Artemisinin-based combination therapy for treating uncomplicated *Plasmodium vivax* malaria (Review)

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[Intervention Review]

Artemisinin-based combination therapy for treating uncomplicated *Plasmodium vivax* malaria

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ABSTRACT

Background

Plasmodium vivax is an important cause of malaria in many parts of Asia and South America, and parasite resistance to the standard treatment (chloroquine) is now high in some parts of Oceania. This review aims to assess the current treatment options in the light of increasing chloroquine resistance.

Objectives

To compare artemisinin-based combination therapies (ACTs) with alternative antimalarial regimens for treating acute uncomplicated *P. vivax* malaria.

Search methods

We searched the Cochrane Infectious Disease Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; EMBASE; LILACS; and the metaRegister of Controlled Trials (mRCT) up to 28 March 2013 using "vivax" and "arte* OR dihydroarte*" as search terms.

Selection criteria

Randomized controlled trials comparing ACTs versus standard therapy, or comparing alternative ACTs, in adults and children with uncomplicated *P. vivax* malaria.

Data collection and analysis

Two authors independently assessed trials for eligibility and risk of bias, and extracted data. We used recurrent parasitaemia prior to day 28 as a proxy for effective treatment of the blood stage parasite, and compared drug treatments using risk ratios (RR) and 95% confidence intervals (CIs). We used trials following patients for longer than 28 days to assess the duration of the post-treatment prophylactic effect of ACTs. We assessed the quality of the evidence using the GRADE approach.

Main results

We included 14 trials, that enrolled 2592 participants, and were all conducted in Asia and Oceania between 2002 and 2011.

ACTs versus chloroquine

ACTs clear parasites from the peripheral blood quicker than chloroquine monotherapy (parasitaemia after 24 hours of treatment: RR 0.42, 95% CI 0.36 to 0.50, four trials, 1652 participants, *high quality evidence*).

In settings where chloroquine remains effective, ACTs are as effective as chloroquine at preventing recurrent parasitaemias before day 28 (RR 0.58, 95% CI 0.18 to 1.90, five trials, 1622 participants, *high quality evidence*). In four of these trials, recurrent parasitaemias before day 28 were very low following treatment with both chloroquine and ACTs. The fifth trial, from Thailand in 2011, found increased recurrent parasitaemias following treatment with chloroquine (9%), while they remained low following ACT (2%) (RR 0.25, 95% CI 0.09 to 0.66, one trial, 437 participants).

ACT combinations with long half-lives probably also provide a longer prophylactic effect after treatment, with significantly fewer recurrent parasitaemias between day 28 and day 42 or day 63 (RR 0.57, 95% CI 0.40 to 0.82, three trials, 1066 participants, *moderate quality evidence*). One trial, from Cambodia, Thailand, India and Indonesia, gave additional primaquine to both treatment groups to reduce the risk of spontaneous relapses. Recurrent parasitaemias after day 28 were lower than seen in the trials that did not give primaquine, but the ACT still appeared to have an advantage (RR 0.27, 95% CI 0.08 to 0.94, one trial, 376 participants, *low quality evidence*).

ACTs versus alternative ACTs

In high transmission settings, dihydroartemisinin-piperaquine is probably superior to artemether-lumefantrine, artesunate plus sulphadoxine-pyrimethamine and artesunate plus amodiaquine at preventing recurrent parasitaemias before day 28 (RR 0.20, 95% CI 0.08 to 0.49, three trials, 334 participants, *moderate quality evidence*).

Dihydroartemisinin-piperaquine may also have an improved post-treatment prophylactic effect lasting for up to six weeks, and this effect may be present even when primaquine is also given to achieve radical cure (RR 0.21, 95% CI 0.10 to 0.46, two trials, 179 participants, *low quality evidence*).

The data available from low transmission settings is too limited to reliably assess the relative effectiveness of ACTs.

Authors' conclusions

ACTs appear at least equivalent to chloroquine at effectively treating the blood stage of *P. vivax* infection. Even in areas where chloroquine remains effective, this finding may allow for simplified protocols for treating all forms of malaria with ACTs. In areas where chloroquine no longer cures the infection, ACTs offer an effective alternative.

