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

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

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the efficacy and safety of alternative primaquine regimens for radical cure of *P. vivax malaria* compared to the standard 14 days of primaquine 0.25 mg/kg/day.

BACKGROUND

Malaria is a potentially life-threatening disease caused by the *Plasmodium* parasite, which is transmitted by the bite of an infected female *Anopheles* mosquito. There are five species of Plasmodium malaria parasites that can cause malaria disease in humans, of these, *Plasmodium vivax* and *Plasmodium falciparum* are generally recognized as the most significant threat to human health (WHO 2016a). In 2015, there were an estimated 212 million cases of malaria worldwide, with 429,000 attributable deaths (WHO 2016b). By 2030, the World Health Organization (WHO) aims to reduce malaria case load and mortality by at least 90% (WHO 2016a).

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

Description of the condition

P. vivax infection caused an estimated 13.8 million cases of malaria in 2015 and is responsible for almost half of the global cases of malaria outside of Sub-Saharan Africa (WHO 2015c). The geographical distribution of *P. vivax* malaria is more widespread than any of the other forms of human malaria - around 35% of the world's population is thought to be at risk, with two-thirds of cases occurring in South-East Asia (WHO 2015a). Co-infection with *P. falciparum* is also common in many regions (Kumar 2007; Mueller 2009). As malaria control accelerates, the *P. vivax* proportion in co-endemic areas tends to rise compared to that of *P. falciparum*, which highlights the importance and challenge of this infection (John 2012).

P. vivax is also important as many countries progress towards malaria elimination, as it is increasingly recognized as a potential roadblock to eradication (Cibulskis 2015; Bassat 2016). Despite a reduction in the number of cases of *P. vivax* malaria over the past 20 years, it has several characteristics that enable it to evade control (Newby 2016). The early appearance of gametocytes in the blood, often prior to symptoms of malaria, increases the chance of onward transmission by mosquitoes (WHO 2015a). *P. vivax* differs to *P. falciparum* in that as well as having a blood stage schizontal infection, hypnozoites develop in the liver that can be dormant for weeks to months before developing into an infection (Llanos-Cuentas 2014). It is not known what triggers these relapses. There is difficulty in distinguishing between relapse, recrudescence (subpar treatment of the initial blood stage infection), and reinfection (new infection with *P. vivax*) (Betuela 2014). A study in Papua New Guinea suggested that relapses cause four-fifths of *P. vivax* infections, so are important in sustaining transmission (Robinson 2015). Parasites show high genetic diversity, even in countries that are at malaria elimination stage, where you would expect reduced transmission to result in reduced diversity (Koepfli 2015). *P. vivax* is likely underestimated worldwide as the dormant liver stage is not detected in routine surveys (Gething 2012). Submicroscopic infections (asymptomatic infection reservoirs) may also lead to underdiagnosis or misdiagnosis. A systematic review showed that across all study sites the polymerase chain reaction (PCR) prevalence of *P. vivax* was significantly higher than that identified by light microscopy (Cheng 2015). The effect that this may have on *P. vivax* malaria studies is unclear. There are different strains of *P. vivax*, which have varying relapse patterns, and this can further complicate matters (White 2016). The Chesson, or tropical, strain is commonly found in South East Asia, Oceania, and parts of the Indian subcontinent and has the shortest relapse interval of about three weeks (if untreated), while the temperate strain may relapse after months (John 2012).

Currently primaquine, an 8-aminoquinoline, is the only drug available on the market for treating the hypnozoite stage of infection (Ashley 2014). One of the main barriers in *P. vivax* treatment is the reluctance to use primaquine due to it causing haemolysis in patients with glucose-6-phosphate-dehydrogenase (G6PD) deficiency. G6PD deficiency is the commonest enzyme deficiency worldwide and affects red blood cells, by leading to their premature lysis (Nkhoma 2009). G6PD deficiency is common in countries where *P. vivax* malaria is endemic, with an estimated population prevalence of 8% (Howes 2012). Within G6PD deficiency there are differing phenotypes, meaning some people may be mildly sensitive to primaquine, while others may be very sensitive and experience life threatening haemolysis (Baird 2015a), which explains the varying responses to primaquine. In many countries where *P. vivax* is pre-dominant, locally available testing for G6PD is not available (Baird 2015b). A newer alternative, tafenoquine, another 8-aminoquinoline, has completed phase III trials and is on track for submission to the Food and Drug Administration (FDA) in 2017 (MMV 2016). Tafenoquine has shown promise in reducing relapses, but there are increased safety concerns in patients with undiagnosed G6PD deficiency compared to primaquine, due to its longer half-life (Rajapakse 2015).

