# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEADER</td>
<td>1</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>1</td>
</tr>
<tr>
<td>PLAIN LANGUAGE SUMMARY</td>
<td>2</td>
</tr>
<tr>
<td>BACKGROUND</td>
<td>2</td>
</tr>
<tr>
<td>OBJECTIVES</td>
<td>4</td>
</tr>
<tr>
<td>METHODS</td>
<td>4</td>
</tr>
<tr>
<td>RESULTS</td>
<td>6</td>
</tr>
<tr>
<td>Figure 1</td>
<td>10</td>
</tr>
<tr>
<td>Figure 2</td>
<td>11</td>
</tr>
<tr>
<td>Figure 3</td>
<td>13</td>
</tr>
<tr>
<td>Figure 4</td>
<td>13</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>13</td>
</tr>
<tr>
<td>AUTHORS’ CONCLUSIONS</td>
<td>14</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>15</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>15</td>
</tr>
<tr>
<td>CHARACTERISTICS OF STUDIES</td>
<td>18</td>
</tr>
<tr>
<td>DATA AND ANALYSES</td>
<td>29</td>
</tr>
<tr>
<td>Analysis 1.1. Comparison 1 Primaquine (5 days) plus chloroquine vs chloroquine, Outcome 1 P. vivax parasitaemia detected &gt; 30 days after starting primaquine.</td>
<td>30</td>
</tr>
<tr>
<td>Analysis 2.1. Comparison 2 Primaquine (14 days) plus chloroquine vs chloroquine, Outcome 1 P. vivax parasitaemia detected &gt; 30 days after starting primaquine.</td>
<td>31</td>
</tr>
<tr>
<td>Analysis 3.1. Comparison 3 Primaquine (5 days) plus chloroquine vs primaquine (14 days) plus chloroquine, Outcome 1 P. vivax parasitaemia detected &gt; 30 days after starting primaquine.</td>
<td>32</td>
</tr>
<tr>
<td>Analysis 3.2. Comparison 3 Primaquine (5 days) plus chloroquine vs primaquine (14 days) plus chloroquine, Outcome 2 P. vivax parasitaemia detected &gt; 30 days after starting primaquine, excluding new infection by PCR.</td>
<td>32</td>
</tr>
<tr>
<td>WHAT’S NEW</td>
<td>32</td>
</tr>
<tr>
<td>HISTORY</td>
<td>33</td>
</tr>
<tr>
<td>CONTRIBUTIONS OF AUTHORS</td>
<td>33</td>
</tr>
<tr>
<td>DECLARATIONS OF INTEREST</td>
<td>33</td>
</tr>
<tr>
<td>SOURCES OF SUPPORT</td>
<td>33</td>
</tr>
<tr>
<td>DIFFERENCES BETWEEN PROTOCOL AND REVIEW</td>
<td>33</td>
</tr>
<tr>
<td>INDEX TERMS</td>
<td>33</td>
</tr>
</tbody>
</table>
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 (Breman 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 people 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 (Breman 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 (Cogwell 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; Kruddood 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 (methaemoglobinemia) 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, methaemoglobinemia, 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

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<th>CIDG SR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>CENTRAL</th>
<th>MEDLINE&lt;sup&gt;b&lt;/sup&gt;</th>
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*a* Cochrane Infectious Diseases Group Specialized Register.

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

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**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.

**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 Coordinating 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**

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

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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.

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Cochrane Infectious Diseases Group Specialized Register.
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 variability (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 1999ii; 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; Raigor 2003); three in Afghan refugee camps in Pakistan (Rowland 1999ii; 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; Raigor 2003; Walsh 2004); nine months (Leslie 2004); and 12 months (Rowland 1999ii; 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; Rowland 1999ii; 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; Rowland 1999ii; 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; Rowland 1999ii; 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 clearance 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; Rowland 1999ii; 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 1999; Rowland 1999ii; 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

