquine: a randomised study. *Lancet* 2000;**355**(9220): 2041–5.

Nasveld 2002 *{published data only}*
Nasveld P, Kitchener S, Edstein M, Rieckmann K. Comparison of tafenoquine (WR238605) and primaquine in the post-exposure (terminal) prophylaxis of vivax malaria in Australian Defence Force personnel. *Transactions of Royal Society of Tropical Medicine and Hygiene* 2002;**96**(6):683–4.

Nasveld 2010 *{published data only}*
Nasveld PE, Edstein MD, Brennan L, Harris IE, Kitchener SJ, Leggat PA, 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.

Shanks 2001 *{published data only}*
Shanks GD, Oloo AJ, Aleman GM, Ohrt C, Klotz FW, Braitman D, et al. A new primaquine analogue, tafenoquine (WR 238605), for prophylaxis against *Plasmodium falciparum* malaria. *Clinical Infectious Diseases* 2001;**33**(12): 1968–74.

Walsh 2004b *{published data only}*
Walsh DS, Eamsila C, Sasiprapha T, Sangkharomya S, Khaewsathien P, Supakalin P, et al. Efficacy of monthly tafenoquine for prophylaxis of *Plasmodium vivax* and multidrug-resistant*P. falciparum* malaria. *Journal of Infectious Diseases* 2004;**190**(8):1456–63.

References to ongoing studies

NCT01205178 *{published data only}*
A Phase I Study to Investigate the Hemolytic Potential of tafenoquine in Healthy Subjects With Glucose-6-phosphate Dehydrogenase Deficiency and the Safety and Tolerability of tafenoquine in Acute *Plasmodium vivax* Malaria Patients With Glucose-6-phosphate Dehydrogenase Deficiency. Ongoing study July 2009.

NCT01290601 *{published data only}*
A Randomized, Active-control, Double-blind, Double-dummy Study to Evaluate the Efficacy and Safety of Tafenoquine for the Treatment of *Plasmodium vivax* in Adults. Ongoing study September 2003.

NCT02216123 *{published data only}*
A Randomized, Double-Blind, Double Dummy, Comparative, Multicenter Study to Assess the Incidence of Hemolysis, Safety, and Efficacy of Tafenoquine (SB-252263, WR238605) Versus Primaquine in the Treatment of Subjects With *Plasmodium Vivax* Malaria. Ongoing study September 2014.

Additional references

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

Brueckner 1998a
Brueckner RP, Coster T, Wesche DL, Shmuklarsky M, Schuster BG. Prophylaxis of *Plasmodium falciparum* infection in a human challenge model with WR 238605, a new 8-aminoquinoline antimalarial. *Antimicrobial Agents and Chemotherapy* 1998;**42**(5):1293-4.

Brueckner 1998b
Brueckner RP, Lasseter KC, Lin ET, Schuster BG. First-time-in-humans safety and pharmacokinetics of WR 238605, a new antimalarial. *American Journal of Tropical Medicine and Hygiene* 1998;**58**(5):645-9.

Carmona-Fonseca 2009
Carmona-Fonseca J, Alvarez 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.

Ehrman 1944
Ehrman FC, Ellis JM, Young MD. *Plasmodium vivax* Chesson strain. *Science* 1945;**101**(2624):377.

Feachem 2010
Feachem RG, Phillips AA, Targett GA, Snow RW. Call to action: priorities for malaria elimination. *Lancet* 2010;**376** (9752):1517–21.

Fernando 2011a
Fernando SD, Rodrigo C, Rajapakse S. Chemoprophylaxis in malaria: drugs, evidence of efficacy and costs. *Asian Pacific Journal of Tropical Medicine* 2011;**4**(4):330–6.

Fernando 2011b
Fernando D, Rodrigo C, Rajapakse S. Primaquine in vivax malaria: an update and review on management issues. *Malaria Journal* 2011;**10**:351.

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

GRADEpro 2014 [Computer program]
McMaster University. GRADEpro. McMaster University, 2014.

Greenland 1994
Greenland S. Quality scores are useless and potentially misleading. *American Journal of Epidemiology* 1994;**140**(3): 300–1.

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

Higgins 2011
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.

Lefebvre 2011
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 [updated March 2011].. *Available from www.cochrane-handbook.org*. The Cochrane Collaboration, 2011.

Prashar 2009
Prashar L, Paul R. Tafenoquine: a new 8- aminoquinoline. *Medical Journal of Zambia* 2009;**36**(4):187–90.

Ramos Júnior 2010
Ramos Júnior WM, Sardinha JF, Costa MR, Santana MS, Alecrim MG, Lacerda MV. Clinical aspects of hemolysis in patients with *P. vivax* malaria treated with primaquine, in the Brazilian Amazon. *Brazilian Journal of Infectious Diseases* 2010;**14**(4):410–2.

Reddy 2006
Reddy P, Flaherty JP. *Plasmodium vivax* malaria relapses after primaquine prophylaxis. *Emerging Infectious Diseases* 2006;**12**(11):1795–6.

RevMan 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rieckmann 1989
Rieckmann KH, Davis DR, Hutton DC. *Plasmodium vivax* resistance to chloroquine?. *Lancet* 1989;**2**(8673):1183–4.

Wells 2010
Wells TN, Burrows JN, Baird JK. Targeting the hypnozoite reservoir of *Plasmodium vivax*: the hidden obstacle to malaria elimination. *Trends in Parasitology* 2010;**26**(3): 145–51.

WHO 2009
World Health Organization. *International travel and health*. Geneva: World Health Organization, 2009.

WHO 2012
World Health Organization. Malaria. Fact sheet N^{0}94. http://www.who.int/mediacentre/factsheets/fs094/en/ December 2014 (Accessed 15 January 2015).

References to other published versions of this review

Rajapakse 2013
Rajapakse S, Rodrigo C, Fernando SD. Tafenoquine for *Plasmodium vivax* malaria infection. *Cochrane Database of Systematic Reviews* 2013, Issue 3. DOI: 10.1002/14651858.CD010458

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Llanos-Cuentas 2014

Methods	Multicentre double blind RCT Trial phase: IIb Trial design: parallel group dose ranging trial
Participants	Number randomized: 329 Inclusion criteria: • Males and females aged 16 or older with clinical symptoms of malaria with *P. vivax* mono infection with an asexual parasite density > 100/µL and < 100,000/µL of blood Exclusion criteria: • Receiving antimalarial treatment within 30 days of screening • Severe malaria, any clinically significant concurrent illness • Severe vomiting or a haemoglobin concentration < 7 g/dL • Pregnancy or G6PD enzyme activity < 70% of the site median
Interventions	All participants received the standard adult dose of CQ (1500 mg) over 3 days to eradicate the current infection plus: 1. TQ 50 mg single dose (n = 55) 2. TQ 100 mg single dose (n = 57) 3. TQ 300 mg single dose (n = 57) 4. TQ 600 mg single dose (n = 56) 5. No further treatment (n = 54) 6. PQ 15 mg/day for 14 days (n = 50)
Outcomes	Outcomes included in this review: • Relapse of microscopically proven *P. vivax* malaria after completing treatment up to 6 months • Adverse events attributable to TQ Outcomes not included in this review: • Time to relapse • Parasite clearance time • Fever clearance time
Notes	Location: Peru, Brazil, India and Thailand Setting: community health centres and hospitals Endemicity: endemic for vivax malaria Resistance: unknown Funding: GlaxoSmithKline, Medicines for Malaria Venture

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computer generated randomisation schedule, stratified by baseline parasite count"

Llanos-Cuentas 2014 (*Continued*)

Allocation concealment (selection bias)	Low risk	"Patients, study staff and GlaxoSmithKline personnel were masked to study treatment allocation"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as "Double blind, double dummy design".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as ""Double blind, double dummy design".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rate in all groups was < 6% of the number randomized
Selective reporting (reporting bias)	Low risk	Absolute number of relapses by 6 months is not mentioned. However it can be calculated from available data. The numbers were confirmed by communicating with the authors
Other bias	Low risk	None identified.

Walsh 1999

Methods	Open label RCT Trial phase: III Trial design: Parallel group
Participants	Number randomized: 44 Inclusion criteria: • Male and female Thai or ethnic Burmese patients aged 18 to 60 years with *P. vivax* infections (*P. vivax* asexual parasitaemia on thin blood film plus one or more clinical features consistent with malaria) Exclusion criteria: • Marked weight discrepancies • Pregnancy • G6PD deficiency
Interventions	All participants received the standard adult dose of CQ (1500 mg) over 3 days to eradicate the current infection plus: 1. TQ 300 mg daily for 7 days (n = 15) 2. TQ 500 mg daily for 3 days, followed by 500 mg daily for 3 days beginning 1 week after the first dose (n = 11) 3. TQ 500 mg as a single dose (n = 9) 4. No further treatment (n = 9)

Walsh 1999 (*Continued*)

Outcomes	Outcomes included in this review: • Relapse of microscopically proven *P. vivax* malaria after completing treatment up to six months • Adverse events recorded during follow-up. Outcomes not included in this review: • Time to relapse
Notes	Location: Thailand Setting: tertiary care referral centre for infectious diseases Endemicity: no malaria transmission in the location (Bangkok) patients were treated Resistance: not mentioned in paper Funding: US Army Medical and Materiel Development Activity (Fort Detrick, Frederick, MD); SmithKline Beecham Pharmaceutical (UK)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomised with a computer generated sequence schedule".
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as "slide readers were unaware of the patients treatment"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as "slide readers were unaware of the patients treatment"
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 50% of participants in group A did not complete follow-up compared to approximately 10% in other groups
Selective reporting (reporting bias)	Low risk	The authors state that they originally planned to only follow-up for two months but patients were followed up for 6 months
Other bias	Low risk	None identified.