Description of the intervention

People with *P. vivax* malaria require treatment with a blood stage antimalarial drug to treat the schizont infection, and a drug to treat the hypnozoite stage (radical cure). The WHO recommends treatment with either chloroquine or an artemisinin-based combination therapy (ACT) for the blood-stage infection, followed by treatment with 0.25 to 0.5 mg/kg primaquine for 14 days (WHO 2015b). ACTs and chloroquine have been shown to be effective and comparable in treating the blood stage infection of *P. vivax* malaria (Gogtay 2013). A previous Cochrane Review showed that primaquine regimes of five days or fewer had similar relapse rates to placebo or no primaquine. Of the comparisons included in the systematic review, a regime of 0.25 mg/kg (15 mg) a day of primaquine for 14 days had the lowest relapse rates of *P. vivax* infection (Galappaththy 2013). There were no trials at that time that compared higher doses of primaquine at 14 or seven days.

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

Adverse effects of primaquine include production of methaemoglobin, an oxidated state of haemoglobin which cannot transport oxygen to tissues. Methaemoglobinaemia (an abnormal build-up of methaemoglobin) can result in cyanosis when levels exceed 10% of the usual haemoglobin level (Vale 2009). As described above, primaquine causes haemolysis in people with G6PD deficiency, which leads to severe intravascular

haemolysis and anaemia (Ashley 2014). When taken on an empty stomach it can cause abdominal pain and gastrointestinal upset (Vale 2009). Primaquine cannot be given in pregnancy or early infancy as the G6PD status of the baby is unknown and there would be risk of haemolysis and possible termination if the foetus was G6PD-deficient. There is currently debate about whether the levels of primaquine in breast milk would be sufficient to cause haemolysis in a G6PD-deficient baby, but it is not recommended at this time.

How the intervention might work

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

has been suggestion of failure of the 0.25 mg/kg/14-day dosing regimen of primaquine for the Chesson strain of *P. vivax*, which is what was behind the suggestion of the increased dosing of 0.5 mg/kg/day. In the last review, Galappaththy 2013, there were no trials found which compared higher doses of primaquine to the 14-day regime. The WHO recommends a weekly dose of 0.75 mg/kg for eight weeks for patients with G6PD deficiency but the evidence for this is low quality as there are few high-quality trials (WHO 2015b).

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

Figure 1. Logic framework: treatment outcome pathways in Plasmodium vivax liver hypnozoite infection
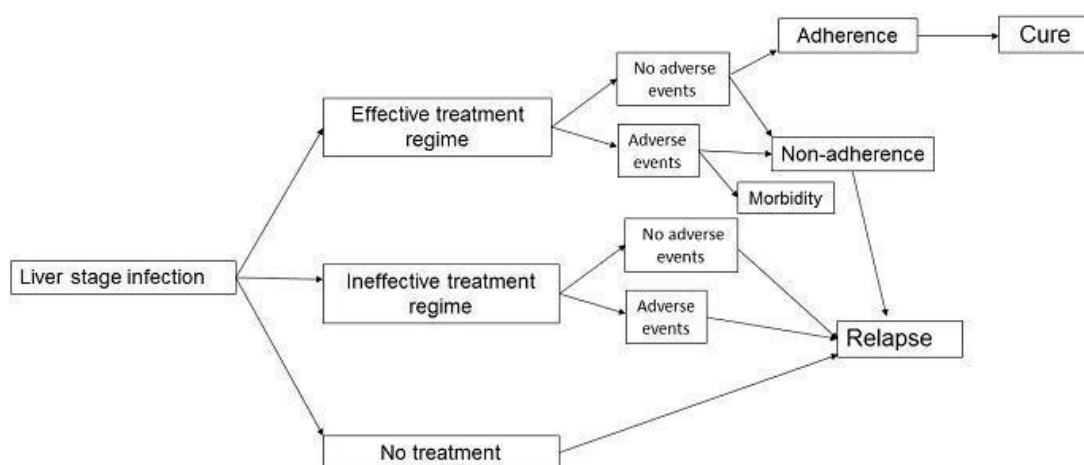
It has long been suggested that it may be the total dose of primaquine that is important in treatment of the hypnozoite stage rather than the length of the course (Schmidt 1977). If a higher dose of primaquine could be administered safely over a shorter period of time, this may improve adherence rates, thus reducing relapse rates and morbidity and mortality resulting from *P. vivax* infection. There are small trials from the 1970s that suggest

