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

Rodrigo C, Rajapakse S, Fernando D

Rodrigo C, Rajapakse S, Fernando D. Tafenoquine for preventing relapse in people with *Plasmodium vivax* malaria. *Cochrane Database of Systematic Reviews* 2020, Issue 9. Art. No.: CD010458. DOI: [10.1002/14651858.CD010458.pub3](http://doi.org/10.1002/14651858.CD010458.pub3).

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[Intervention Review]

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

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Editorial group: Cochrane Infectious Diseases Group.

Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 9, 2020.

Citation: Rodrigo C, Rajapakse S, Fernando D. Tafenoquine for preventing relapse in people with *Plasmodium vivax* malaria. *Cochrane Database of Systematic Reviews* 2020, Issue 9. Art. No.: CD010458. DOI: 10.1002/14651858.CD010458.pub3.

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**ABSTRACT**

**Background**

*Plasmodium vivax* malaria has a persistent liver stage that causes relapse of the disease and continued *P vivax* transmission. Primaquine (PQ) is used to clear the liver stage of the parasite, but treatment is required for 14 days. Primaquine also causes haemolysis in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Tafenoquine (TQ) is a new alternative to PQ with a longer half-life and can be used as a single-dose treatment.

**Objectives**

To assess the effects of tafenoquine 300 mg (single dose) on preventing *P vivax* relapse.

**Search methods**

We searched the following up to 3 June 2020: the Cochrane Infectious Diseases Group Specialized Register; CENTRAL; MEDLINE; Embase; and three other databases. We also searched the WHO International Clinical Trial Registry Platform and the metaRegister of Controlled Trials for ongoing trials using "tafenoquine" and "malaria" as search terms up to 3 June 2020.

**Selection criteria**

Randomized controlled trials (RCTs) that gave TQ to prevent relapse in people with *P vivax* malaria. We planned to include trials irrespective of whether participants had been screened for G6PD enzyme deficiency.

**Data collection and analysis**

All review authors independently extracted data and assessed risk of bias. As true relapse and reinfection are difficult to differentiate in people living in endemic areas, studies report "recurrences" of infection as a proxy for relapse. We carried out meta-analysis where appropriate, and gave estimates as risk ratios (RR) with 95% confidence intervals (CI). We assessed the certainty of the evidence using the GRADE approach.
Main results
Three individually randomized RCTs met our inclusion criteria, all in endemic areas, and thus reporting recurrence. Trials compared TQ with PQ or placebo, and all participants received chloroquine (CQ) to treat the asexual infection. In all trials, pregnant and G6PD-deficient people were excluded.

Tafenoquine 300 mg single dose versus no treatment for relapse prevention
Two trials assessed this comparison. TQ 300 mg single dose reduces P vivax recurrences compared to no antihypnozoite treatment during a six-month follow-up, but there is moderate uncertainty around effect size (RR 0.32, 95% CI 0.12 to 0.88; 2 trials, 504 participants; moderate-certainty evidence).

In people with normal G6PD status, there is probably little or no difference in any type of adverse events (2 trials, 504 participants; moderate-certainty evidence). However, we are uncertain if TQ causes more serious adverse events (2 trials, 504 participants; very low-certainty evidence). Both RCTs reported a total of 23 serious adverse events in TQ groups (One RCT reported 21 events) and a majority (15 events) were a drop in haemoglobin level by >3g/dl (or >30% reduction from baseline).

Tafenoquine 300 mg single dose versus primaquine 15 mg/day for 14 days for relapse prevention
Three trials assessed this comparison. There is probably little or no difference between TQ and PQ in preventing recurrences (proxy measure for relapse) up to six months of follow-up (RR 1.04, 95% CI 0.8 to 1.34; 3 trials, 747 participants; moderate-certainty evidence).

In people with normal G6PD status, there is probably little or no difference in any type of adverse events (3 trials, 747 participants; moderate-certainty evidence). We are uncertain if TQ can cause more serious adverse events compared to PQ (3 trials, 747 participants; very low-certainty evidence). Two trials had higher point estimates against TQ while the other showed the reverse. Most commonly reported serious adverse event in TQ group was a decline in haemoglobin level (19 out of 29 events). Some other serious adverse events, though observed in the TQ group, are unlikely to be caused by it (Hepatitis E infection, limb abscess, pneumonia, menorrhagia).

Authors' conclusions
TQ 300 mg single dose prevents relapses after clinically parasitologically confirmed P vivax malaria compared to no antihypnozoite treatment, and with no difference detected in studies comparing it to PQ to date. However, the inability to differentiate a true relapse from a recurrence in the available studies may affect these estimates. The drug is untested in children and in people with G6PD deficiency. Single-dose treatment is an important practical advantage compared to using PQ for the same purpose without an overall increase in adverse events in non-pregnant, non-G6PD-deficient adults.

PLAIN LANGUAGE SUMMARY
Tafenoquine for preventing relapse in people with vivax malaria
What was the aim of this review?
The aim of this review was to see if tafenoquine could prevent relapses of vivax infections and if this effect is equivalent to that of standard-dose primaquine. Standard-dose primaquine is defined as 15 mg/day for 14 days for adults.

Key messages
Tafenoquine prevents vivax malaria relapses (measured as recurrences of infection in all studies as it is not possible to differentiate a true relapse from a reinfection) in adults compared to no relapse prevention treatment (placebo). There is also probably little or no difference between tafenoquine and primaquine in preventing relapses. The evidence was of moderate certainty due to the low number of studies and few data. There is probably little or no difference in the overall adverse events with tafenoquine compared to placebo or primaquine. However, we are uncertain if tafenoquine causes more serious adverse events such as a drop in blood haemoglobin.

What was studied in this review?
Vivax malaria is caused by the parasite Plasmodium vivax. The disease includes a dormant (inactive) stage of liver infection and this can cause relapse (worsening) unless it is treated.

The most frequently used medicine for relapse prevention until recently was primaquine, but now there is a new alternative named tafenoquine. The US agency responsible for protecting public health, the Food and Drug Administration (FDA), recommends tafenoquine for relapse prevention at a single 300 mg dose. Compared to primaquine, which is usually given daily for 14 days, single-day dosing provides a significant advantage. However, both primaquine and tafenoquine can cause rupture or destruction of red blood cells (called haemolysis) in people with a hereditary condition called glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency.

We conducted a Cochrane Review on the effect of tafenoquine on clearing the dormant P vivax parasites in infected people to prevent a relapse. However, it is difficult to differentiate between a true relapse and a new infection in the same individual unless the person was...
removed from a malaria-endemic area after initial treatment. All trials included in this review did not do that and have actually measured recurrences as a proxy measure to infer on relapses. While acknowledging this limitation, in giving recommendations and results in this review we used the word 'relapse' as preventing relapses is the intention for using tafenoquine as a single dose in these trials.

What are the main results of the review?

We examined the research published up to 3 June 2020. We identified three trials conducted in nine countries in 747 adults with confirmed *Plasmodium vivax* malaria. All adults received chloroquine (to clear the parasites from the blood) and some groups received either tafenoquine in a single dose of 300 mg, primaquine or placebo (an inactive tablet matched for the duration of primaquine). All were observed for recurrences of *Plasmodium vivax* malaria (up to six months) and all trials tested people for G6PD activity and excluded people who were deficient. Pregnant women and children were also excluded.

Adults receiving tafenoquine 300 mg had fewer relapses (inferred from the lower number of recurrences of infection) than adults who had placebo (moderate-certainty evidence). There was probably little or no difference between Tafenoquine 300 mg and primaquine for relapse prevention (moderate-certainty evidence). There is probably little or no difference in overall side effects between tafenoquine and primaquine (moderate-certainty evidence). We are uncertain though if tafenoquine causes more serious adverse events compared to placebo or primaquine (for example, haemolysis; very low-certainty evidence).
### SUMMARY OF FINDINGS

**Summary of findings 1. Summary of findings table 1**

| Outcomes | Illustrative comparative risks* (95% CI) | Relative effect (95% CI) | No of participants (trials) | Certainty of the evidence (GRADE) | Comments |
| --- | --- | --- | --- | --- | --- |
| **P. vivax parasitaemia during 6 months of follow-up** | | | | | |
| CQ alone | 636 per 1000 (76 to 560) | 204 per 1000 | RR 0.32 (0.12 to 0.88) | 504 (2 trials) | Moderate a,b,c |
| TQ + CQ | 204 per 1000 | | | | |
| **Serious adverse events** | 53 per 1000 (34 to 152) | 72 per 1000 | RR 1.34 (0.63 to 2.84) | 504 (2 trials) | Very low a,d,e |
| **Any adverse event** | 567 per 1000 (459 to 641) | 544 per 1000 | RR 0.96 (0.81 to 1.13) | 504 (2 trials) | Moderate a,d |

*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; RR: risk ratio; TQ: tafenoquine.

**GRADE Working Group grades of evidence**

- **High certainty**: further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate certainty**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low certainty**: 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.
Tafenoquine for preventing relapse in people with *Plasmodium vivax* malaria (Review)

*Very low certainty:* we are very uncertain about the estimate.

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No serious risk of bias: all trials were at low risk of selection and reporting bias.

No serious indirectness: all trials when combined enrolled adults with *P. vivax* malaria in Peru, Thailand, India, Ethiopia, Cambodia, Philippines and Brazil. CQ was given in the standard adult dose to all participants.

Downgraded one level for high heterogeneity: one of the trials was small and had few events during six months, as such this result is at high risk of overestimating the true effect.

Downgraded one level for serious indirectness: all trials excluded children.

Downgraded by two for serious imprecision (wide CI of risk estimate). Note: 14 participants in TQ group had Hb falls < 3 g, compared to 2 in control group.

**Summary of findings 2. Summary of findings table 2**

**Tafenoquine versus primaquine in people with *Plasmodium vivax* malaria**

**Patient or population:** adults and children with *P. vivax* malaria

**Settings:** *P. vivax* endemic areas

**Intervention:** tafenoquine 300 mg single dose. Both intervention and control received chloroquine treatment

**Comparison:** primaquine (15 mg/day for 14 days)

| Outcomes                                      | Illustrative comparative risks* (95% CI) | Relative effect (95% CI) | No of participants (trials) | Certainty of the evidence (GRADE) | Comments                                                                 |
|-----------------------------------------------|-----------------------------------------|--------------------------|------------------------------|----------------------------------|--------------------------------------------------------------------------|
| *P. vivax* parasitaemia during 6 months of follow-up | PQ + CQ: 258 per 1000 (206 to 345)        | RR 1.04 (0.8 to 1.34)    | 747 (3 trials)               | ⊕⊕⊕⊝ Moderate a,b,c               | TQ is probably as effective as PQ for vivax relapse prevention up to 6 months. |
| Serious adverse events                        | PQ + CQ: 45 per 1000 (32 to 129)         | RR 1.41 (0.7 to 2.83)    | 747 (3 trials)               | ⊕⊕⊝⊝⊝ Very low a,d,e              | We are uncertain if TQ + CQ causes more serious adverse events than standard-dose PQ + CQ. |
| Any adverse event                             | PQ + CQ: 591 per 1000 (526 to 674)       | RR 1.01 (0.89 to 1.14)   | 747 (3 trials)               | ⊕⊕⊕⊕ Moderate a,d                 | TQ + CQ probably has little or no difference in adverse events (any type) compared to standard-dose PQ + CQ. |

*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: primaquine; RR: risk ratio; TQ: tafenoquine.

GRADE Working Group grades of evidence

High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: 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 certainty: we are very uncertain about the estimate.

a No serious risk of bias: two trials were at low risk of selection bias (selection bias in Llanos-Cuentas 2019 was unclear), while all trials were at low risk of reporting bias.
b No serious indirectness: all trials when combined enrolled adults with P vivax malaria in Peru, Thailand, India, Ethiopia, Cambodia, Philippines, Colombia, Vietnam and Brazil. CQ was given in the standard adult dose to all participants.
c Downgraded one level for high heterogeneity.
d Downgraded one level for serious indirectness: these trials excluded children.
e Downgraded by two levels for serious imprecision. Point estimate indicated 41% increase in harms, but there were wide CI of risk estimate.
B A C K G R O U N D

Malaria remains an important cause of illness and death in many tropical countries. In 2017, 219 million cases of malaria were estimated to have occurred globally with 435,000 deaths (WHO 2018). Malaria eradication efforts have been successful in reducing malaria mortality and morbidity since 2000 and many countries have been declared malaria-free (WHO 2018). Most malaria cases are caused by the species Plasmodium falciparum and Plasmodium vivax. *P falciparum* causes a more severe form of malaria with multiorgan involvement (Fernando 2011a). *P vivax* is less virulent but still accounts for around 40% of global malaria burden (50% of cases in Asia) (Douglas 2014; Price 2007). The notion of vivax malaria being a 'benign' illness is increasingly contested as mortality from vivax monoinfections has been demonstrated (Baird 2013; Douglas 2014). The incidence of *P vivax* infection has become particularly important in countries aiming for malaria elimination (WHO 2018). *P vivax* infection has been treated with chloroquine (CQ) but resistance to this widely available drug has been reported on all continents in which vivax malaria is endemic (Price 2014; WHO 2015).