Walsh 2004a

Methods	Open label RCT Trial phase: III Trial design: Parallel group
Participants	Number randomized: 80 Inclusion criteria: • Male and female Thai or ethnic Burmese patients aged 18 to 55 years with *P. vivax* infections (*P. vivax* asexual parasitaemia on thin blood film plus one or more clinical features consistent with malaria) • Weight within 20% of the standards of the population • Ability to take oral medication • Not having received an antimalarial agent for last 14 days Exclusion criteria: • Pregnancy and G6PD deficiency • Mixed infections • Haematocrit < 25% • Protracted vomiting • Oliguria • Systolic blood pressure < 90 mmHg • Lactation • Concomitant systemic disease
Interventions	All participants received the standard adult dose of CQ (1500 mg) over 3 days to eradicate the current infection plus: 1. TQ, 300 mg per day for 7 days (n = 18) 2. TQ, 600 mg per day for 3 days (n = 19) 3. TQ, 600 mg as a single dose (n = 18) 4. No further treatment (n = 13) 5. PQ, 15 mg per day for 14 days (n = 12)
Outcomes	Outcomes included in this review: • Relapse of microscopically proven *P. vivax* malaria after completing treatment. Participants were tested daily during drug administration and then two weekly till week 8 and 4 weekly till week 24 • Adverse events recorded during follow-up Outcomes not included in this review: • Plasma TQ concentrations of participants
Notes	Location: Thailand Setting: tertiary care referral centre for infectious diseases Endemicity: no malaria transmission in the location (Bangkok) patients were treated Resistance: not mentioned in paper Funding: US Army Medical and Materiel Development Activity and GlaxoSmithKline (formerly SmithKline Beecham)

Risk of bias

Bias	Authors' judgement	Support for judgement

Walsh 2004a (*Continued*)

Random sequence generation (selection bias)	Unclear risk	This was a randomized trial with a computer generated block randomization. However, following randomization some patients had been moved between groups and nearly 10 randomizations had been eliminated
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Despite being an open label trial, if the microscopists were blinded performance bias would be low. This fact is not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Despite being an open label trial, if the microscopists were blinded detection bias would be low. This fact is not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rate was < 25% in all groups for 2 month follow-up. There was no attrition in group 5
Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	None identified.

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

Study	Reason for exclusion
Dow 2014	Assesses the efficacy of TQ with regard to prevention of vivax and falciparum malaria during a period of exposure in an endemic area in healthy participants
Edstein 2003	Describes the same trial by Walsh 2004b
Elmes 2008	Assess the efficacy of TQ for preventing recurrences of vivax malaria in participants without baseline vivax parasitaemia after leaving an endemic area
Green 2014	Assesses QT prolongation with TQ in healthy volunteers.
Hale 2003	Assesses the efficacy of TQ with regard to prevention of falciparum malaria
Kitchener 2007	Uncontrolled study.
Lacerda 2013	Conference proceeding describing the same trial (DETECTIVE) as Llanos-Cuentas 2014.

(*Continued*)

Lell 2000	Assesses the efficacy of TQ with regard to prevention of falciparum malaria
Nasveld 2002	Assess efficacy of TQ for hypnozoite clearance of participants leaving an endemic area (who did not have baseline vivax parasitaemia)
Nasveld 2010	Assess the efficacy of TQ for preventing vivax malaria infections in healthy participants during a period of exposure in an endemic area
Shanks 2001	Assesses the efficacy of TQ with regard to falciparum malaria
Walsh 2004b	Assess the efficacy of TQ for preventing vivax and falciparum malaria during a period of exposure in an endemic area in healthy participants

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

NCT01205178

Trial name or title	A Phase I Study to Investigate the Hemolytic Potential of tafenoquine in Healthy Subjects With Glucose-6-phosphate Dehydrogenase Deficiency and the Safety and Tolerability of tafenoquine in Acute *Plasmodium vivax* Malaria Patients With Glucose-6-phosphate Dehydrogenase Deficiency
Methods	Randomized open label study
Participants	Inclusion criteria: • Age 18 to 45 years • Non-pregnant non-lactating women • WHO class III G6PD-deficiency or G6PD-normal status must be documented by enzyme activity and cytochemical staining • Positive GIEMSA smear for *P. vivax* with parasite density between 500 to 200,000/µL
Interventions	CQ and PQ versus TQ
Outcomes	To evaluate the safety, tolerability, and haemolytic potential of TQ in G6PD-deficient female healthy volunteers compared with G6PD-normal female healthy volunteers. This will be done by measuring maximum absolute decline in haemoglobin from baseline (time frame: 2 years)
Starting date	July 2009
Contact information	US GSK Clinical Trials Call Center (GSKClinicalSupportHD@gsk.com), USA
Notes	Location: Thailand Funding: GlaxoSmithKline Pharmaceuticals Ltd.

NCT01290601

Trial name or title	A Randomized, Active-control, Double-blind, Double-dummy Study to Evaluate the Efficacy and Safety of Tafenoquine for the Treatment of *Plasmodium vivax* in Adults
Methods	Randomized, active-control, double-blind, double-dummy study
Participants	Inclusion criteria: • Age 20 to 60 years • Positive GIEMSA smear for *P. vivax* with parasite density between 500 to 200,000/µL • Willing to be hospitalized for 29 days and remain in a malaria-free area for 60 days Exclusion criteria: • Lactating and pregnant females
Interventions	CQ and PQ for the control arm and TQ for the trial arm for treatment
Outcomes	Primary outcome; adequate clinical response
Starting date	September 2003
Contact information	Sornchai Looareesuwan, Mahidol University, Thailand
Notes	Location: Thailand Funding: U.S. Army Medical Research and Materiel Command and GlaxoSmithKline Pharmaceuticals Ltd

NCT02216123

Trial name or title	A Randomized, Double-Blind, Double Dummy, Comparative, Multicenter Study to Assess the Incidence of Hemolysis, Safety, and Efficacy of Tafenoquine (SB-252263, WR238605) Versus Primaquine in the Treatment of Subjects With *Plasmodium Vivax* Malaria
Methods	Randomized, double-blind, double dummy, comparative, multicentre study
Participants	Inclusion criteria: • Age > 16 years • Positive GIEMSA smear for *P. vivax* with parasite density between 100 to 100,000/µL • Willing to follow study protocol • Hb level > 7 g/dL (for those with a G6PD level > 70% of site median) or > 8 g/dL (or those with a G6PD level 40 to 70% of site median) Exclusion criteria: • Lactating, pregnant and sexually active females not using a contraceptive method • Any patient with 4- or 8-aminoquinoline allergy, liver impairment or any other significant illness including QT prolongation on ECG, severe vivax malaria, mixed malaria infection and substance abuse
Interventions	CQ and TQ (trial arm) compared with CQ and primaquine and CQ and placebo (control arms)
Outcomes	Primary outcome(s): • Proportion of all subjects with *P. vivax* experiencing clinically relevant haemolysis up to 180 days. • Proportion of female subjects with *P. vivax* who are moderately (40 to 70 percent) G6PD deficient experiencing clinically relevant haemolysis.

NCT02216123 (*Continued*)

	Secondary outcomes: • Adverse events caused by treatment. • *P. vivax* relapses within 6 months post treatment. • Fever clearance time • Gametocyte clearance time • Total parasite clearance time • Correlation between plasma TQ levels and haemoglobin • MHb levels • Treatment efficacy
Starting date	September 2014
Contact information	US GSK Clinical Trials Call Center
Notes	Location: Not mentioned Funding: GlaxoSmithKline Pharmaceuticals Ltd and Medicines for Malaria Venture

DATA AND ANALYSES

Comparison 1. Tafenoquine versus no hypnozoite treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrent *P. vivax* parasitaemia by 6 months	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Tafenoquine 50 to 100 mg single dose	1	162	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.55, 1.04]
1.2 Tafenoquine 300 mg single dose	1	110	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.08, 0.41]
1.3 Tafenoquine 500 to 600 mg single dose	2	122	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.06, 0.34]
1.4 Tafenoquine 1800 to 3000 mg split doses	2	63	Risk Ratio (M-H, Fixed, 95% CI)	0.05 [0.01, 0.23]
2 Recurrent *P. vivax* parasitaemia by 6 months (excluding tafenoquine doses < 300 mg)	3	250	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.08, 0.22]
3 Serious adverse events	3	358	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.34, 2.56]
4 Any adverse event by tafenoquine dose	1	272	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.78, 1.10]
5 Comparison by type of adverse event for tafenoquine 300 mg	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Abdominal pain	1	110	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.38, 3.57]
5.2 Nausea	1	110	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [0.40, 6.40]
5.3 Vomiting	1	110	Risk Ratio (M-H, Fixed, 95% CI)	4.82 [0.24, 98.24]
5.4 Diarrhoea	1	110	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.17, 3.08]
5.5 Chills	1	110	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.10, 0.60]
5.6 Vertigo/dizziness	1	110	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.30, 3.14]
5.7 Headache	1	110	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.25, 0.93]
5.8 Myalgia	1	110	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.03, 3.00]
5.9 Rash/pruritus	1	110	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.43, 2.83]
5.10 Weakness/asthenia	1	110	Risk Ratio (M-H, Fixed, 95% CI)	2.89 [0.12, 69.55]
5.11 Cough	1	110	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.25, 3.66]
5.12 Arthralgia	1	110	Risk Ratio (M-H, Fixed, 95% CI)	1.93 [0.18, 20.65]
5.13 Insomnia	1	110	Risk Ratio (M-H, Fixed, 95% CI)	4.82 [0.58, 39.94]
5.14 Anaemia/drop in Hb	1	110	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.06, 15.03]
5.15 QT prolongation	1	110	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.17, 3.08]
6 Comparison by type of adverse event for tafenoquine 600 mg	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Abdominal pain	1	108	Risk Ratio (M-H, Fixed, 95% CI)	1.2 [0.39, 3.70]
6.2 Nausea	1	108	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.42, 6.63]
6.3 Vomiting	1	108	Risk Ratio (M-H, Fixed, 95% CI)	7.0 [0.37, 132.35]
6.4 Diarrhoea	1	108	Risk Ratio (M-H, Fixed, 95% CI)	2.25 [0.74, 6.87]
6.5 Chills	1	108	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.23, 0.90]
6.6 Vertigo/dizziness	1	108	Risk Ratio (M-H, Fixed, 95% CI)	0.8 [0.23, 2.82]
6.7 Headache	1	108	Risk Ratio (M-H, Fixed, 95% CI)	0.8 [0.47, 1.37]
6.8 Myalgia	1	108	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.21, 4.74]

6.9 Rash/pruritus	1	108	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.06, 1.31]
6.10 Weakness/asthenia	1	108	Risk Ratio (M-H, Fixed, 95% CI)	11.0 [0.62, 194.17]
6.11 Cough	1	108	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.16]
6.12 Arthralgia	1	108	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.32, 27.94]
6.13 Insomnia	1	108	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.32, 27.94]
6.14 Anaemia/drop in Hb	1	108	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 15.58]
6.15 QT prolongation	1	108	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.16]