that shorter, higher dose regimes were as efficacious as the 14-day courses (Clyde 1977), and there is also evidence of similar efficacy (Saint-Yves 1977). At the time of the last review (Galappaththy 2013) there were no recent large high-quality trials that had investigated the use of higher doses given over seven days. We plan to include any such trials in this Cochrane Review.

Why it is important to do this review

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

From the previous systematic review on primaquine with chloroquine for radical cure (Galappaththy 2013), we know 14 days of 0.25 mg/kg or 15 mg/day (210 mg total dose) is better than shorter regimens of similar daily doses and placebo. A major problem with the radical cure of *P. vivax* is difficulty with the adherence of the 14-day course of primaquine, which has led to many countries shortening the regime. Peru was once such example, although a study revealed that patients often still discontinued the therapy after around three days, when they started to feel better (Grietens 2010). A study that compared directly observed therapy (DOT) for 14 days of primaquine, versus non-DOT primaquine found that the vivax relapse rate was significantly lower in the DOT group (Takeuchi 2010). These problems have led to a more urgent call for shorter treatment regimes. Various trials are investigating regimens that improves dosing and duration of treatment, to improve adherence and reduce the potential for incomplete treatment and development of resistance. As mentioned previously, the significance of the total cumulative primaquine dose given, rather than length of course, is one avenue of investigation. In areas where G6PD screening is present, using higher dosing regimes over shorter time periods, if at least similarly efficacious, could improve adherence and reduce morbidity associated with *P. vivax* parasitaemia.

WHO guidelines suggest a higher dosing regimen of primaquine for areas with the tropical strain of *P. vivax* (WHO 2015b), although the previous Cochrane Review, Galappaththy 2013, did not find any trials that assessed this. Therefore investigating the evidence base for this is important. The 2015 WHO guidelines also suggest an alternate dosing regimen of weekly primaquine, which may be safer in patients with G6PD. In the last Cochrane Review, only data from one trial assessed this, so it will be useful to see if there is any further evidence to substantiate this guidance. In this Cochrane Review, we will exclude comparisons between blood stage drug (chloroquine/ACT) with and without primaquine as the rationale for primaquine use has been sufficiently demonstrated in a previous Cochrane Review (Galappaththy 2013). Similarly, we will not include comparisons that look at different blood stage drugs compared using the same dose of primaquine as an update to an existing Cochrane Review will address this (Gogtay 2013). However, we will stratify our results according to partner drug, as there is increasing evidence that primaquine is metabolized via the CYP2D6 pathway and efficacy may thus be affected if the blood stage antimalarial drug is a CYP2D6 inhibitor

(Bennett 2013). This review will exclude comparisons of regimens that do not use the control of 14 days of primaquine at 0.25 mg/kg/day. Also, it will not include comparisons of primaquine regimens of 0.25 mg/kg daily for less than 14 days as Galappaththy 2013 has already assessed these shorter, same daily dose regimens. Currently there is a lack of consensus among studies as to what the minimum time frame for follow-up of relapse in *P. vivax* malaria should be. The WHO guidance on clinical trials in malaria sets out standard follow-up for blood (or schizontal) stage infection as 28 days after treatment commencement, but has no clear definition on the follow-up period for radical cure in primaquine studies. It states that "follow up varies from three months to a year in the literature, and should be adapted to regional parasite characteristics" (WHO 2009). In a recent review, John 2012 described relapse of the tropical strain of *P. vivax* as typically three weeks, but this varies according to blood stage treatment: "three weeks following quinine therapy" and "six to eight weeks following chloroquine" (White 2011). With exposure to primaquine - even if radical cure is not achieved - relapses may be at longer intervals (Sutanto 2013). In the Cochrane Review (Galappaththy 2013), the period of follow-up was 30 days after starting primaquine treatment. Despite this, the definition of relapse used in the review was the presence of *P. vivax* parasites more than 28 to 30 days after the full course of primaquine in people living in a non-endemic area (Murphy 1993; Looareesuwan 1997). Because of the varying lengths of relapse time in *P. vivax* malaria, as well as the longer schizonticidal half-life in ACTs, 28 days from treatment commencement may not allow true assessment of radical cure. It also makes assessment of the weekly primaquine regime difficult, as the follow-up time is before the eight-week treatment course has finished. In this Cochrane Review we plan to assess parasitaemia at 3, 6, and 12 months follow-up, in keeping with WHO guidance. We intend to describe the length of follow-up across studies, and then group them into meaningful lengths of follow-up, depending on the regimen.

