

Primaquine for preventing relapses in people with *Plasmodium vivax* malaria (Review)

Galappaththy GNL, Omari AAA, Tharyan P



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[Intervention Review]

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

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ABSTRACT

Background

Plasmodium vivax infections contribute to a significant proportion of the malaria infections in many countries. Primaquine is the most widely used drug for treating the dormant liver stage. Different primaquine dosing regimens are in use.

Objectives

To compare primaquine regimens for preventing relapses in people with *P. vivax* malaria.

Search strategy

In 2006, we searched the Cochrane Infectious Diseases Group's Specialized Register (January), CENTRAL (*The Cochrane Library* 2006, Issue 3), MEDLINE (October), EMBASE (January), LILACS (January). We also checked conference proceedings and reference lists, and contacted researchers, the World Health Organization (WHO), malaria mailing lists, and pharmaceutical companies.

Selection criteria

Randomized and quasi-randomized controlled trials comparing primaquine plus chloroquine with chloroquine alone, and the standard primaquine regimen (15 mg/day for 14 days) with other primaquine-containing regimens in people with vivax malaria.

Data collection and analysis

All authors independently assessed trial eligibility and quality, and extracted data. We calculated odds ratios (OR) with 95% confidence intervals (CI) for dichotomous data, and used the random-effects model if there was significant heterogeneity.

Main results

Nine trials (3423 participants) met the inclusion criteria. Compared with chloroquine alone, five-day primaquine plus chloroquine was no better at preventing relapses (OR 1.04, 95% CI 0.64 to 1.69, random-effects model; 2104 participants; 3 trials), while 14-day primaquine plus chloroquine was significantly better (OR 0.24, 95% CI 0.12 to 0.45, random-effects model; 1071 participants, 6 trials). Limited data suggest the advantage for the 14-day primaquine regimen persisted for over six months (OR 0.41, 95% CI 0.29

to 0.60; 585 participants, 2 trials). Direct comparisons of the 14-day and five-day primaquine plus chloroquine regimens also confirm the superiority of the longer course (OR 13.33, 95% CI 3.45 to 51.44; 186 participants, 2 trials).

Adverse effects were poorly reported, with three trials reporting skin rash, vertigo, headache, abdominal pain and/or nausea, and two trials reporting that primaquine was well tolerated.

Authors' conclusions

Primaquine (15 mg/day for 14 days) plus chloroquine is more effective than chloroquine alone or primaquine (15 mg/day for 5 days) plus chloroquine in preventing relapses of vivax malaria. Primaquine (five days) plus chloroquine appears no better than chloroquine. Countries should follow the WHO's recommendation for 14-day primaquine plus chloroquine regimen. Alternative regimens need to be evaluated in randomized controlled trials, which should also consider variations in regional *P. vivax* strains and the possibility of primaquine resistance, reinfection, and adherence in those who relapse.

PLAIN LANGUAGE SUMMARY

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

P. vivax infections contribute to a significant proportion of the malaria infections in many Asian-Pacific and South American countries. Primaquine is the most frequently used drug for treating the dormant liver stage of the infection and is given in combination with chloroquine. Different primaquine dosing regimens are used to prevent relapses of the disease. The review included nine randomized controlled trials, comparing either primaquine plus chloroquine with chloroquine or the 14-day primaquine plus chloroquine regimen with a 5-day primaquine plus chloroquine regimen.

Compared with chloroquine alone, primaquine (for five days) plus chloroquine was no better in preventing relapses of *P. vivax* infection, while primaquine (for 14 days) plus chloroquine resulted in significantly fewer relapses. The 14-day primaquine regimen was also significantly better than the five-day primaquine regimen at preventing relapses. Adverse effects were poorly reported; three trials reported skin rash, vertigo, headache, abdominal pain and/or nausea in some participants, and two trials reported that primaquine was well tolerated.

Since the five-day primaquine plus chloroquine does not prevent relapses, countries should follow the World Health Organization's recommendation of the 14-day primaquine plus chloroquine regimen.

BACKGROUND

Malaria is one of the most common parasitic diseases and a major public health problem in many tropical and subtropical countries. *Plasmodium vivax*, *P. falciparum*, *P. malariae*, and *P. ovale* cause malaria in humans. The estimated global burden of malaria due to *P. vivax* is approximately 70 to 80 million cases annually, with about 80% to 90% of cases in the Middle East, Asia, and Western Pacific, 10% to 15% in Central and South America, and 10% to 20% in sub-Saharan Africa (Bremam 2001; Mendis 2001).

The transmission rate of *P. vivax* is relatively low in most areas where *P. vivax* is prevalent, but it can cause large epidemics. *P. vivax* is a poor stimulant of the immune system in many peo-

ple and thus reinfection is a major problem. This means people of all ages are susceptible to infection and *P. vivax* malaria is an acute illness. In endemic populations, repeated attacks of *P. vivax* through childhood and adult life can result in chronic anaemia. This rarely causes death but can have a major deleterious effect on personal well being, growth, and on economic performance at the individual, family, community, and national level (Bremam 2001; Mendis 2001).

P. vivax is a relapsing type of malaria. This means that in addition to the pre-erythrocytic and erythrocytic stages found in *P. falciparum* and *P. malariae*, there is an additional stage in the liver called the hypnozoite. These dormant forms can be activated weeks to

years after the initial infection causing relapses of the infection. The timing of the relapse varies depending on the infecting strain. It occurs within one to six months with most tropical strains, such as the Chesson strain (from New Guinea) and the Saint Elizabeth strain (from North America), and usually much later with temperate strains, such as the North Korean strain (Collins 1996). The relapse patterns appear to be independent of the infected person's immune response (Cogswell 1992). It has therefore been suggested that the timing of relapses is strain dependent and determined by the genetic makeup of the individual sporozoites (infective stage of parasite found in mosquito salivary glands) (Craig 1996). In Thailand, relapses usually occur within six months of treatment (Looareesuwan 1997). A study from Sri Lanka reported that most relapses of *P. vivax* malaria occurred in the first 24 months and of those who suffered subsequent relapses, these occurred within the first month in 22%, within the second month in 44%, and within six months in 22% (Fonseka 1987).

A new (primary) infection and a relapse of the initial infection can be differentiated using the polymerase chain reaction (PCR) technique, which compares parasite genotypes (gene types) (Looareesuwan 1997). Parasites collected on the first day of the infection are compared with those that reappear during the follow-up period. Parasites causing relapses are identical to or closely related to those circulating during the initial infection (Craig 1996). Therefore, a true relapse is confirmed when the genotypes are similar, and a new infection when the genotypes are different.

Primaquine, an 8-aminoquinoline, is the most frequently used drug for treating hypnozoites. More recently, trials involving tafenoquine (Walsh 2004) and bulaquine (also called elubaquine CDRI 80/53) (Adak 2001; Krudsood 2006), longer acting synthetic analogues of primaquine, have been conducted, but these drugs are not yet in common use. Primaquine is taken orally and is rapidly absorbed from the gut, with peak plasma concentrations after one to two hours, after which it rapidly falls (elimination half life of three to six hours) (Parfitt 1999). High doses of primaquine may cause adverse effects such as a decrease in the white blood cell count (leucopenia), high blood pressure (hypertension), irregular heart beat (cardiac arrhythmia), nausea, and vomiting. It also causes the destruction of red blood cells (haemolysis) in people with an enzyme deficiency affecting red blood cells known as glucose-6-phosphate dehydrogenase enzyme deficiency (G6PD deficiency) (Parfitt 1999). The severity of haemolytic anaemia caused by primaquine in people with this deficiency seems to be related to the dose of primaquine and the variant of the G6PD enzyme, that is, the degree of G6PD deficiency (Hill 2006). This deficiency can be detected by various tests, though these may not always be affordable or feasible in parts of the developing world. Less commonly primaquine use can result in abnormal haemoglobin (methaemoglobinaemia) that can lead to cyanosis when the methaemoglobin level exceeds 15 to 20 g/L of blood (around 10% of the normal level of haemoglobin), though in usual

practice this increase in methaemoglobin levels with primaquine is mild, self-limited, and well tolerated in otherwise healthy people (Hill 2006).

A combination of chloroquine and primaquine is used to treat *P. vivax* malaria. Chloroquine acts on the blood stages of the parasite and primaquine eliminates the liver forms. Treatment failure in people with recurrent *P. vivax* malaria may be due either to a failure of the chloroquine or of the primaquine. Primaquine treatment failure or relapse is defined as the presence of *P. vivax* parasites more than 30 days after the full course of primaquine in a non-endemic area (Looareesuwan 1997). Chloroquine treatment failure is defined as the presence of *P. vivax* parasitaemia during the 30-day follow-up period after the full course of chloroquine in a non-endemic area (Looareesuwan 1997).

Several dosing regimens are used for primaquine, such as 15 mg/day for five, seven, or 14 days. The World Health Organization recommends the 14-day course of primaquine as the standard treatment for preventing relapses (WHO 2001), as does the US Food and Drug Administration (FDA) (Hill 2006), while some National Malaria Control Programmes advocate treatment for five days, such as in Sri Lanka and India. This may be because people find it difficult to adhere to the 14-day therapy. Primaquine is not recommended for pregnant women and children under four years (WHO 2001). For people with G6PD deficiency and *P. vivax* malaria, different National Malaria Control Programmes advocate different treatment regimens; for example, the National Malaria Control Programme in Sri Lanka recommends only chloroquine.

Resistance to primaquine has emerged in some *P. vivax* strains, particularly those from the Western Pacific, South-East Asia, South America, and parts of Africa (Charoenlarp 1973; Hill 2006). In Thailand, where *P. vivax* now causes about half of all malaria infections, relapses occur in up to 18% of people treated with the standard primaquine regimens (Looareesuwan 1997), which is 15 mg primaquine for 14 days with an increased dose of primaquine for 14 days as a second-line treatment. Higher doses of primaquine or longer treatment periods may be used after a conventional course has failed. In Thailand, 30 mg of primaquine for 14 days is used when the standard treatment has failed (Looareesuwan 1997) and 30 mg per day for 14 days is now recommended by the Centers for Disease Control (CDC 2005) as standard therapy for presumptive anti-relapse therapy (PART) in people who have travelled to an area of the world where *P. vivax* or *P. ovale* occurs, or for radical cure in people infected with *P. vivax* malaria. This higher dose has not been approved by the FDA (Hill 2006).