Comparison 2. Tafenoquine versus primaquine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrent *P. vivax* parasitaemia by 6 months (excluding tafenoquine doses < 300 mg)	2	215	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.15, 0.59]
1.1 Tafenoquine 300 mg single dose	1	79	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.15, 1.14]
1.2 Tafenoquine 600 mg single dose	2	98	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.10, 0.84]
1.3 Tafenoquine 1800 to 2100 mg split doses	1	38	Risk Ratio (M-H, Fixed, 95% CI)	0.06 [0.00, 1.10]
2 Serious adverse events	2	323	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.20, 1.08]
3 Any adverse event by tafenoquine dose	2	323	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.87, 1.28]
4 Comparison by type of adverse event for tafenoquine 300 mg	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Abdominal pain	1	103	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.26, 1.99]
4.2 Nausea	1	103	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.30, 3.68]
4.3 Vomiting	1	103	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.07, 1.65]
4.4 Diarrhoea	1	103	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.15, 2.67]
4.5 Chills	1	103	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.15, 1.14]
4.6 Vertigo/dizziness	1	103	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.26, 2.72]
4.7 Headache	1	103	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.29, 1.22]
4.8 Myalgia	1	103	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.04, 4.48]
4.9 Rash/pruritus	1	103	Risk Ratio (M-H, Fixed, 95% CI)	2.24 [0.63, 7.96]
4.10 Weakness/asthenia	1	103	Risk Ratio (M-H, Fixed, 95% CI)	2.53 [0.11, 60.60]
4.11 Cough	1	103	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.22, 3.18]
4.12 Arthralgia	1	103	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [0.16, 17.94]
4.13 Insomnia	1	103	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.35, 5.55]
4.14 Anaemia/drop in Hb	1	103	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.05, 13.06]
4.15 QT prolongation	1	103	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.13, 2.00]
5 Comparison by type of adverse event for tafenoquine 600 mg	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Abdominal pain	2	129	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.27, 2.06]
5.2 Nausea	2	129	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.39, 3.90]
5.3 Vomiting	2	129	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.21, 2.32]
5.4 Diarrhoea	2	129	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [0.62, 4.68]
5.5 Chills	2	129	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.35, 1.76]

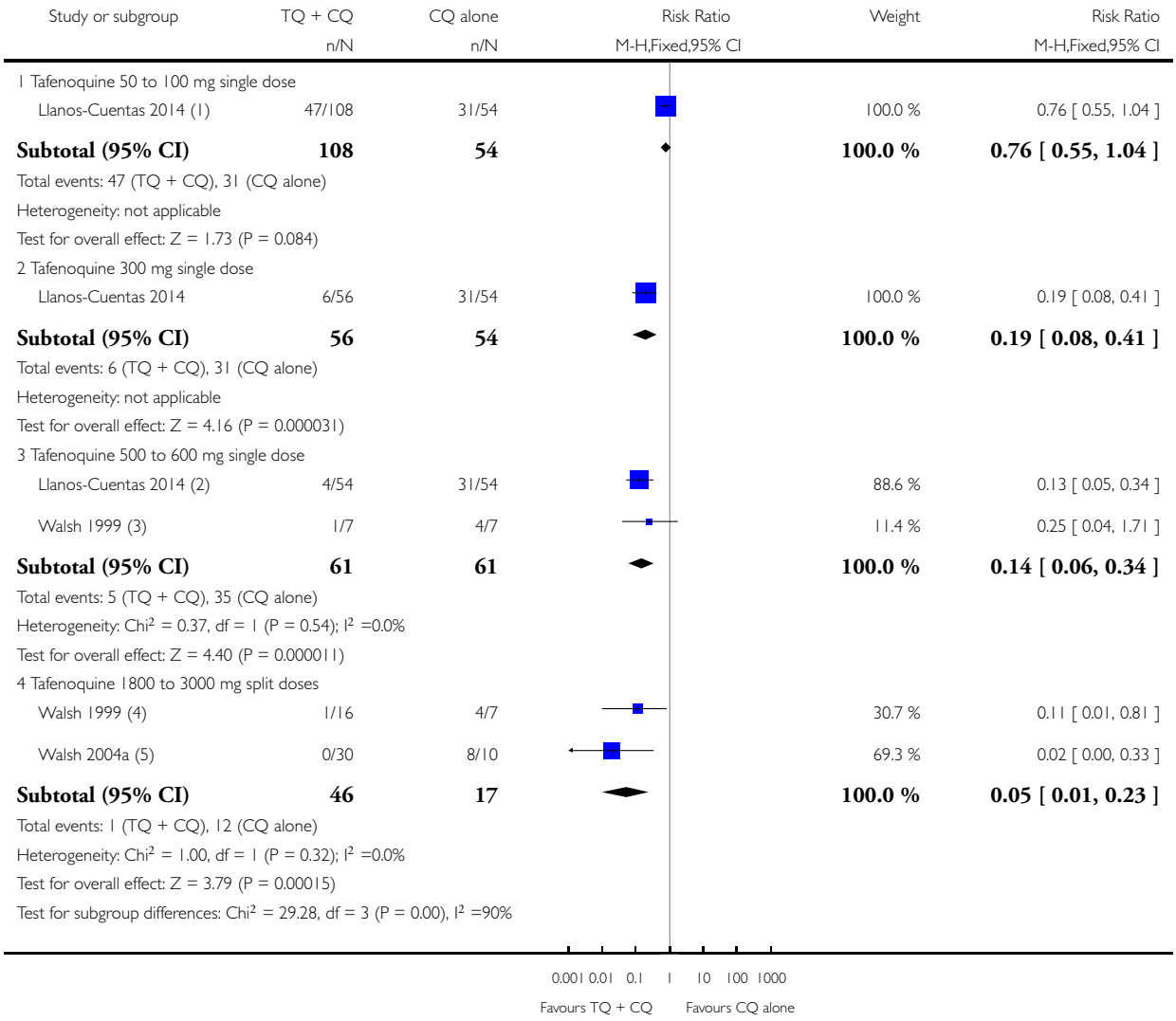
5.6 Vertigo/dizziness	2	129	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.33, 2.01]
5.7 Headache	2	129	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.49, 1.48]
5.8 Myalgia	2	129	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.23, 7.48]
5.9 Rash/pruritus	2	129	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.18, 3.11]
5.10 Weakness/asthenia	2	129	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.41, 1.92]
5.11 Cough	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.03, 1.88]
5.12 Arthralgia	1	101	Risk Ratio (M-H, Fixed, 95% CI)	2.61 [0.28, 24.26]
5.13 Insomnia	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.18, 4.11]
5.14 Anaemia/drop in Hb	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.06, 13.53]
5.15 QT prolongation	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.02, 1.44]
6 Comparison by type of adverse event for tafenoquine doses > 600 mg	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Abdominal pain	1	42	Risk Ratio (M-H, Fixed, 95% CI)	3.77 [0.22, 65.19]
6.2 Nausea	1	42	Risk Ratio (M-H, Fixed, 95% CI)	3.77 [0.22, 65.19]
6.3 Vomiting	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.4 Diarrhoea	1	42	Risk Ratio (M-H, Fixed, 95% CI)	1.6 [0.20, 12.89]
6.5 Chills	1	42	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.05, 28.90]
6.6 Vertigo/dizziness	1	42	Risk Ratio (M-H, Fixed, 95% CI)	2.13 [0.76, 6.01]
6.7 Headache	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.8 [0.30, 2.17]
6.8 Myalgia	1	46	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [0.07, 38.22]
6.9 Rash/pruritus	1	46	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [0.18, 14.16]
6.10 Weakness/asthenia	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.9 [0.55, 1.48]

Analysis 1.1. Comparison 1 Tafenoquine versus no hypnozoite treatment, Outcome 1 Recurrent *P. vivax* parasitaemia by 6 months.

Review: Tafenoquine for preventing relapse in people with *Plasmodium vivax* malaria

Comparison: 1 Tafenoquine versus no hypnozoite treatment

Outcome: 1 Recurrent *P. vivax* parasitaemia by 6 months



(1) Llanos-Cuentas 2013: The study had two trial arms that were given 50mg and 100mg of tafenoquine respectively. The two arms are combined and compared with placebo.

(2) Llanos-Cuentas 2013: This study arm gave 600mg single dose and is compared with placebo

(3) Walsh 1999: This study arm gave 500mg single dose and is compared with placebo

(4) Walsh 1999: This study had two arms which gave 600mg daily for three days or two doses of 1500mg one week apart. The two arms are combined and compared with placebo.

(5) Walsh 2004a: This study had two arms which gave 600 mg daily for three days or 300mg daily for 7 days. The two arms are combined and compared with placebo.

Analysis 1.2. Comparison 1 Tafenoquine versus no hypnozoite treatment, Outcome 2 Recurrent *P. vivax* parasitaemia by 6 months (excluding tafenoquine doses < 300 mg).

Review: Tafenoquine for preventing relapse in people with *Plasmodium vivax* malaria

Comparison: 1 Tafenoquine versus no hypnozoite treatment

Outcome: 2 Recurrent *P. vivax* parasitaemia by 6 months (excluding tafenoquine doses < 300 mg)

Study or subgroup	TQ + CQ n/N	CQ alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Llanos-Cuentas 2014 (1)	11/110	34/54		70.3 %	0.16 [0.09, 0.29]
Walsh 1999	2/23	4/7		9.5 %	0.15 [0.03, 0.66]
Walsh 2004a	1/46	8/10		20.3 %	0.03 [0.00, 0.19]
Total (95% CI)	**179**	**71**		**100.0 %**	**0.13 [0.08, 0.22]**
Total events: 14 (TQ + CQ), 46 (CQ alone)					
Heterogeneity: Chi^2 = 2.90, df = 2 (P = 0.23); I^2 =31%					
Test for overall effect: Z = 7.69 (P < 0.00001)					
Test for subgroup differences: Not applicable					

(1) The trial groups that used low doses of tafenoquine (50 and 100 mg) were excluded from the analysis

Analysis 1.3. Comparison 1 Tafenoquine versus no hypnozoite treatment, Outcome 3 Serious adverse events.

Review: Tafenoquine for preventing relapse in people with *Plasmodium vivax* malaria

Comparison: 1 Tafenoquine versus no hypnozoite treatment

Outcome: 3 Serious adverse events

Study or subgroup	TQ + CQ n/N	CQ alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Llanos-Cuentas 2014 (1)	5/54	1/14		22.2 %	1.30 [0.16, 10.22]
Llanos-Cuentas 2014 (2)	2/56	1/13		22.7 %	0.46 [0.05, 4.74]
Llanos-Cuentas 2014 (3)	2/54	1/14		22.2 %	0.52 [0.05, 5.32]
Llanos-Cuentas 2014 (4)	6/54	1/13		22.5 %	1.44 [0.19, 10.98]
Walsh 1999 (5)	1/23	0/7		10.5 %	1.00 [0.05, 22.18]
Walsh 2004a	0/46	0/10			Not estimable
Total (95% CI)	**287**	**71**		**100.0 %**	**0.94 [0.34, 2.56]**

Total events: 16 (TQ + CQ), 4 (CQ alone)

Heterogeneity: $Chi^2 = 0.87$, df = 4 (P = 0.93); $I^2 = 0.0\%$

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

Test for subgroup differences: Not applicable

(1) Llanos-Cuentas 2013; TQ 600mg group

(2) Llanos-Cuentas 2013; TQ 300mg group

(3) Llanos-Cuentas 2013; TQ 500mg group

(4) Llanos-Cuentas 2013; TQ 100mg group

(5) Walsh 1999; Only serious event was reported in the TQ 2100mg group

Analysis 1.4. Comparison 1 Tafenoquine versus no hypnozoite treatment, Outcome 4 Any adverse event by tafenoquine dose.