We intend to answer the following questions by comparing the new regimens to the standard regimen of 14 days of primaquine at 0.25 mg/kg (15 mg adult dose).

- Are higher doses (0.5 mg/kg or 30 mg primaquine/day for 14 days) more efficacious and safe compared to standard therapy (0.25 mg/kg/day for 14 days), in all areas, or only in areas where they are standard treatment (for tropical *P. vivax* strains in Asia, Pacific)?

- Are shorter, higher dose regimes (0.5 mg/kg or 30 mg primaquine/day for 7 days) as efficacious and safe compared to standard therapy (0.25 mg/kg/day for 14 days)?

- Are weekly dosing regimens (0.75 mg/kg or 45 mg/week for 8 weeks) as efficacious and safe compared to standard therapy (0.25 mg/kg/day for 14 days)?

OBJECTIVES

To assess the efficacy and safety of alternative primaquine regimens for radical cure of *P. vivax malaria* compared to the standard 14 days of primaquine 0.25 mg/kg/day.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCT). We will exclude quasi-RCTs.

Types of participants

Adults and children with confirmed clinical and parasitological (light microscopy or polymerase chain reaction (PCR), or both) diagnosis of *P. vivax* malaria. We will include trials that have excluded people with glucose-6-phosphate-dehydrogenase (G6PD) deficiency, and trials that included populations that had not been screened for G6PD deficiency.

Types of interventions

Intervention

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

- Higher daily doses for 14 days.
- Shorter regimens with the same total dose.
- Using weekly dosing regimens.

Control

Standard regimen of 14 days of primaquine at 0.25 mg/kg (15 mg adult dose) plus either chloroquine or an ACT.
We will include trials that use chloroquine or ACT as the treatment for blood-borne infection, and we will stratify by the schizonticidal agent.

Types of outcome measures

Primary outcomes

- *P. vivax* parasitaemia detected (by light microscopy or polymerase chain reaction (PCR), or both) at 3 months, 6 months, and 12 months follow-up.

Secondary outcomes

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

Adverse effects

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

Search methods for identification of studies

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

Electronic searches

We will search the following databases: the Cochrane Infectious Diseases Group (CIDG) Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library; MEDLINE (PubMed); Embase (OVID); and LILACS (BIREME), using the search terms detailed in Appendix 1 (Lefebvre 2011). We will also search the World Health Organization (WHO) International Clinical Trials Registry Platform (http://www.who.int/ictrp/search/en/) and ClinicalTrials.gov (https://clinicaltrials.gov/), to identify ongoing trials, using "vivax" and "primaquine" as search terms.

Searching other resources

We will check the reference lists of all studies identified by the above methods for other potentially relevant studies. We will contact researchers working in the field and the World Health Organization (WHO) for unpublished and ongoing trials. We will also search the reference lists and included studies of the Cochrane review by Galappaththy 2013.

Data collection and analysis

Selection of studies

Two review authors will independently screen the titles and abstracts of the search results to identify potentially eligible trials, and will code the articles as either 'retrieve' or 'do not retrieve'. We will obtain the full-text reports of potentially eligible trials and will assess them for inclusion in the review using a predesigned eligibility form based on the inclusion criteria. We will resolve discrepancies through discussion or, if required, we will consult a third review author. Where necessary we will contact the trial authors for clarification of trial methods. We will list the excluded trials and the reasons for exclusion in a 'Characteristics of excluded studies' table. Where there are multiple reports relating to the same trial, we will include all reports. However, we will only extract data from the most up-to-date report that includes the specified outcome. We will detail the trial selection process in a PRISMA diagram.

Data extraction and management

Two review authors will independently extract data from the included trials using a data extraction form, designed for this review, in keeping with Cochrane guidance (Higgins 2011).
For each included trial we plan to extract a minimum of the following data if available.