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, months or even years. 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 relapses. 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. However, it is difficult to identify a true relapse from a reinfection even with genetic studies of the parasite across the two infections. For example, if both infections are by a homologous strain it can still be a reinfection (instead of a relapse) in regions of low endemicity if the genomic diversity of circulating parasite variants is low. Interpretation of homologous infections as a relapse also depends on which part of the genome was sequenced (conserved versus variable regions). Similarly, a heterologous infection can still be a relapse (instead of a reinfection) if the first infection was caused by multiple variants and if two variants were sequenced at two time points (Beck 2016). This is more likely in regions of high endemicity. More reliable data on relapses can be obtained if the patients were moved to a non-endemic area after the first infection. Unless a trial fulfilled this criterion, we cannot differentiate a relapse from a reinfection.

Description of the intervention

The first drug used to treat vivax malaria was the hypnozoitocide, plasmochin (pamaquine), which was introduced in 1926 (Fletcher 1927). In the 1950s, primaquine (PQ), an 8-aminoquinoline, was licensed for this use by the US Food and Drug Administration (FDA) and became the most popular choice (Hill 2006). Without administration of PQ in adequate doses, complete cure of people with *P vivax* infection is difficult, and people often have relapses of clinical disease (Baird 2004; Fernando 2011b). Tafenoquine (TQ) is the most extensively studied and a newly licensed alternative to PQ. It is an 8-aminoquinoline (Wells 2010), and is a synthetic analogue of PQ (Crockett 2007). It is shown to be useful in regimens for prophylaxis and radical cure of *P vivax* malaria.

Tafenoquine can precipitate haemolysis (which can be life-threatening) in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency, an X-linked recessive condition (Ramos Júnior 2010). However, PQ could still be prescribed in men and non-pregnant women with G6PD deficiency in a modified dosing regimen under close medical supervision as this was the only relapse prevention treatment available until recently (WHO 2016). In addition, PQ has other undesirable adverse effects such as methaemoglobinemia and gastrointestinal disturbances (Carmona-Fonseca 2009). PQ is metabolized to active metabolites by cytochrome P450 2D6 enzyme (CYP2D6) and its activity phenotype may partly influence efficacy in instances where administration in standard doses have not been able to prevent relapses (Chen 2019; Goller 2007; Reddy 2006). Hence, the World Health Organization (WHO) currently recommends two PQ dose regimens based on the geographical location; 30 mg/day for adults (0.5 mg/kg/day) in East Asia and Oceania and 15 mg/day for adults (0.25 mg/kg/day) elsewhere (WHO 2015). PQ treatment has to be continued for 14 days, which often leads to poor compliance (Hill 2006; WHO 2015). The modified regimen in G6PD deficiency (< 30% of enzyme activity) is 0.75 mg base/kg weekly for 8 weeks (WHO 2016).

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: 1. a shorter duration of treatment; 2. better efficacy in clearing hypnozoites; 3. being free from the significant adverse effects of PQ such as haemolysis in people with G6PD deficiency; and 4. being free from variation of susceptibility of the parasite (partially contributed by host genetic polymorphisms). 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). TQ is currently licensed by the FDA and the Therapeutic Goods Administration, Australia for hypnozoite clearance and prophylaxis of vivax malaria (Berman 2019). TQ also causes haemolysis, and its longer half-life makes any haemolytic effect more prolonged and thus potentially more serious. This Cochrane Review will pool the evidence from all randomized controlled trials (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 relapse prevention treatment or PQ.

How the intervention might work

The mechanism of action of TQ is unknown. Based on early in vitro and animal studies, it is believed to be longer acting and more effective than PQ (Crockett 2007). Preclinical studies showed better activity of TQ compared to PQ against both hepatic and erythrocytic forms of the parasite. Phase I, II and III trials have been conducted to evaluate its safety (Brueckner 1998a; Brueckner 1998b; Lacerda 2019; Llanos-Cuentas 2014).

Why it is important to do this review

PQ is a unique drug in combating vivax malaria but has adverse effects that can sometimes be serious in people with G6PD deficiency. The long duration of treatment also leads to poor adherence. TQ has already shown promise in having efficacy for the same indications when administered as a single dose. Therefore, it is important to analyze the efficacy and safety data of TQ in preventing relapses of vivax malaria. Since TQ 300 mg single dose is approved by FDA for relapse prevention of vivax malaria, this analysis focused on this dose only.
OBJECTIVES
To assess the effect of tafenoquine 300 mg (single dose) in preventing *P. vivax* relapses.

METHODS
Criteria for considering studies for this review
Types of studies
RCTs. We excluded quasi-RCTs.

Types of participants
Adults and children with confirmed (clinical and parasitological) diagnosis of *P. vivax* malaria (as a single infection or as part of a mixed infection alongside *P. falciparum*).

Types of interventions
Intervention
Tafenoquine at the FDA approved dose of 300 mg.

Control
No drug or placebo.

Primaquine in a WHO-recommended 14-day regimen.

Cointerventions
Both intervention and control groups must have received the same treatment, either CQ or an artemisinin-based combination therapy (ACT), for the blood-borne stage of the *P. vivax* infection.

Types of outcome measures
- Recurrent (as a proxy measure of relapse when patients remained in the endemic area during follow-up) *P. vivax* parasitaemia by six months.
- Serious adverse events: death, symptomatic haemolysis, symptomatic methaemoglobinemia, 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 participants or elicited by investigators during treatment and follow-up.

Search methods for identification of studies
We identified all relevant new trials regardless of language or publication status (published, unpublished, in press and in progress) from the last date of search (13 April 2015) of the previously published version of this review (Rajapakse 2015). We combined these with the included studies of the previous version of the review (after evaluating them against the current inclusion criteria).

Electronic searches
We searched 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 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 3 June 2020 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 2015 onwards for new trial information.

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
Three review authors (CR, SR, 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. Any disagreement was resolved by consensus. We listed the ineligible trials and the reasons for their exclusion in the Characteristics of excluded studies table.

Data extraction and management
We extracted data from the selected trials and independently recorded the outcomes. We used a data extraction and assessment form suited for the needs of this review according to the instructions provided by Cochrane by updating the same form used in the previous version of the review (Higgins 2011). We used Review Manager 5 for data analysis and storage (Review Manager 2014), 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, geographic location, co-administered schizonticidal drugs, G6PD status of the participants, 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. We presented information in the Characteristics of included studies table.

Assessment of risk of bias in included studies
Three review authors (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.

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, recurrent infections of vivax malaria). For all results, we calculated 95% confidence intervals (CIs) and performed a meta-analyses if sufficient data were available (if the control groups and follow-up duration were similar across studies).

Unit of analysis issues

When trials reported multiple doses of TQ (for example, dose-ranging studies published prior to 2015), only the treatment groups receiving the currently approved 300 mg dose of TQ were included in this review. We split the control groups between trial arms of a single trial as appropriate during a meta-analysis to avoid duplication in data entry.

Dealing with missing data

We planned to contact study authors in the event of missing data. However, no trials were excluded due to missing data.

Assessment of heterogeneity

We visually inspected the Forest plots and looked at the Chi² values of meta-analyses for evidence of heterogeneity. We assessed heterogeneity using the I² statistic, which examines the percentage of total variation across studies that are due to heterogeneity rather than chance (Higgins 2003).

Assessment of reporting biases

As there were fewer than 10 trials, we did not use Funnel plots to assess publication bias.

Data synthesis

We analyzed data using Review Manager 5 (Review Manager 2014). One review author (CR) performed the initial analyses, and two review authors (SR and SDF) independently checked and performed recalculations. We compared recurrences following treatment between groups treated with TQ-containing drug regimens against CQ/ACT alone or CQ/ACT plus PQ. We also compared the reported adverse events between TQ and PQ (or no antirelapse treatment). We performed all analyses using a fixed-effect model except when there was high heterogeneity in results (I² statistic greater than 70%), in which case we used a random-effects model.

We used GRADE working group 2013 recommendations to estimate the certainty of evidence for each effect estimate (Schünemann 2013).

Subgroup analysis and investigation of heterogeneity

When several trials were combined in a meta-analysis, we estimated the heterogeneity regarding the treatment effect of TQ and CQ/ACT versus CQ/ACT alone or CQ/ACT plus PQ. In case of high heterogeneity, results were reanalyzed and reported using a random-effects model. We also considered the following subgroup analyses to explain any heterogeneity: G6PD status, geographical location, age (adults versus children) of participants and the schizonticidal drug administered (CQ or ACT).

Sensitivity analysis

The main results are reported using an intention-to-treat analysis. All participants who were randomized but did not complete treatment were included in the denominator with the intention-to-treat model. The numbers randomized were taken from the study flow diagrams in each trial. We also performed a sensitivity analysis using a per-protocol analysis. Here, only those who completed the protocol were included in the denominator for each trial group. We performed a worst-case scenario analysis by assuming all participants who were randomized but did not complete the study had a recurrence and those missing in control/comparator groups did not have a recurrence.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; and Characteristics of ongoing studies tables. 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 search for new articles published since 13 April 2015, after excluding duplicate and irrelevant articles, yielded three papers that we deemed potentially useful for this Cochrane Review. However, only two trials met the inclusion criteria. Furthermore, according to the revised inclusion criteria, two studies that were included in the previous version of the review were not eligible for this version (as these studies did not use the now-approved single dose 300 mg TQ dose in any of their treatment arms) (Walsh 1999; Walsh 2004a). Figure 1 shows a combined PRISMA flow chart for both versions of this review.
Included studies

Three RCTs met the inclusion criteria; Phase IIb DETECTIVE study (Llanos-Cuentas 2014), Phase III DETECTIVE study (Lacerda 2019), and GATHER study (Llanos-Cuentas 2019). All the data required for this analysis originated from the cited publications. Another publication (a conference abstract related to Llanos-Cuentas 2014 was noted but it did not have any new information relevant to the analysis (Lacerda 2013).

All participants in these trials received a full course of CQ to treat their *P. vivax* infection (1500 mg over three days). For relapse prevention, comparisons included TQ plus CQ versus CQ only (two trials) and TQ plus CQ versus CQ plus PQ (three trials). No trials used ACTs as the background treatment. All trials were in symptomatic people with uncomplicated vivax malaria, and all trials excluded people with G6PD deficiency, pregnant women, and children.

All trials were multicentre conducted in Thailand, India, Peru, Ethiopia, Cambodia, Philippines, Colombia, Vietnam and Brazil. All three studies were conducted by the same principal investigators. Llanos-Cuentas 2014 tested single doses of TQ at strengths of 50 mg, 100 mg, 300 mg and 600 mg versus PQ or placebo. The follow-up trial tested TQ 300 mg single dose versus PQ or placebo (Lacerda 2019). The third trial compared TQ 300 mg single dose versus PQ (Llanos-Cuentas 2019). The main outcomes assessed were: recurrences of vivax malaria up to six months’ follow-up and adverse events. In the earlier version of the review, we contacted the authors of Llanos-Cuentas 2014 for details not published in the paper (exact number of recurrences during follow-up). All outcome data were reported for Llanos-Cuentas 2019 and Lacerda 2019.

Excluded studies

We excluded randomized trials on prophylaxis and randomized trials that did not use TQ 300 mg single dose, non-controlled trials and randomized pharmacokinetic studies performed on healthy individuals (see Characteristics of excluded studies table).
Risk of bias in included studies

For a summary of risk of bias, 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, while two of them specified method of randomization as computer-generated sequence allocation. The methodology of the remaining trial (Llanos-Cuestas 2019) was mentioned to be similar to Lacerda.
Collaboration.