Review: Tafenoquine for preventing relapse in people with *Plasmodium vivax* malaria

Comparison: 1 Tafenoquine versus no hypnozoite treatment

Outcome: 4 Any adverse event by tafenoquine dose

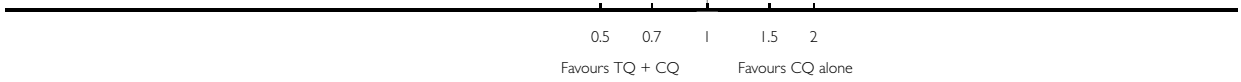
Study or subgroup	TQ + CQ n/N	CQ alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Llanos-Cuentas 2014 (1)	42/54	11/13		27.0 %	0.92 [0.70, 1.21]
Llanos-Cuentas 2014 (2)	37/54	10/14		24.2 %	0.96 [0.66, 1.40]
Llanos-Cuentas 2014 (3)	38/56	10/13		24.7 %	0.88 [0.62, 1.25]
Llanos-Cuentas 2014 (4)	37/54	10/14		24.2 %	0.96 [0.66, 1.40]
Total (95% CI)	**218**	**54**		**100.0 %**	**0.93 [0.78, 1.10]**

Total events: 154 (TQ + CQ), 41 (CQ alone)

Heterogeneity: $Chi^2 = 0.15$, df = 3 (P = 0.99); $I^2 = 0.0\%$

Test for overall effect: Z = 0.84 (P = 0.40)

Test for subgroup differences: Not applicable



(1) Llanos-Cuentas 2013; TQ 100mg group

(2) Llanos-Cuentas 2013; TQ 50mg group

(3) Llanos-Cuentas 2013; TQ 300mg group

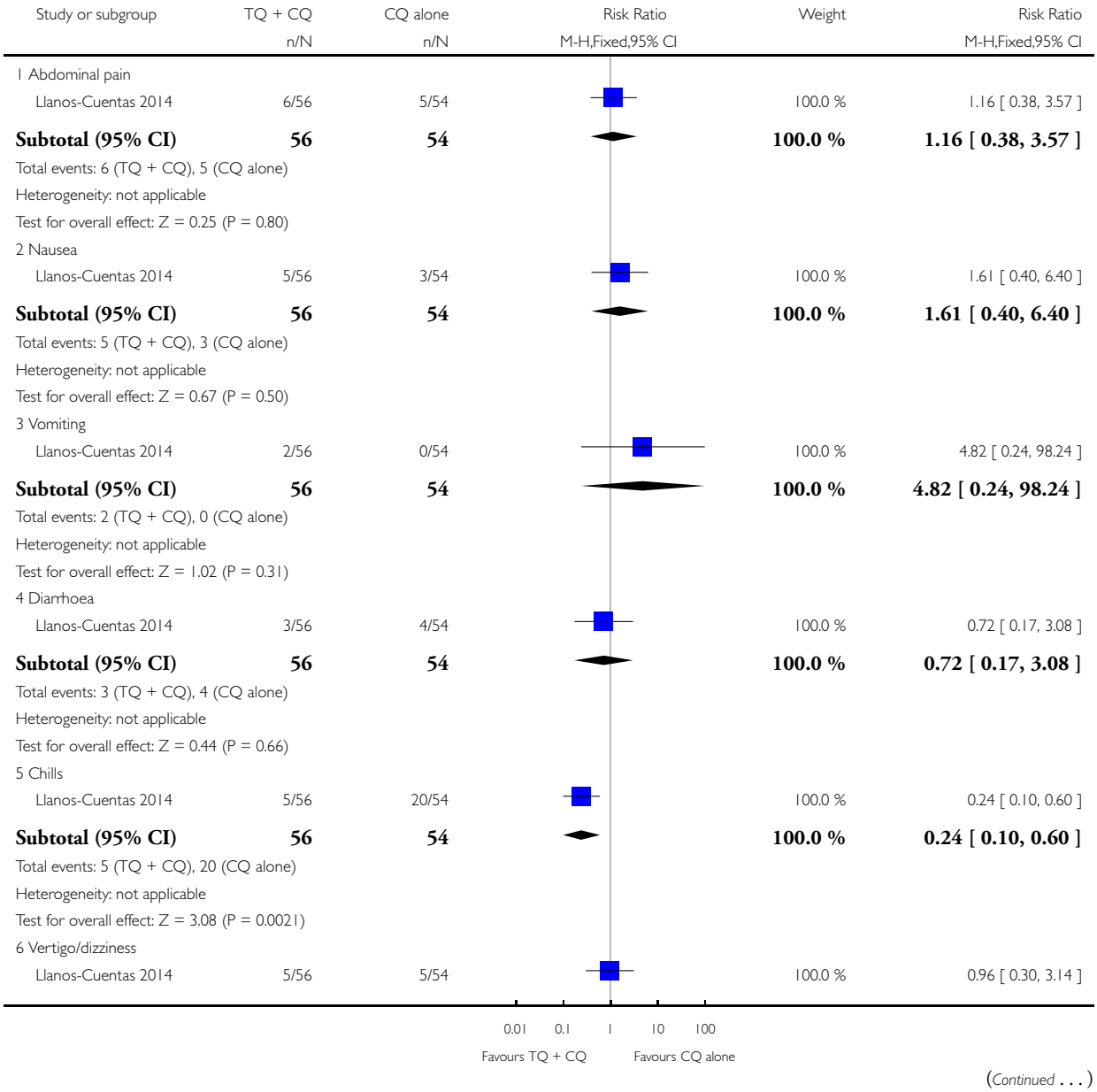
(4) Llanos-Cuentas 2013; TQ 600mg group

Analysis 1.5. Comparison 1 Tafenoquine versus no hypnozoite treatment, Outcome 5 Comparison by type of adverse event for tafenoquine 300 mg.

Review: Tafenoquine for preventing relapse in people with *Plasmodium vivax* malaria

Comparison: 1 Tafenoquine versus no hypnozoite treatment

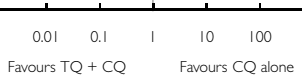
Outcome: 5 Comparison by type of adverse event for tafenoquine 300 mg



(*Continued . . .*)

(. . . *Continued*)

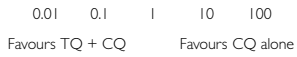
Study or subgroup	TQ + CQ n/N	CQ alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**56**	**54**		**100.0 %**	**0.96 [0.30, 3.14]**
Total events: 5 (TQ + CQ), 5 (CQ alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.06 (P = 0.95)					
7 Headache					
Llanos-Cuentas 2014	10/56	20/54		100.0 %	0.48 [0.25, 0.93]
Subtotal (95% CI)	**56**	**54**		**100.0 %**	**0.48 [0.25, 0.93]**
Total events: 10 (TQ + CQ), 20 (CQ alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.16 (P = 0.030)					
8 Myalgia					
Llanos-Cuentas 2014	1/56	3/54		100.0 %	0.32 [0.03, 3.00]
Subtotal (95% CI)	**56**	**54**		**100.0 %**	**0.32 [0.03, 3.00]**
Total events: 1 (TQ + CQ), 3 (CQ alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.00 (P = 0.32)					
9 Rash/pruritus					
Llanos-Cuentas 2014	8/56	7/54		100.0 %	1.10 [0.43, 2.83]
Subtotal (95% CI)	**56**	**54**		**100.0 %**	**1.10 [0.43, 2.83]**
Total events: 8 (TQ + CQ), 7 (CQ alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.20 (P = 0.84)					
10 Weakness/asthenia					
Llanos-Cuentas 2014	1/56	0/54		100.0 %	2.89 [0.12, 69.55]
Subtotal (95% CI)	**56**	**54**		**100.0 %**	**2.89 [0.12, 69.55]**
Total events: 1 (TQ + CQ), 0 (CQ alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.66 (P = 0.51)					
11 Cough					
Llanos-Cuentas 2014	4/56	4/54		100.0 %	0.96 [0.25, 3.66]
Subtotal (95% CI)	**56**	**54**		**100.0 %**	**0.96 [0.25, 3.66]**
Total events: 4 (TQ + CQ), 4 (CQ alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.05 (P = 0.96)					
12 Arthralgia					
Llanos-Cuentas 2014	2/56	1/54		100.0 %	1.93 [0.18, 20.65]
Subtotal (95% CI)	**56**	**54**		**100.0 %**	**1.93 [0.18, 20.65]**
Total events: 2 (TQ + CQ), 1 (CQ alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.54 (P = 0.59)					
13 Insomnia					



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	TQ + CQ n/N	CQ alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Llanos-Cuentas 2014	5/56	1/54		100.0 %	4.82 [0.58, 39.94]
Subtotal (95% CI)	**56**	**54**		**100.0 %**	**4.82 [0.58, 39.94]**
Total events: 5 (TQ + CQ), 1 (CQ alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.46 (P = 0.14)					
14 Anaemia/drop in Hb					
Llanos-Cuentas 2014	1/56	1/54		100.0 %	0.96 [0.06, 15.03]
Subtotal (95% CI)	**56**	**54**		**100.0 %**	**0.96 [0.06, 15.03]**
Total events: 1 (TQ + CQ), 1 (CQ alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.03 (P = 0.98)					
15 QT prolongation					
Llanos-Cuentas 2014	3/56	4/54		100.0 %	0.72 [0.17, 3.08]
Subtotal (95% CI)	**56**	**54**		**100.0 %**	**0.72 [0.17, 3.08]**
Total events: 3 (TQ + CQ), 4 (CQ alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.44 (P = 0.66)					
Test for subgroup differences: Chi^2 = 16.76, df = 14 (P = 0.27), I^2 =16%					