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

We will resolve any differences in data extraction through discussion and consult a third review author if there is any discrepancy. We will enter the extracted data into Review Manager 5 (RevMan 5) (RevMan 2014). We will contact the authors of primary trials in case of any doubts regarding missing data or methodological details of the trial. We will note the limitations in the included studies.
We will group comparisons as illustrated in Table 1.

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias of each included trial using the Cochrane 'Risk of bias' assessment tool, and discuss any differences of opinion. In the case of missing or unclear information, we will contact the trial authors for clarification. We will summarize the results using Cochrane 'Risk of bias' tables (Higgins 2011).

Measures of treatment effect

For dichotomous data, we will compare interventions using risk ratios to measure treatment effect. Where trial authors present data as odds ratios, we will recalculate the effect. We will define statistical significance as $P < 0.05$ and for all results we will calculate 95% confidence intervals (CIs). For comparable trials, we will perform meta-analyses if there is sufficient data.

Unit of analysis issues

For this Cochrane Review, cluster-randomized designs would be inappropriate for evaluating the research questions. If trials that have used cluster-randomization meet our inclusion criteria we would expect the results to have been controlled for clustering. If they have not, we will contact the trial authors for an estimate of the intra-cluster correlation coefficient (ICC) value. We will analyse clustered data using the methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will split trials that include more than two comparison groups and will analyse them as individual pair-wise comparisons. If there is a shared control group we will split the control group so that participants are only counted once in the overall meta-analysis.

Dealing with missing data

We will analyse missing data using available case analysis if we judge the trial to be at low risk of bias for incomplete outcome data. We will attempt to contact trial authors to obtain missing or unclear data. If the missing data render the result uninterpretable, we will exclude the data from meta-analyses and clearly state the reason for exclusion. If the missing data means that results are interpretable but likely to be at high risk of bias, we may use imputation methods to investigate the impact of the missing data. We will analyse extracted data on an intention-to-treat basis where there is no missing data.

Assessment of heterogeneity

We will inspect forest plots for overlapping CIs. We will also apply the Chi² test as a statistical test for the presence of heterogeneity, with a P value of 0.10 used to indicate statistical significance, and we will compute the I² statistic to quantify the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). We will investigate possible causes of heterogeneity by subgroup analysis. If substantive heterogeneity persists, which we define as an I² statistic value of greater than 50%, we will use a random-effects meta-analysis.

Assessment of reporting biases

We will examine the likelihood of reporting bias using funnel plots provided that there is a sufficient number of included trials.

Data synthesis

We will analyse the data using Review Manager 5 (RevMan 5) (RevMan 2014). We will assess the certainty of the evidence for each outcome measure using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and we will construct 'Summary of findings' tables using GRADEpro Guideline Development Tool (GDT) (GRADEpro GDT 2014). We will stratify results according to blood stage partner drug. Length of follow-up will vary with regimes and between studies. We will describe regimes and follow-up periods and define sensible groupings for follow-up. If there is sufficient data, we will also perform subgroup analyses according to CYP2D6 status (when available), geographical region/endemicity, length of follow-up, and directly observed therapy (DOT) or non-DOT.

Subgroup analysis and investigation of heterogeneity

We will group the analysis by drug regimen. We will describe the interventions and outcomes in all included trials. We will conduct an inventory of length of follow-up against each drug regimen and then group *P. vivax* parasitaemia relapse by appropriate groupings

for length of follow-up.

Sensitivity analysis

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

ACKNOWLEDGEMENTS

REFERENCES

Additional references

Arévalo-Herrera 2015

Arévalo-Herrera M, Lopez-Perez M, Medina L, Moreno A, Gutierrez JB, Herrera S. Clinical profile of Plasmodium falciparum and Plasmodium vivax infections in low and unstable malaria transmission settings of Colombia. *Malaria Journal* 2015;**14**:154.

Ashley 2014

Ashley EA, Recht J, White NJ. Primaquine: the risks and the benefits. *Malaria Journal* 2014;**13**:418.

Baird 2003

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

Baird 2004

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

Baird 2013

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

Baird 2015a

Baird JK. Origins and implications of neglect of G6PD deficiency and primaquine toxicity in Plasmodium vivax malaria. *Pathogens and Global Health* 2015;**109**(3):93–106.