<table>
<thead>
<tr>
<th>Trial</th>
<th>Generation of allocation sequence</th>
<th>Allocation concealment</th>
<th>Blinding</th>
<th>Inclusion of all randomized participants in the analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gogtay 1999</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Single blind</td>
<td>Inadequate</td>
</tr>
<tr>
<td>Leslie 2004</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unsupervised group blinded, unsupervised group not blinded</td>
<td>Adequate</td>
</tr>
<tr>
<td>Pukrittayakamee 1994</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unsupervised group blinded, unsupervised group not blinded</td>
<td>Adequate</td>
</tr>
<tr>
<td>Rowland 1999i</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Single blind</td>
<td>Adequate</td>
</tr>
<tr>
<td>Rowland 1999i</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Single blind</td>
<td>Adequate</td>
</tr>
<tr>
<td>Rajgor 2003</td>
<td>Adequate</td>
<td>Unclear</td>
<td>Single blind</td>
<td>Inadequate</td>
</tr>
<tr>
<td>Villalobos 2000</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Adequate</td>
</tr>
<tr>
<td>Walsh 2004</td>
<td>Adequate</td>
<td>Partly adequate</td>
<td>Open</td>
<td>Inadequate</td>
</tr>
<tr>
<td>Yadav 2002</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Adequate</td>
</tr>
</tbody>
</table>
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 1999ii; 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 homogeneous 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).
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 1999; Leslie 2004; Raigor 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.
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)

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. participants relapsing</th>
<th>Odds ratio</th>
<th>Log odds ratio</th>
<th>Standard error of log odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primaquine-14 chloroquine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pukrittayakamee 1994</td>
<td>n/N = 2/25</td>
<td>(2<em>26)/(23</em>4) = 2.8794</td>
<td>-2.8732</td>
<td>Square root of (1/2+ 1/26 + 1/23 + 1/4) = 0.912274164</td>
</tr>
<tr>
<td>Gogtay 1999</td>
<td>n/N = 0/63</td>
<td>(0.5<em>53.5)/(63.5</em>7.5) = 0.565217391</td>
<td>-2.8794</td>
<td>Square root of (1/0.5 + 1/53.5 + 1/7.5 + 1/63.5) = 1.472335883</td>
</tr>
<tr>
<td>Rowland 1999i</td>
<td>n/N = 32/100</td>
<td>(32<em>51)/(68</em>49) = 0.4897959 = -0.7138</td>
<td>0.565217391</td>
<td>Square root of (1/33 + 1/51 + 1/68 + 1/49) = 0.29322346</td>
</tr>
</tbody>
</table>

---

Primaquine for preventing relapses in people with Plasmodium vivax malaria (Review)
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### Table 3. Data used for generic inverse variance (Analysis 02.01) (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>n/N = 6/131</th>
<th>n/N = 13/142</th>
<th>(\frac{(6\times129)}{(125\times13)} = 0.107076923)</th>
<th>-2.2342</th>
<th>Square root of ((\frac{1}{6} + \frac{1}{125} + \frac{1}{13} + \frac{1}{129}) = 0.5089)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rajgor 2003</td>
<td>n/N = 34/173</td>
<td>n/N = 86/212</td>
<td>(0.35^*) (95% CI 0.23 to 0.59) (adjusted OR and 95% CI from report) (-0.9942)</td>
<td>0.2425</td>
<td></td>
</tr>
<tr>
<td>Leslie 2004</td>
<td>n/N = 3/12</td>
<td>n/N = 11/13</td>
<td>(\frac{(3\times2)}{(9\times11)} = 0.060606066) (-1.2175)</td>
<td>Square root of ((\frac{1}{3} + \frac{1}{2} + \frac{1}{11} + \frac{1}{13}) = 1.004489920)</td>
<td></td>
</tr>
</tbody>
</table>

### Adverse events

Rowland 1999i and Rowland 1999ii 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.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PO-5 days plus CO Events</th>
<th>Total</th>
<th>PO-14 days plus CO Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M.I. Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gogtay 1999</td>
<td>18</td>
<td>82</td>
<td>0</td>
<td>63</td>
<td>20.2%</td>
<td>45.06 [2.64, 770.46]</td>
</tr>
<tr>
<td>Villalobos 2006</td>
<td>8</td>
<td>38</td>
<td>2</td>
<td>31</td>
<td>79.8%</td>
<td>5.21 [1.02, 27.33]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>24</td>
<td>92</td>
<td></td>
<td>94</td>
<td>100.0%</td>
<td>13.33 [3.45, 51.44]</td>
</tr>
</tbody>
</table>

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 blindness; some had high levels of attrition (Gogtay 1999; Pukrittayakamee 1994; Raigor 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-
Primaquine 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 (Qingjue 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 1999; Rowland 1999; 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.