Tafenoquine for preventing relapse in people with symptomatic cases in the TQ 300 mg single-dose group (Table 2). The maximum Hb levels except that there were no cases of symptomatic cases in the TQ 300 mg single-dose group (Table 2). There was an increase in methaemoglobin (MHB) levels in TQ-treated patients. There was probably little or no difference between groups regarding the number or type of any adverse events reported (2 trials, 504 participants; Analysis 1.2). There were no deaths reported in any of the trials during treatment or follow-up. One RCT (Lacerda 2019) reported 21 serious adverse events in the TQ group out of which 14 were significant drops in Hb level (>3g/dl or >30% from baseline). Some other events reported may be attributable to TQ (one case each of diarrhoea and drug induced liver injury) while for others a direct contributory role of TQ is doubtful (one case each of limb abscess, menorrhagia, urinary tract infection, hepatitis E infection and spontaneous abortion). In the other RCT (Llanos-Cuentas 2014), two serious adverse events were reported in the TQ group (one case each of a drop in Hb level and QT prolongation on ECG).

Any adverse events

There was probably little or no difference between groups regarding the number or type of any adverse events reported (2 trials, 504 participants; Analysis 1.3) including anaemia/drop in Hb level.

There was an increase in methaemoglobin (MHB) levels in TQ-treated groups with a maximum of 13% in Lacerda 2019. All cases were asymptomatic. Llanos-Cuentas 2014 did not report the maximum MHB levels except that there were no cases of symptomatic cases in the TQ 300 mg single-dose group (Table 2).

Recurrence Plasmodium vivax parasitaemia by six months

TQ 300 mg single dose reduced P vivax relapses (as demonstrated by a reduction in recurrent infections) compared to no antihypnozoite treatment during a six-month follow-up according to an intention-to-treat analysis (RR 0.32, 95% CI 0.12 to 0.88; 2 trials, 504 participants; Analysis 1.1; Figure 3). However, the range where the actual effect may be (the “margin of error”) is wide, and the size of the difference may be small. The findings did not change when a per-protocol analysis or a worst-case scenario was considered (Analysis 1.4; Analysis 1.5). Subgroup analysis based on the geographical region of participants (Asia, Africa or South America) showed similar results to the main analysis (Analysis 1.6; Analysis 1.7; Analysis 1.8).

Serious adverse events

We are uncertain if TQ+CQ combination causes more serious adverse events (2 trials, 504 participants; Analysis 1.2). There were no deaths reported in any of the trials during treatment or follow-up. One RCT (Lacerda 2019) reported 21 serious adverse events in the TQ group out of which 14 were significant drops in Hb level (>3g/dl or >30% from baseline). Some other events reported may be attributable to TQ (one case each of diarrhoea and drug induced liver injury) while for others a direct contributory role of TQ is doubtful (one case each of limb abscess, menorrhagia, urinary tract infection, hepatitis E infection and spontaneous abortion). In the other RCT (Llanos-Cuentas 2014), two serious adverse events were reported in the TQ group (one case each of a drop in Hb level and QT prolongation on ECG).

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

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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). CQ: chloroquine; PQ: primaquine; TQ: tafenoquine.

| Study or Subgroup | TQ + CQ | PQ + CQ | Risk Ratio | Risk Ratio |
|-------------------|---------|---------|------------|------------|
|                   | Events | Total   | Events | Total   | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Lacerda 2019      | 85     | 260     | 36     | 129     | 1.17 [0.84, 1.63] |
| Llanos-Cuentas 2014 | 6     | 57      | 12     | 50      | 0.44 [0.18, 1.08] |
| Llanos-Cuentas 2019 | 42    | 166     | 20     | 85      | 1.08 [0.68, 1.71] |
| **Total (95% CI)** | **483** | **264** | **100.0%** | **1.04 [0.80, 1.34]** |

Serious adverse events

We are uncertain if TQ plus CQ causes more serious adverse events than PQ plus CQ (3 trials, 747 participants; Analysis 2.2). The type of serious adverse events reported in the TQ group in two RCTs (Lacerda 2019; Llanos-Cuentas 2014) was mentioned in the previous section. In the remaining RCT (Llanos-Cuentas 2019), six serious adverse events were reported in the TQ group (4 instances of Hb drop, one case each of pneumonia and fever).

Any adverse events

There is probably little or no difference across groups for the number or type of any adverse events reported (3 trials, 747 participants; Analysis 2.3) including anaemia/drop in Hb level. There were increased Mhb levels with both TQ and PQ but there were no symptomatic cases in any of the treatment groups (Table 2).

DISCUSSION

Summary of main results

See Summary of findings 1 and Summary of findings 2.

TQ 300 mg single dose reduced relapse of vivax malaria (up to six months of observation) when combined with a standard dose of CQ compared to CQ only. However, there is moderate uncertainty regarding the effect size. TQ 300 mg single dose and CQ combination probably has little or no difference compared to PQ 15 mg/day for 14 days and CQ combination (moderate-certainty evidence) for the same purpose. There was probably little or no difference regarding overall adverse events between the TQ group and other groups (moderate-certainty evidence).

Overall completeness and applicability of evidence

All trials were multicentre, double-blind RCTs collectively conducted in nine countries across three continents mostly by the same group of investigators with consistency in methods and reporting. All trials measured recurrences as a proxy measure of relapse as the participants remained in the endemic area during follow-up, with the risk of reinfection. Llanos-Cuentas 2014 showed that TQ in single low doses (50 mg and 100 mg) is ineffective in preventing recurrences compared to CQ monotherapy and that 300 mg may be more suitable for this indication. Lacerda 2019 tested this hypothesis with a larger sample size and confirmed the same.

The pooled results of three trials that compared PQ versus TQ 300 mg single dose suggest probable equal efficacy in relapse prevention. However, the subgroup analysis for Asia, which consisted of people recruited from India, Vietnam, Philippines and Cambodia, showed TQ may be less effective than PQ. While this result was heavily influenced by a single trial (Lacerda 2019), a higher dose of TQ in fact be necessary for some parts of Asia. WHO already recommends a higher than standard dose of PQ for East Asia and Oceania (30 mg/day for 14 days) and the same may be required for TQ. This needs to be confirmed with further evidence.

The dose of PQ used in the control arm in both trials was 15 mg/day for 14 days. Efficacy of TQ is untested against the higher dose of PQ recommended for East Asia and Oceania. Haemolysis with G6PD deficiency is a risk with PQ and the structurally similar TQ (Rueangwearerayut 2017), and same cautions apply for prescription. All RCTs on TQ to-date, have excluded people with G6PD deficiency and, therefore, safety of TQ in this population was not explored. However, PQ is not absolutely contraindicated in G6PD deficiency. When the enzyme activity is less than 30% of normal, a modified regimen (0.75 mg base/kg/d weekly for 8 weeks) can be prescribed under close medical supervision for both men and non-pregnant women (WHO 2016). Therefore there may be a future role for RCTs to compare TQ and PQ (in modified dosing regimens) under these circumstances, depending on outcomes of phase I studies. Pregnant women were also excluded from trials but, given that the G6PD status of the foetus cannot be determined and the preliminary observations from TQ-induced haemolysis in people with G6PD deficiency, TQ is very unlikely to be tested in pregnant women. Consistent observations from included studies demonstrate that at 300 mg single dose, TQ is probably unlikely to cause symptomatic methaemoglobinemia.

Certainty of the evidence

Recurrent *Plasmodium vivax* parasitaemia at six months

Considering the overall picture, we conclude that TQ is more effective than placebo in preventing relapses of vivax malaria for...
A follow-up of six months (moderate-certainty evidence). There is probably little or no difference between TQ 300 mg single dose and standard-dose PQ for the same indication. This is an improvement from the evidence of our previous review where certainty for this comparison was low. However, relapses of vivax malaria can occur even later, probably up to one year. All included trials were randomized prospective double-blind clinical trials. As mentioned previously, the evidence from these trials spanned three continents and nine countries. The inclusion and exclusion criteria and outcome measurements were consistent.

Serious adverse events

We are uncertain if TQ causes more serious adverse events compared to placebo or PQ. The certainty of this evidence was downgraded as very low since safety of TQ has not been tested in children and wide confidence intervals of the estimate (serious imprecision). Most common type of serious adverse event reported was a drop in Hb level in patients and clinicians should be alert to monitoring this TQ prescribed patients who have a low baseline Hb level.

Any adverse events

There is moderate-certainty evidence from three trials that TQ probably has little or no difference in all types of adverse events compared to PQ or placebo when administered as 300 mg single dose. Neither TQ nor PQ is likely to cause symptomatic methaemoglobinemia at these doses though the MHB percentage was observed to increase with both. The certainty of evidence was downgraded for indirectness. TQ is unlikely to be used in pregnant women as the G6PD status of the foetus cannot be determined.

Potential biases in the review process

We searched trial registries using specific search strategies to uncover any unpublished trials with negative results; however, we found none.

Agreements and disagreements with other studies or reviews

A per-protocol, individual participant level meta-analysis of Lacerda 2019 and Llanos-Cuentas 2019 came to the same conclusion as ours though non-inferiority of TQ against PQ could not be demonstrated (based on a preset non-inferiority margin calculated from the results of Llanos-Cuentas 2014). Given the differences in analysis method (ours was based on an intention-to-treat analysis), the CIs observed by Llanos-Cuentas 2019 were wider. Adverse events were not compared in the above-mentioned meta-analysis. On adverse events, we agreed 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 people in the dose ranges tested.

AUTHORS’ CONCLUSIONS

Implications for practice

Tafenoquine (TQ) is effective in preventing Plasmodium vivax relapses up to six months by clearing vivax hypnozoites when used at a single dose of 300 mg (moderate-certainty evidence). However, the margin of error is wide and the size of the difference may be small. Evidence from three studies suggest that it probably has little or no difference to standard-dose PQ for hypnozoite clearance (moderate-certainty evidence). The ability to administer TQ as a single dose is a significant advantage in terms of compliance. Children and people with G6PD deficiency were excluded from the studies so recommendations are not valid for these groups. It is very likely that pregnancy will remain a contraindication for TQ. Though the overall incidence of adverse events are probably not higher with TQ (compared to PQ or placebo), we are uncertain if it causes more serious adverse events, mainly haemolysis. The practitioners need to be alert to this possibility.

Implications for research

Further randomized controlled clinical trials will help to establish whether a higher single dose of TQ is better in relapse prevention compared to primaquine (PQ) with comparable adverse events particularly in Asia accounting for CYP2D6 polymorphisms (as TQ may also be metabolized via the same enzyme). Such trials should compare PQ at a higher than standard dose which is the current recommendation for East Asia and Oceania. In addition, all studies conducted to-date in endemic areas cannot differentiate a relapse or recrudescence from a reinfection. It will be interesting to note if equivalent efficacy of TQ versus PQ can be demonstrated once the reinfection risk is eliminated (people isolated or removed from an endemic region after first infection). Future studies should also have a longer follow-up period (extending to one year). Safety and efficacy of TQ in children is also unassessed at the moment.

ACKNOWLEDGEMENTS

The Academic Editor is Dr Patricia Graves.

CR is supported by the National Health and Medical Research Council of Australia (investigator grant no. 1173666).

The editorial base of the Cochrane Infectious Diseases Group is funded by UK aid from the UK government for the benefit of low- and middle-income countries (project number 300342-104). The views expressed do not necessarily reflect the UK government’s official policies. GlaxoSmithKline (GSK) is acknowledged for providing access to unpublished trial data.
References to studies included in this review

Lacerda 2019 \textit{(published and unpublished data)}
Lacerda MG, Llanos-Cuentas A, Krudsood S, Lon C, Saunders DL, Mohammed R, et al. Single-dose tafenoquine to prevent relapse of Plasmodium vivax malaria. \textit{New England Journal of Medicine} 2019;\textit{380}(3):215-28.

Llanos-Cuentas 2014 \textit{(published and unpublished data)}
Lacerda M, Ugwugebula 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. \textit{American Journal of Tropical Medicine and Hygiene} 2013;\textit{89}(5 Suppl 1):14.

\* 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. \textit{Lancet} 2014;\textit{383}(9922):1049-58.

Llanos-Cuentas 2019 \textit{(published and unpublished data)}
Llanos-Cuentas A, Lacerda MG, Hien TT, Velez JD, Naimak-Larp C, Chu CS, et al. Tafenoquine versus primaquine to prevent relapse of Plasmodium vivax malaria. \textit{New England Journal of Medicine} 2019;\textit{380}(3):229-41.

References to studies excluded from this review

Ackert 2019 \textit{(published data only)}
Ackert J, Mohamed K, Slakter JS, El-Harazi S, Berni A, Gevorkyan H et al. Randomized Placebo-Controlled Trial Evaluating the Ophthalmic Safety of Single-Dose Tafenoquine in Healthy Volunteers. \textit{Drug Safety} 2019;\textit{42}(9):1103-14.