Dihydroartemisinin-piperaquine is the most studied ACT. It may provide a longer period of post-treatment prophylaxis than artemether-lumefantrine or artesunate plus amodiaquine. This effect may be clinically important in high transmission settings whether primaquine is also given or not.

PLAIN LANGUAGE SUMMARY

Artemisinin-based combination therapy (ACT) for treating non-severe malaria due to *Plasmodium vivax*

What is *P. vivax* malaria and how do ACTs work?

P. vivax is one of five species of the malaria parasite known to cause clinical illness. It is a common cause of malaria in Asia, South America and Oceania. Unlike *P. falciparum* (the commonest cause of malaria in Africa), *P. vivax* has a liver stage which is not treated by most common antimalarial drugs. This liver stage can become active and cause a relapse of clinical illness weeks or even years after the initial illness.

The standard treatment for vivax malaria has been chloroquine to treat the clinical illness, and a 14-day course of primaquine to clear the liver stage. In some parts of Oceania the *P. vivax* parasite in now highly resistant to chloroquine, which makes this treatment ineffective.

Artemisinin-based combination therapies (ACTs) are now the recommended treatment for *P. falciparum* malaria worldwide. As the effectiveness of chloroquine for *P. vivax* declines, alternative therapies are needed. If ACTs are also effective against *P. vivax* they could become the standard treatment for all forms of malaria.

Current ACT combinations do not contain drugs effective against the liver stage of *P. vivax* so primaquine would still be necessary to achieve complete cure.

What the research says about the effect of using ACTs

We examined the research published up to 28 March 2013.

Compared to chloroquine

People who are treated with an ACT are probably less likely to have another episode of *P. vivax* malaria during the next six to eight weeks than those treated with chloroquine (only dihydroartemisinin-piperaquine, artesunate plus sulphadoxine-pyrimethamine, and artesunate-pyronaridine have been compared with chloroquine). It is not clear whether this advantage is still present when primaquine is given to achieve a complete cure.

Compared to alternative ACTs

People who are treated with dihydroartemisinin-piperaquine are probably less likely to have another episode of *P. vivax* malaria during the next six weeks than those treated with alternative ACTs (only artemether-lumefantrine, artesunate plus sulphadoxine-pyrimethamine and artesunate plus amodiaquine have been compared). This advantage may be present even when additional primaquine is given to achieve a complete cure.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Artemisinin-based combination therapy compared with chloroquine for uncomplicated *P. vivax* malaria

Patient or population: Adults and children with uncomplicated *P. vivax* malaria
Settings: Endemic areas where chloroquine is still an effective treatment for the first 28 days
Intervention: Artemisinin-based combination therapy
Comparison: Chloroquine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Chloroquine	ACT			
Remaining parasitaemic at 24 hours	**52 per 100**	**22 per 100** (19 to 26)	**RR 0.42** (0.36 to 0.50)	1652 (4 studies[1])	**high**[2,3,4,5]
Remaining febrile after 24 hours	**29 per 100**	**16 per 100** (12 to 20)	**RR 0.55** (0.43 to 0.7)	990 (2 studies[6])	**moderate**[2,4,5,7]
Effective treatment of the blood stage parasite As assessed by: Recurrent parasitaemia before day 28	**3 per 100**	**2 per 100** (1 to 6)	**RR 0.58** (0.18 to 1.90)	1622 (5 studies[8])	**high**[2,3,4,9]
Post-treatment prophylaxis As assessed by: Recurrent parasitaemia between day 28 and day 42/56/63	**With primaquine**		**RR 0.27** (0.08 to 0.94)	376 (1 study[10])	**low**[11,12]
	6 per 100	**2 per 100** (0 to 6)			
	Without primaquine		**RR 0.57** (0.40 to 0.82)	1066 (3 studies[13])	**moderate**[3,5,14]
	40 per 100	**23 per 100** (16 to 33)			

Serious adverse events	**0 per 100**	**0 per 100** (0 to 2)	**RR 1** (0.14 to 7.04)	1775 (5 studies[8])	**high**[2,3,4,9]

*The basis for the **assumed risk** (for example, the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; ACT: artemisinin-based combination therapy