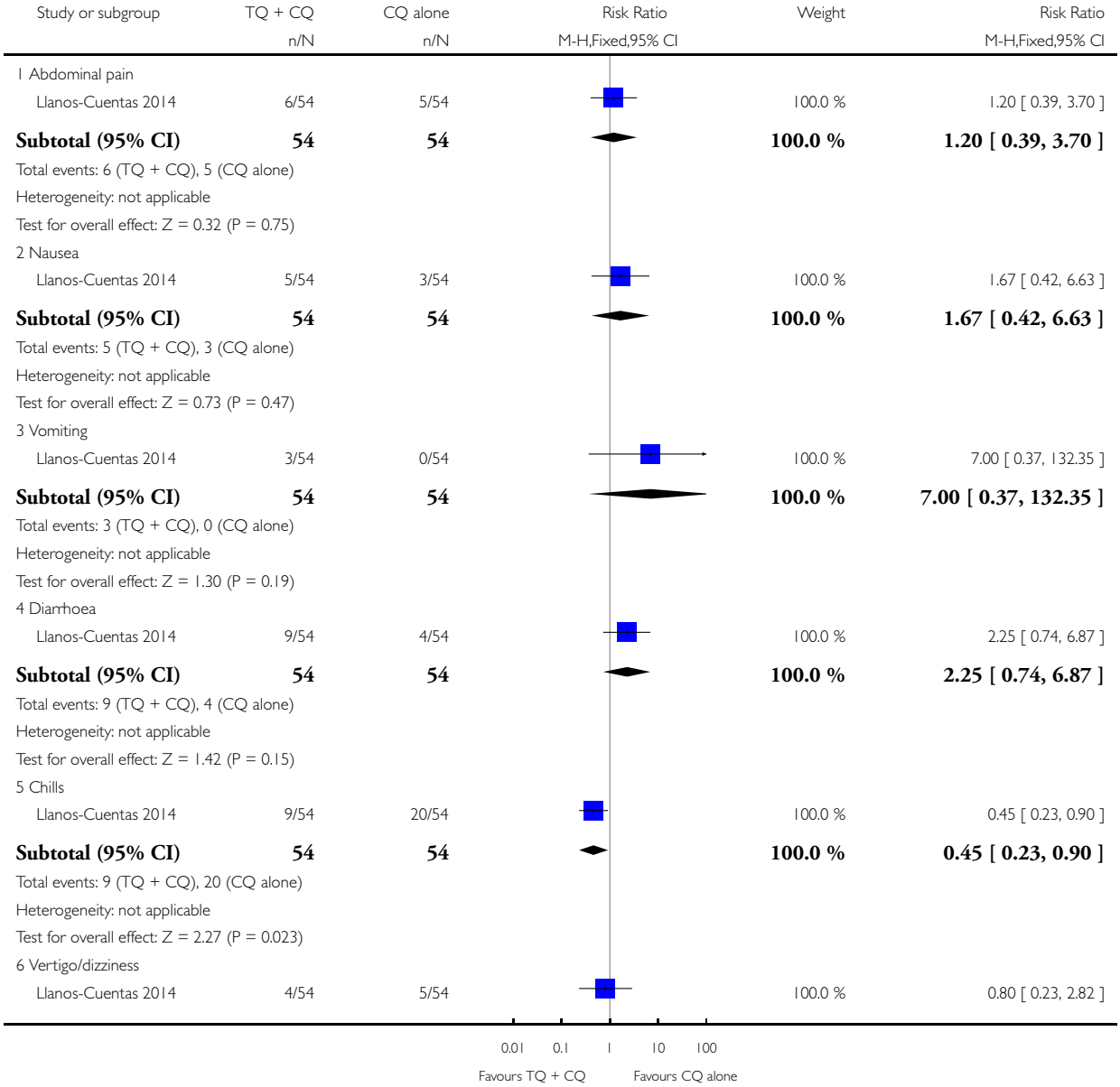


Analysis 1.6. Comparison 1 Tafenoquine versus no hypnozoite treatment, Outcome 6 Comparison by type of adverse event for tafenoquine 600 mg.

Review: Tafenoquine for preventing relapse in people with *Plasmodium vivax* malaria

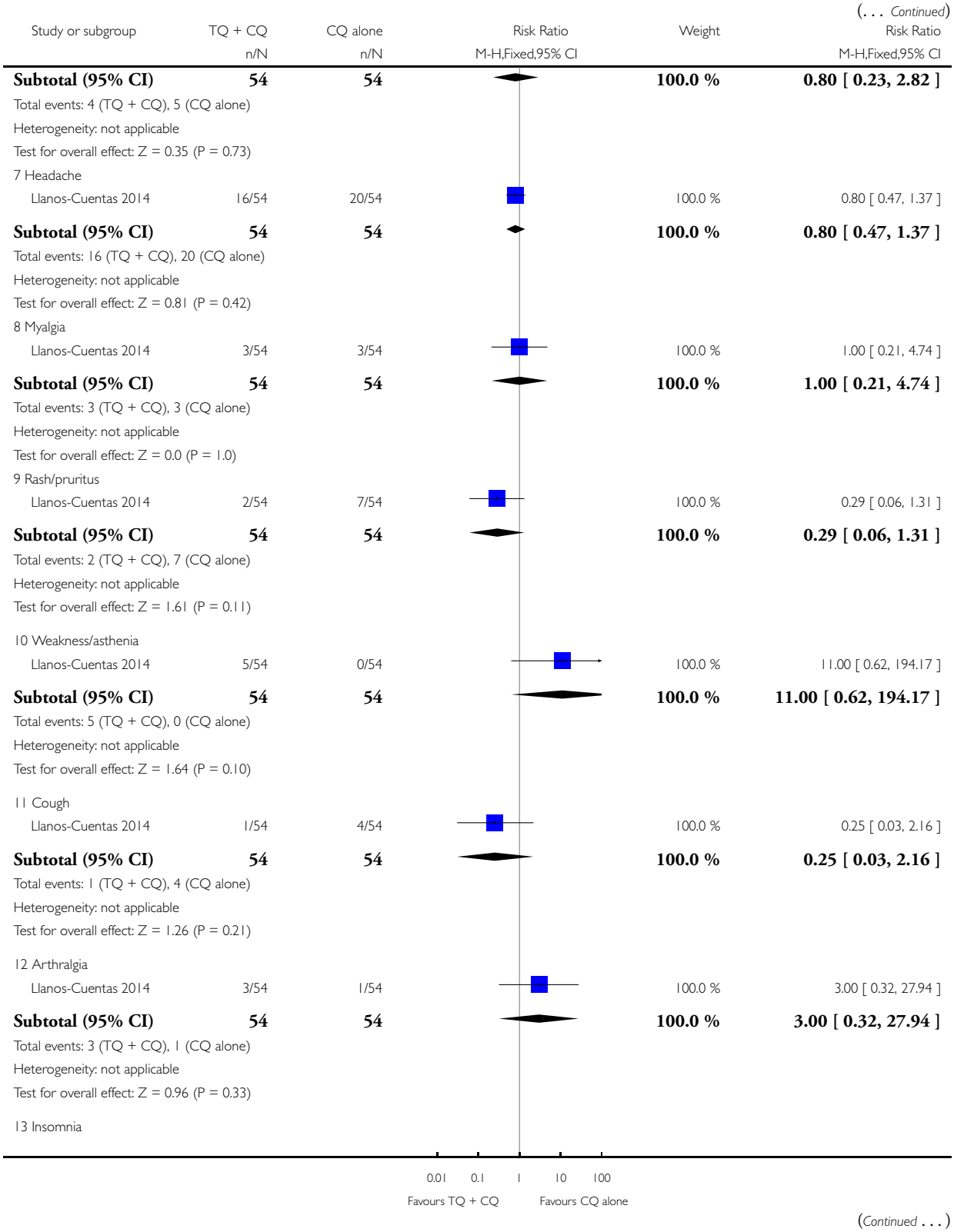
Comparison: 1 Tafenoquine versus no hypnozoite treatment

Outcome: 6 Comparison by type of adverse event for tafenoquine 600 mg



(*Continued . . .*)

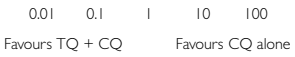
(. . . *Continued*)



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	TQ + CQ n/N	CQ alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Llanos-Cuentas 2014	3/54	1/54		100.0 %	3.00 [0.32, 27.94]
Subtotal (95% CI)	**54**	**54**		**100.0 %**	**3.00 [0.32, 27.94]**
Total events: 3 (TQ + CQ), 1 (CQ alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.96 (P = 0.33)					
14 Anaemia/drop in Hb					
Llanos-Cuentas 2014	1/54	1/54		100.0 %	1.00 [0.06, 15.58]
Subtotal (95% CI)	**54**	**54**		**100.0 %**	**1.00 [0.06, 15.58]**
Total events: 1 (TQ + CQ), 1 (CQ alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
15 QT prolongation					
Llanos-Cuentas 2014	1/54	4/54		100.0 %	0.25 [0.03, 2.16]
Subtotal (95% CI)	**54**	**54**		**100.0 %**	**0.25 [0.03, 2.16]**
Total events: 1 (TQ + CQ), 4 (CQ alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.26 (P = 0.21)					
Test for subgroup differences: Chi^2 = 19.49, df = 14 (P = 0.15), I^2 =28%					



Analysis 2.1. Comparison 2 Tafenoquine versus primaquine, Outcome 1 Recurrent *P. vivax* parasitaemia by 6 months (excluding tafenoquine doses < 300 mg).

Review: Tafenoquine for preventing relapse in people with *Plasmodium vivax* malaria

Comparison: 2 Tafenoquine versus primaquine

Outcome: 1 Recurrent *P. vivax* parasitaemia by 6 months (excluding tafenoquine doses < 300 mg)

Study or subgroup	TQ + CQ n/N	PQ + CQ n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Tafenoquine 300 mg single dose					
Llanos-Cuentas 2014 (1)	6/56	6/23		38.2 %	0.41 [0.15, 1.14]
Subtotal (95% CI)	**56**	**23**		**38.2 %**	**0.41 [0.15, 1.14]**
Total events: 6 (TQ + CQ), 6 (PQ + CQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.71 (P = 0.088)					
2 Tafenoquine 600 mg single dose					
Llanos-Cuentas 2014 (2)	4/54	6/24		37.3 %	0.30 [0.09, 0.95]
Walsh 2004a (3)	1/16	1/4		7.2 %	0.25 [0.02, 3.19]
Subtotal (95% CI)	**70**	**28**		**44.5 %**	**0.29 [0.10, 0.84]**
Total events: 5 (TQ + CQ), 7 (PQ + CQ)					
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.91); I^2 =0.0%					
Test for overall effect: Z = 2.29 (P = 0.022)					
3 Tafenoquine 1800 to 2100 mg split doses					
Walsh 2004a (4)	0/30	2/8		17.4 %	0.06 [0.00, 1.10]
Subtotal (95% CI)	**30**	**8**		**17.4 %**	**0.06 [0.00, 1.10]**
Total events: 0 (TQ + CQ), 2 (PQ + CQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.89 (P = 0.058)					
Total (95% CI)	**156**	**59**		**100.0 %**	**0.30 [0.15, 0.59]**
Total events: 11 (TQ + CQ), 15 (PQ + CQ)					
Heterogeneity: Chi^2 = 1.59, df = 3 (P = 0.66); I^2 =0.0%					
Test for overall effect: Z = 3.44 (P = 0.00058)					
Test for subgroup differences: Chi^2 = 1.55, df = 2 (P = 0.46), I^2 =0.0%					

(1) Llanos-Cuentas 2013; TQ 300 mg group

(2) Llanos-Cuentas 2013; TQ 600 mg group

(3) Walsh 2004; TQ 600 mg group

(4) Walsh 2004; two groups combined: TQ total dose 1800 mg (600 mg daily for 3 days), TQ total dose 2100 mg (300 mg daily for 7 days)

Analysis 2.2. Comparison 2 Tafenoquine versus primaquine, Outcome 2 Serious adverse events.