Dow 2014 \textit{(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. \textit{Malaria Journal} 2014;\textit{13}(9):49.

Edstein 2003 \textit{(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. \textit{Clinical Infectious Diseases} 2003;\textit{37}(12):1654-8.

Elmes 2008 \textit{(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. \textit{Transactions of Royal Society of Tropical Medicine and Hygiene} 2008;\textit{102}(11):1095-101.

Fukuda 2017 \textit{(published data only)}
Fukuda MM, Krudsood S, Mohamed K, Green JA, Warrasak S, Noedl H, et al. A randomized, double-blind, active-control trial to evaluate the efficacy and safety of a three day course of tafenoquine monotherapy for the treatment of Plasmodium vivax malaria. \textit{PloS One} 2017;\textit{12}(11):e0187376.

Green 2014 \textit{(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. \textit{Journal of Clinical Pharmacology} 2014;\textit{54}(9):995-1005.

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

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

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

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

Nasveld 2010 \textit{(published data only)}
Nasveld PE, Edstein MD, Brennan L, Harris IE, Kitchener SJ, Leggate PA, et al. Randomized, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. \textit{Antimicrobial Agents and Chemotherapy} 2010;\textit{54}(2):792-8.

Shanks 2001 \textit{(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. \textit{Clinical Infectious Diseases} 2001;\textit{33}(12):1968-74.

Walsh 1999 \textit{(published data only)}
Walsh DS, Loaareesuwan S, Wilairatanapa 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. \textit{Journal of Infectious Diseases} 1999;\textit{180}(4):1282-7.
Collaboration.

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References to ongoing studies

NCT02802501 [published data only]
NCT02802501. Efficacy and safety study of tafenoquine (TQ) co-administered with dihydroartemisinin-piperaquine (DHA-PQP) for the radical cure of Plasmodium vivax (P. vivax) malaria [Study 200894: A double-blind, double-dummy, randomized, parallel group, placebo-controlled superiority study to evaluate the efficacy and safety of tafenoquine (SB-252263, WR238605) co-administered with dihydroartemisinin-piperaquine (DHA-PQP) for the radical cure of Plasmodium vivax malaria]. clinicaltrials.gov/ct2/show/NCT02802501 (first received 16 June 2016).

NCT04411836 [published data only]
NCT04411836. Effectiveness of novel approaches to radical cure with tafenoquine and primaquine (EFFORT) [Effectiveness of novel approaches to radical cure with tafenoquine and primaquine - a randomized controlled trial in P. vivax patients]. clinicaltrials.gov/ct2/show/NCT04411836 (first received 2 June 2020).

Additional references

Baird 2004
Baird JK, Hoffman SL. Primaquine therapy for malaria. Clinical Infectious Diseases 2004;39(8):1336-45.

Baird 2013
Baird JK. Evidence and implications of mortality associated with acute Plasmodium vivax malaria. Clinical Microbiology Reviews 2013;26(1):36-57.

Beck 2016
Beck HP, Wampfler R, Carter N, Koh G, Osorio R, Rueangweerayut S, et al. Estimation of the antirelapse efficacy of tafenoquine, using Plasmodium vivax genotyping. Journal of Infectious Diseases 2016;213(5):794-99.

Berman 2019
Berman JD. Approval of tafenoquine for malaria chemoprophylaxis. American Journal of Tropical Medicine and Hygiene 2019;100(6):1301-4.

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.

Chen 2019
Chen N, Dowd S, Gatton ML, Auliff A, Edstein MD, Cheng Q. Cytochrome P450 2D6 profiles and their relationship with outcomes of primaquine anti-relapse therapy in Australian Defence Force personnel deployed to Papua New Guinea and East Timor. Malaria Journal 2019;18(1):140.

Crockett 2007
Crockett M, Kain KC. Tafenoquine: a promising new antimalarial agent. Expert Opinion on Investigational Drugs 2007;16(5):705-15.

Douglas 2014
Douglas NM, Pontororing GJ, Lampah DA, Yeo TW, Kenangalem E, Poepoprodjo AP, et al. Mortality attributable to Plasmodium vivax malaria: a clinical audit from Papua, Indonesia. BMC Medicine 2014;12(1):217.

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.

Fletcher 1927
Fletcher W, Kanagarayer K. Plasmochin in the treatment of malaria. Indian Medical Gazette 1927;62(9):499-506.

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.
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GRADEpro 2014 [Computer program]
McMaster University (developed by Evidence Prime) GRADEpro GDT. Hamilton (ON): McMaster University (developed by Evidence Prime), 2014. Available at gradepro.org.

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 JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.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.

Lacerda 2013
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* 2013;89(Suppl 1):14.

Lefebvre 2011
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

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

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

Price 2014
Price RN, von Seidlein L, Valecha N, Nosten F, Baird JK, White NJ. Global extent of chloroquine-resistant Plasmodium vivax: a systematic review and meta-analysis. *Lancet Infectious Diseases* 2014;14(10):982-91.

Ramos Júnior 2010
Ramos Júnior WM, Sardinha JF, Costa MR, Santana MS, Alecrim MG, Lacerda MV. Clinical aspects of hemolysis in patients with *Plasmodium 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.

Review Manager 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.

Rueangwearerayut 2017
Rueangwearerayut R, Bancone G, Harrell EJ, Beelen AP, Kongpatanakul S, Mohrle JJ, et al. Hemolytic potential of tafenoquine in female volunteers heterozygous for glucose-6-phosphate dehydrogenase (G6PD) deficiency (G6PD Mahidol variant) versus G6PD-normal volunteers. *American Journal of Tropical Medicine and Hygiene* 2017;97(3):702-11.

Schünemann 2013
Schünemann H, Brozek J, Guyatt G, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. Available from guidelinedevelopment.org/handbook, Updated October 2013.

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 2015
World Health Organization. Guidelines for the Treatment of Malaria. 3 edition. Geneva: World Health Organization, 2015.

WHO 2016
World Health Organization. Testing for G6PD deficiency for safe use of primaquine in radical cure of *P. vivax* and *P. ovale* malaria; Policy brief. Geneva, Switzerland: World Health organization, 2016.

WHO 2018
World Health Organization. World Malaria Report 2018. www.who.int/malaria/publications/world-malaria-report-2018/report/en/ (accessed 15 May 2019).

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. Art. No: CD010458. [DOI: 10.1002/14651858.CD010458]

Rajapakse 2015
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]

* Indicates the major publication for the study
# Characteristics of Studies

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

**Lacerda 2019**

### Study characteristics

| Methods          | Multicentre, double-blind, double-dummy RCT |
|------------------|--------------------------------------------|
|                  | Trial phase: III                           |
|                  | Trial design: parallel-group trial         |

| Participants     | Number randomized: 522                     |
|------------------|--------------------------------------------|
|                  | Inclusion criteria:                        |
|                  | • males and females aged ≥ 16 years with clinical symptoms of malaria with *P. vivax* monoinfection 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 Hb < 7 g/dL           |
|                  | • pregnancy, breastfeeding or G6PD enzyme activity < 70% of the site median |
|                  | • mixed malaria                            |
|                  | • prolonged QT interval on ECG or elevation of ALT < 2 times upper normal limit |

| Interventions    | All participants received the standard adult dose of CQ 1500 mg over 3 days to eradicate the current infection plus: |
|------------------|---------------------------------------------------------------|
|                  | • TQ 300 mg single dose (n = 260)                             |
|                  | • PQ 15 mg/day for 14 days (n = 129)                          |
|                  | • TQ/PQ matched placebo (n = 133)                            |

| Outcomes         | Outcomes included in this review:                          |
|------------------|-------------------------------------------------------------|
|                  | • recurrence of microscopically confirmed *P. vivax* malaria after completing treatment up to 6 months |
|                  | • adverse events attributable to TQ (including a drop in Hb > 3 g/dL or 30% from baseline) |

| Outcomes         | Outcomes not included in this review:                     |
|------------------|------------------------------------------------------------|
|                  | • number of recurrences at 33 days and 4 months           |
|                  | • time to recurrence                                       |
|                  | • time to parasite clearance                               |
|                  | • time to fever clearance                                  |
|                  | • *P. vivax* gametocyte clearance                           |

| Notes            | Location: Ethiopia, Peru, Thailand, Cambodia, Brazil, Philippines |
|------------------|------------------------------------------------------------------|
|                  | Setting: local 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           | Quote: “With the use of a computer-generated randomisation schedule provided by GlaxoSmithKline, on day 1 eligible participants were randomly assigned, in a 2:1:1 ratio...” |
| Allocation concealment (selection bias)       | Low risk           | Quote: “Patients and trial staff were unaware of the group assignments.” |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk           | Double-blind, double-dummy study.                                   |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk           | Double-blind study.                                                  |
| Incomplete outcome data (attrition bias) All outcomes | Low risk           | Attrition rate in all groups < 5% of number randomized.              |
| Selective reporting (reporting bias)           | Low risk           | All participants were accounted for.                                 |
| Other bias                                     | Low risk           | None identified.                                                    |

### Study characteristics

**Lacerda 2019**

**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 years with clinical symptoms of malaria with *P. vivax* monoinfection 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 Hb < 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:
  - TQ 50 mg single dose (*n* = 55)

**Llanos-Cuentas 2014**

**Methods**
- Multicentre, double-blind RCT
- Trial phase: IIb
- Trial design: parallel-group, dose-ranging trial

**Participants**
- Number randomized: 329

**Interventions**
- All participants received the standard adult dose of CQ (1500 mg) over 3 days to eradicate the current infection plus:
  - TQ 50 mg single dose (*n* = 55)
Llanos-Cuentes 2014 (Continued)

- TQ 100 mg single dose (n = 57)
- TQ 300 mg single dose (n = 57)
- TQ 600 mg single dose (n = 56)
- TQ/PQ matched placebo (n = 54)
- PQ 15 mg/day for 14 days (n = 50)

### Outcomes

Outcomes included in this review:

- recurrence of microscopically confirmed *P. vivax* malaria after completing treatment up to 6 months
- adverse events attributable to TQ

Outcomes not included in this review:

- time to recurrence
- 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           | Quote: “A computer generated randomisation schedule, stratified by baseline parasite count.” |
| Allocation concealment (selection bias)   | Low risk           | Quote: “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 < 6% of the number randomized. |
| Selective reporting (reporting bias)      | Low risk           | Absolute number of recurrences by 6 months not mentioned. However, it could be calculated from available data. The numbers were confirmed by communication with the authors. |
| Other bias                                | Low risk           | None identified.                                                                       |
| Study characteristics |
|-----------------------|
| **Methods**           | Multicentre, double-blind, double-dummy RCT |
|                       | Trial phase: III |
|                       | Trial design: parallel-group trial assessing primary safety outcomes |
| **Participants**      | Number randomized: 251 |
|                       | Inclusion criteria: |
|                       | • males and females aged ≥ 16 years with clinical symptoms of malaria with *P. vivax* monoinfection 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 Hb < 7 g/dL |
|                       | • pregnancy, breastfeeding or G6PD enzyme activity < 70% of the site median for males (< 40% for females) |
|                       | • mixed malaria |
|                       | • prolonged QT interval on ECG or elevation of ALT < 2 times upper normal limit |
| **Interventions**     | All participants received the standard adult dose of CQ (1500 mg) over 3 days to eradicate the current infection plus: |
|                       | • TQ 300 mg single dose + PQ matched placebo (n = 166) |
|                       | • PQ 15 mg/day for 14 days (n = 85) |
| **Outcomes**          | Outcomes included in this review: |
|                       | • recurrence of microscopically confirmed *P. vivax* malaria after completing treatment up to 6 months |
|                       | • adverse events attributable to TQ (including a drop in Hb > 3 g/dL or 30% from baseline) |
|                       | Outcomes not included in this review: |
|                       | • number of recurrences at 4 months |
| **Notes**             | Location: Peru, Thailand, Colombia, Brazil, Vietnam |
|                       | Setting: local hospitals |
|                       | Endemicity: endemic for vivax malaria |
|                       | Resistance: unknown |
|                       | Funding: GlaxoSmithKline, Medicines for Malaria Venture |
|                       | This study was designated as an ongoing study in the previous version of our review (NCT02216123) |

### Risk of bias

| Bias                             | Authors' judgement | Support for judgement |
|----------------------------------|--------------------|-----------------------|
| Random sequence generation (selection bias) | Unclear risk       | Method of sequence generation not mentioned. |
|                                  |                    | Quote: "The methods were similar to those used in the phase 3 DETECTIVE trial (Lacerda 2019)." |
### Characteristics of excluded studies [ordered by study ID]

| Study       | Reason for exclusion                                                                 |
|-------------|--------------------------------------------------------------------------------------|
| Ackert 2019 | Assessed ophthalmic safety of tafenoquine in healthy people                           |
| Dow 2014    | Assessed the efficacy of TQ with regard to prevention of vivax and falciparum malaria during a period of exposure in an endemic area. |
| Edstein 2003| Described the same trial as Walsh 2004b.                                              |
| Elmes 2008  | Assessed the efficacy of TQ for preventing recurrences of vivax malaria in participants without baseline vivax parasitaemia after leaving an endemic area. |
| Fukuda 2017 | TQ 300 mg single dose not tested in any of the treatment arms. TQ monotherapy used to clear both schizonts and hypnozoites. |
| Green 2014  | Assessed QT prolongation with TQ in healthy volunteers.                               |
| Hale 2003   | Assessed the efficacy of TQ with regard to prevention of falciparum malaria.          |
| Kitchener 2007 | Uncontrolled study.                                                               |
| Lell 2000   | Assessed the efficacy of TQ with regard to prevention of falciparum malaria.          |
| Nasveld 2002| Assessed efficacy of TQ for hypnozoite clearance of participants leaving an endemic area (who did not have baseline vivax parasitaemia). |
| Nasveld 2010| Assessed the efficacy of TQ for preventing vivax malaria infections in healthy participants during a period of exposure in an endemic area. |

ALT: alanine aminotransferase; CQ: chloroquine; ECG: electrocardiogram; Hb: haemoglobin; G6PD: glucose-6-phosphate dehydrogenase; n: number of participants; PQ: primaquine; RCT: randomized controlled trial; TQ: tafenoquine.
TQ: tafenoquine.