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Awab 2010 AFG (Afghanistan), Kolaczinski 2007 AFG (Afghanistan), Poravuth 2010 ASIA (multi-site), and Phyo 2011 THA (Thailand).
[2] No serious study limitations: Awab 2010 AFG , Poravuth 2010 ASIA and Phyo 2011 THA adequately concealed allocation, Kolaczinski 2007 AFG did not, and Krudsood 2007 THA did not adequately describe allocation concealment.
[3] No serious inconsistency: The findings of all the trials are consistent.
[4] No serious indirectness: The findings of these three studies can reasonably be applied to other settings with similar transmission and resistance patterns.
[5] No serious imprecision: The finding is of a clinically and statistically significant benefit with ACTs.
[6] Awab 2010 AFG (Afghanistan) and Poravuth 2010 ASIA (multi-site).
[7] Downgraded by 1 for serious inconsistency: The two additional trials (Kolaczinski 2007 AFG; Krudsood 2007 THA) report that fever clearance was not significantly different between the groups.
[8] Awab 2010 AFG (Afghanistan), Kolaczinski 2007 AFG (Afghanistan), Krudsood 2007 THA (Thailand), Poravuth 2010 ASIA (multi-site), and Phyo 2011 THA (Thailand).
[9] No serious imprecision: The finding is of no clinically important difference between ACTs and CQ. Although the 95% CI around the relative effect is very wide, recurrent parasitaemia before day 28 and serious adverse events were very rare and consequently the 95% CI around the absolute effect is very narrow.
[10] Poravuth 2010 ASIA.
[11] Downgraded by 1 for serious indirectness: Poravuth 2010 ASIA delayed primaquine until day 28 and so the course will not have completed until day 42 the last day of the trial. The effect seen may not be present if primaquine is given in the usual way (on completion of 3 days of ACT). The period of follow-up is also not long enough to fully assess this effect, the inevitable relapse may simply be delayed, rather than a reduction in clinical episodes.
[12] Downgraded by 1 for serious imprecision: Although statistically significant the 95% CI is wide and includes the possibility of no appreciable benefit.
[13] Awab 2010 AFG continued until day 56, Kolaczinski 2007 AFG to day 42 and Phyo 2011 THA to day 63 (Primaquine was administered to the participants after day 63).

[14] Downgraded by 1 for serious indirectness: Both studies are from Afghanistan Awab 2010 AFG and Kolaczinski 2007 AFG where primaquine is not recommended due to a high prevalence of G6PD. The period of follow-up is also not long enough to fully assess this effect, the inevitable relapse may simply be delayed, rather than a reduction in clinical episodes.

BACKGROUND

Malaria is a disease of global public health importance whose social and economic burden is a major obstacle to human development in many of the worlds' poorest countries (WHO 2012). Transmission occurs from person to person via the bite of female mosquitoes infected with the protozoan parasite *Plasmodium,* of which five species are capable of causing disease in humans: *P. falciparum*,*P. vivax*, *P. malariae*, *P. ovale*, and (rarely)*P. knowlesi* (WHO 2010).

Although *P. falciparum* remains the dominant species worldwide, outside Africa *P. vivax* is often equally prevalent, and co-infections in a single clinical episode are also common (Mayxay 2004; Price 2007b). The relative importance of *P. vivax* has increased over recent years as control efforts against *P. falciparum* have shown signs of success, and as evidence accumulates that *P. vivax* malaria is not an entirely benign illness (Anstey 2009; Price 2009). *P. vivax* accounts for approximately 50% of all malaria episodes in southern Asia and the Western Pacific, and up to 80% in South America and the eastern Mediterranean region (Mendis 2001; Price 2007b). Estimates for the total burden of *P. vivax* are uncertain, ranging from 72 to 390 million clinical episodes per year (Price 2007b), but 2.48 billion people are estimated to be living in the areas at risk of *P. vivax* malaria (Gething 2012).