Baird 2015b

Baird JK. Point-of-care G6PD diagnostics for Plasmodium vivax malaria is a clinical and public health urgency. *BMC Medicine* 2015;**13**:296.

Bassat 2016

Bassat Q, Velarde M, Mueller I, Lin J, Leslie T, Wongsrichanalai C, et al. Key knowledge gaps for Plasmodium vivax control and elimination. *American Journal of Tropical Medicine and Hygiene* 2016;**95**(6 Suppl): 62–71.

Battle 2014

Battle KE, Karhunen MS, Bhatt S, Gething PW, Howes RE, Golding N, et al. Geographical variation in Plasmodium vivax relapse. *Malaria Journal* 2014;**13**:144.

Bennett 2013

Bennett JW, Pybus BS, Yadava A, Tosh D, Sousa JC, McCarthy WF, et al. Primaquine failure and cytochrome P-450 2D6 in Plasmodium vivax malaria. *New England Journal of Medicine* 2013;**369**(14):1381–2.

Betuela 2014

Betuela IN, Robinson LJ, Hetzel MW, Laman MO, Siba PM, Bassat QU, et al. Primaquine treatment for Plasmodium vivax - an essential tool for malaria control and elimination in Papua New Guinea. *Papua and New Guinea Medical Journal* 2014;**57**((1-4)):68–74.

Bhattacharjee 2013

Bhattacharjee P, Dubey S, Gupta VK, Agarwal P, Mahato MP. The clinicopathologic manifestations of Plasmodium

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vivax malaria in children: a growing menace. *Journal of Clinical and Diagnostic Research* 2013;**7**(5):861–67.

Brutus 2013

Brutus L, Santalla J, Schneider D, Avila JC, Deloron P. Plasmodium vivax malaria during pregnancy, Bolivia. *Emerging Infectious Diseases* 2013;**19**(10):1605–11.

Cheng 2015

Cheng Q, Cunningham J, Gatton ML. Systematic review of sub-microscopic P. vivax infections: prevalence and determining factors. *PLoS Neglected Tropical Diseases* 2015;**9**(1):e3413.

Cibulskis 2015

Cibulskis R. Plasmodium vivax: a roadblock on the quest to eliminate malaria. *Lancet Infectious Diseases* 2015;**15**(10):1127–8.

Clyde 1977

Clyde DF, McCarthy VC. Radical cure of Chesson strain vivax malaria in man by 7, not 14, days of treatment with primaquine. *American Journal of Tropical Medicine and Hygiene* 1977;**26**(3):562–3.

Douglas 2014

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

Galappaththy 2013

Galappaththy GNL, Tharyan P, Kirubakaran R. Primaquine for preventing relapse in people with Plasmodium vivax malaria treated with chloroquine. *Cochrane Database of Systematic Reviews* 2013, Issue 10. [DOI: 10.1002/14651858.CD004389.pub3]

Gething 2012

Gething PW, Elyazar IR, Moyes CL, Smith DL, Battle KE, Guerra CA, et al. A long neglected world malaria map: Plasmodium vivax endemicity in 2010. *PLoS Neglected Tropical Diseases* 2012;**6**(9):e1814.

Gogtay 2013

Gogtay N, Kannan S, Thatte UM, Olliaro PL, Sinclair D. Artemisinin-based combination therapy for treating uncomplicated Plasmodium vivax malaria. *Cochrane Database of Systematic Reviews* 2013, Issue 10. [DOI: 10.1002/14651858.CD008492.pub3]

GRADEpro GDT 2014 [Computer program]

GRADE Working Group, McMaster University. GRADEpro GDT. Version accessed 19 April 2017. Hamilton (ON): GRADE Working Group, McMaster University, 2014.

Grietens 2010

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

Higgins 2011

Higgins JPT, 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. The Cochrane Collaboration. Available from www.cochrane–handbook.org.

Howes 2012

Howes RE, Piel FB, Patil AP, Nyangiri OA, Gething PW, Dewi M, et al. G6PD deficiency prevalence and estimates of affected populations in malaria endemic countries: a geostatistical model-based map. *PLoS Medicine* 2012;**9**(11):e1001339.