P. vivax infection contributes to a significant proportion of malaria infections in many countries in South-East Asia and other parts of the world. The burden of disease on infected individuals and the substantial amount of money governments have to spend to treat relapsed infections makes effective treatment a priority. With several primaquine regimens currently in use, it is important to

determine the effectiveness and safety of the different regimens.

OBJECTIVES

1. To compare primaquine plus chloroquine with chloroquine alone for preventing relapses in people with *P. vivax* malaria.
2. To compare the standard primaquine regimen (15 mg/day for 14 days) recommended by the World Health Organization with other primaquine regimens for preventing relapses in people with *P. vivax* malaria.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized and quasi-randomized controlled trials.

Types of participants

Adults and children with microscopically confirmed asexual *P. vivax* malaria. People with mixed infections are excluded, and those with G6PD deficiency should have been excluded.

Types of interventions

Objective 1

Intervention: primaquine (any dose or duration) plus chloroquine*.

Control: placebo or no intervention plus chloroquine*.

Objective 2

Intervention: primaquine (any dose or duration other than used in control group) plus chloroquine*.

Control: primaquine (15 mg/day for 14 days) plus chloroquine*.

*same dose in each group

Types of outcome measures

Primary

P. vivax parasitaemia detected more than 30 days after starting primaquine.

Secondary

P. vivax parasitaemia detected more than 30 days after starting of primaquine, corrected for new infections using PCR analysis.

Adverse events

- Serious adverse events (fatal, life threatening, or requiring hospitalization).

- Adverse events that result in the discontinuation of treatment. Adverse events known to occur with primaquine (cyanosis, leucopenia, methaemoglobinaemia, hypertension, cardiac arrhythmia, nausea, vomiting, and haemolysis).

- Other adverse events.

Search methods for identification of studies

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

Databases

We searched the following databases using the search terms and strategies described in Table 1: Cochrane Infectious Diseases Group Specialized Register (January 2006); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2006, Issue 3); MEDLINE (1966 to October 2006); EMBASE (1974 to January 2006); and LILACS (1982 to January 2006).

Table 1. Detailed search strategies

Search set	CIDG SR ^a	CENTRAL	MEDLINE ^b	EMBASE ^b	LILACS ^b
1	Plasmodium vivax	primaquine	primaquine	primaquine	primaquine

Table 1. Detailed search strategies (Continued)

2	vivax malaria	PRIMAQUINE	PRIMAQUINE	PRIMAQUINE	malaria
3	primaquine	1 or 2	1 or 2	1 or 2	Plasmodium vivax
4	-	Plasmodium vivax	MALARIA, VIVAX	malaria vivax	-
5	-	vivax malaria	Plasmodium vivax	PLASMODIUM VIVAX	-
6	-	4 or 5	4 or 5	4 or 5	-
7	-	3 and 6	3 and 6	3 and 6	-

^aCochrane Infectious Diseases Group Specialized Register.

^bSearch terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Higgins 2005); upper case: MeSH or Emtree heading; lower case: free text term.

Conference proceedings

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

Researchers, organizations, and pharmaceutical companies

In June 2005, we contacted individual researchers working in the field, the World Health Organization, and the pharmaceutical companies GlaxoSmithKline and Novartis for unpublished data. We also consulted postings in malaria mailing lists.

Reference lists

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

Data collection and analysis

Trial selection

We independently assessed the full report of all potentially relevant studies for inclusion in the review using an eligibility form based on the inclusion criteria. Trial reports were scrutinized for multiple publications from the same data set. We stated the reason for excluding studies in the 'Characteristics of excluded studies', and resolved differences in opinion through discussion or by consulting the Co-ordinating Editor of the Cochrane Infectious Diseases Group (Paul Garner).

Assessment of methodological quality

We independently assessed the generation of allocation sequence and allocation concealment as adequate, inadequate, or unclear according to Juni 2001. We classified blinding as double (neither the participant or care provider/assessor know which treatment is given; eg trial uses placebo or double dummy technique), single (participant or care provider/assessor aware of treatment given), or open (all parties aware of treatment). We considered follow up to be adequate if more than 90% of the randomized participants were included in the final analysis.

Data extraction

All authors independently extracted and recorded data on study characteristics including methods, participants, interventions, and outcomes using data extraction forms. We resolved any disagreements by referring to the trial report and through discussion, or by consulting Paul Garner. Where data were insufficient or missing, we contacted authors for additional information.

Where possible, we extracted data to allow an intention-to-treat analysis, in which all randomized participants should be analysed in the groups to which they were originally assigned. If there was a discrepancy in the number randomized and the numbers analysed in each treatment group, we calculated the percentage loss to follow up in each group and reported this information.

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

For cluster-randomized trials, we recorded the number of clusters in the trial, the average size of clusters and the unit of randomization (eg household or institution). We also documented the statistical methods used to analyse the trial, along with details describing whether these methods adjusted for clustering or other covariates. When reported, we recorded estimates of the intra-cluster correlation (ICC) coefficient for each outcome. Where results had been adjusted for clustering, we extracted the point estimate and the 95% confidence interval. Had the results not been adjusted for clustering, we would have extracted the data as for the individually randomized trials and used it in a sensitivity analysis.

Data analysis

We analysed data using [Review Manager 4.2](#). For individually randomized trials, we compared dichotomous data using odds ratios (OR) and 95% confidence intervals (CI). When cluster-randomized trials had adjusted for clustering, we combined them with the individually randomized trials using the generic inverse variance method ([Deeks 2005](#)). We intended to carry out a sensitivity analysis by subgrouping the analyses by unit of randomizations, that is, cluster versus individual, but this review included only one cluster-randomized trial and there were only two trials in the relevant comparison, one of each type, so we did not do this.

We assessed heterogeneity amongst trials by inspecting the forest plots and using the chi-squared test (10% level of statistical significance). We also used the I^2 statistic, which was not available when we prepared the protocol, and which is a method of quantifying the proportion of heterogeneity due to inter-trial variability as opposed to chance ([Higgins 2003](#); [Deeks 2005](#)). We used a 50% limit to indicate substantial levels of inter-study variability ([Deeks 2005](#)), and had the result exceeded 50%, we intended to explore reasons for heterogeneity, not add data from the responsible trials to the data synthesis, and test their exclusion in a sensitivity analysis. However, there were too few trials in the relevant comparisons to render this a meaningful exercise and when heterogeneity was detected ($P < 0.10$) and/or I^2 revealed moderate inter-trial vari-

ability (50% or greater), we used the random-effects model and suggested a cautious interpretation of the results.

We intended to investigate heterogeneity by subgrouping tropical and temperate strains of *P. vivax*, but none of the trials took this into account. We will consider subgrouping by different regions if enough trials are available in the future. We stratified the data by length of follow up: less than or equal to six months; and greater than six months.

To consider the impact of the methodological quality of the included trials, we intended to conduct subgroup analyses for allocation concealment according to whether they were classed as adequate, unclear, or inadequate, but this was not possible because all trials were classed as unclear.

We intended to investigate publication bias using funnel plots, but the limited number of trials with similar comparisons and outcomes precluded this. Heterogeneity, methodological quality, or publication bias may cause funnel plot asymmetry.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#).

Trial selection

We identified 38 potentially relevant trials, of which nine randomized controlled trials met the inclusion criteria (see 'Characteristics of included studies') and are summarized below. Two trials were reported in a single publication ([Rowland 1999i](#) compared 14 days of primaquine following chloroquine and [Rowland1999ii](#) compared five days of primaquine after treatment with chloroquine). The reasons for excluding studies are given in the 'Characteristics of excluded studies'. One ongoing trial sponsored by the Gates Malaria Partnership and HealthNet International ([Rowland 2004](#)) is described in the 'Characteristics of ongoing studies'.

Location and length of follow up

Eight trials were conducted in Asia: three in India ([Gogtay 1999](#); [Yadav 2002](#); [Rajgor 2003](#)); three in Afghan refugee camps in Pakistan ([Rowland 1999i](#); [Rowland1999ii](#); [Leslie 2004](#)); and two in Thailand ([Pukrittayakamee 1994](#); [Walsh 2004](#)). The other was conducted in South America in Brazil ([Villalobos 2000](#)). The trials used different lengths of follow up: three months ([Pukrittayakamee 1994](#); [Villalobos 2000](#)); six months ([Gogtay 1999](#); [Rajgor 2003](#); [Walsh 2004](#)); nine months ([Leslie 2004](#)); and 12 months ([Rowland 1999i](#); [Rowland1999ii](#); [Yadav 2002](#)).

Participants

The trials included 3423 participants, all blood smear-positive for *P. vivax*. People with mixed infections were excluded. Some trials excluded those with G6PD deficiency, while others did not provide this information; we attempted to contact the trial authors without success.

Interventions

Eight trials compared primaquine (15 mg/day) plus chloroquine (25 mg/kg) with chloroquine plus placebo or no additional intervention (Pukrittayakamee 1994; Gogtay 1999; Rowland 1999i; Rowland1999ii; Yadav 2002; Rajgor 2003; Leslie 2004; Walsh 2004). Two trials compared five versus 14 days of primaquine plus chloroquine (Gogtay 1999; Villalobos 2000). Gogtay 1999 had three arms comparing chloroquine alone with chloroquine plus primaquine for five or 14 days. Pukrittayakamee 1994 also had three arms: chloroquine versus chloroquine plus primaquine versus primaquine. Walsh 2004 had five arms of which three were given different doses of tafenoquine following chloroquine, one used chloroquine alone and one used primaquine for 14 days after chloroquine; data from the latter two arms were used in this review. Chloroquine was administered for three days in seven trials; Yadav 2002 used a single dose (600 mg), and Villalobos 2000 used five days of chloroquine with the five-day primaquine arm. Three trials administered primaquine for five days (Gogtay 1999; Rowland1999ii; Yadav 2002), and six trials gave primaquine for 14 days (Pukrittayakamee 1994; Gogtay 1999; Rowland 1999i; Rajgor 2003; Leslie 2004; Walsh 2004). Seven trials ensured compliance by supervising treatment for all participants (Gogtay 1999; Rowland 1999i; Rowland1999ii; Pukrittayakamee 1994; Villalobos 2000; Rajgor 2003; Walsh 2004). Leslie 2004 directly compared the effects of unsupervised and supervised treatments. Yadav 2002 did not provide details regarding supervision of treatment.