Review: Tafenoquine for preventing relapse in people with *Plasmodium vivax* malaria

Comparison: 2 Tafenoquine versus primaquine

Outcome: 2 Serious adverse events

Study or subgroup	TQ + CQ n/N	PQ + CQ n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Llanos-Cuentas 2014 (1)	6/54	2/12		28.5 %	0.67 [0.15, 2.91]
Llanos-Cuentas 2014 (2)	2/54	2/12		28.5 %	0.22 [0.03, 1.42]
Llanos-Cuentas 2014 (3)	2/56	1/11		14.5 %	0.39 [0.04, 3.96]
Llanos-Cuentas 2014 (4)	5/54	2/12		28.5 %	0.56 [0.12, 2.53]
Walsh 2004a	0/46	0/12			Not estimable
Total (95% CI)	**264**	**59**		**100.0 %**	**0.47 [0.20, 1.08]**

Total events: 15 (TQ + CQ), 7 (PQ + CQ)

Heterogeneity: $Chi^2 = 0.91$, df = 3 (P = 0.82); $I^2 = 0.0\%$

Test for overall effect: Z = 1.78 (P = 0.076)

Test for subgroup differences: Not applicable

(1) Llanos-Cuentas 2013; TQ 100mg group

(2) Llanos-Cuentas 2013; TQ 50mg group

(3) Llanos-Cuentas 2013; TQ 300mg group

(4) Llanos-Cuentas 2013; TQ 600mg group

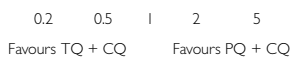
Analysis 2.3. Comparison 2 Tafenoquine versus primaquine, Outcome 3 Any adverse event by tafenoquine dose.

Review: Tafenoquine for preventing relapse in people with *Plasmodium vivax* malaria

Comparison: 2 Tafenoquine versus primaquine

Outcome: 3 Any adverse event by tafenoquine dose

Study or subgroup	TQ + CQ n/N	PQ + CQ n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Llanos-Cuentas 2014 (1)	38/56	8/12		20.2 %	1.02 [0.66, 1.58]
Llanos-Cuentas 2014 (2)	42/54	8/12		20.0 %	1.17 [0.76, 1.78]
Llanos-Cuentas 2014 (3)	37/54	8/11		20.3 %	0.94 [0.63, 1.41]
Llanos-Cuentas 2014 (4)	37/54	8/12		20.0 %	1.03 [0.66, 1.59]
Walsh 2004a (5)	8/16	3/4		7.3 %	0.67 [0.32, 1.41]
Walsh 2004a (6)	14/15	3/4		7.2 %	1.24 [0.70, 2.23]
Walsh 2004a (7)	13/15	2/4		4.8 %	1.73 [0.64, 4.71]
Total (95% CI)	**264**	**59**		**100.0 %**	**1.06 [0.87, 1.28]**
Total events: 189 (TQ + CQ), 40 (PQ + CQ)					
Heterogeneity: Chi^2 = 3.27, df = 6 (P = 0.77); I^2 =0.0%					
Test for overall effect: Z = 0.59 (P = 0.56)					
Test for subgroup differences: Not applicable					



(1) Llanos-Cuentas 2013; TQ 300mg group

(2) Llanos-Cuentas 2013; TQ 100mg group

(3) Llanos-Cuentas 2013; TQ 600mg group

(4) Llanos-Cuentas 2013; TQ 50mg group

(5) Walsh 2004; TQ 600mg single dose

(6) Walsh 2004; TQ 1800 mg total dose (600mg X 3 days)

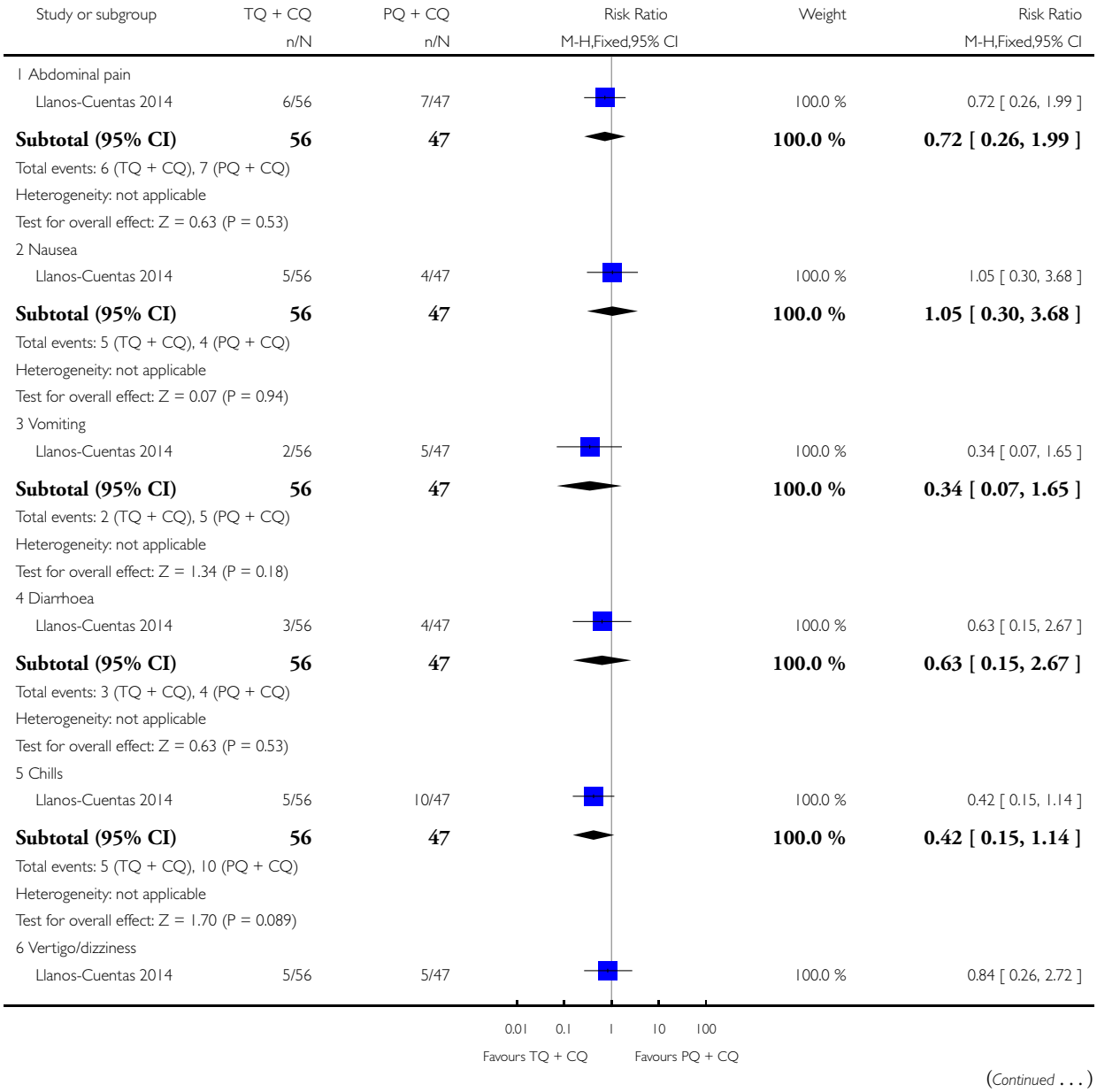
(7) Walsh 2004; TQ 2100mg total dose (300mg X 7 days)

Analysis 2.4. Comparison 2 Tafenoquine versus primaquine, Outcome 4 Comparison by type of adverse event for tafenoquine 300 mg.

Review: Tafenoquine for preventing relapse in people with *Plasmodium vivax* malaria

Comparison: 2 Tafenoquine versus primaquine

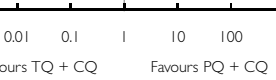
Outcome: 4 Comparison by type of adverse event for tafenoquine 300 mg



(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	TQ + CQ n/N	PQ + CQ n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**56**	**47**		**100.0 %**	**0.84 [0.26, 2.72]**
Total events: 5 (TQ + CQ), 5 (PQ + CQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.29 (P = 0.77)					
7 Headache					
Llanos-Cuentas 2014	10/56	14/47		100.0 %	0.60 [0.29, 1.22]
Subtotal (95% CI)	**56**	**47**		**100.0 %**	**0.60 [0.29, 1.22]**
Total events: 10 (TQ + CQ), 14 (PQ + CQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.41 (P = 0.16)					
8 Myalgia					
Llanos-Cuentas 2014	1/56	2/47		100.0 %	0.42 [0.04, 4.48]
Subtotal (95% CI)	**56**	**47**		**100.0 %**	**0.42 [0.04, 4.48]**
Total events: 1 (TQ + CQ), 2 (PQ + CQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.72 (P = 0.47)					
9 Rash/pruritus					
Llanos-Cuentas 2014	8/56	3/47		100.0 %	2.24 [0.63, 7.96]
Subtotal (95% CI)	**56**	**47**		**100.0 %**	**2.24 [0.63, 7.96]**
Total events: 8 (TQ + CQ), 3 (PQ + CQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.24 (P = 0.21)					
10 Weakness/asthenia					
Llanos-Cuentas 2014	1/56	0/47		100.0 %	2.53 [0.11, 60.60]
Subtotal (95% CI)	**56**	**47**		**100.0 %**	**2.53 [0.11, 60.60]**
Total events: 1 (TQ + CQ), 0 (PQ + CQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.57 (P = 0.57)					
11 Cough					
Llanos-Cuentas 2014	4/56	4/47		100.0 %	0.84 [0.22, 3.18]
Subtotal (95% CI)	**56**	**47**		**100.0 %**	**0.84 [0.22, 3.18]**
Total events: 4 (TQ + CQ), 4 (PQ + CQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.26 (P = 0.80)					
12 Arthralgia					
Llanos-Cuentas 2014	2/56	1/47		100.0 %	1.68 [0.16, 17.94]
Subtotal (95% CI)	**56**	**47**		**100.0 %**	**1.68 [0.16, 17.94]**
Total events: 2 (TQ + CQ), 1 (PQ + CQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.43 (P = 0.67)					
13 Insomnia					



(*Continued* . . .)