John 2012

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

Kochar 2014

Kochar DK, Das A, Kochar A, Middha S, Acharya J, Tanwar GS, et al. A prospective study on adult patients of severe malaria caused by *Plasmodium falciparum*, *Plasmodium vivax* and mixed infection from Bikaner, northwest India. *Journal of Vector Borne Diseases* 2014;**51**(3):200–10.

Koepfli 2015

Koepfli C, Rodrigues PT, Antao T, Orjuela-Sánchez P, Van den Eede P, Gamboa D, et al. Plasmodium vivax diversity and population structure across four continents. *PLoS Neglected Tropical Diseases* 2015;**9**(6):e0003872.

Kumar 2007

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

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. The Cochrane Collaboration.

Llanos-Cuentas 2014

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

Looareesuwan 1997

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

McGready 2012

McGready R, Lee S, Wiladphaingern J, Ashley E, Rijken M, Boel M, et al. Adverse effects of falciparum and vivax malaria and the safety of antimalarial treatment in early

pregnancy: a population-based study. *Lancet Infectious Diseases* 2012;**12**(5):388–96.

Mendis 2001

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

Mikolajczak 2015

Mikolajczak SA, Vaughan AM, Kangwanrangsan N, Roobsoong W, Fishbaugher M, Yimamnuaychok N, et al. Plasmodium vivax liver stage development and hypnozoite persistence in human liver-chimeric mice. *Cell Host & Microbe* 2015;**17**(4):526–35.

MMV 2016

Reddy D (Medicines for Malaria Venture). End of Year Review 2016. www.mmv.org/sites/default/files/uploads/docs/news/2016˙end˙of˙year˙review.pdf 22 December 2016 (accessed 19 April 2017).

Mueller 2009

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

Murphy 1993

Murphy GS, Basri H, Purnomo, Andersen EM, Bangs MJ, Mount DL, et al. Vivax malaria resistant to treatment and prophylaxis with chloroquine. *Lancet* 1993;**341**(8837):96–100.

Newby 2016

Newby G, Bennett A, Larson E, Cotter C, Shretta R, Phillips AA, et al. The path to eradication: a progress report on the malaria-eliminating countries. *Lancet* 2016;**387**(10029):1775–84.

Nkhoma 2009

Nkhoma ET, Poole C, Vannappagari V, Hall SA, Beutler E. The global prevalence of glucose-6-phosphate dehydrogenase deficiency: a systematic review and meta-analysis. *Blood Cells, Molecules, and Diseases* 2009;**42**(3):267–78.

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. [DOI: 10.1002/14651858.CD010458.pub2]

RevMan 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rijken 2012

Rijken MJ, McGready R, Boel ME, Poespoprodjo R, Singh N, Syafruddin D, et al. Malaria in pregnancy in the Asia-Pacific region. *Lancet Infectious Diseases* 2012;**12**(1):75-88.

Rizvi 2013

Rizvi I, Tripathi DK, Chughtai AM, Beg M, Zaman S, Zaidi N. Complications associated with Plasmodium vivax malaria: a retrospective study from a tertiary care hospital based in western Uttar Pradesh, India. *Annals of African Medicine* 2013;**12**(3):155–9.

Robinson 2015

Robinson LJ, Wampfler R, Betuela I, Karl S, White MT, Li Wai Suen CS, et al. Strategies for understanding and reducing the Plasmodium vivax and Plasmodium ovale hypnozoite reservoir in Papua New Guinean children: a randomised placebo-controlled trial and mathematical model. *PLoS Medicine* 2015;**12**(10):e1001891.

Saint-Yves 1977

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

Schmidt 1977

Schmidt LH, Fradkin R, Vaughan D, Rasco J. Radical cure of infections with Plasmodium cynomolgi: a function of total 8-aminoquinoline dose. *American Journal of Tropical Medicine and Hygiene* 1977;**26**(6 Pt 1):1116–28.

Singh 2013

Singh J, Purohit B, Desai A, Savardekar L, Shanbag P, Kshirsagar N. Clinical manifestations, treatment, and outcome of hospitalized patients with Plasmodium vivax malaria in two Indian States: a retrospective study. *Malaria Research and Treatment* 2013;**2013**:341862.

Sutanto 2013

Sutanto I, Tjahjono B, Basri H, Taylor WR, Putri FA, Meilia RA, et al. Randomized, open-label trial of primaquine against vivax malaria relapse in Indonesia. *Antimicrobial Agents and Chemotherapy* 2013;**57**(3):1128–35.