Outcomes

All nine trials reported relapses of smear positive *P. vivax* malaria; all relapses, except for two in Gogtay 1999, one in Yadav 2002, and one in Rajgor 2003 occurred 30 days after starting primaquine, which corresponds to our outcome “of parasitaemia detected more than 30 days after starting primaquine”. Pukrittayakamee 1994, Gogtay 1999, Villalobos 2000, and Walsh 2004 confirmed clear-

ance of *P. vivax* in peripheral blood smear after chloroquine treatment. Villalobos 2000 and Rajgor 2003 used PCR analysis, but Rajgor 2003 only used it on those who relapsed on primaquine. In most trials it was not clear whether follow up was active (regular planned screening with blood films) or passive. Four trials provided sparse information on adverse events (Gogtay 1999; Rowland 1999i; Rowland1999ii; Villalobos 2000), while one trial, Walsh 2004, provided systematically ascertained details of adverse events, including methaemoglobin levels.

Five trials reported the number of participants who relapsed (Pukrittayakamee 1994; Gogtay 1999; Villalobos 2000; Rajgor 2003; Leslie 2004), while four reported both the cumulative number of relapses over the period of follow up as well as the relapse rate (Yadav 2002; Rowland 1999i; Rowland1999ii; Walsh 2004). The number of episodes of relapses are not independent for a trial. If a patient has already had one relapse the chance of them having another relapse may be different to the chance that a patient relapses if he/she has not already relapsed. Statistically, this consequence of analysing observations that are not independent is that the standard deviations for the measure of effect estimate will be under-estimated; therefore, the confidence intervals will be unduly narrow and the interpretation of the results will be mistakenly over precise. To avoid a unit of analysis error in interpreting cumulative episodes of relapses (count data) as relapse rates (Deeks 2005), we extracted data for relapse rates only and subgrouped them according to whether follow up was for more or less than six months.

Leslie 2004 used cluster randomizations of families in their trial. Studies increasingly employ cluster randomizations (such as randomizations by clinician or practice), but pooling of clustered data poses problems if the reported analyses have not accounted for the clustering effect. Failing to account for intra-class correlation (clustering effect) in clustered studies, leads to a unit of analysis error (Divine 1992) whereby P values are spuriously low and, confidence intervals unduly narrow. Leslie 2004 presented results adjusted for clustering; hence we were able to extract the results adjusted for clustering. We used only the adjusted odds ratios and 95% confidence intervals from the unsupervised primaquine and placebo arms of this report as they were considered comparable, and did not use the data for the supervised primaquine intervention arm.

Risk of bias in included studies

See Table 2 for details.

Table 2. Methodological quality of included trials

Trial	Generation of allocation sequence	Allocation concealment	Blinding	Inclusion of all randomized participants in the analysis
Gogtay 1999	Unclear	Unclear	Single blind	Inadequate
Leslie 2004	Unclear	Unclear	Unsupervised group blinded, unsupervised group not blinded	Adequate
Pukrittayakamee 1994	Unclear	Unclear	Unclear	Inadequate
Rowland 1999i	Unclear	Unclear	Single blind	Adequate
Rowland 1999ii	Unclear	Unclear	Single blind	Adequate
Rajgor 2003	Adequate	Unclear	Single blind	Inadequate
Villalobos 2000	Unclear	Unclear	Unclear	Adequate
Walsh 2004	Adequate	Partly adequate	Open	Inadequate
Yadav 2002	Unclear	Unclear	Unclear	Adequate

Two trials were considered adequate for generation of the allocation sequence as they used computer-generated random numbers (Rajgor 2003; Walsh 2004); the remaining trials did not describe the method used for allocation. Only Walsh 2004 reported on attempts at allocation concealment. Five trials were single blind (assessor blinded) (Gogtay 1999; Rowland 1999i; Rowland1999ii; Rajgor 2003; Leslie 2004); one trial was open (Walsh 2004); and the remaining trials did not report on this. Five trials included more than 90% of randomized participants in the final analysis (Rowland 1999i; Rowland1999ii; Villalobos 2000; Yadav 2002; Leslie 2004). Rowland 1999i and Rowland1999ii included all participants, Pukrittayakamee 1994 included 71%, and Rajgor 2003 followed up 75%. Gogtay 1999 reported results for 185/244 (76%) randomized participants who completed six months follow up. Walsh 2004 reported results for 22/25 (88%) of those in the two arms that were used for this review of the five-arm trial.

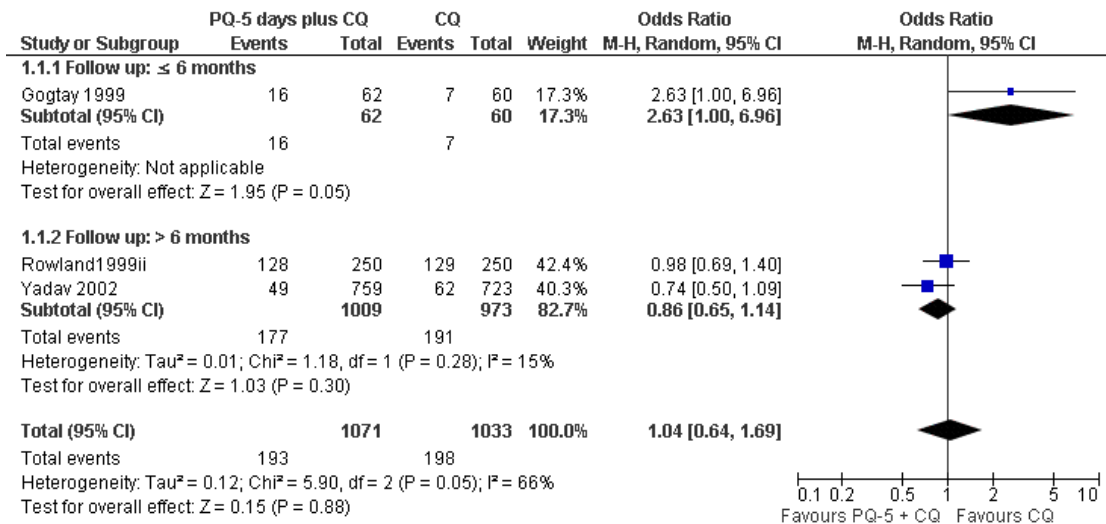
Effects of interventions

1. Primaquine plus chloroquine versus chloroquine

Parasitaemia detected more than 30 days after starting primaquine

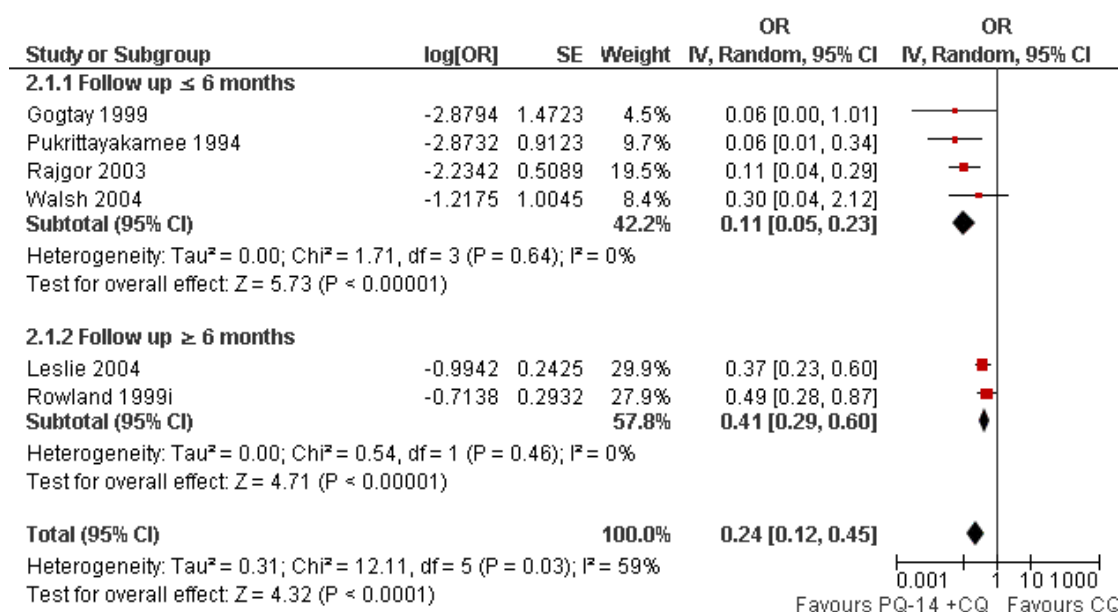
Three trials that compared primaquine for five days reported this outcome (Gogtay 1999; Rowland1999ii; Yadav 2002). Pooled heterogeneous data from the three trials did not favour primaquine for five days plus chloroquine over chloroquine alone (OR 1.04, 95% CI 0.64 to 1.69, random-effects model; 2104 participants, Figure 1, Analysis 1.1). The results, though homogenous within subgroups, showed that there was still no evidence that five days of primaquine prevented relapses when data for this comparison were subgrouped according to duration of follow up less than six months (OR 2.63, 95% CI 1.00 to 6.96; 122 participants, Gogtay 1999) or greater than six months (OR 0.86, 95% CI 0.65 to 1.14, 1982 participants, Rowland1999ii; Yadav 2002).