Resistance of *P. vivax* to chloroquine, a cheap and simple treatment, is now widespread and has rendered this drug ineffective in parts of Indonesia and Papua New Guinea (Sumawinata 2003; Ratcliff 2007a; Karunajeewa 2008; Sutanto 2009). Low levels of resistance have also been reported from Burma, South Korea, Vietnam, India, Turkey, Ethiopia, and parts of southern Africa and South America (Baird 2009; Price 2009; WHO 2010). In 2010, the World Health Organization (WHO) recommended artemisinin-based combination therapy (ACTs) for treating for chloroquine-resistant *P. vivax* malaria (WHO 2012).

Description of the condition

Clinical syndromes

The clinical symptoms of malaria are caused by the direct and indirect effects of the blood stage parasite (Anstey 2009). Uncomplicated malaria is the milder form of the disease which presents as an acute febrile illness with headache, tiredness, muscle pains, abdominal pains, rigors, sweats, nausea, and vomiting (WHO 2010). In the absence of adequate treatment, uncomplicated malaria can progress to severe or fatal forms of the disease characterized by severe anaemia, respiratory distress, renal failure, thrombocytopenia, and coma (Anstey 2009). Such severe disease with *P. vivax* has traditionally been considered extremely rare; however, the development of more accurate diagnostic tests, particularly polymerase chain reaction (PCR) techniques capable of reliably excluding *P. falciparum* as a cause, have revealed that severe disease due to *P. vivax* may cause significant morbidity (Barcus 2007; Genton 2008; Tjitra 2008; Baird 2009; Kochar 2009; Price 2009).

A clinical diagnosis of *P. vivax* malaria can be confirmed by detection and identification of the malaria parasite in the patient's blood using light microscopy, by rapid antigen testing kits, or by PCR techniques (rarely used in a clinical context) (WHO 2010).

The hypnozoite as the cause of spontaneous relapses

P. vivax differs from *P. falciparum* in having a liver stage, known as a hypnozoite, which can lie dormant in the liver following an acute infection. These hypnozoites are not susceptible to the antimalarial drugs used to treat the acute illness (which act upon the circulating blood stage parasite), and are the cause of spontaneous relapses which may occur weeks, months, or even years after the initial episode (Galappaththy 2007; WHO 2010). The frequency and timing of these relapses varies geographically, reflecting variations in the behaviour of locally prevalent strains (Collins 1996; White 2002; Baird 2007). In the tropical regions of southeast Asia and Oceania the risk of relapse is highest, with the first relapse occurring at around three to five weeks and often recurring repeatedly in the same patient (Collins 1996; Baird 1997; Baird 2007; Imwong 2007). Relapses in temperate regions are less common, often occur 6 to 12 months later, and usually only once (Galappaththy 2007; Imwong 2007; Baird 2009).

Radical cure (complete removal of all stages of the malaria parasite from the infected patient) therefore requires additional therapy targeted at the hypnozoite. The only drug in common use for this purpose is primaquine, an 8-aminoquinolone. The current regimen recommended by the World Health Organization (WHO) is 15 mg/kg/day for 14 days, with higher doses necessary is some parts of southeast Asia and Oceania (Galappaththy 2007; WHO 2010). Of note, primaquine is known to cause haemolysis in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency, a condition that can be frequent in some malaria endemic areas. These reactions can range from mild and transient to severe and life-threatening.

Assessing antimalarial efficacy in P. vivax

The hypnozoite causes considerable difficulty in the design and interpretation of *P. vivax* intervention trials. When *P. vivax* parasites reappear in the peripheral blood, which we will term a 'recurrence', there are no reliable methods to distinguish a recrudescence of the original infection (due to failure to adequately clear the schizont from the peripheral blood), from a spontaneous relapse (due to activation of the hypnozoite in the liver) or a re-infection (due to a new infection acquired from a subsequent mosquito bite) (Baird 2009; WHO 2010).

The most accurate test of a drugs ability to clear the blood stage would be to measure treatment failure prior to day 16, as post-

treatment recurrent parasitaemia at this time-point will almost certainly be due to a recrudescence (Baird 2009; WHO 2010). This outcome however, may have little ability to discriminate between drugs, and is too early to exclude the possibility of subsequent recrudescence. Trials of ACT in the treatment of *P. falciparum* have recorded proven recrudescence well beyond 14 or even 28 days (Bloland 2003; Sinclair 2009).