ACKNOWLEDGEMENTS

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REFERENCES

References to studies included in this review

Gogtay 1999 (published data only)

Leslie 2004 (published data only)

Pukrittayakamee 1994 (published data only)

Rajgor 2003 (published data only)
Primaquine for preventing relapses in people with Plasmodium vivax malaria (Review)

Basavaraj 1960 [published data only]

Buchachart 2001 [published data only]

Bunnag 1994 [published data only]

Cedillos 1978 [published data only]

Clyde 1977 [published data only]

Contacos 1974 [published data only]

da Silva 2003 [published data only]

Dua 2001 [published data only]

Fryauff 1997 [published data only]

Gogtay 1998 [published data only]

Gogtay 1996 [published data only]

Gogtay 2000 [published data only]

Basavaraj 1960 [published data only]

Buchachart 2001 [published data only]

Bunnag 1994 [published data only]

References to studies excluded from this review

Abdon 2001 [published data only]

Appavo 1984 [published data only]

Baird 1995 [published data only]

Baird 2001 [published data only]

Baird 2003 [published data only]

Walsh 2004 [published data only]

Yaday 2002 [published data only]

Baird 1999 [published data only]

Baird 1999ii [published data only]

Villalobos 2000 [published data only]

Walsh 2004 [published data only]

Yaday 2002 [published data only]

References to studies excluded from this review

Abdon 2001 [published data only]

Appavo 1984 [published data only]

Baird 1995 [published data only]

Baird 2001 [published data only]

Baird 2003 [published data only]
Primaquine for preventing relapses in people with Plasmodium vivax malaria (Review)

References

Valibayov 2003 (published data only)

References to ongoing studies

Rowland 2004 (published data only)

Additional references

Adak 2001

Baird 2004

Beutler 1994

Bremner 2001

CDC 2005

Charoenlarp 1973

Cogswell 1992

Collins 1996

Craig 1996

Deeks 2005
Divine 1992

Fonseka 1987

Haynes 2005

Higgins 2003

Higgins 2005

Hill 2006

Juni 2001

Krudsood 2006

Looareesuwan 1997

Mendis 2001

Moher 2001

Orton 2005

Parfitt 1999

Qingjun 1998

WHO 2001

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

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

**Gogtay 1999**

<table>
<thead>
<tr>
<th>Methods</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized controlled trial</td>
<td></td>
</tr>
<tr>
<td>Generation of allocation sequence: unclear</td>
<td></td>
</tr>
<tr>
<td>Allocation concealment: unclear</td>
<td></td>
</tr>
<tr>
<td>Blinding: assessor blinded</td>
<td></td>
</tr>
<tr>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number: 244 recruited</td>
<td></td>
</tr>
<tr>
<td>Inclusion criteria: patients attending K.E.M. Hospital; smear positive for <em>P. vivax</em>; and willing to be hospitalized</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: mixed infection and G6PD deficiency participants</td>
<td></td>
</tr>
<tr>
<td>Age range: 16 to 63 years</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. CQ (3 days): 83 participants</td>
<td></td>
</tr>
<tr>
<td>2. PQ (5 days) plus CQ (3 days): 80 participants</td>
<td></td>
</tr>
<tr>
<td>3. PQ (14 days) plus CQ (3 days): 81 participants</td>
<td></td>
</tr>
<tr>
<td>CQ dose: 25 mg/kg</td>
<td></td>
</tr>
<tr>
<td>PQ dose: 0.25 mg/kg</td>
<td></td>
</tr>
<tr>
<td>All participants hospitalized for intervention</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Number of participants relapsing during the 6-month follow-up period</td>
<td></td>
</tr>
<tr>
<td>2. Adverse events</td>
<td></td>
</tr>
<tr>
<td>Parasitic clearance after intervention was confirmed</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Location: K.E.M. Hospital in Mumbai, India</td>
<td></td>
</tr>
<tr>
<td>Date: October 1997</td>
<td></td>
</tr>
<tr>
<td>Malaria endemicity: 80% of infections are <em>P. vivax</em> malaria</td>
<td></td>
</tr>
</tbody>
</table>

<p>| Risk of bias                                  | |</p>
<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

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

Copyright © 2008 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
**Leslie 2004**

| Methods | 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 |
|---|---|
| Participants | Number: 595  
Inclusion criteria: clinical cases with blood smear positive for *P. vivax* 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 |
| Interventions | 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 |
| Outcomes | 1. Number of participants relapsing during the 9-month follow-up period  
Parasitic clearance after intervention was not confirmed |
| Notes | Location: Afghan refugee camp, North-West Frontier Province, Pakistan  
Date: June 2000 to August 2001  
Malaria endemicity: highly endemic for *P. vivax* and *P. falciparum* 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 |

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>
### Pulkritayakamee 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 *P. vivax* 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 *P. falciparum* malaria

#### Risk of bias

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

### 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 *P. vivax*; normal G6PD status; consented to trial and follow up; haemoglobin > 10 g/dL
- Excluded: < 16 years; G6PD deficiency; pregnant and lactating women; mixed infections
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 *P. vivax* 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 *P. vivax*