Figure 1. Primaquine (5 days) plus chloroquine vs chloroquine: *P. vivax* parasitaemia detected > 30 days after starting primaquine.



Data from the six trials that used primaquine for 14 days found that primaquine plus chloroquine significantly reduced the number of relapses compared with chloroquine alone (OR 0.24, 95% CI 0.12 to 0.45, random-effects model; 1071 participants, [Figure 2, Analysis 2.1](#)) ([Pukrittayakamee 1994](#); [Gogtay 1999](#); [Rowland 1999i](#); [Leslie 2004](#); [Rajgor 2003](#); [Walsh 2004](#)). We used the random-effects model for data synthesis due to the presence of heterogeneity and moderate degrees of inter-trial variability in the overall results. When the outcome was subgrouped according to length of follow up, data synthesis results were homogenous within subgroups.

Figure 2. Primaquine (14 days) plus chloroquine vs chloroquine: *P. vivax* parasitaemia detected > 30 days after starting primaquine.



Limited data suggest that the significant advantage of primaquine (14 days) plus chloroquine in preventing relapses persisted beyond six months after treatment (OR 0.41, 95% CI 0.29 to 0.60, random-effects model; 585 participants, Figure 2, Analysis 2.1, Rowland 1999i; Leslie 2004). Table 3 provides details of the data and methods used for this comparison using the generic inverse variance method.

Table 3. Data used for generic inverse variance (Analysis 02.01)

Trial	No. participants relapsing		Odds ratio	Log odds ratio	Standard error of log odds ratio
	Primaquine-14 + chloroquine	Chloroquine			
Pukrittayakamee 1994	n/N = 2/25	n/N = 4/30	$(2*26)/(23*4)$ 0.565217391	= -2.8732	Square root of $(1/2 + 1/26 + 1/23 + 1/4) = 0.912274164$
Gogtay 1999	n/N = 0/63	n/N = 7/60	$(0.5*53.5)/(63.5*7.5)$ =0.056167979	-2.8794	Square root of $(1/0.5 + 1/53.5 + 1/7.5 + 1/63.5) = 1.472335883$
Rowland 1999i	n/N = 32/100	n/N = 49/100	$(32*51)/(68*49)$ 0.4897959	= -0.7138	Square root of $(1/33 + 1/51 + 1/68 + 1/49) = 0.29322346$

Table 3. Data used for generic inverse variance (Analysis 02.01) (Continued)

Rajgor 2003	n/N = 6/131	n/N = 13/142	$(6*129)/(125*13) = 0.107076923$	-2.2342	Square root of $(1/6 + 1/125 + 1/13 + 1/129) = 0.5089$
Leslie 2004	n/N = 34/ 173	n/N = 86/212	0.35* (95% CI 0.23 to 0.59) (adjusted OR and 95% CI from report)	-0.9942	0.2425
Walsh 2004	n/N = 3/12	n/N = 11/13	$(3*2)/(9*11) = 0.0606060606$	-1.2175	Square root of $(1/3 + 1/2 + 1/11 + 1/13) = 1.004489920$

Adverse events

Rowland 1999i and Rowland1999ii reported that participants tolerated primaquine well. Gogtay 1999 reported that participants experienced mild adverse events of nausea and skin rash. Walsh 2004 reported numerical data for the group given both chloroquine and primaquine; neurological adverse effects were the most common with transient vertigo and headache reported by three and four participants respectively. Gastrointestinal adverse effects were infrequent with one person reporting diarrhoea and none reporting abdominal pain, nausea or vomiting. Two people reported skin rash/itching and eight reported weakness.

2. Primaquine (5 days) plus chloroquine versus primaquine (14 days) plus chloroquine

Parasitaemia detected more than 30 days after starting primaquine

Two trials contributed data to this comparison (Gogtay 1999; Villalobos 2000). Pooled analysis of the homogenous data showed the number of relapses was significantly higher for the five days compared with 14 days of primaquine (OR 13.33, 95% CI 3.45 to 51.44, fixed-effect model; 186 participants, 2 trials, Figure 3, Analysis 3.1). When PCR was used to exclude new infections, results from one of the trials were equivocal (OR 2.23, 95% CI 0.38 to 13.20; 61 participants, Villalobos 2000, Figure 4, Analysis 3.2).

Figure 3. Primaquine (5 days) plus chloroquine vs primaquine (14 days) plus chloroquine: *P. vivax* parasitaemia detected > 30 days after starting primaquine.

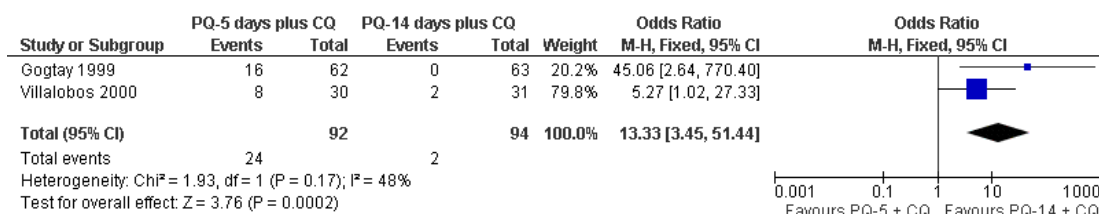
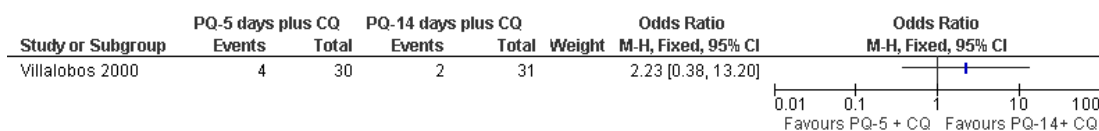


Figure 4. Primaquine (5 days) plus chloroquine vs primaquine (14 days) plus chloroquine: *P. vivax* parasitaemia detected > 30 days after starting primaquine, excluding new infection by PCR.



Adverse events

Gogtay 1999 reported mild adverse events of nausea and skin rash. Villalobos 2000 reported frequent, mild, transient headache, vertigo, abdominal pain and/or nausea. Neither trial provided numerical data.

3. Publication bias

Due to the small number of trials in each of the comparisons (less than five), it was not possible to construct funnel plots to investigate for potential publication bias.

DISCUSSION

This review was designed to assess the effects of primaquine added to chloroquine and the different dosing regimens in preventing relapses of *P. vivax* malaria. All trials primarily assessed the effectiveness of primaquine in preventing relapses and compared regimens of five days or 14 days of primaquine.

Most trials had methodological limitations such as inadequate reporting of generation of random sequence and allocation concealment and lack of blinding; some had high levels of attrition (Gogtay 1999; Pukrittayakamee 1994; Rajgor 2003). Only one trial gave placebo in addition to chloroquine to the control group

(Leslie 2004). This lack of participant blinding could have affected the methodological quality of trials. Participants in the control group may not adhere to the treatment or hide or exaggerate symptoms of their illness if they know they are not receiving the experimental treatment. However, the use of an objective measure such as parasitaemia detected after one month as the primary outcome would mitigate the effects of lack of participant blinding on the validity of results. Inadequate methodological quality may produce systemic errors and reduce the robustness of the findings.

The three trials that evaluated primaquine (five days) plus chloroquine versus chloroquine randomized 2104 participants. Pooled data did not provide evidence to support the efficacy of five days of primaquine in preventing relapses. The 14-day course recommended by the World Health Organization significantly reduced the relapse rate compared with chloroquine alone. This comparison included a reasonable number of randomized participants (1061 participants, six trials); moreover the magnitude of the effect and the lack of overlap in the confidence limits of the point estimates between the two dosing regimens of primaquine strengthens our interpretation that the 14-day course is superior to the five-day course of primaquine or no primaquine. This is further supported by data from two trials that compared the different regimens of primaquine favouring the longer course.

The characterization by PCR of specific alleles of polymorphic genes of *P. vivax* isolates collected before and after treatment can help distinguish relapses from reinfections. The secondary outcome measure of the review was to evaluate the efficacy of pri-

maquine therapy after excluding instances of new infections by PCR. Villalobos 2000 used PCR to differentiate new infections from true relapses in all participants. The results are inconclusive as the sample size was relatively small (61 participants) and also because PCR was successfully performed on only eight of 10 people with relapses. Rajgor 2003 also used PCR but only on six participants (out of 13) who relapsed; two of the six relapses were reinfections. Interpretation of the results of this trial is limited as one sample of the six failed to amplify and the 13 participants who relapsed on chloroquine alone were not subjected to PCR. The remaining trials did not attempt to distinguish between relapses and reinfections. The trialists argued that the low endemicity of malaria in the trial areas and the absence of infections during the follow up of one treatment group would indicate that most, if not all, of the infections seen during the follow-up period were the result of relapses. However, this may not always be the case, as some trials were done in malaria endemic areas.

Assessing compliance to primaquine was not an objective of this review, but it is important to consider if governments are to be encouraged to switch to the 14-day regimen. All trials (apart from Yadav 2002) provided supervised primaquine, but only Leslie 2004 formally evaluated the effects of supervised treatments wherein 346 participants given chloroquine plus 14-days of primaquine were randomized equally to supervised therapy or unsupervised therapy. Both groups had significant reductions in relapse rates compared with the 212 participants taking chloroquine plus placebo. The supervised group was significantly less likely to relapse in the long term. Although poor compliance with primaquine is reported as a major cause of relapse (Baird 2004; Hill 2006), a policy of 14 days should not be dismissed on grounds of compliance alone. Of concern is that shortened courses or poor compliance would accelerate the selection of primaquine-resistant strains (Collins 1996). Adequate and timely measures, such as health education messages, are essential to improve compliance and to prolong the effective life of this unique drug (Leslie 2004). Fears that primaquine is toxic and poorly tolerated are not widely supported (Baird 2004). Ensuring compliance may not be difficult as, unlike with long-term interventions, improving short-term adherence to interventions is relatively successful with a variety of simple interventions (Haynes 2005). The evidence specific to improving adherence in malaria, such as unit-dose packaging supported by educational interventions, though promising (Qingjun 1998), requires further evaluation (Orton 2005).