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

**NCT02802501**

**Study name**

Efficacy and safety study of tafenoquine (TQ) co-administered with dihydroartemisinin-piperazine (DHA-PQP) for the radical cure of *Plasmodium vivax* (*P vivax*) malaria

**Methods**

Double-blind, double-dummy, randomized, parallel-group, placebo-controlled superiority study

**Participants**

Inclusion criteria:

- men aged \( \geq 18 \) years
- positive Giemsa smear for *P vivax*
- parasite density \( > 20/\mu L \)
- normal G6PD enzyme status
- QT interval \( < 450 \) millisecond

Exclusion criteria:

- severe *P vivax* malaria
- severe vomiting (no food or inability to take food during previous 8 hours)
- screening haemoglobin \( < 8 \) g/dL
- liver function test ALT \( > 2 \) times upper limit of normal
- clinically significant concurrent illness or history of hypersensitivity
- previous treatment with TQ or other antimalarials within 30 days or any other drug known to have significant interactions with study drugs,
- illicit drug use
- any other contraindication to study drugs

**Interventions**

- DHA-PQP + TQ
- DHA-PQP + PQ (control)

**Outcomes**

Primary outcome: relapse-free efficacy 6 months post-dosing

**Starting date**

April 2018

**Contact information**

GSK Clinical Trials

**Notes**

Location: Indonesia

Funding: GlaxoSmithKline Pharmaceuticals Ltd.
NCT04411836

Study name: Effectiveness of Novel Approaches to Radical Cure With Tafenoquine and Primaquine (EFFORT)

Methods: Health care facility based, randomized, controlled, open label, superiority trial with 3 arms

Participants

Inclusion criteria

- *P. vivax* peripheral parasitaemia (mono-infection) as determined by microscopy
- G6PD normal status (G6PD activity ≥ 70% of the adjusted male median as determined by the Biosensor™ (SD Bioline, ROK))
- Fever (temperature ≥37.5°C) or history of fever in the preceding 48 hours
- Age ≥18 years
- Written informed consent
- Living in the study area and willing to be followed for six months

Exclusion criteria

- Danger signs or symptoms of severe malaria
- Anaemia (defined as Hb <8g/dl)
- Pregnant or lactating females
- Known hypersensitivity to any of the study drugs

Interventions

- Schizontocidal treatment plus low dose PQ (total dose 3.5mg/kg) unsupervised over 14 days
- Schizontocidal treatment plus high dose PQ (total dose 7 mg/kg) unsupervised over 7 days
- Schizontocidal treatment plus a single dose of Tafenoquine (TQ) 300mg

Outcomes

Primary outcome: the incidence risk (time to first event) of symptomatic *P. vivax* parasitaemia during the 6-month follow up period as determined by microscopy

Starting date: January 2021

Contact information
Sophie Weston (sophie.weston@menzies.edu.au), Menzies School of Health Research

Notes
Location: Not provided
Sponsor: Menzies School of Health Research

ALT: alanine aminotransferase; DHA-PQP: dihydroartemisinin-piperaquine; G6PD: glucose-6-phosphate dehydrogenase; PQ: primaquine; TQ: tafenoquine.

**DATA AND ANALYSES**

Comparison 1. Tafenoquine (TQ) 300 mg single dose versus no hypnozoite treatment (chloroquine (CQ))

| Outcome or subgroup title                           | No. of studies | No. of participants | Statistical method     | Effect size          |
|-----------------------------------------------------|----------------|---------------------|------------------------|----------------------|
| 1.1 Recurrent *P. vivax* parasitaemia by 6 months (intention to treat) | 2              | 504                 | Risk Ratio (M-H, Random, 95% CI) | 0.32 [0.12, 0.88] |
| 1.2 Serious adverse events                          | 2              | 504                 | Risk Ratio (M-H, Fixed, 95% CI)   | 1.34 [0.63, 2.84] |
| 1.3 Adverse events by type                          | 2              |                     | Risk Ratio (M-H, Fixed, 95% CI)   | Subtotals only      |

Tafenoquine for preventing relapse in people with *Plasmodium vivax* malaria (Review)
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---------------------------|----------------|---------------------|--------------------|-------------|
| 1.3.1 Any adverse event   | 2              | 504                 | Risk Ratio (M-H, Fixed, 95% CI) | 0.96 [0.81, 1.13] |
| 1.3.2 Abdominal pain      | 2              | 504                 | Risk Ratio (M-H, Fixed, 95% CI) | 0.66 [0.33, 1.33] |
| 1.3.3 Nausea              | 2              | 504                 | Risk Ratio (M-H, Fixed, 95% CI) | 1.05 [0.53, 2.07] |
| 1.3.4 Vomiting            | 2              | 504                 | Risk Ratio (M-H, Fixed, 95% CI) | 1.29 [0.57, 2.93] |
| 1.3.5 Diarrhoea           | 2              | 504                 | Risk Ratio (M-H, Fixed, 95% CI) | 1.03 [0.42, 2.50] |
| 1.3.6 Vertigo/dizziness   | 2              | 504                 | Risk Ratio (M-H, Fixed, 95% CI) | 1.89 [0.88, 4.08] |
| 1.3.7 Headache            | 2              | 504                 | Risk Ratio (M-H, Fixed, 95% CI) | 0.55 [0.33, 0.92] |
| 1.3.8 Rash/pruritus       | 2              | 504                 | Risk Ratio (M-H, Fixed, 95% CI) | 0.92 [0.57, 1.50] |
| 1.3.9 QT prolongation     | 2              | 504                 | Risk Ratio (M-H, Fixed, 95% CI) | 0.37 [0.12, 1.20] |
| 1.3.10 Anaemia/drop in haemoglobin | 2 | 504 | Risk Ratio (M-H, Fixed, 95% CI) | 2.84 [0.80, 10.09] |
| 1.4 Recurrent *P. vivax* parasitaemia by 6 months (per protocol) | 2 | 408 | Risk Ratio (M-H, Random, 95% CI) | 0.31 [0.13, 0.77] |
| 1.5 Recurrent *P. vivax* parasitaemia by 6 months (worst-case scenario) | 2 | 504 | Risk Ratio (M-H, Random, 95% CI) | 0.36 [0.14, 0.90] |
| 1.6 Recurrent *P. vivax* parasitaemia by region – Asia | 2 | 130 | Risk Ratio (M-H, Fixed, 95% CI) | 0.44 [0.28, 0.69] |
| 1.7 Recurrent *P. vivax* parasitaemia by region – Africa | 1 | 42   | Risk Ratio (M-H, Fixed, 95% CI) | 0.38 [0.16, 0.87] |
| 1.8 Recurrent *P. vivax* parasitaemia by region – South America | 2 | 332 | Risk Ratio (M-H, Fixed, 95% CI) | 0.43 [0.34, 0.55] |

**Analysis 1.1. Comparison 1: Tafenoquine (TQ) 300 mg single dose versus no hypnozoite treatment (chloroquine (CQ)), Outcome 1: Recurrent *P. vivax* parasitaemia by 6 months (intention to treat)**

| Study or Subgroup            | TQ + CQ Events | TQ + CQ Total | CQ alone Events | CQ alone Total | Risk Ratio M-H, Random, 95% CI |
|-----------------------------|----------------|---------------|----------------|---------------|--------------------------------|
| Lacerda 2019                | 85             | 260           | 88             | 133           | 0.49 [0.40, 0.61]               |
| Llanos-Cuentas 2014         | 6              | 57            | 31             | 54            | 0.18 [0.08, 0.40]               |
| Total (95% CI)              | 91             | 317           | 187            | 100.0%        | 0.32 [0.12, 0.88]               |

Total events: 91

Heterogeneity: $\tau^2 = 0.45; \chi^2 = 6.19, df = 1 (P = 0.01); I^2 = 84%$

Test for overall effect: $Z = 2.20 (P = 0.03)$

Test for subgroup differences: Not applicable
### Analysis 1.2. Comparison 1: Tafenoquine (TQ) 300 mg single dose versus no hypnozoite treatment (chloroquine (CQ)), Outcome 2: Serious adverse events

| Study or Subgroup | TQ + CQ | CQ alone | Risk Ratio |
|-------------------|---------|----------|------------|
|                   | Events  | Total    | Events     | Total   | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Lacerda 2019      | 21      | 260      | 6          | 133     | 65.9%  | 1.79 [0.74, 4.33]  |
| Llanos-Cuentas 2014 (1) | 2      | 57       | 4          | 54      | 34.1%  | 0.47 [0.09, 2.48]  |
| **Total (95% CI)** | 23      | 260      | 10         | 187     | 100.0% | 1.34 [0.63, 2.84]  |

**Heterogeneity:** Chi² = 1.93, df = 1 (P = 0.16); I² = 48%
**Test for overall effect:** Z = 0.77 (P = 0.44)
**Test for subgroup differences:** Not applicable