(. . . *Continued*)

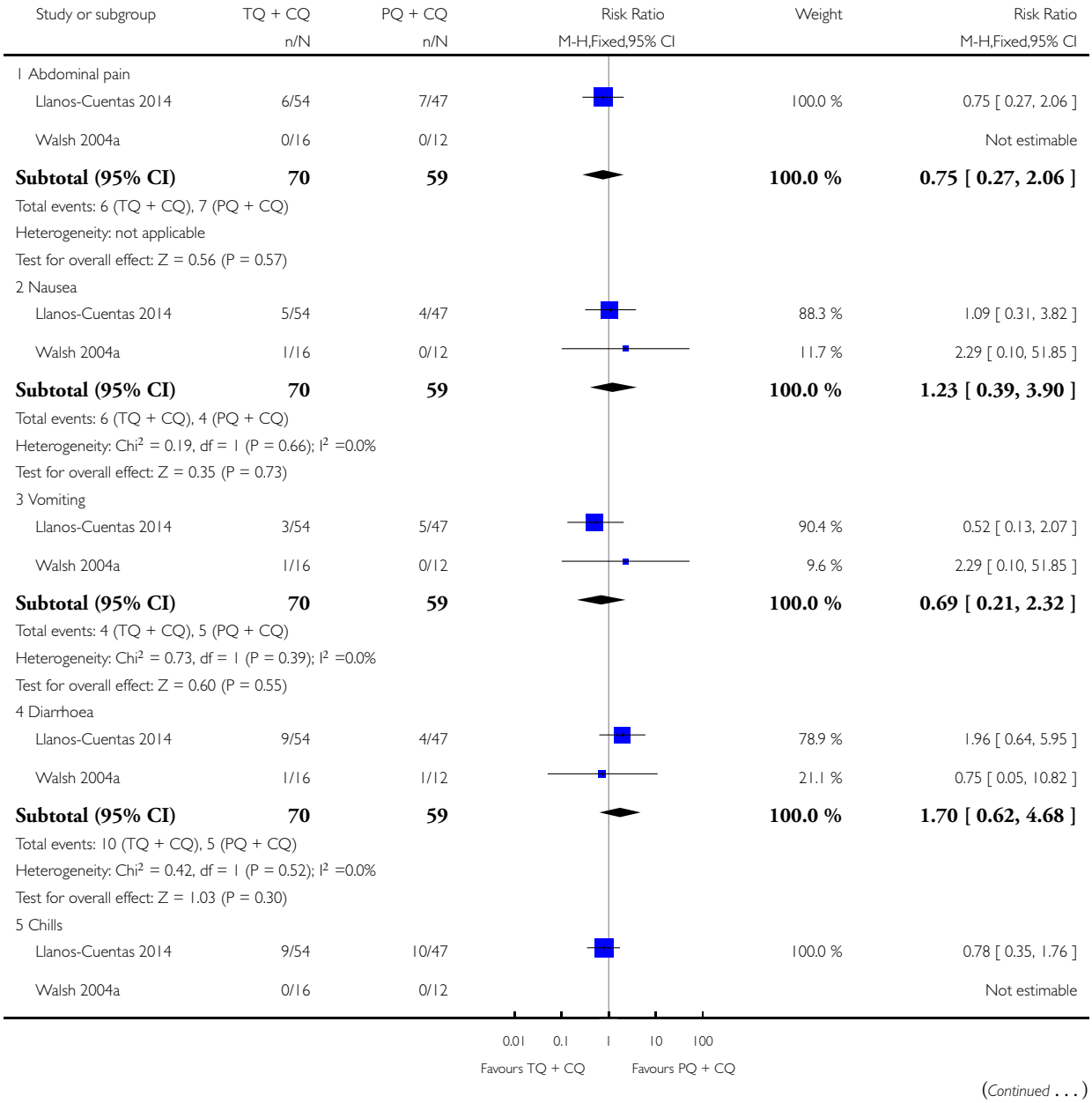
Study or subgroup	TQ + CQ n/N	PQ + CQ n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Llanos-Cuentas 2014	5/56	3/47		100.0 %	1.40 [0.35, 5.55]
Subtotal (95% CI)	**56**	**47**		**100.0 %**	**1.40 [0.35, 5.55]**
Total events: 5 (TQ + CQ), 3 (PQ + CQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.48 (P = 0.63)					
14 Anaemia/drop in Hb					
Llanos-Cuentas 2014	1/56	1/47		100.0 %	0.84 [0.05, 13.06]
Subtotal (95% CI)	**56**	**47**		**100.0 %**	**0.84 [0.05, 13.06]**
Total events: 1 (TQ + CQ), 1 (PQ + CQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.13 (P = 0.90)					
15 QT prolongation					
Llanos-Cuentas 2014	3/56	5/47		100.0 %	0.50 [0.13, 2.00]
Subtotal (95% CI)	**56**	**47**		**100.0 %**	**0.50 [0.13, 2.00]**
Total events: 3 (TQ + CQ), 5 (PQ + CQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.98 (P = 0.33)					
Test for subgroup differences: Chi^2 = 8.24, df = 14 (P = 0.88), I^2 =0.0%					

Analysis 2.5. Comparison 2 Tafenoquine versus primaquine, Outcome 5 Comparison by type of adverse event for tafenoquine 600 mg.

Review: Tafenoquine for preventing relapse in people with *Plasmodium vivax* malaria

Comparison: 2 Tafenoquine versus primaquine

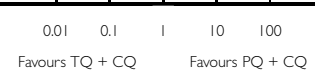
Outcome: 5 Comparison by type of adverse event for tafenoquine 600 mg



(*Continued . . .*)

(. . . *Continued*)

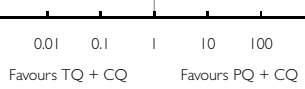
Study or subgroup	TQ + CQ n/N	PQ + CQ n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**70**	**59**		**100.0 %**	**0.78 [0.35, 1.76]**
Total events: 9 (TQ + CQ), 10 (PQ + CQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.59 (P = 0.56)					
6 Vertigo/dizziness					
Llanos-Cuentas 2014	4/54	5/47		60.9 %	0.70 [0.20, 2.44]
Walsh 2004a	4/16	3/12		39.1 %	1.00 [0.27, 3.66]
Subtotal (95% CI)	**70**	**59**		**100.0 %**	**0.81 [0.33, 2.01]**
Total events: 8 (TQ + CQ), 8 (PQ + CQ)					
Heterogeneity: Chi^2 = 0.16, df = 1 (P = 0.69); I^2 =0.0%					
Test for overall effect: Z = 0.44 (P = 0.66)					
7 Headache					
Llanos-Cuentas 2014	16/54	14/47		76.6 %	0.99 [0.55, 1.81]
Walsh 2004a	2/16	4/12		23.4 %	0.38 [0.08, 1.72]
Subtotal (95% CI)	**70**	**59**		**100.0 %**	**0.85 [0.49, 1.48]**
Total events: 18 (TQ + CQ), 18 (PQ + CQ)					
Heterogeneity: Chi^2 = 1.37, df = 1 (P = 0.24); I^2 =27%					
Test for overall effect: Z = 0.58 (P = 0.56)					
8 Myalgia					
Llanos-Cuentas 2014	3/54	2/47		100.0 %	1.31 [0.23, 7.48]
Walsh 2004a	0/12	0/16			Not estimable
Subtotal (95% CI)	**66**	**63**		**100.0 %**	**1.31 [0.23, 7.48]**
Total events: 3 (TQ + CQ), 2 (PQ + CQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.30 (P = 0.76)					
9 Rash/pruritus					
Llanos-Cuentas 2014	2/54	3/47		78.9 %	0.58 [0.10, 3.33]
Walsh 2004a	1/12	1/16		21.1 %	1.33 [0.09, 19.23]
Subtotal (95% CI)	**66**	**63**		**100.0 %**	**0.74 [0.18, 3.11]**
Total events: 3 (TQ + CQ), 4 (PQ + CQ)					
Heterogeneity: Chi^2 = 0.26, df = 1 (P = 0.61); I^2 =0.0%					
Test for overall effect: Z = 0.41 (P = 0.68)					
10 Weakness/asthenia					
Llanos-Cuentas 2014	5/54	0/47		5.5 %	9.60 [0.54, 169.16]
Walsh 2004a	4/16	8/12		94.5 %	0.38 [0.15, 0.96]
Subtotal (95% CI)	**70**	**59**		**100.0 %**	**0.88 [0.41, 1.92]**
Total events: 9 (TQ + CQ), 8 (PQ + CQ)					
Heterogeneity: Chi^2 = 5.86, df = 1 (P = 0.02); I^2 =83%					
Test for overall effect: Z = 0.31 (P = 0.76)					
11 Cough					



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	TQ + CQ n/N	PQ + CQ n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Llanos-Cuentas 2014	1/54	4/47		100.0 %	0.22 [0.03, 1.88]
Subtotal (95% CI)	**54**	**47**		**100.0 %**	**0.22 [0.03, 1.88]**
Total events: 1 (TQ + CQ), 4 (PQ + CQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.39 (P = 0.17)					
12 Arthralgia					
Llanos-Cuentas 2014	3/54	1/47		100.0 %	2.61 [0.28, 24.26]
Subtotal (95% CI)	**54**	**47**		**100.0 %**	**2.61 [0.28, 24.26]**
Total events: 3 (TQ + CQ), 1 (PQ + CQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.84 (P = 0.40)					
13 Insomnia					
Llanos-Cuentas 2014	3/54	3/47		100.0 %	0.87 [0.18, 4.11]
Subtotal (95% CI)	**54**	**47**		**100.0 %**	**0.87 [0.18, 4.11]**
Total events: 3 (TQ + CQ), 3 (PQ + CQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.18 (P = 0.86)					
14 Anaemia/drop in Hb					
Llanos-Cuentas 2014	1/54	1/47		100.0 %	0.87 [0.06, 13.53]
Subtotal (95% CI)	**54**	**47**		**100.0 %**	**0.87 [0.06, 13.53]**
Total events: 1 (TQ + CQ), 1 (PQ + CQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.10 (P = 0.92)					
15 QT prolongation					
Llanos-Cuentas 2014	1/54	5/47		100.0 %	0.17 [0.02, 1.44]
Subtotal (95% CI)	**54**	**47**		**100.0 %**	**0.17 [0.02, 1.44]**
Total events: 1 (TQ + CQ), 5 (PQ + CQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.62 (P = 0.10)					
Test for subgroup differences: Chi^2 = 7.37, df = 14 (P = 0.92), I^2 =0.0%					