Most governments in South-East Asia and Latin America, where *P. vivax* is prevalent, administer primaquine for five days due to the perceived lack of compliance by patients for the 14-day course (Leslie 2004). The results of this systematic review suggest a revision of this policy is warranted since the administration of five days of primaquine appears not to prevent relapses. Narrative reviews have also called for such a change in policy (Baird 2004).

The timing of the relapse varies depending on the infecting strain

and is determined by the genetic make up of the individual sporozoites. In different regions relapses occur within one to six months with most tropical strains and usually much later with temperate strains (Collins 1996). The duration of follow up varied from two months to one year. We grouped follow up into less than six months and above six months. There was no significant difference in the number of relapses between chloroquine plus primaquine (administered for five days) with the chloroquine alone group over shorter and longer follow-up periods. Chloroquine with primaquine administered for 14 days was more effective than chloroquine alone irrespective of the length of follow up. None of the trials in this review assessed the relationship between different regional strains and relapse patterns.

The included trials, except for Villalobos 2000 and Yadav 2002, explicitly mentioned the exclusion of people with G6PD deficiency because primaquine can cause haemolysis in people with this deficiency. Many low-income countries have limited facilities to detect this condition before administering primaquine. G6PD deficiency can be detected with either a quantitative determination of the enzyme level or a qualitative screening test; the latter is less expensive and is sufficient to identify individuals with a G6PD deficiency in most instances (Beutler 1994). It is important to screen all patients for G6PD deficiency before administering primaquine for a duration as long as 14 days, though there are insufficient data from the reports included in this review to reveal how feasible, or necessary, this may be on a routine basis.

Five of the nine trials reported adverse events (Gogtay 1999; Rowland 1999i; Rowland 1999ii; Villalobos 2000; Walsh 2004), but only Walsh 2004 ascertained this systematically. Both chloroquine and primaquine are well tolerated by people (without G6PD deficiency) with *P. vivax* malaria with few adverse events. However, it is a matter of concern that primaquine was administered for long periods without systematically evaluating adverse events. The majority of the trials reported adverse effects poorly and four did not report adverse effects as an outcome.

AUTHORS' CONCLUSIONS

Implications for practice

We found no evidence to support the practice of administering primaquine for five days along with chloroquine as an effective strategy to prevent relapses of *P. vivax* malaria. This review provides evidence to support the World Health Organization's recommended course of primaquine (15 mg/day for 14 days) plus chloroquine. National Malaria Control Programmes that currently advocate the five-day primaquine regimen should consider the findings of this review and switch to the 14-day primaquine regimen. Malaria control programmes that decide to switch to the 14-day regimen should consider routine screening for G6PD deficiency and enhance health education activities to improve adherence.

Implications for research

Large randomized controlled trials that adhere to CONSORT guidelines for reporting (Moher 2001) are needed to determine the optimum dose and duration of primaquine for preventing relapses of different strains of *P. vivax* malaria in different regions. Trials on the efficacy and safety of higher doses of primaquine given for periods between five and 14 days appear warranted. The CDC 2005 recommendation of 30 mg/day of primaquine for 14 days also needs to be evaluated in the context of trials. Further trials evaluating five days of primaquine are unlikely to be beneficial unless higher doses of primaquine are used. Future trials should also consider the effects of variations in regional strains of *P. vivax* malaria as well as the possibility of primaquine resistance and reinfection in those who relapse. The utility and validity of PCR analyses to exclude reinfections from relapses of *P. vivax* malaria need evaluation in such trials. The adherence of people given longer courses of primaquine as well as methods to improve adherence also need to be systematically assessed.

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REFERENCES

References to studies included in this review

Gogtay 1999 *{published data only}*

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

Leslie 2004 *{published data only}*

Leslie T, Rab MA, Ahmadzai H, Durrani N, Fayaz M, Kolaczinski J, et al. Compliance with 14-day primaquine therapy for radical cure of vivax malaria—a randomized placebo-controlled trial comparing

unsupervised with supervised treatment. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2004;**98**(3):168–73.

Pukrittayakamee 1994 *{published data only}*

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

Rajgor 2003 *{published data only}*

Rajgor DD, Gogtay NJ, Kadam VS, Kamtekar KD, Dalvi SS, Chogle AR, et al. Efficacy of a 14-day primaquine regimen in preventing relapses in patients with Plasmodium vivax malaria in

Mumbai, India. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2003;**1997**:438–40.

Rowland 1999i {published data only}

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

Rowland 1999ii {published data only}

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

Villalobos 2000 {published data only}

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

Walsh 2004 {published data only}

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

Yadav 2002 {published data only}

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

References to studies excluded from this review

Abdon 2001 {published data only}

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

Appavoo 1984 {published data only}

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

Baird 1995 {published data only}

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

Baird 2001 {published data only}

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

Baird 2003 {published data only}

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

Basavaraj 1960 {published data only}

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

Buchachart 2001 {published data only}

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

Bunnag 1994 {published data only}

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

Cedillos 1978 {published data only}

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

Clyde 1977 {published data only}

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

Contacos 1974 {published data only}

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

da Silva 2003 {published data only}

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

Dua 2001 {published data only}

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

Fryauff 1997 {published data only}

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

Gogtay 1998 {published data only}

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

Looareesuwan 1999 {published data only}

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

Luxemburger 1999 *{published data only}*

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

Pinto 1998 *{published data only}*

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

Prasad 1991 *{published data only}*

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

Roy 1977 *{published data only}*

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

Saint-Yves 1977 *{published data only}*

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

Schwartz 2000 *{published data only}*

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

Sharma 1973 *{published data only}*

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

Singh 1990 *{published data only}*

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

Sinha 1989 *{published data only}*

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

Soto 1998 *{published data only}*

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

Soto 1999 *{published data only}*

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

Valibayov 2003 *{published data only}*

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

References to ongoing studies**Rowland 2004** *{published data only}*

Rowland M, Leslie T, Durrani NM (Gates Malaria Partnership & HealthNet International). “A Placebo Controlled, Randomised Evaluation of an Eight Week Primaquine Regimen for the Treatment of Vivax Malaria” [ClinicalTrials.gov Identifier: NCT00158587]. www.clinicaltrials.gov/ct/show/NCT00158587 2005.

Additional references**Adak 2001**

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

Baird 2004

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

Beutler 1994

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

Breman 2001

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

CDC 2005

Centers for Disease Control and Prevention, Kozarsky PE, Arguin PM, Navin AW. *Health Information for International Travel 2005–2006*. Philadelphia: Elsevier, 2005.

Charoenlarp 1973

Charoenlarp P, Harinasuta T. Relapses of vivax malaria after a conventional course of primaquine and chloroquine: report of 2 cases. *Southeast Asian Journal of Tropical Medicine and Public Health* 1973;**4**(1):135–6.

Cogswell 1992

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

Collins 1996

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

Craig 1996

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

Deeks 2005

Deeks JJ, Higgins JPT, Altman DG, editors. In: Higgins JPT, Green S (editors). Appendix 5b: Analysing and presenting results. *Cochrane Handbook for Systematic Reviews of Interventions* 4.2.5 (updated May 2005). The Cochrane Collaboration, 2005. Available from www.cochrane-handbook.org.

- Divine 1992**
Divine GW, Brown JT, Frazier LM. The unit of analysis error in studies about physicians' patient care behavior. *Journal of General Internal Medicine* 1992;7(6):623–9.
- Fonseka 1987**
Fonseka J, Mendis KN. A metropolitan hospital in a non-endemic area provides a sampling pool for epidemiological studies on vivax malaria in Sri Lanka. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1987;81(3):360–4.
- Haynes 2005**
Haynes RB, Yao X, Degani A, Kripalani S, Garg A, McDonald HP. Interventions to enhance medication adherence. *Cochrane Database of Systematic Reviews* 2005, Issue 4.
- Higgins 2003**
Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327(7414):557–60.
- Higgins 2005**
Higgins JPT, Green S, editors. Highly sensitive search strategies for identifying reports of randomized controlled trials in MEDLINE. *Cochrane Handbook for Systematic Reviews of Interventions* [4.2.5] updated [May 2005]; Appendix 5b. www.cochrane.org/resources/handbook/hbook.htm (accessed 1 January 2006).
- 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.
- Juni 2001**
Juni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. *BMJ* 2001;323(7303):42–6.
- Krudsood 2006**
Krudsood S, Wilairatana P, Tangpukdee N, Chalermrut K, Srivilairit S, Thanachartwet V, et al. Safety and tolerability of elubaquine (bulaquine, CDRI 80/53) for treatment of Plasmodium vivax malaria in Thailand. *Korean Journal of Parasitology* 2006;44(3):221–8.
- 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.
- Mendis 2001**
Mendis K, Sina JB, Marchesini P, Carter R. The neglected burden of P. vivax malaria. *American Journal of Medicine and Hygiene* 2001; 64 Suppl 1-2:97–106.
- Moher 2001**
Moher D, Schulz KF, Altman D, CONSORT Group (Consolidated Standards of Reporting Trials). The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA* 2001;285(15):1987–91.
- Orton 2005**
Orton L, Barnish G. Unit-dose packaged drugs for treating malaria. *Cochrane Database of Systematic Reviews* 2005, Issue 2. [DOI: 10.1002/14651858.CD004614.pub2]
- Parfitt 1999**
Parfitt K, editor. *Martindale: the complete drug reference*. 2nd Edition. London: Pharmaceutical Press, 1999.
- Qingjun 1998**
Qingjun L, Jihui D, Laiyi T, Xiangjun Z, Jun L, Hay A, et al. The effect of drug packaging on patients' compliance with treatment for Plasmodium vivax malaria in China. *Bulletin of the World Health Organization* 1998;76 Suppl 1:21–7.
- Review Manager 4.2**
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 4.2 for Windows. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2003.
- WHO 2001**
World Health Organization, Global Partnership to Roll Back Malaria. *The use of antimalarial drugs: report of a WHO informal consultation, 13-17 November 2000 [WHO/CDS/RBM/2001.33]*. Geneva: World Health Organization, 2001.
- * Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Gogtay 1999