Measuring recurrent parasitaemia at time-points later than 16 days will include failures due to both recrudescences and relapses (Baird 2009). This distinction is important in understanding the therapeutic value of a given treatment, though it may be of little interest to the patient as both may result in a further episodes of clinical illness.

Demonstration of radical cure requires longer periods of follow-up, ideally up to one year, but is further complicated by the possibility that the observed recurrence is not due to recrudescence or relapse but to re-infections (White 2002; WHO 2010). The follow-up period needed to make conclusions on radical cure, rather than delayed relapse, must exceed both the individual drug clearance time (the time taken to effectively reduce the drug levels to undetectable), and the expected relapse time of local strains (Bloland 2003; Baird 2009).

Drug resistance

Chloroquine resistance is a major problem, and there is further evidence of resistance developing among *P. vivax* strains to sulphadoxine-pyrimethamine (a common second-line treatment), and of decreased primaquine efficacy in parts of southeast Asia (Baird 2009).

A 28-day test has been devised to assess chloroquine resistance in vivo. This defines resistance as the recurrence of *P. vivax* parasitaemia before day 28 in the presence of adequate chloroquine drug levels, regardless of the nature of the recurrence (recrudescence, relapse, or re-infection). Prior to the development of resistance, recurrent *P. vivax* parasitaemia following chloroquine treatment was rarely seen before 28 days (Baird 1997; Baird 2009). It seems reasonable therefore to expect a replacement drug to also prevent recurrence (of any cause) for at least 28 days.

To combat the growing problem of resistance among *P. falciparum* strains, the WHO has now recommended that *P. falciparum* malaria is always treated using a combination of two drugs which act at different biochemical sites within the parasite. Parasites carrying a mutation producing resistance arising spontaneously during treatment, should then be killed by the partner drug, reducing or delaying the development of resistance and increasing the useful lifetime of each individual drug (White 1996; White 1999; WHO 2010). The availability of effective (and cheap) monotherapies for *P. vivax*, has until now negated the need for a similar approach with *P. vivax*. However, there are several reasons why ACT treatment for both species might now be desirable:

- both parasites are co-endemic is parts of the world, and individuals can be infected with both species;
- many malaria episodes continue to be diagnosed clinically without identification of the species;
- it would simplify national treatment protocols, and provide a rational approach to both proven, and undetected, *P. falciparum* and *P. vivax* co-infections;
- it may decrease the market availability of monotherapies, and aid in the combat of drug-resistance.

Description of the intervention

Artemisinin and its derivatives (artesunate, artemether, and dihydroartemisinin) are short-acting antimalarial drugs which have been shown to produce rapid relief from clinical symptoms and rapid clearance of the parasite from the peripheral blood (Pukrittayakamee 2000; WHO 2010). They are usually combined with a longer-acting partner drug to produce ACTs. Until recently there was no known resistance to the artemisinin derivatives but some resistance among *P. falciparum* species has now been reported in southeast Asia and is being investigated (Dondorp 2009).

Artemisinin derivatives are generally reported as being well-tolerated, and the safety profile of ACTs may be largely determined by the partner drug (Taylor 2004). Studies of artemisinin derivatives in animals have reported significant neurotoxicity (brain damage), but this has not been seen in human studies (Price 1999). Animal studies have also shown adverse effects on the early development of the foetus, but the artemisinin derivatives have not been fully evaluated during early pregnancy in humans. Other reported adverse events include gastrointestinal disturbance (stomach upset), dizziness, tinnitus (ringing in the ears), neutropenia (low levels of white blood cells), elevated liver enzymes (a marker for liver damage), and electrocardiographic (ECG) abnormalities (changes in cardiac conduction). Most studies, however, have found no evidence of ECG changes, and only non-significant changes in liver enzymes (Nosten 2007; WHO 2010). The incidence of type 1 hypersensitivity (allergic) reactions is reported to be approximately 1 in 3000 patients (Nosten 2007).