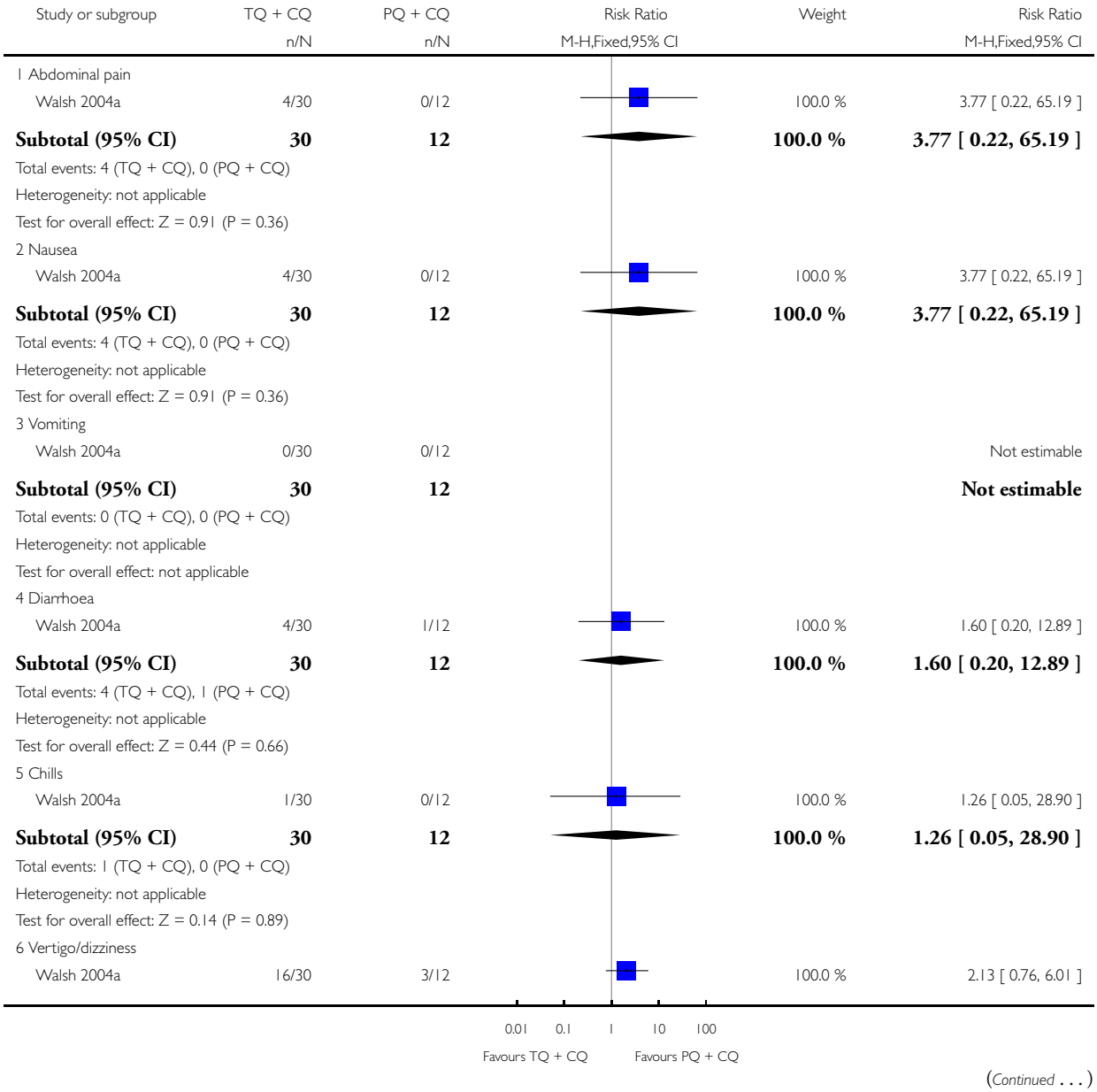


Analysis 2.6. Comparison 2 Tafenoquine versus primaquine, Outcome 6 Comparison by type of adverse event for tafenoquine doses > 600 mg.

Review: Tafenoquine for preventing relapse in people with *Plasmodium vivax* malaria

Comparison: 2 Tafenoquine versus primaquine

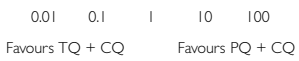
Outcome: 6 Comparison by type of adverse event for tafenoquine doses > 600 mg



(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	TQ + CQ n/N	PQ + CQ n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**30**	**12**		**100.0 %**	**2.13 [0.76, 6.01]**
Total events: 16 (TQ + CQ), 3 (PQ + CQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.43 (P = 0.15)					
7 Headache					
Walsh 2004a	8/30	4/12		100.0 %	0.80 [0.30, 2.17]
Subtotal (95% CI)	**30**	**12**		**100.0 %**	**0.80 [0.30, 2.17]**
Total events: 8 (TQ + CQ), 4 (PQ + CQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.44 (P = 0.66)					
8 Myalgia					
Walsh 2004a	1/30	0/16		100.0 %	1.65 [0.07, 38.22]
Subtotal (95% CI)	**30**	**16**		**100.0 %**	**1.65 [0.07, 38.22]**
Total events: 1 (TQ + CQ), 0 (PQ + CQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.31 (P = 0.76)					
9 Rash/pruritus					
Walsh 2004a	3/30	1/16		100.0 %	1.60 [0.18, 14.16]
Subtotal (95% CI)	**30**	**16**		**100.0 %**	**1.60 [0.18, 14.16]**
Total events: 3 (TQ + CQ), 1 (PQ + CQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.42 (P = 0.67)					
10 Weakness/asthenia					
Walsh 2004a	18/30	8/12		100.0 %	0.90 [0.55, 1.48]
Subtotal (95% CI)	**30**	**12**		**100.0 %**	**0.90 [0.55, 1.48]**
Total events: 18 (TQ + CQ), 8 (PQ + CQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.42 (P = 0.68)					
Test for subgroup differences: Chi^2 = 4.34, df = 8 (P = 0.83), I^2 =0.0%					



ADDITIONAL TABLES

Table 1. Summary of doses of drugs used in each of the trial arms

Trial	Trial groups and tafenoquine doses	Comments
Llanos-Cuentas 2014	1. 50 mg single dose 2. 100 mg single dose 3. 300 mg single dose 4. 600 mg as a single dose 5. No TQ; CQ followed by PQ 15 mg/day for 14 days 6. No TQ; CQ only	In all trials, all patients received the standard treatment of CQ 1500 mg over 3 days to clear the initial parasitaemia There were no reports of CQ resistance.
Walsh 1999	1. 300 mg/day for 7 days (total dose 2100 mg) 2. 500 mg/day for 3 days, two courses separated by 1 week (total dose 3000 mg) 3. 500 mg as a single dose 4. No TQ; CQ only	
Walsh 2004a	1. 300 mg/day for 7 days (total dose 2100 mg) 2. 600 mg/day for 3 days (total dose 1800 mg) 3. 600 mg as a single dose 4. No TQ; CQ only 5. No TQ; CQ followed by PQ 15 mg/day for 14 days	

CQ: Chloroquine; PQ: Primaquine; TQ: Tafenoquine

APPENDICES

Appendix 1. Search strategies

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]	CINAHL, SCOPUS
1	malaria	Malaria ti, ab, MeSH	Malaria ti, ab, MeSH	Malaria ti, ab, Emtree	malaria	malaria
2	Tafenoquine	Tafenoquine ti, ab	Tafenoquine ti, ab	Tafenoquine ti, ab, Emtree	Tafenoquine	Tafenoquine
3	1 and 2	1 and 2	1 and 2	1 and 2	1 and 2	1 and 2

(*Continued*)

4						(randomised controlled trial) or placebo or randomly
5						3 and 4

[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 (Lefebvre 2011).

CONTRIBUTIONS OF AUTHORS

CR, SR and SDF independently screened all articles to identify relevant trials for inclusion in the review. CR, SR and SDF then compared results of article screening and resolved any disagreements through discussion. CR performed the initial data synthesis which was independently verified by SR and SDF. CR wrote the first draft of the manuscript in consultation with SR and SDF. We all read and approved the final draft of the review before submission for publication.

DECLARATIONS OF INTEREST

SR: none declared.

CR: none declared.

SDF: none declared.

SOURCES OF SUPPORT

Internal sources

- University of Colombo, Sri Lanka.

Provided institutional access to databases

External sources

- NHS Lincolnshire Trust, UK.

Provided access to databases

- Cochrane Infectious Diseases Group editorial team, UK.

Guided the restructuring of the review

- Effective Health Care Research Consortium funded by Department of International Development, UK.

Funded CR for a two week fellowship at CIDG to restructure and finalize the review

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the title from "Tafenoquine for *Plasmodium vivax* malaria infection" in the protocol to "Tafenoquine for preventing relapse in people with *Plasmodium vivax* malaria" with the concurrence of the CIDG.

The protocol mentions that the efficacy of TQ is to be assessed on three domains: a) radical cure, b) primary prophylaxis and c) terminal prophylaxis. Since then, we restructured the review with the agreement of the CIDG. During the restructuring process it was decided that assessing three different indications for one drug in a single review is complicated. Therefore this Cochrane review is restricted to trials on relapse prevention of patients with *P. vivax* parasitaemia (radical cure). We have changed the methodology accordingly but search strategies remain the same.

INDEX TERMS

Medical Subject Headings (MeSH)

*Primary Prevention; Aminoquinolines [*administration & dosage; adverse effects]; Antimalarials [*administration & dosage; adverse effects]; Glucosephosphate Dehydrogenase Deficiency [complications]; Malaria, Vivax [*drug therapy]; Primaquine [administration & dosage]; Randomized Controlled Trials as Topic; Recurrence

MeSH check words

Adult; Humans