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**Footnotes**

(1) Llanos-Cuentas 2013; TQ 600mg group
Analysis 1.3.  Comparison 1: Tafenoquine (TQ) 300 mg single dose versus no hypnozoite treatment (chloroquine (CQ)), Outcome 3: Adverse events by type

| Study or Subgroup | TQ + CQ | CQ alone | Risk Ratio | Weight | Risk Ratio |
|-------------------|---------|----------|------------|--------|------------|
|                   | Events  | Total    | Events     | Total  |            | M-H, Fixed, 95% CI |
| 1.3.1 Any adverse event |        |          |            |        |            |
| Lacerda 2019      | 127     | 260      | 65         | 133    | 67.1%      | 1.00 [0.81 , 1.24] |
| Llanos-Cuentas 2014 | 38     | 57       | 41         | 54     | 32.9%      | 0.88 [0.69 , 1.11] |
| Subtotal (95% CI) | 317     | 187      | 100.0%     |        |            | 0.96 [0.81 , 1.13] |
| Total events:     | 165     | 106      |            |        |            |               |
| Heterogeneity: Chi² = 0.68, df = 1 (P = 0.41); I² = 0% |
| Test for overall effect: Z = 0.49 (P = 0.62) |
| 1.3.2 Abdominal pain |        |          |            |        |            |
| Lacerda 2019      | 8       | 260      | 9          | 133    | 69.9%      | 0.45 [0.18 , 1.15] |
| Llanos-Cuentas 2014 | 6      | 57       | 5          | 54     | 30.1%      | 1.14 [0.37 , 3.51] |
| Subtotal (95% CI) | 317     | 187      | 100.0%     |        |            | 0.66 [0.33 , 1.33] |
| Total events:     | 14      | 14       |            |        |            |               |
| Heterogeneity: Chi² = 1.51, df = 1 (P = 0.22); I² = 34% |
| Test for overall effect: Z = 1.16 (P = 0.24) |
| 1.3.3 Nausea |        |          |            |        |            |
| Lacerda 2019      | 16      | 260      | 9          | 133    | 79.4%      | 0.91 [0.41 , 2.00] |
| Llanos-Cuentas 2014 | 5      | 57       | 3          | 54     | 20.6%      | 1.58 [0.40 , 6.29] |
| Subtotal (95% CI) | 317     | 187      | 100.0%     |        |            | 1.05 [0.53 , 2.07] |
| Total events:     | 21      | 12       |            |        |            |               |
| Heterogeneity: Chi² = 0.46, df = 1 (P = 0.50); I² = 0% |
| Test for overall effect: Z = 0.13 (P = 0.89) |
| 1.3.4 Vomiting |        |          |            |        |            |
| Lacerda 2019      | 15      | 260      | 7          | 133    | 94.7%      | 1.10 [0.46 , 2.62] |
| Llanos-Cuentas 2014 | 2      | 57       | 0          | 54     | 5.3%       | 4.74 [0.23 , 96.56] |
| Subtotal (95% CI) | 317     | 187      | 100.0%     |        |            | 1.29 [0.57 , 2.93] |
| Total events:     | 17      | 7        |            |        |            |               |
| Heterogeneity: Chi² = 0.85, df = 1 (P = 0.36); I² = 0% |
| Test for overall effect: Z = 0.60 (P = 0.55) |
| 1.3.5 Diarrhoea |        |          |            |        |            |
| Lacerda 2019      | 10      | 260      | 4          | 133    | 56.3%      | 1.28 [0.41 , 4.00] |
| Llanos-Cuentas 2014 | 3      | 57       | 4          | 54     | 43.7%      | 0.71 [0.17 , 3.03] |
| Subtotal (95% CI) | 317     | 187      | 100.0%     |        |            | 1.03 [0.42 , 2.50] |
| Total events:     | 13      | 8        |            |        |            |               |
| Heterogeneity: Chi² = 0.39, df = 1 (P = 0.53); I² = 0% |
| Test for overall effect: Z = 0.07 (P = 0.95) |
| 1.3.6 Vertigo/dizziness |        |          |            |        |            |
| Lacerda 2019      | 22      | 260      | 4          | 133    | 50.8%      | 2.81 [0.99 , 8.00] |
| Llanos-Cuentas 2014 | 5      | 57       | 5          | 54     | 49.2%      | 0.95 [0.29 , 3.09] |
| Subtotal (95% CI) | 317     | 187      | 100.0%     |        |            | 1.89 [0.88 , 4.08] |
| Total events:     | 27      | 9        |            |        |            |               |
| Heterogeneity: Chi² = 1.87, df = 1 (P = 0.17); I² = 47% |
| Test for overall effect: Z = 1.63 (P = 0.10) |
| 1.3.7 Headache |        |          |            |        |            |
| Lacerda 2019      | 12      | 260      | 9          | 133    | 36.7%      | 0.68 [0.29 , 1.58] |
| Llanos-Cuentas 2014 | 10     | 57       | 20         | 54     | 63.3%      | 0.47 [0.24 , 0.92] |
| Subtotal (95% CI) | 317     | 187      | 100.0%     |        |            | 0.55 [0.33 , 0.92] |
Analysis 1.3. (Continued)

| Subtotal (95% CI) | 317 | 187 | 100.0% | 0.55 [0.33 , 0.92] |
|-------------------|-----|-----|---------|------------------|

Total events: 22
Heterogeneity: Chi² = 0.45, df = 1 (P = 0.50); I² = 0%
Test for overall effect: Z = 2.26 (P = 0.02)

1.3.8 Rash/pruritus

| Lacerda 2019 | 29 | 260 | 17 | 133 | 75.8% | 0.87 [0.50 , 1.53] |
|-------------|----|-----|----|-----|-------|------------------|
| Llanos-Cuentas 2014 | 8 | 57 | 7 | 54 | 24.2% | 1.08 [0.42 , 2.78] |

Subtotal (95% CI) | 317 | 187 | 100.0% | 0.92 [0.57 , 1.50] |
|-------------------|-----|-----|---------|------------------|

Total events: 37
Heterogeneity: Chi² = 0.15, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 0.32 (P = 0.75)

1.3.9 QT prolongation

| Lacerda 2019 | 0 | 260 | 3 | 133 | 53.0% | 0.07 [0.00 , 1.41] |
|-------------|---|-----|---|-----|-------|------------------|
| Llanos-Cuentas 2014 | 3 | 57 | 4 | 54 | 47.0% | 0.71 [0.17 , 3.03] |

Subtotal (95% CI) | 317 | 187 | 100.0% | 0.37 [0.12 , 1.20] |
|-------------------|-----|-----|---------|------------------|

Total events: 3
Heterogeneity: Chi² = 1.92, df = 1 (P = 0.17); I² = 48%
Test for overall effect: Z = 1.65 (P = 0.10)

1.3.10 Anaemia/drop in haemoglobin

| Lacerda 2019 | 14 | 260 | 2 | 133 | 72.0% | 3.58 [0.83 , 15.52] |
|-------------|----|-----|---|-----|-------|------------------|
| Llanos-Cuentas 2014 | 1 | 57 | 1 | 54 | 28.0% | 0.95 [0.06 , 14.77] |

Subtotal (95% CI) | 317 | 187 | 100.0% | 2.84 [0.80 , 10.09] |
|-------------------|-----|-----|---------|------------------|

Total events: 15
Heterogeneity: Chi² = 0.71, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 1.62 (P = 0.11)
Test for subgroup differences: Chi² = 14.41, df = 9 (P = 0.01), I² = 37.5%

Analysis 1.4. Comparison 1: Tafenoquine (TQ) 300 mg single dose versus no hypnozoite treatment (chloroquine (CQ)), Outcome 4: Recurrent *P. vivax* parasitaemia by 6 months (per protocol)

| Study or Subgroup | TQ + CQ | CQ alone | Risk Ratio |
|-------------------|---------|----------|------------|
| TQ + CQ | Events | Total | Events | Total | Weight | M-H, Random, 95% CI |
| Lacerda 2019 | 52      | 192      | 63      | 106   | 58.2% | 0.46 [0.34 , 0.60] |
| Llanos-Cuentas 2014 | 6    | 56       | 31      | 54    | 41.8% | 0.19 [0.08 , 0.41] |

Subtotal (95% CI) | 248 | 160 | 100.0% | 0.31 [0.13 , 0.77] |
|-------------------|-----|-----|---------|------------------|

Total events: 58
Heterogeneity: Tau² = 0.34; Chi² = 4.71, df = 1 (P = 0.03); I² = 79%
Test for overall effect: Z = 2.53 (P = 0.01)
Test for subgroup differences: Not applicable
### Analysis 1.5. Comparison 1: Tafenoquine (TQ) 300 mg single dose versus no hypnozoite treatment (chloroquine (CQ)), Outcome 5: Recurrent *P. vivax* parasitaemia by 6 months (worst-case scenario)

| Study or Subgroup       | TQ + CQ | CQ alone | Risk Ratio |
|-------------------------|---------|----------|------------|
|                         | Events  | Total    | Events     | Total    | Weight | M-H, Random, 95% CI |
| Lacerda 2019            | 95      | 260      | 92         | 133      | 57.2%   | 0.53 [0.43, 0.64] |
| Llanos-Cuestas 2014     | 7       | 57       | 31         | 54       | 42.8%   | 0.21 [0.10, 0.44] |
| Total (95% CI)          | 317     | 187      | 100.0%     | 102      | 0.36 [0.14, 0.90] |
| Heterogeneity:          |         |          |            |          |         | Tau² = 0.37; Chi² = 6.02, df = 1 (P = 0.01); I² = 83% |
| Test for overall effect |         |          |            |          |         | Z = 2.19 (P = 0.03) |
| Test for subgroup       |         |          |            |          |         | differences: Not applicable |

### Analysis 1.6. Comparison 1: Tafenoquine (TQ) 300 mg single dose versus no hypnozoite treatment (chloroquine (CQ)), Outcome 6: Recurrent *P. vivax* parasitaemia by region – Asia

| Study or Subgroup       | TQ + CQ | CQ alone | Risk Ratio |
|-------------------------|---------|----------|------------|
|                         | Events  | Total    | Events     | Total    | Weight | M-H, Fixed, 95% CI |
| Lacerda 2019            | 19      | 50       | 18         | 26       | 74.1%   | 0.55 [0.35, 0.85] |
| Llanos-Cuestas 2014     | 1       | 28       | 8          | 26       | 25.9%   | 0.12 [0.02, 0.87] |
| Total (95% CI)          | 78      | 52       | 100.0%     | 20       | 0.44 [0.28, 0.69] |
| Heterogeneity:          |         |          |            |          |         | Chi² = 2.72, df = 1 (P = 0.10); I² = 63% |
| Test for overall effect |         |          |            |          |         | Z = 3.60 (P = 0.0003) |
| Test for subgroup       |         |          |            |          |         | differences: Not applicable |

### Analysis 1.7. Comparison 1: Tafenoquine (TQ) 300 mg single dose versus no hypnozoite treatment (chloroquine (CQ)), Outcome 7: Recurrent *P. vivax* parasitaemia by region – Africa

| Study or Subgroup       | TQ + CQ | CQ alone | Risk Ratio |
|-------------------------|---------|----------|------------|
|                         | Events  | Total    | Events     | Total    | Weight | M-H, Fixed, 95% CI |
| Lacerda 2019            | 6       | 28       | 8          | 14       | 100.0% | 0.38 [0.16, 0.87] |
| Total (95% CI)          | 28      | 14       | 100.0%     | 6        | 0.38 [0.16, 0.87] |
| Heterogeneity:          |         |          |            |          |         | Not applicable |
| Test for overall effect |         |          |            |          |         | Z = 2.28 (P = 0.02) |
| Test for subgroup       |         |          |            |          |         | differences: Not applicable |
Analysis 1.8. Comparison 1: Tafenoquine (TQ) 300 mg single dose versus no hypnozoite treatment (chloroquine (CQ)), Outcome 8: Recurrent *P. vivax* parasitaemia by region – South America

| Study or Subgroup | TQ + CQ | CQ alone | Risk Ratio | Risk Ratio |
|-------------------|---------|----------|------------|------------|
|                   | Events  | Total    |            | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Lacerda 2019      | 60      | 182      | 93         | 77.8%       | 0.49 [0.38, 0.64]   |
| Llanos-Cuentas 2014 | 5       | 29       | 23         | 28          | 22.2%               | 0.21 [0.09, 0.47]   |
| Total (95% CI)    | 65      | 211      | 121        | 100.0%      | 0.43 [0.34, 0.55]   |

Heterogeneity: *Chi² = 4.12, df = 1 (P = 0.04); I² = 76%*
Test for overall effect: *Z = 6.72 (P < 0.00001)*
Test for subgroup differences: Not applicable

Comparison 2. Tafenoquine (TQ) 300 mg single dose versus primaquine (PQ) 15 mg/day for 14 days (chloroquine (CQ))