Methods	Randomized controlled trial Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: assessor blinded Inclusion of all randomized participants in final analysis: 6 months follow up was completed by only 60/83 (72%) in CQ group, 62/80 (77%) in PQ (5 days) plus CQ group, and 63/81 (77%) in PQ (14 days) plus CQ group	
Participants	Number: 244 recruited Inclusion criteria: patients attending K.E.M. Hospital; smear positive for <i>P. vivax</i> ; and willing to be hospitalized Exclusion criteria: mixed infection and G6PD deficiency participants Age range: 16 to 63 years	
Interventions	1. CQ (3 days): 83 participants 2. PQ (5 days) plus CQ (3 days): 80 participants 3. PQ (14 days) plus CQ (3 days): 81 participants CQ dose: 25 mg/kg PQ dose: 0.25 mg/kg All participants hospitalized for intervention	
Outcomes	1. Number of participants relapsing during the 6-month follow-up period 2. Adverse events Parasitic clearance after intervention was confirmed	
Notes	Location: K.E.M. Hospital in Mumbai, India Date: October 1997 Malaria endemicity: 80% of infections are <i>P. vivax</i> malaria	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Leslie 2004

Methods	<p>Cluster-randomized controlled trial: unit of allocation = family Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: unsupervised group and those on placebo were blinded; supervised group was not blinded Inclusion of all randomized participants in final analysis: > 90% of 595 participants enrolled from 290 families; 98 families (212 individuals) in placebo group and 192 families (383 individuals) in PQ group - supervised: 105 families; unsupervised: 87 families)</p>	
Participants	<p>Number: 595 Inclusion criteria: clinical cases with blood smear positive for <i>P. vivax</i> malaria; temperature > 37.5 °C and or recent history of fever Exclusion criteria: G6PD deficiency; < 3 years old; pregnancy; severe anaemia; mixed infections Average age: 11.7 years for CQ plus placebo; 14 and 13.1 years for the supervised group and unsupervised PQ plus CQ groups, respectively</p>	
Interventions	<p>1. CQ (3 days) and placebo: 212 participants 2. PQ (14 days) plus CQ (3 days): supervised (210 participants) and unsupervised (173 participants) CQ dose: 25 mg/kg PQ dose: 0.25 mg/kg</p>	
Outcomes	<p>1. Number of participants relapsing during the 9-month follow-up period Parasitic clearance after intervention was not confirmed</p>	
Notes	<p>Location: Afghan refugee camp, North-West Frontier Province, Pakistan Date: June 2000 to August 2001 Malaria endemicity: highly endemic for <i>P. vivax</i> and <i>P. falciparum</i> malaria with active transmission from June to November Data analysed in report by random effects logistic regression; adjusted odds ratios and 95% confidence intervals reported Data used in meta-analysis were adjusted odds ratios and 95% confidence intervals for relapse at 9 months for unsupervised primaquine group (n = 34/210; 19.7%) and in placebo group (n = 86/212; 40.6%). Data for supervised primaquine groups not used; results not notably different from unsupervised group compared to placebo</p>	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Pukrittayakamee 1994

Methods	Randomized controlled trial Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: unclear Inclusion of all randomized participants in final analysis: 61 of the 85 (71%) enrolled participants returned for follow up after 2 months
Participants	Number: 85 male patients Inclusion criteria: confirmed <i>P. vivax</i> infection Exclusion criteria: history of taking any antimalarials within the past 48 h; urine positive for sulphonamides or 4-aminoquinoline; and G6PD deficiency Age range: 15 to 50 years
Interventions	1. CQ (3 days): 30 participants 2. PQ (14 days) plus CQ (3 days): 25 participants 3. PQ only (not included in review): 30 participants CQ dose: 25 mg/kg PQ dose: 0.25 mg/kg 71/85 participants were hospitalized during intervention
Outcomes	1. Number of participants relapsing during the 2-month follow-up period Parasitic clearance after intervention was confirmed
Notes	Location: Bangkok Hospital for Tropical Diseases, Thailand Date: 1992 to 1993 Malaria endemicity: very high endemicity with multiple-drug resistant <i>P. falciparum</i> malaria

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Rajgor 2003

Methods	Randomized controlled trial Generation of allocation sequence: computer-generated Allocation concealment: unclear Blinding: assessor blind Inclusion of all randomized participants in final analysis: 41/142 (28.8%) in chloroquine group and 28/131 (21.4 %) in the chloroquine plus 14-day primaquine group dropped out before 6 months
Participants	Number: 273 Inclusion criteria: age > 16 years; smear-positive for asexual forms of <i>P. vivax</i> ; normal G6PD status; consented to trial and follow up; haemoglobin > 10 g/dL Excluded: < 16 years; G6PD deficiency; pregnant and lactating women; mixed infections

Rajgor 2003 (Continued)

Interventions	1. CQ (3 days): 142 participants 2. PQ (14 days plus CQ (3 days): 131 participants CQ dose: 25 mg/kg PQ dose: 15 mg/day Interventions were supervised
Outcomes	1. Number of participants relapsing during the 6-month follow up period Genotyping of <i>P. vivax</i> infection with PCR to differentiate new infections from relapses was done only in people given PQ PCR was successful in 5/6 cases of presumed relapses; of these 2 were confirmed as re-infections and 3 as true relapses The PCR data were not used in meta-analysis as similar data for CQ group were not available Parasitic clearance after intervention was not confirmed
Notes	Location: Seth GS Medical College & KEM Hospital, Mumbai, India July 1998 to April 2000 Malaria endemicity: 80% of infections are due to <i>P. vivax</i>

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Rowland 1999i

Methods	Randomized controlled trial Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: assessor blinded Inclusion of all randomized participants in final analysis: no losses (100%)
Participants	Number: 200 enrolled Inclusion criteria: positive for <i>P. vivax</i> with temperature > 37.5 °C Exclusion criteria: mixed infections; pregnant women; G6PD deficiency; severe anaemia; < 3 years; very elderly; recent antimalarial intake Average age: 11 to 12 years
Interventions	1. CQ (3 days) plus placebo: 100 participants 2. PQ (14 days) plus CQ (3 days): 100 participants CQ dose: 25 mg/kg PQ dose: 0.25 mg/kg Interventions were supervised
Outcomes	1. Number of participants relapsing during 12-month follow-up period 2. Parasitaemic episodes during the 12-month follow-up period (not used) 2. Adverse events Parasitic clearance after treatment was not confirmed

Rowland 1999i (Continued)

Notes	Location: Adizai refugee camp, Afghanistan Date: August 1997 to June 1998 Malaria endemicity: predominant species is <i>P. vivax</i> malaria Data analysed were number of participants relapsing over 12 months	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Rowland1999ii

Methods	Randomized controlled trial Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: assessor blinded Inclusion of all randomized participants in final analysis: no losses (100%)	
Participants	Number: 500 enrolled Inclusion criteria: <i>P. vivax</i> positive with temperature > 37.5 °C Exclusion criteria: mixed infections; pregnant women; G6PD deficiency; severe anaemia; < 3 years; very elderly; recent antimalarial intake Average age: 10 to 10.4 years	
Interventions	1. CQ (3 days) plus placebo: 250 participants 2. PQ (5 days) plus CQ (3 days): 250 participants CQ dose: 25 mg/kg PQ dose: 0.25 mg/kg Interventions were supervised	
Outcomes	1. Number of participants relapsing during the 12-month follow-up period 2. Parasitaemic episodes during the 12-month follow-up period (not used) PCR not used to adjust for re-infections 3. Adverse events Parasitic clearance after treatment was confirmed	
Notes	Location: Adizai refugee camp, Afghanistan Date: August 1996 to June 1997 Malaria endemicity: <i>P. vivax</i> predominant species Data analysed were number of clinical-parasitic episodes over 12 months	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Villalobos 2000

Methods	Randomized controlled trial Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: unclear Inclusion of all randomized participants in final analysis: treatment outcome was investigated for 73 of the 79 enrolled participants (92%); of the 73 participants, 61 (84%) were followed up for 90 days, while 12 were followed up for 35 days
Participants	Number: 79 participants included in the study Inclusion criteria: <i>P. vivax</i> uncomplicated malaria; > 12 years; no history of antimalarials for the last 15 days; and no history of haemolytic anaemia Exclusion criteria: pregnant women; Negroid Mean age: 30.7 years for intervention 1 and 32.7 years for intervention 2
Interventions	1. PQ (14 days) plus CQ (3 days): 39 participants 2. PQ (5 days) plus CQ (5 days): 40 participants CQ total dose: 25 mg/kg PQ dose: 0.25 mg/kg Interventions were supervised
Outcomes	1. Number of participants with parasitaemia between days 30 and 90 2. Genotyping of <i>P. vivax</i> infection with PCR to differentiate new infections from relapses. PCR was successful in 8/10 cases of presumed relapses; of these 2 were confirmed as re-infections and 6 as true relapses 3. Adverse effects Parasitic clearance after treatment was confirmed
Notes	Location: Centre de Pesquisa em Medicina Tropical in Rondonia, Brazil Date: April to December 1998 Malaria endemicity: malaria transmission is low and seasonal

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Walsh 2004

Methods	Randomized controlled trial Generation of allocation sequence: computer-generated list with block size of 5 Allocation concealment: randomization list kept by an off-site investigator Blinding: open Inclusion of all randomized participants in final analysis: 13 participants were enrolled in the CQ group and 10 completed trial (77%); 12 were enrolled and followed up in CQ+PQ group (100%)
Participants	Number: 25 included (from two arms of a 6-arm trial that randomized 130 people) Inclusion criteria: smear positive for <i>P. vivax</i> ; weight within 20% of population standards; normal G6PD screening; no antimalarials in previous 14 days; negative pregnancy test; consent to participate; ability to