Takeuchi 2010

Takeuchi R, Lawpoolsri S, Imwong M, Kobayashi J, Kaewkungwal J, Pukrittayakamee S, et al. Directly-observed therapy (DOT) for the radical14-day primaquine treatment of Plasmodium vivax malaria on the Thai-Myanmar border. *Malaria Journal* 2010;**9**:308.

Vale 2009

Vale N, Moreira R, Gomes P. Primaquine revisited six decades after its discovery. *European Journal of Medicinal Chemistry* 2009;**44**(3):937–53.

White 2011

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

White 2016

White MT, Shirreff G, Karl S, Ghani AC, Mueller I. Variation in relapse frequency and the transmission potential of *Plasmodium vivax* malaria. *Proceedings. Biological Sciences* 2016;**283**(1827):20160048.

WHO 2009

World Health Organization. Methods for surveillance of antimalarial drug efficacy. http://www.who.int/iris/handle/10665/44048 (accessed October 2016).

WHO 2015a

World Health Organization. Control and elimination of Plasmodium vivax malaria. A technical brief.

---

http://apps.who.int/iris/bitstream/10665/181162/1/
9789241509244˙eng.pdf?ua=1&ua=1 (accessed October
2016).

WHO 2015b
World Health Organization. *Guidelines for the Treatment of
Malaria*. 3rd Edition. Geneva: World Health Organization,
2015.

WHO 2016a
World Health Organization. Eliminating malaria.
http://apps.who.int/iris/bitstream/10665/205565/1/
WHO˙HTM˙GMP˙2016.3˙eng.pdf (accessed October
2016).

WHO 2016b
World Health Organization. World Malaria Report
2016. http://apps.who.int/iris/bitstream/10665/252038/1/
9789241511711-eng.pdf?ua=1 (accessed April 2017).

* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Data extraction: Grouping of comparisons to address the review objectives

Objective	Intervention	Control
Are higher doses more effective (0.5 mg/kg or 30 mg primaquine/day for 14 days), in all areas, or only in areas where they are standard treatment (Asia, Pacific)?	Blood-stage antimalarial drug with primaquine 0.5 mg/kg (30 mg) per day for 14 days (total dose 420 mg) Both intervention and control groups must have received the same treatment: either CQ or ACT for the blood-borne stage of infection	Blood-stage antimalarial drug with primaquine 0.25 mg/kg (15 mg) per day for 14 days (total dose 210 mg) Both intervention and control groups must have received the same treatment: either CQ or ACT for the blood-borne stage of infection
Are shorter, higher dose regimes of primaquine over 7 days as effective as treatment over 14 days (is the total dose rather than the length of treatment the important factor)?	Blood-stage antimalarial drug with primaquine 0.5 mg/kg (30 mg) per day for 7 days (total dose 210 mg) Both intervention and control groups must have received the same treatment: either CQ or ACT for the blood-borne stage of infection	
Are weekly dosing regimens (0.75 mg/kg or 45 mg/week for 8 weeks) as effective?	Blood-stage antimalarial drug with primaquine 0.75/kg (45 mg) per week for 8 weeks (total dose 360 mg)	

CQ = Chloroquine
ACT = Artemisinin-based combination therapy

APPENDICES

Appendix 1. Detailed search strategy

Search set	Search terms
1	primaquine [Title/Abstract]
2	"Primaquine"[Mesh]
3	1 or 2
4	"Plasmodium vivax " [Title/Abstract]
5	"Plasmodium vivax"[Mesh]
6	"vivax malaria " [Title/Abstract]
7	"Malaria, Vivax"[Mesh]
8	4 or 5 or 6
9	3 and 8

Search terms used in combination with the search strategy for retrieving trials developed by the Cochrane Collaboration (Lefebvre 2011).

This is the preliminary search strategy for MEDLINE (PubMed). We will adapt it for other electronic databases and we will report all search strategies in full in the final version of the review.

CONTRIBUTIONS OF AUTHORS

Patricia Graves (PMG), Paul Garner (CIDG Co-ordinating Editor) and Rachael Milligan (RM) contributed to the conception of the research question.

All protocol authors contributed to the protocol design and approved the final version.

DECLARATIONS OF INTEREST

RM has no known conflicts of interest.

AD has no known conflicts of interest.

PMG has no known conflicts of interest.

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