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---------------------------|----------------|---------------------|--------------------|-------------|
| 2.1 Recurrent *P. vivax* parasitaemia by 6 months (intention to treat) | 3 | 747 | Risk Ratio (M-H, Fixed, 95% CI) | 1.04 [0.80, 1.34] |
| 2.2 Serious adverse events | 3 | 747 | Risk Ratio (M-H, Fixed, 95% CI) | 1.41 [0.70, 2.83] |
| 2.3 Adverse events by type | 3 | 747 | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 2.3.1 Any adverse event | 3 | 747 | Risk Ratio (M-H, Fixed, 95% CI) | 1.01 [0.89, 1.14] |
| 2.3.2 Abdominal pain | 3 | 747 | Risk Ratio (M-H, Fixed, 95% CI) | 1.05 [0.56, 1.97] |
| 2.3.3 Nausea | 3 | 747 | Risk Ratio (M-H, Fixed, 95% CI) | 1.14 [0.61, 2.13] |
| 2.3.4 Vomiting | 3 | 747 | Risk Ratio (M-H, Fixed, 95% CI) | 0.93 [0.56, 1.56] |
| 2.3.5 Diarrhoea | 3 | 747 | Risk Ratio (M-H, Fixed, 95% CI) | 1.43 [0.68, 3.01] |
| 2.3.6 Vertigo/dizziness | 3 | 747 | Risk Ratio (M-H, Fixed, 95% CI) | 1.03 [0.68, 1.55] |
| 2.3.7 Headache | 3 | 747 | Risk Ratio (M-H, Fixed, 95% CI) | 0.83 [0.56, 1.25] |
| 2.3.8 Arthralgia | 2 | 358 | Risk Ratio (M-H, Fixed, 95% CI) | 2.46 [0.39, 15.53] |
| 2.3.9 Rash/pruritus | 3 | 747 | Risk Ratio (M-H, Fixed, 95% CI) | 1.18 [0.70, 1.99] |
| 2.3.10 Myalgia | 2 | 358 | Risk Ratio (M-H, Fixed, 95% CI) | 0.67 [0.33, 1.34] |
| 2.3.11 Cough | 2 | 358 | Risk Ratio (M-H, Fixed, 95% CI) | 0.74 [0.25, 2.19] |
| 2.3.12 QT prolongation | 3 | 747 | Risk Ratio (M-H, Fixed, 95% CI) | 0.53 [0.13, 2.09] |
| 2.3.13 Anaemia/drop in haemoglobin | 3 | 747 | Risk Ratio (M-H, Fixed, 95% CI) | 2.55 [0.86, 7.60] |
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---------------------------|----------------|---------------------|--------------------|-------------|
| 2.3.14 High creatinine phosphokinase | 2 | 358 | Risk Ratio (M-H, Fixed, 95% CI) | 1.15 [0.39, 3.36] |
| 2.3.15 High alanine aminotransferase | 3 | 747 | Risk Ratio (M-H, Fixed, 95% CI) | 0.98 [0.39, 2.44] |
| 2.4 Recurrent \( P \) vivax parasitaemia by 6 months (per protocol) | 3 | 516 | Risk Ratio (M-H, Fixed, 95% CI) | 1.08 [0.83, 1.39] |
| 2.5 Recurrent \( P \) vivax parasitaemia by 6 months (worst-case scenario) | 3 | 747 | Risk Ratio (M-H, Fixed, 95% CI) | 1.01 [0.80, 1.27] |
| 2.6 Recurrent \( P \) vivax parasitaemia by region – South America | 3 | 516 | Risk Ratio (M-H, Fixed, 95% CI) | 0.88 [0.67, 1.15] |
| 2.7 Recurrent \( P \) vivax parasitaemia by region – Asia | 3 | 190 | Risk Ratio (M-H, Fixed, 95% CI) | 2.88 [1.15, 7.24] |
| 2.8 Recurrent \( P \) vivax parasitaemia by region – Africa | 1 | 41 | Risk Ratio (M-H, Fixed, 95% CI) | 1.39 [0.32, 5.99] |

**Analysis 2.1. Comparison 2: Tafenoquine (TQ) 300 mg single dose versus primaquine (PQ) 15 mg/day for 14 days (chloroquine (CQ)), Outcome 1: Recurrent \( P \) vivax parasitaemia by 6 months (intention to treat)**

| Study or Subgroup | TQ + CQ Events | TQ + CQ Total | PQ + CQ Events | PQ + CQ Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|----------------|--------------|----------------|--------------|--------|-----------------------------|
| Lacerda 2019      | 85             | 260          | 36             | 129          | 55.1%  | 1.17 [0.84, 1.63]           |
| Llanos-Cuentas 2014 | 6              | 57           | 12             | 50           | 14.6%  | 0.44 [0.18, 1.08]           |
| Llanos-Cuentas 2019 | 42             | 166          | 20             | 85           | 30.3%  | 1.08 [0.68, 1.71]           |
| Total (95% CI)    | 483            | 264          | 100.0%         |              | 1.04 [0.80, 1.34]           |

Total events: 133

Heterogeneity: Chi² = 4.04, df = 2 (P = 0.13); I² = 51%

Test for overall effect: Z = 0.27 (P = 0.79)

Test for subgroup differences: Not applicable
### Analysis 2.2. Comparison 2: Tafenoquine (TQ) 300 mg single dose versus primaquine (PQ) 15 mg/day for 14 days (chloroquine (CQ)), Outcome 2: Serious adverse events

| Study or Subgroup | TQ + CQ Events | TQ + CQ Total | PQ + CQ Events | PQ + CQ Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|----------------|---------------|----------------|---------------|--------|-----------------------------|
| Lacerda 2019      | 21             | 260           | 4              | 129           | 37.8%  | 2.60 [0.91, 7.43]           |
| Llanos-Cuentas 2014 | 2              | 57            | 7              | 70            | 52.8%  | 0.25 [0.05, 1.15]           |
| Llanos-Cuentas 2019 | 6              | 166           | 1              | 85            | 9.4%   | 3.07 [0.38, 25.11]          |
| **Total (95% CI)** | **483**        | **264**       | **129**        | **483**       | 100.0% | **1.41 [0.70, 2.83]**       |

Total events: 291

Heterogeneity: Chi² = 6.77, df = 2 (P = 0.03); I² = 70%

Test for overall effect: Z = 0.95 (P = 0.34)

Test for subgroup differences: Not applicable
### Analysis 2.3. Comparison 2: Tafenoquine (TQ) 300 mg single dose versus primaquine (PQ) 15 mg/day for 14 days (chloroquine (CQ)), Outcome 3: Adverse events by type

#### Study or Subgroup

| TQ + CQ | PQ + CQ | Risk Ratio M-H, Fixed, 95% CI |
|---------|---------|-------------------------------|
| Events  | Total   | Events | Total | Weight | M-H, Fixed, 95% CI |

#### 2.3.1 Any adverse event

- **Lacerda 2019**: 127 events, 60 participants, weight 40.3%
- **Llanos-Cuentas 2014**: 38 events, 50 participants, weight 41.1%
- **Llanos-Cuentas 2019**: 119 events, 85 participants, weight 42.5%

Subtotal (95% CI): 483 events, 264 participants, weight 100.0%

- Total events: 284
- Subtotal: 156

Heterogeneity: Chi² = 0.70, df = 2 (P = 0.71); I² = 0%

Test for overall effect: Z = 0.11 (P = 0.91)

#### 2.3.2 Abdominal pain

- **Lacerda 2019**: 8 events, 6 participants, weight 44.3%
- **Llanos-Cuentas 2014**: 6 events, 5 participants, weight 41.1%
- **Llanos-Cuentas 2019**: 12 events, 8 participants, weight 14.6%

Subtotal (95% CI): 483 events, 264 participants, weight 100.0%

- Total events: 26
- Subtotal: 15

Heterogeneity: Chi² = 3.21, df = 2 (P = 0.20); I² = 38%

Test for overall effect: Z = 0.15 (P = 0.88)

#### 2.3.3 Nausea

- **Lacerda 2019**: 16 events, 7 participants, weight 53.2%
- **Llanos-Cuentas 2014**: 5 events, 4 participants, weight 24.2%
- **Llanos-Cuentas 2019**: 7 events, 8 participants, weight 22.6%

Subtotal (95% CI): 483 events, 264 participants, weight 100.0%

- Total events: 28
- Subtotal: 14

Heterogeneity: Chi² = 0.01, df = 2 (P = 1.00); I² = 0%

Test for overall effect: Z = 0.41 (P = 0.68)

#### 2.3.4 Vomiting

- **Lacerda 2019**: 15 events, 9 participants, weight 43.1%
- **Llanos-Cuentas 2014**: 2 events, 5 participants, weight 19.1%
- **Llanos-Cuentas 2019**: 21 events, 8 participants, weight 37.9%

Subtotal (95% CI): 483 events, 264 participants, weight 100.0%

- Total events: 38
- Subtotal: 22

Heterogeneity: Chi² = 2.39, df = 2 (P = 0.30); I² = 16%

Test for overall effect: Z = 0.27 (P = 0.79)

#### 2.3.5 Diarrhoea

- **Lacerda 2019**: 10 events, 3 participants, weight 32.8%
- **Llanos-Cuentas 2014**: 3 events, 4 participants, weight 34.8%
- **Llanos-Cuentas 2019**: 12 events, 3 participants, weight 32.4%

Subtotal (95% CI): 483 events, 264 participants, weight 100.0%

- Total events: 25
- Subtotal: 10

Heterogeneity: Chi² = 1.48, df = 2 (P = 0.48); I² = 0%

Test for overall effect: Z = 0.96 (P = 0.34)

#### 2.3.6 Vertigo/dizziness

- **Lacerda 2019**: 22 events, 8 participants, weight 27.8%
- **Llanos-Cuentas 2014**: 5 events, 5 participants, weight 13.8%
- **Llanos-Cuentas 2019**: 30 events, 17 participants, weight 58.4%

Subtotal (95% CI): 483 events, 264 participants, weight 100.0%

- Total events: 57
- Subtotal: 30

Heterogeneity: Chi² = 0.80, df = 2 (P = 0.67); I² = 0%
Analysis 2.3. (Continued)

Total events: 57
Heterogeneity: \( \chi^2 = 0.80, \text{df} = 2 (P = 0.67); I^2 = 0\% \)
Test for overall effect: \( Z = 0.13 (P = 0.90) \)

2.3.7 Headache

Lacerda 2019 12 260 5 129 15.6\% 1.19 [0.43, 3.31]
Llanos-Cuentas 2014 10 57 14 50 34.9\% 0.63 [0.31, 1.28]
Llanos-Cuentas 2019 27 166 16 85 49.5\% 0.86 [0.49, 1.51]
Subtotal (95\% CI) 483 264 100.0\% 0.83 [0.56, 1.25]

Total events: 49
Heterogeneity: \( \chi^2 = 1.09, \text{df} = 2 (P = 0.58); I^2 = 0\% \)
Test for overall effect: \( Z = 0.89 (P = 0.37) \)

2.3.8 Arthralgia

Llanos-Cuentas 2014 2 57 1 50 61.7\% 1.75 [0.16, 18.77]
Llanos-Cuentas 2019 3 166 0 85 38.3\% 3.60 [0.19, 68.99]
Subtotal (95\% CI) 223 135 100.0\% 2.46 [0.39, 15.53]

Total events: 5
Heterogeneity: \( \chi^2 = 0.14, \text{df} = 1 (P = 0.71); I^2 = 0\% \)
Test for overall effect: \( Z = 0.96 (P = 0.34) \)

2.3.9 Rash/pruritus

Lacerda 2019 29 260 14 129 80.5\% 1.03 [0.56, 1.88]
Llanos-Cuentas 2014 8 57 3 50 13.8\% 2.34 [0.66, 8.34]
Llanos-Cuentas 2019 1 166 1 85 5.7\% 0.51 [0.03, 8.09]
Subtotal (95\% CI) 483 264 100.0\% 1.18 [0.70, 1.99]

Total events: 38
Heterogeneity: \( \chi^2 = 1.67, \text{df} = 2 (P = 0.43); I^2 = 0\% \)
Test for overall effect: \( Z = 0.61 (P = 0.54) \)

2.3.10 Myalgia

Llanos-Cuentas 2014 1 57 2 50 12.8\% 0.44 [0.04, 4.69]
Llanos-Cuentas 2019 15 166 11 85 87.2\% 0.70 [0.34, 1.45]
Subtotal (95\% CI) 223 135 100.0\% 0.67 [0.33, 1.34]

Total events: 16
Heterogeneity: \( \chi^2 = 0.14, \text{df} = 1 (P = 0.71); I^2 = 0\% \)
Test for overall effect: \( Z = 1.14 (P = 0.25) \)

2.3.11 Cough

Llanos-Cuentas 2014 4 57 4 50 61.7\% 0.88 [0.23, 3.33]
Llanos-Cuentas 2019 2 166 2 85 38.3\% 0.51 [0.07, 3.57]
Subtotal (95\% CI) 223 135 100.0\% 0.74 [0.25, 2.19]

Total events: 6
Heterogeneity: \( \chi^2 = 0.20, \text{df} = 1 (P = 0.65); I^2 = 0\% \)
Test for overall effect: \( Z = 0.55 (P = 0.58) \)

2.3.12 QT prolongation

Lacerda 2019 0 260 0 129 Not estimable
Llanos-Cuentas 2014 3 57 5 50 100.0\% 0.53 [0.13, 2.09]
Llanos-Cuentas 2019 0 166 0 85 Not estimable
Subtotal (95\% CI) 483 264 100.0\% 0.53 [0.13, 2.09]

Total events: 3
Heterogeneity: Not applicable
Test for overall effect: \( Z = 0.91 (P = 0.36) \)

3.3.12 Anaemia/drop in haemoglobin

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

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### Analysis 2.3. (Continued)