How the intervention might work

Therapy for *P. vivax* is divided into two components. First, there is removal of the blood stage of the parasite by a drug with schizonticidal activity, traditionally chloroquine. Second, there is treatment of the liver stage using a hypnozonticidal drug, usually primaquine, to achieve a radical cure. The artemisinin derivatives do not have a substantial effect on the liver stage of the parasite and therefore the primary aim of ACT treatment is eradication of the blood stage parasite, and relief of clinical symptoms (Pukrittayakamee 2000; WHO 2010).

In areas of high transmission where the risk of new infections is high, the risks associated with primaquine, particularly the risk of haemolysis in patients with G6PD deficiency, may outweigh the

clinical benefits (WHO 2010). In this scenario, where primaquine is not routinely given, treatments which delay or prevent the initial relapses could have public health benefits such as; reduced clinical episodes, reduced loss of work, and reduction in malaria-associated anaemia.

A secondary aim of ACT treatment therefore might be to delay clinical relapse, and there are now several trials which have investigated this (Hasugian 2007; Ratcliff 2007b). However, the ability of an ACT to delay the first relapse is critically dependent on the half-life of the partner drug, with long half-life drugs still being present (in sufficient concentration) at the time of the first spontaneous relapse to clear the resultant blood stage parasites and prevent a recurrent clinical illness. This may be a desirable property in a drug combination from a patient perspective, but could contribute to further resistance developing as the partner drug is left unprotected by the rapidly eliminated artemisinin derivative.

Alternatively an ACT co-administered with the recommended 14 days of primaquine could demonstrate superiority to monotherapies plus primaquine if the ACT had fewer recrudescent failures, if it prevented re-infections (as a function of its long half-life), or if it delayed relapses due to primaquine failure.

In addition, the artemisinin derivatives have been shown to have an effect on developing *Plasmodium* gametocytes, which are the stage of the parasite capable of infecting mosquitoes and therefore an important stage in the transmission cycle (Price 1996). The interpretation of this indirect measure for reduced transmission is however unclear; there is evidence that even submicroscopic (undetectable) gametocytes are capable of transmission, and there is no consensus on what might constitute a clinically relevant reduction (Targett 2001). We have included it as an outcome here for completeness.

Why it is important to do this review

ACTs are now the recommended therapy for *P. falciparum* malaria worldwide and despite the initial financial and programmatic hurdles they are now being used in the majority of malaria endemic countries (WHO 2010).

This review seeks to assess the comparative effectiveness of ACTs for treating *P. vivax* malaria.

OBJECTIVES

To compare ACTs with alternative antimalarial regimens for treating acute, uncomplicated *P. vivax* malaria and the prevention of relapses.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials.

Types of participants

Adults and children (including pregnant or lactating women and infants) with symptomatic, microscopically confirmed, uncomplicated *P. vivax* malaria.

In studies recruiting patients with *P. falciparum* and *P. vivax* mono- or co-infections, only the data from patients with proven *P. vivax* (+/- *P. falciparum*) at baseline were included.

Types of interventions

Intervention

- A 3-day course of an ACT.

Control

- A recognized non-ACT antimalarial therapy (chloroquine, sulphadoxine-pyrimethamine, amodiaquine, mefloquine, quinine, or combinations).

Or:

- A 3-day course of an alternative ACT.

Types of outcome measures

Primary outcomes

- Recurrence of *P. vivax* parasitaemia by days 14 and 28.

(The term recurrence simply refers to reappearance of *P. vivax* parasites in the peripheral blood. It may include recrudescences, relapses, and re-infections).

Secondary outcomes

- Parasite clearance: the proportion of patients clear of parasites on each day, or the mean or median time to first negative blood smear.
- Fever clearance: the proportion of patients afebrile on each day, or the mean or median time to becoming afebrile.
- Recurrence of *P. vivax* parasitaemia at one to 12 months.
- Haematological recovery: changes in haemoglobin from baseline to last day of follow-up.
- Measures of gametocyte carriage.
- Serious adverse events that require patients to stop treatment or be admitted to hospital.

Search methods for identification of studies

All relevant studies regardless of language or publication status were considered (published, unpublished, in press, or ongoing).