Walsh 2004 (Continued)

	take oral medication Exclusion criteria: mixed infection with <i>P. vivax</i> and <i>P. falciparum</i> ; hematocrit < 25%; protracted vomiting; oliguria; systolic blood pressure < 90 mm mercury; lactation; concomitant systemic disease Age: CQ median age 21 years (range 18 to 31), CQ+PQ median age 23 years (range 18 to 37 years)	
Interventions	1. CQ (1500 mg over 3 days): 13 participants 2. CQ (1500 mg over 3 days) + PQ 15 mg/day for 14 days: 12 participants Interventions were supervised	
Outcomes	1. Number of participants with parasitaemia between 8 to 24 weeks 2. Incidence (per person-year) of relapse (not used) 3. Cumulative risk of relapse (not used) 4. Adverse effects Parasitic clearance after treatment with chloroquine was confirmed by 2 consecutive negative blood smears	
Notes	Location: Bangkok Hospital for Tropical Diseases, Thailand Date: August 1998 to June 1999 Malaria endemicity: no local transmission of vivax malaria	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Yadav 2002

Methods	Randomized controlled trial Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: unclear Inclusion of all randomized participants in final analysis: 723 participants were enrolled and followed up for 1 year in the CQ group; 759 participants were enrolled and also followed up for 1 year in CQ plus PQ group	
Participants	Number: 1482 included Inclusion criteria: smear positive for <i>P. vivax</i> Exclusion criteria: mixed infections; pregnant women; infants Age range equal numbers in both groups from age 1 year to > 49 years	
Interventions	1. CQ (single dose of 600 mg): 723 participants 2. PQ (5 days) plus CQ (single dose of 600 mg): 759 participants CQ dose: single dose of 600 mg PQ dose: 0.25 mg/kg Primaquine dose unsupervised	

Yadav 2002 (Continued)

Outcomes	1. Number of participants relapsing during the 1-year follow up 2. Episodes of clinical- parasitaemia during the 1-year follow-up period (not used) Parasitic clearance after treatment not confirmed	
Notes	Location: Orissa State, India Date: 1998 to 1991 Malaria endemicity: malaria mesoendemic and seasonal	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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

Characteristics of excluded studies [ordered by study ID]

Abdon 2001	Different doses of chloroquine was given to control and experimental groups
Appavoo 1984	Participants were not randomly assigned
Baird 1995	Not randomized; compared primaquine with chloroquine in healthy people
Baird 2001	Healthy participants randomized to 30 mg primaquine or placebo
Baird 2003	Not a trial
Basavaraj 1960	Case series
Buchachart 2001	Case series
Bunnag 1994	Randomized controlled trial that compared chloroquine + primaquine (15 mg/day for 14 days) with chloroquine + primaquine (22.5 mg/day for 14 days). Only 33/81 (40%) in 15 mg/day primaquine arm and 40/86 (47%) in 22.5 mg/day primaquine arm completed 6 months follow up; only 19 in each arm completed 18 months follow up; no usable data
Cedillos 1978	Compared 2 regimens of primaquine with amodiaquine versus amodiaquine
Clyde 1977	No comparison group

(Continued)

Contacos 1974	No comparison group
da Silva 2003	Compared artemisinin and primaquine with chloroquine and primaquine
Dua 2001	Not randomized
Fryauff 1997	Compared 1 year of weekly chloroquine, daily primaquine, or placebo
Gogtay 1998	Not randomized
Looareesuwan 1999	Randomized participants to chloroquine + primaquine for 14 days or chloroquine alone. Followed participants for 28 days to assess failure of initial therapy. Further follow up beyond 28 days only for 4 participants with reappearance of parasitaemia in first 28 days who were retreated with chloroquine
Luxemburger 1999	Not randomized
Pinto 1998	Low dose of chloroquine and primaquine was given for 2 groups for 5 days and 7 days respectively
Prasad 1991	No comparison group
Roy 1977	No comparison group
Saint-Yves 1977	Presumptive treatment of 45 mg primaquine given to all participants before randomization
Schwartz 2000	Retrospective study
Sharma 1973	Not a randomized trial
Singh 1990	Not randomized
Sinha 1989	No comparison group
Soto 1998	Compared 30 mg primaquine for 16 weeks against placebo in healthy people.
Soto 1999	Compared 30 mg primaquine for 16 weeks against placebo in healthy people
Valibayov 2003	No comparison group

Characteristics of ongoing studies [ordered by study ID]

Rowland 2004

Trial name or title	“ A Placebo Controlled, Randomised Evaluation of an Eight Week Primaquine Regimen for the Treatment of Vivax Malaria”
Methods	Randomized controlled trial
Participants	Vivax-positive individuals from Adizai and Baghicha refugee camps, Pakistan, and Jalalabad, Afghanistan Inclusion criteria: 1. Diagnosed with <i>Plasmodium vivax</i> parasitaemia 2. Over 3 years old 3. With G6PD deficiency to a safety trial 4. Without G6PD deficiency to all other groups Exclusion criteria: 1. Children under the age of 3 2. Pregnant or breastfeeding women 3. Severe clinical anaemia (haemoglobin < 7 g/dL) 4. <i>Plasmodium falciparum</i> 5. Unavailable for the duration of study 6. Antimalarial drugs in the 2 weeks before consultation 7. Concomitant infections or whose general health is considered too poor
Interventions	1. Initial 3-day chloroquine with supervised weekly placebo for 8 wk 2. Initial 3-day chloroquine followed by supervised 14-day primaquine treatment 3. Initial 3-day chloroquine followed by supervised 8-wk primaquine treatment (45 mg/wk) 4. A safety arm G6PD-deficient participants; this will be used to compare packed cell volume with group 3 (above)
Outcomes	Primary efficacy variable: proportion with relapse(s) of <i>P. vivax</i> in 12 months of follow up Secondary efficacy variables: time to subsequent relapse episode; number of relapse episodes in 12 months; side effects/adverse events
Starting date	April 2004 Duration: 3 years
Contact information	Principal Investigator: Mark Rowland, PhD, London School of Hygiene and Tropical Medicine
Notes	Location: Adizai and Baghicha refugee camps, Pakistan, and Jalalabad, Afghanistan ClinicalTrials.gov Identifier: NCT00158587 Sponsors and collaborators: Gates Malaria Partnership; HealthNet International

G6PD: glucose-6-phosphate dehydrogenase

DATA AND ANALYSES

Comparison 1. Primaquine (5 days) plus chloroquine vs chloroquine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 <i>P. vivax</i> parasitaemia detected > 30 days after starting primaquine	3	2104	Odds Ratio (M-H, Random, 95% CI)	1.04 [0.64, 1.69]
1.1 Follow up: ≤ 6 months	1	122	Odds Ratio (M-H, Random, 95% CI)	2.63 [1.00, 6.96]
1.2 Follow up: > 6 months	2	1982	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.65, 1.14]

Comparison 2. Primaquine (14 days) plus chloroquine vs chloroquine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 <i>P. vivax</i> parasitaemia detected > 30 days after starting primaquine	6		OR (Random, 95% CI)	0.24 [0.12, 0.45]
1.1 Follow up ≤ 6 months	4		OR (Random, 95% CI)	0.11 [0.05, 0.23]
1.2 Follow up ≥ 6 months	2		OR (Random, 95% CI)	0.41 [0.29, 0.60]

Comparison 3. Primaquine (5 days) plus chloroquine vs primaquine (14 days) plus chloroquine

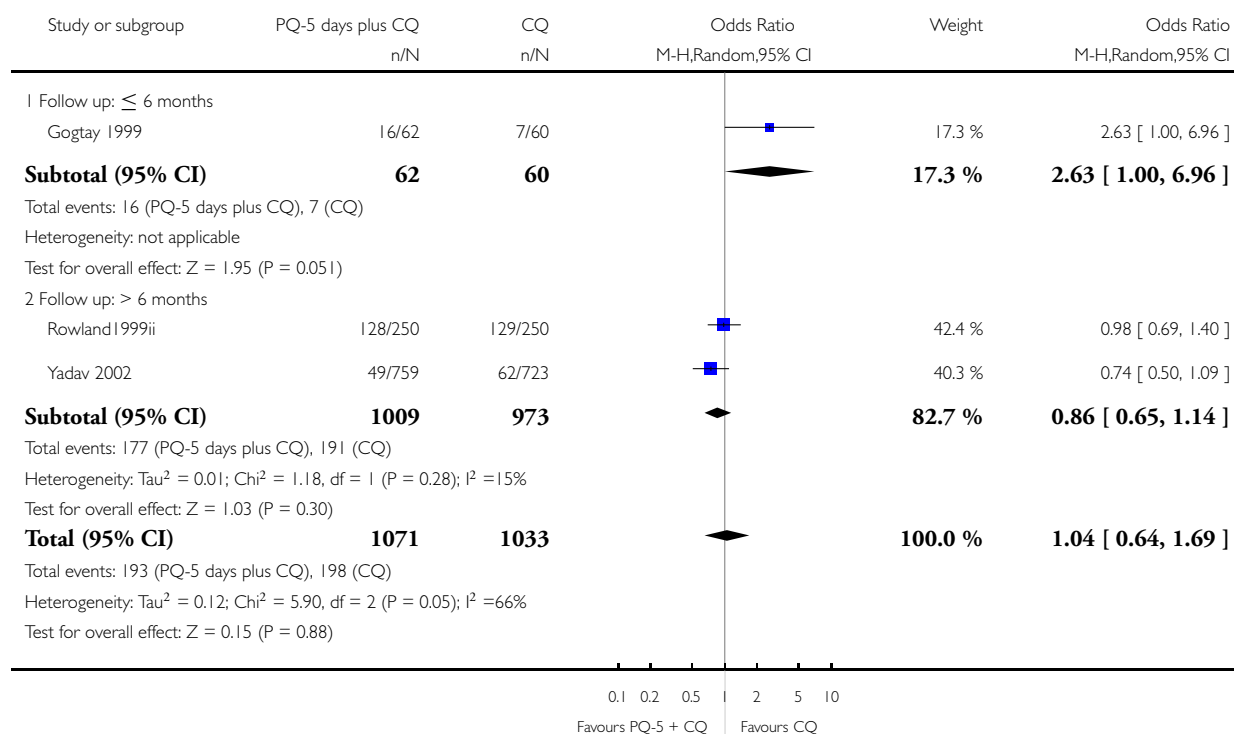
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 <i>P. vivax</i> parasitaemia detected > 30 days after starting primaquine	2	186	Odds Ratio (M-H, Fixed, 95% CI)	13.33 [3.45, 51.44]
2 <i>P. vivax</i> parasitaemia detected > 30 days after starting primaquine, excluding new infection by PCR	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 Primaquine (5 days) plus chloroquine vs chloroquine, Outcome 1 *P. vivax* parasitaemia detected > 30 days after starting primaquine.