#### 2.3.13 Anaemia/drop in haemoglobin

| Study or Subgroup | TQ + CQ | PQ + CQ | Weight | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|---------|---------|--------|-----------------------------|
| Lacerda 2019      | 14      | 260     | 2      | 129 34.9% 4.90 (0.25, 9.90)  |
| Llanos-Cuentas 2014 | 1      | 57      | 1      | 50 21.0% 0.88 (0.06, 13.66) |
| Llanos-Cuentas 2019 | 4      | 166     | 1      | 85 26.1% 2.05 (0.23, 18.04) |
| **Subtotal (95% CI)** | **483** | **264** | **199** | **100.0%** 1.15 (0.39, 2.36) |
| Total events: | 19      | 4       | 4       | |
| Heterogeneity: Chi² = 0.79, df = 2 (P = 0.67); I² = 0% |
| Test for overall effect: Z = 0.91 (P = 0.36) |

#### 2.3.14 High creatinine phosphokinase

| Study or Subgroup | TQ + CQ | PQ + CQ | Weight | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|---------|---------|--------|-----------------------------|
| Llanos-Cuentas 2014 | 5      | 57      | 3      | 50 54.7% 1.46 (0.37, 5.81)  |
| Llanos-Cuentas 2019 | 3      | 166     | 2      | 85 45.3% 0.77 (0.13, 4.51)  |
| **Subtotal (95% CI)** | **223** | **135** | **107** | **100.0%** 1.15 (0.39, 2.36) |
| Total events: | 8       | 5       | 5       | |
| Heterogeneity: Chi² = 0.32, df = 1 (P = 0.57); I² = 0% |
| Test for overall effect: Z = 0.25 (P = 0.80) |

#### 2.3.15 High alanine aminotransferase

| Study or Subgroup | TQ + CQ | PQ + CQ | Weight | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|---------|---------|--------|-----------------------------|
| Lacerda 2019      | 6      | 260     | 3      | 129 44.9% 0.99 (0.25, 3.90)  |
| Llanos-Cuentas 2014 | 4      | 57      | 4      | 50 47.7% 0.88 (0.23, 3.33)  |
| Llanos-Cuentas 2019 | 1      | 166     | 0      | 85 7.4% 1.54 (0.06, 37.52)  |
| **Subtotal (95% CI)** | **483** | **264** | **199** | **100.0%** 0.98 (0.39, 2.44) |
| Total events: | 11      | 7       | 7       | |
| Heterogeneity: Chi² = 0.10, df = 2 (P = 0.95); I² = 0% |
| Test for overall effect: Z = 0.05 (P = 0.96) |

Test for subgroup differences: Chi² = 14.87, df = 14 (P = 0.90)

### Analysis 2.4. Comparison 2: Tafenoquine (TQ) 300 mg single dose versus primaquine (PQ) 15 mg/day for 14 days (chloroquine (CQ)), Outcome 4: Recurrent P vivax parasitaemia by 6 months (per protocol)

| Study or Subgroup | TQ + CQ Events | PQ + CQ Events | Weight | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|---------------|---------------|--------|-----------------------------|
| Lacerda 2019      | 66 199        | 126 199       | 77 51.5% 1.30 (0.95, 1.79)  |
| Llanos-Cuentas 2014 | 6      | 56        | 12 47 17.5% 0.42 (0.17, 1.03) |
| Llanos-Cuentas 2019 | 35     | 135       | 18 75 31.0% 1.08 (0.66, 1.77) |
| **Total (95% CI)** | **317** | **199**     | **107** | **100.0%** 1.08 (0.83, 1.39) |
| Total events: | 107      | 61       | 61       | |
| Heterogeneity: Chi² = 5.55, df = 2 (P = 0.06); I² = 64% |
| Test for overall effect: Z = 0.58 (P = 0.56) |
| Test for subgroup differences: Not applicable |
### Analysis 2.5. Comparison 2: Tafenoquine (TQ) 300 mg single dose versus primaquine (PQ) 15 mg/day for 14 days (chloroquine (CQ)), Outcome 5: Recurrent *P vivax* parasitaemia by 6 months (worst-case scenario)

| Study or Subgroup | TQ + CQ | PQ + CQ | Risk Ratio |
|-------------------|---------|---------|------------|
|                    | Total   | Total   | M-H, Fixed, 95% CI |
| Lacerda 2019       | 95      | 260     | 1.12 [0.84, 1.51]  |
| Llanos-Cuentas 2014| 7       | 57      | 0.41 [0.18, 0.92]  |
| Llanos-Cuentas 2019| 48      | 166     | 1.12 [0.73, 1.72]  |
| Total (95% CI)     | 483     | 264     | 1.01 [0.80, 1.27]  |

Heterogeneity: Ch² = 5.45, df = 2 (P = 0.07); I² = 63%
Test for overall effect: Z = 0.07 (P = 0.94)
Test for subgroup differences: Not applicable

### Analysis 2.6. Comparison 2: Tafenoquine (TQ) 300 mg single dose versus primaquine (PQ) 15 mg/day for 14 days (chloroquine (CQ)), Outcome 6: Recurrent *P vivax* parasitaemia by region – South America

| Study or Subgroup | TQ + CQ | PQ + CQ | Risk Ratio |
|-------------------|---------|---------|------------|
|                    | Total   | Total   | M-H, Fixed, 95% CI |
| Lacerda 2019       | 60      | 182     | 0.93 [0.66, 1.31]  |
| Llanos-Cuentas 2014| 5       | 29      | 0.44 [0.17, 1.10]  |
| Llanos-Cuentas 2019| 36      | 125     | 0.99 [0.62, 1.60]  |
| Total (95% CI)     | 336     | 180     | 0.88 [0.67, 1.15]  |

Heterogeneity: Ch² = 2.53, df = 2 (P = 0.28); I² = 21%
Test for overall effect: Z = 0.96 (P = 0.34)
Test for subgroup differences: Not applicable

### Analysis 2.7. Comparison 2: Tafenoquine (TQ) 300 mg single dose versus primaquine (PQ) 15 mg/day for 14 days (chloroquine (CQ)), Outcome 7: Recurrent *P vivax* parasitaemia by region – Asia

| Study or Subgroup | TQ + CQ | PQ + CQ | Risk Ratio |
|-------------------|---------|---------|------------|
|                    | Total   | Total   | M-H, Fixed, 95% CI |
| Lacerda 2019       | 19      | 50      | 4.94 [1.25, 19.59] |
| Llanos-Cuentas 2014| 1       | 28      | 0.79 [0.05, 11.87] |
| Llanos-Cuentas 2019| 6       | 41      | 1.68 [0.37, 7.67]  |
| Total (95% CI)     | 119     | 71      | 2.88 [1.15, 7.24]  |

Heterogeneity: Ch² = 1.95, df = 2 (P = 0.38); I² = 0%
Test for overall effect: Z = 2.25 (P = 0.02)
Test for subgroup differences: Not applicable

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

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Analysis 2.8. Comparison 2: Tafenoquine (TQ) 300 mg single dose versus primaquine (PQ) 15 mg/day for 14 days (chloroquine (CQ)), Outcome 8: Recurrent \textit{P} \textit{vivax} parasitaemia by region – Africa

| Study or Subgroup | TQ + CQ | PQ + CQ | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|---------|---------|-----------------------------|
| Events            | Total   | Events  | Total                       | Weight |
| Lacerda 2019      | 6       | 28      | 13                           | 100.0% | 1.39 [0.32, 5.99] |
| Total (95% CI)    | 28      | 13      | 100.0%                       | 1.39 [0.32, 5.99] |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.66)
Test for subgroup differences: Not applicable

**ADDITIONAL TABLES**

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

| Trial            | Trial groups and tafenoquine doses                                                                 |
|------------------|----------------------------------------------------------------------------------------------------|
| Lacerda 2019     | • TQ 300 mg single dose                                                                               |
|                  | • PQ 15 mg/day for 14 days                                                                           |
|                  | • Placebo                                                                                           |
|                  | In all trials, all participants received the standard treatment of CQ 1500 mg over 3 days to clear the initial parasitaemia. |
| Llanos-Cuentas 2014 | • TQ 50 mg single dose                                                                               |
|                  | • TQ 100 mg single dose                                                                               |
|                  | • TQ 300 mg single dose                                                                               |
|                  | • TQ 600 mg as a single dose                                                                         |
|                  | • No TQ; CQ followed by PQ 15 mg/day for 14 days                                                     |
|                  | • CQ followed by placebo                                                                             |
|                  | There were no reports of CQ resistance.                                                             |
| Llanos-Cuentas 2019 | • TQ 300 mg single dose                                                                               |
|                  | • PQ 15 mg/day for 14 days                                                                           |

CQ: chloroquine; PQ: primaquine; TQ: tafenoquine.

**Table 2. Maximum methaemoglobin percentages reported in each trial with tafenoquine 300 mg single dose and standard-dose primaquine**

| Trial            | Drug | Maximum methaemoglobin percentage |
|------------------|------|-----------------------------------|
| Lacerda 2019     | TQ   | 13%                               |
|                  | PQ   | 14.7%                             |
| Llanos-Cuentas 2014 | TQ   | Not reported for TQ 300 mg group  |
| Llanos-Cuentas 2019 | TQ   | 1.9%                              |
|                  | PQ   | 4.1%                              |

PQ: primaquine; TQ: tafenoquine.
APPENDICES

Appendix 1. Search strategy

| Search set | CIDG SR | CENTRAL | MEDLINE | Embase | LILACS | 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 |
| 4          |          |          |          |        | 3 and 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).

WHAT'S NEW

| Date          | Event                                           | Description                                                                                                                                 |
|---------------|-------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| 2 September 2020 | New search has been performed                   | We updated the date of search to 3 June 2020.                                                                                           |
| 2 September 2020 | New citation required and conclusions have changed | This is an update of the previous review version with new study data. The US FDA has licenced tafenoquine 300 mg single dose for preventing relapse in vivax malaria. This update includes studies at this dose, excluding comparisons at other doses from the earlier dose-ranging trials. |

HISTORY

Protocol first published: Issue 3, 2013
Review first published: Issue 4, 2015

CONTRIBUTIONS OF AUTHORS

CR, SR, and SDF independently screened all articles to identify relevant trials for inclusion in the review.
CR, SR, and SDF 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.
All review authors read and approved the final draft of the review before submission for publication.
DEclarations of Interest
SR: none.
CR: none.
SDF: none.

Sources of Support
Internal sources
• Liverpool School of Tropical Medicine, UK
• University of New South Wales, Australia
  Provided institutional access to databases

External sources
• Foreign, Commonwealth and Development Office (FCDO), UK
  Project number 300342-104
• NHS Lincolnshire Trust, UK
  Provided access to databases
• National Health and Medical Research Council, Australia

CR is supported by a NHMRC Investigator grant (no. 1173666)

Differences Between Protocol and Review
Differences between review and review update
The previous version of this review, Rajapakse 2013, included several dose-ranging studies that had tested TQ against CQ only or PQ plus CQ (Llanos-Cuentas 2014; Walsh 1999; Walsh 2004a). We concluded that TQ at a single dose above 300 mg is probably more effective than CQ only for relapse prevention (moderate-certainty evidence). We also concluded that TQ 300 mg single dose may be as effective as PQ 15 mg/day for 14 days in relapse prevention while TQ 600 mg single dose may be better (low-certainty evidence). TQ may have little or no difference with regard to adverse event profile compared to CQ only or PQ plus CQ.

Since the publication of Rajapakse 2013, TQ has been licensed by the FDA (USA) for relapse prevention at 300 mg single dose.

This review update only considers the approved TQ 300 mg single dose for all comparisons. Hence both Walsh 1999 and Walsh 2004a were excluded. Two new studies published in 2019 were included (Lacerda 2019; Llanos-Cuentas 2019). The findings for the 300 mg single dose is similar to the previous review except that the certainty of evidence has been upgraded to moderate for the TQ versus PQ comparison and for both adverse event comparisons (TQ plus CQ versus CQ; TQ plus CQ versus PQ plus CQ).

Index Terms
Medical Subject Headings (MeSH)
Aminoquinolines [*administration & dosage] [adverse effects]; Antimalarials [*administration & dosage] [adverse effects]; Chloroquine [administration & dosage] [adverse effects]; Drug Administration Schedule; Glucosephosphate Dehydrogenase Deficiency [complications]; Malaria, Vivax [*drug therapy]; Parasitemia [drug therapy]; Placebos; Primaquine [*administration & dosage] [adverse effects]; Randomized Controlled Trials as Topic; Recurrence; *Secondary Prevention

MeSH check words
Adult; Humans

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