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

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 *P. vivax* 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
### Notes

Location: Adizai refugee camp, Afghanistan  
Date: August 1997 to June 1998  
Malaria endemicity: predominant species is *P. vivax* malaria  
Data analysed were number of participants relapsing over 12 months

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

### 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: *P. vivax* 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: *P. vivax* predominant species  
Data analysed were number of clinical-parasitic episodes over 12 months

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>
### 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: *P. vivax* 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 *P. vivax* 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

<table>
<thead>
<tr>
<th>Item</th>
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<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

### 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 *P. vivax*; 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)

| 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**

<table>
<thead>
<tr>
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<tbody>
<tr>
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<td>B - Unclear</td>
</tr>
</tbody>
</table>

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 *P. vivax*
|                            | 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
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

<table>
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<tr>
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</tbody>
</table>

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]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdon 2001</td>
<td>Different doses of chloroquine was given to control and experimental groups</td>
</tr>
<tr>
<td>Appavoo 1984</td>
<td>Participants were not randomly assigned</td>
</tr>
<tr>
<td>Baird 1995</td>
<td>Not randomized; compared primaquine with chloroquine in healthy people</td>
</tr>
<tr>
<td>Baird 2001</td>
<td>Healthy participants randomized to 30 mg primaquine or placebo</td>
</tr>
<tr>
<td>Baird 2003</td>
<td>Not a trial</td>
</tr>
<tr>
<td>Basavaraj 1960</td>
<td>Case series</td>
</tr>
<tr>
<td>Buchachart 2001</td>
<td>Case series</td>
</tr>
<tr>
<td>Bunnag 1994</td>
<td>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</td>
</tr>
<tr>
<td>Cedillos 1978</td>
<td>Compared 2 regimens of primaquine with amodiaquine versus amodiaquine</td>
</tr>
<tr>
<td>Clyde 1977</td>
<td>No comparison group</td>
</tr>
<tr>
<td>Study</td>
<td>Comparator(s)</td>
</tr>
<tr>
<td>--------------------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Contacos 1974</td>
<td>No comparison group</td>
</tr>
<tr>
<td>da Silva 2003</td>
<td>Compared artemisinin and primaquine with chloroquine and primaquine</td>
</tr>
<tr>
<td>Dua 2001</td>
<td>Not randomized</td>
</tr>
<tr>
<td>Fryauff 1997</td>
<td>Compared 1 year of weekly chloroquine, daily primaquine, or placebo</td>
</tr>
<tr>
<td>Gogtay 1998</td>
<td>Not randomized</td>
</tr>
<tr>
<td>Looareesuwan 1999</td>
<td>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</td>
</tr>
<tr>
<td>Luxemburger 1999</td>
<td>Not randomized</td>
</tr>
<tr>
<td>Pinto 1998</td>
<td>Low dose of chloroquine and primaquine was given for 2 groups for 5 days and 7 days respectively</td>
</tr>
<tr>
<td>Prasad 1991</td>
<td>No comparison group</td>
</tr>
<tr>
<td>Roy 1977</td>
<td>No comparison group</td>
</tr>
<tr>
<td>Saint-Yves 1977</td>
<td>Presumptive treatment of 45 mg primaquine given to all participants before randomization</td>
</tr>
<tr>
<td>Schwartz 2000</td>
<td>Retrospective study</td>
</tr>
<tr>
<td>Sharma 1973</td>
<td>Not a randomized trial</td>
</tr>
<tr>
<td>Singh 1990</td>
<td>Not randomized</td>
</tr>
<tr>
<td>Sinha 1989</td>
<td>No comparison group</td>
</tr>
<tr>
<td>Soto 1998</td>
<td>Compared 30 mg primaquine for 16 weeks against placebo in healthy people.</td>
</tr>
<tr>
<td>Soto 1999</td>
<td>Compared 30 mg primaquine for 16 weeks against placebo in healthy people.</td>
</tr>
<tr>
<td>Valibayov 2003</td>
<td>No comparison group</td>
</tr>
</tbody>
</table>
### Characteristics of ongoing studies [ordered by study ID]

**Rowland 2004**

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

G6PD: glucose-6-phosphate dehydrogenase
**DATA AND ANALYSES**

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

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

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

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

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

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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>PQ-5 days plus CQ</th>
<th>CQ</th>
<th>Odds Ratio M-H,Random 95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H,Random 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Follow up: ≤ 6 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gogtay 1999</td>
<td>16/62</td>
<td>7/60</td>
<td>17.3 % 2.63 [1.00, 6.96]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>62</td>
<td>60</td>
<td>17.3 % 2.63 [1.00, 6.96]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable

Test for overall effect: Z = 1.95 (P = 0.051)

| Follow up: > 6 months |                   |     |                               |        |                               |
|-----------------------|                   |     |                               |        |                               |
| Rowland 1999ii        | 128/250           | 129/250 | 42.4 % 0.98 [0.69, 1.40]  |        |                               |
| Yadav 2002            | 49/759            | 62/723 | 40.3 % 0.74 [0.50, 1.09]  |        |                               |
| Subtotal (95% CI)     | 1009              | 973  | 82.7 % 0.86 [0.65, 1.14]  |        |                               |

Heterogeneity: Tu^2 = 0.12; Ch^2 = 5.90, df = 2 (P = 0.05); I^2 = 66%

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

Total (95% CI) 1071 1033 100.0 % 1.04 [0.64, 1.69]
### 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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>log [OR] (SE)</th>
<th>OR (IV/Random, 95% CI)</th>
<th>Weight</th>
<th>OR (IV/Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Follow up ≤ 6 months</td>
<td></td>
<td></td>
<td>4.5 %</td>
<td>0.06 [0.00, 1.01]</td>
</tr>
<tr>
<td>Gogtay 1999</td>
<td>-2.8794 (1.4723)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pakrittayakamee 1994</td>
<td>-2.8732 (0.9123)</td>
<td></td>
<td>9.7 %</td>
<td>0.06 [0.01, 0.34]</td>
</tr>
<tr>
<td>Rajgor 2003</td>
<td>-2.2342 (0.5089)</td>
<td></td>
<td>19.5 %</td>
<td>0.11 [0.04, 0.29]</td>
</tr>
<tr>
<td>Walsh 2004</td>
<td>-1.2175 (1.0045)</td>
<td></td>
<td>8.4 %</td>
<td>0.30 [0.04, 2.12]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td>42.2 %</td>
<td>0.11 [0.05, 0.23]</td>
</tr>
<tr>
<td>2 Follow up ≥ 6 months</td>
<td></td>
<td></td>
<td>29.9 %</td>
<td>0.37 [0.23, 0.60]</td>
</tr>
<tr>
<td>Leslie 2004</td>
<td>-0.9942 (0.2425)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rowland 1999i</td>
<td>-0.7138 (0.2932)</td>
<td></td>
<td>27.9 %</td>
<td>0.49 [0.28, 0.87]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td>57.8 %</td>
<td>0.41 [0.29, 0.60]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td>100.0 %</td>
<td>0.24 [0.12, 0.45]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.0$; $\chi^2 = 1.71, df = 3 (P = 0.64); I^2 = 0.0$

Test for overall effect: $Z = 5.73 (P < 0.00001)$

Heterogeneity: $\tau^2 = 0.31; \chi^2 = 12.1, df = 5 (P = 0.03); I^2 = 59$

Test for overall effect: $Z = 4.32 (P = 0.000016)$
### 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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>PQ-5 days plus CQ</th>
<th>PQ-14 days plus CQ</th>
<th>Odds Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gogtay 1999</td>
<td>16/62</td>
<td>0/63</td>
<td>20.2 % 45.06 [ 2.64, 770.40 ]</td>
<td>45.06</td>
</tr>
<tr>
<td>Villalobos 2000</td>
<td>8/30</td>
<td>2/31</td>
<td>79.8 % 5.27 [ 1.02, 27.33 ]</td>
<td>5.27</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>92</strong></td>
<td><strong>94</strong></td>
<td><strong>100.0 % 13.33 [ 3.45, 51.44 ]</strong></td>
<td><strong>13.33</strong></td>
</tr>
</tbody>
</table>

Total events: 24 (PQ-5 days plus CQ), 2 (PQ-14 days plus CQ)

Heterogeneity: Chisq = 1.93, df = 1 (P = 0.17); I^2 = 48%

Test for overall effect: Z = 3.76 (P = 0.00017)

### 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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>PQ-5 days plus CQ</th>
<th>PQ-14 days plus CQ</th>
<th>Odds Ratio M-H,Fixed 95% CI</th>
<th>Odds Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Villalobos 2000</td>
<td>4/30</td>
<td>2/31</td>
<td>2.23 [ 0.38, 13.20 ]</td>
<td></td>
</tr>
</tbody>
</table>

**WHAT'S NEW**

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

24 March 2008 Amended Dosage figures corrected.
HISTORY

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.
- 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