Review: Primaquine for preventing relapses in people with Plasmodium vivax malaria

Comparison: 1 Primaquine (5 days) plus chloroquine vs chloroquine

Outcome: 1 *P. vivax* parasitaemia detected > 30 days after starting primaquine

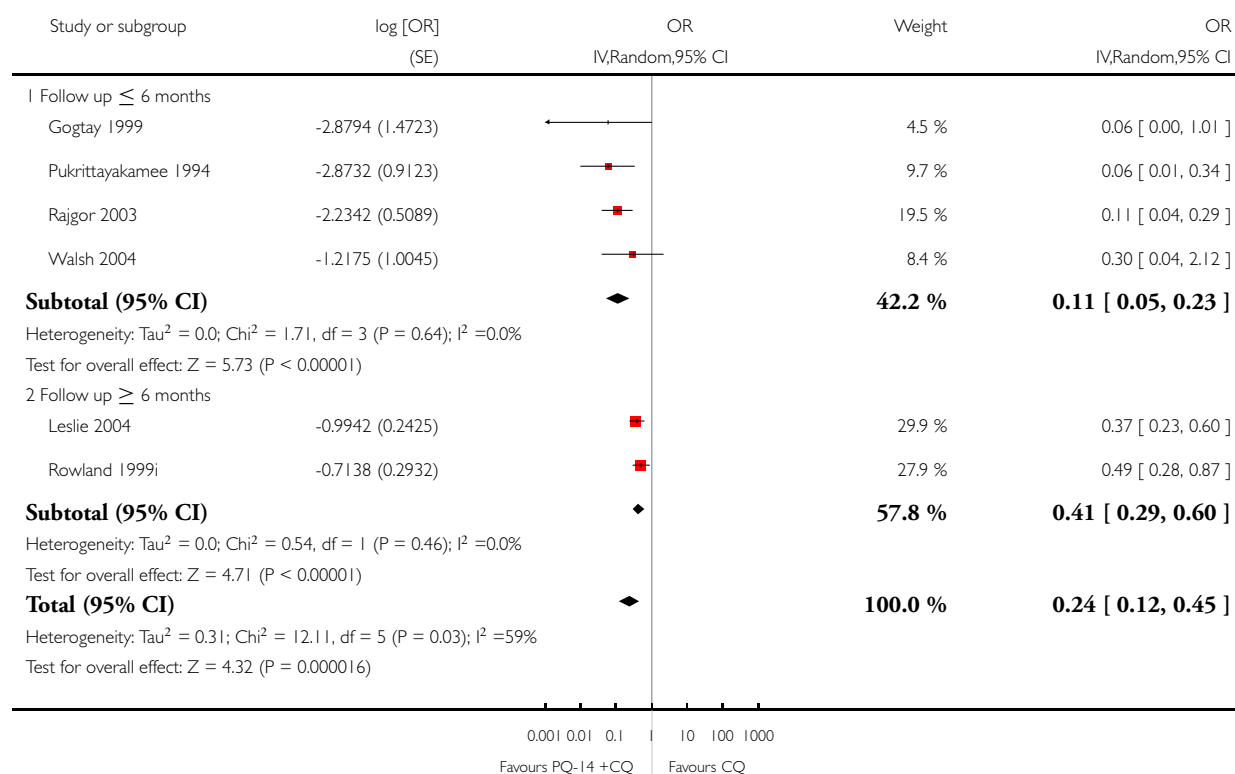


Analysis 2.1. Comparison 2 Primaquine (14 days) plus chloroquine vs chloroquine, Outcome 1 *P. vivax* parasitaemia detected > 30 days after starting primaquine.

Review: Primaquine for preventing relapses in people with Plasmodium vivax malaria

Comparison: 2 Primaquine (14 days) plus chloroquine vs chloroquine

Outcome: 1 *P. vivax* parasitaemia detected > 30 days after starting primaquine

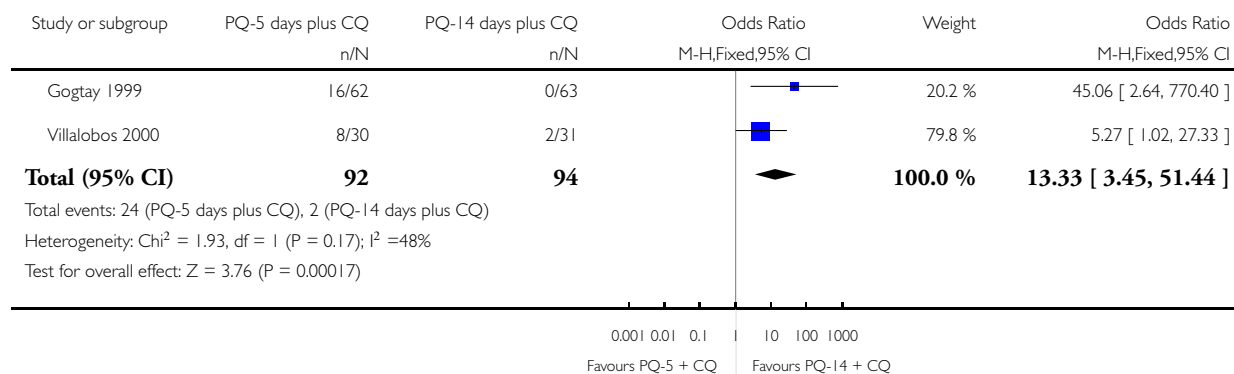


Analysis 3.1. Comparison 3 Primaquine (5 days) plus chloroquine vs primaquine (14 days) plus chloroquine, Outcome 1 *P. vivax* parasitaemia detected > 30 days after starting primaquine.

Review: Primaquine for preventing relapses in people with Plasmodium vivax malaria

Comparison: 3 Primaquine (5 days) plus chloroquine vs primaquine (14 days) plus chloroquine

Outcome: 1 *P. vivax* parasitaemia detected > 30 days after starting primaquine

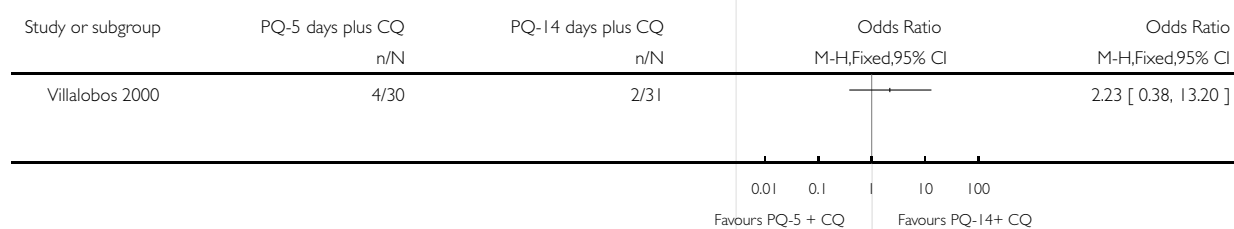


Analysis 3.2. Comparison 3 Primaquine (5 days) plus chloroquine vs primaquine (14 days) plus chloroquine, Outcome 2 *P. vivax* parasitaemia detected > 30 days after starting primaquine, excluding new infection by PCR.

Review: Primaquine for preventing relapses in people with Plasmodium vivax malaria

Comparison: 3 Primaquine (5 days) plus chloroquine vs primaquine (14 days) plus chloroquine

Outcome: 2 *P. vivax* parasitaemia detected > 30 days after starting primaquine, excluding new infection by PCR



WHAT'S NEW

Last assessed as up-to-date: 30 October 2006.

24 March 2008	Amended	Dosage figures corrected.
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HISTORY

Protocol first published: Issue 3, 2003

Review first published: Issue 1, 2007

CONTRIBUTIONS OF AUTHORS

Gawrie Galappaththy conceived the review, wrote the protocol, selected studies, assessed quality, extracted and entered data, synthesized data, interpreted results, wrote the draft of the review, and approved the final version. Aika Omari helped write the protocol, selected studies, assessed quality, extracted data, interpreted data, helped write the draft of the review, and approved the final version. Prathap Tharyan revised the protocol, selected studies, checked quality, extracted and entered data, synthesized data, interpreted results, and wrote the final version of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.
- National Malaria Control Programme, Sri Lanka.
- Christian Medical College, Vellore, India.

External sources

- Department for International Development (DFID), UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2007, Issue 1 (review): We stated in the protocol that we intended to stratify the results by length of follow up: 40 days, 90 days, 120 days, six months, nine months, one year, and greater than one year. We could not do this because only nine trials met the inclusion criteria; so instead we analysed the length of follow up as less than or equal to six months and greater than six months. Prathap Tharyan joined the team as a co-author of this review after publication of the protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

Antimalarials [*therapeutic use]; Chloroquine [therapeutic use]; Malaria, Vivax [*prevention & control]; Primaquine [*therapeutic use]; Randomized Controlled Trials as Topic; Recurrence [prevention & control]

MeSH check words

Adult; Child; Humans