Electronic searches

We conducted a search of the following databases up to 28 March 2013: Cochrane Infectious Disease Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library*; MEDLINE; EMBASE; and LILACS, using the search terms we have detailed in Table 1. We also searched the metaRegister of Controlled Trials (mRCT) using "vivax" and "arte* OR dihydroarte*" as search terms.

Searching other resources

We reviewed the reference lists of all trials identified by the methods described above for any further trials, and contacted individual researchers working in the field.

Data collection and analysis

Selection of studies

David Sinclair (DS) and Kannan Sridharan (KS) independently reviewed the results of the literature search and obtained full text copies of all trials thought relevant to this review.
DS, KS, and Urmila Thatte (UT) then independently assessed the eligibility of each trial for inclusion in this review using an eligibility form based on the inclusion criteria stated above, and reported the reasons for their exclusion in the 'Characteristics of excluded studies' table. Disagreements were resolved through discussion.

Data extraction and management

Two authors (Nithya Gogtay (NG), DS, and KS) independently extracted data using a pre-tested data extraction form, and extracted data on trial characteristics including: trial site, year, local malaria prevalence and transmission, trial methods, participants, interventions, and outcomes. Disagreements were resolved through discussion and review of the trial report.
For each outcome we extracted the number randomized and the number analysed in each treatment group, and calculated and reported the loss to follow-up in each group.
For dichotomous outcomes we extracted the number of participants experiencing the event, and for continuous outcomes we extracted the arithmetic means and standard deviations for each treatment group.
We analysed the data using Review Manager 5.

Assessment of risk of bias in included studies

Two authors (NG and KS) independently assessed the methodological quality of each trial, using The Cochrane Collaboration's tool for assessing the risk of bias (Review Manager 5). We followed the guidance to assess whether trials took adequate steps to reduce the risk of bias across six domains: sequence generation, allocation concealment, blinding (of participants, personnel, and outcome assessors), incomplete outcome data, selective outcome reporting, and other sources of bias. We categorized our judgements as 'yes' (low risk of bias), 'no' (high risk of bias), or 'unclear'. Where a trial was at unclear risk of bias, we attempted to contact the authors for clarification.

Measures of treatment effect

Dichotomous data are combined using risk ratios and continuous data using mean differences. Both measures are presented with 95% confidence intervals (CIs). Medians and ranges are only reported in tables.

Dealing with missing data

The primary analysis is a complete-case analysis. We excluded participants who were lost to follow-up or who developed *P. falciparum* parasitaemia during follow-up, and conducted a sensitivity analyses as described below to evaluate the robustness of this methodology. Participants who developed mixed parasitaemia during follow-up were treated as failure in the same way as recurrence of *P. vivax* mono-infections.
If data from the trial reports were insufficient, unclear, or missing, we attempted to contact the authors for additional information.

Assessment of heterogeneity

We assessed heterogeneity amongst trials by inspecting the forest plots (to detect overlapping CIs), the I^2 statistic with a level of 50% to denote moderate levels of heterogeneity, and applying the Chi^2 test with a P value of 0.10 to indicate statistical significance.

Assessment of reporting biases

There were too few included trials to assess publication bias.

Data synthesis

We analysed the data using Review Manager 5, and compared treatments directly using pair-wise meta-analyses. We stratified by time-point, and for some analyses, further stratified the results by transmission intensity and known presence of resistance.
When pooling data from comparisons including different combinations (such as any ACT versus chloroquine) we used the random-effects model as we were looking for an 'average' effect rather than one true underlying effect. Where pooling only within a single comparison we used the fixed-effect model when there was

no statistically significant heterogeneity, and the random-effects model when there was moderate heterogeneity. Where a pooled meta-analysis was considered to be meaningless because of clinical or substantial heterogeneity the results were presented in a forest plot without a pooled estimate of effect.

Subgroup analysis and investigation of heterogeneity

The small number of included trials precluded subgroup analysis.

Sensitivity analysis

We conducted four sensitivity analyses to restore the integrity of the randomization process and test the robustness of our results.

- Sensitivity analysis 1: *P. falciparum* cases added in as failures.
- Sensitivity analysis 2: All exclusions added in as failures.
- Sensitivity analysis 3: *P. falciparum* cases added in as successes.
- Sensitivity analysis 4: All exclusions added in as successes.

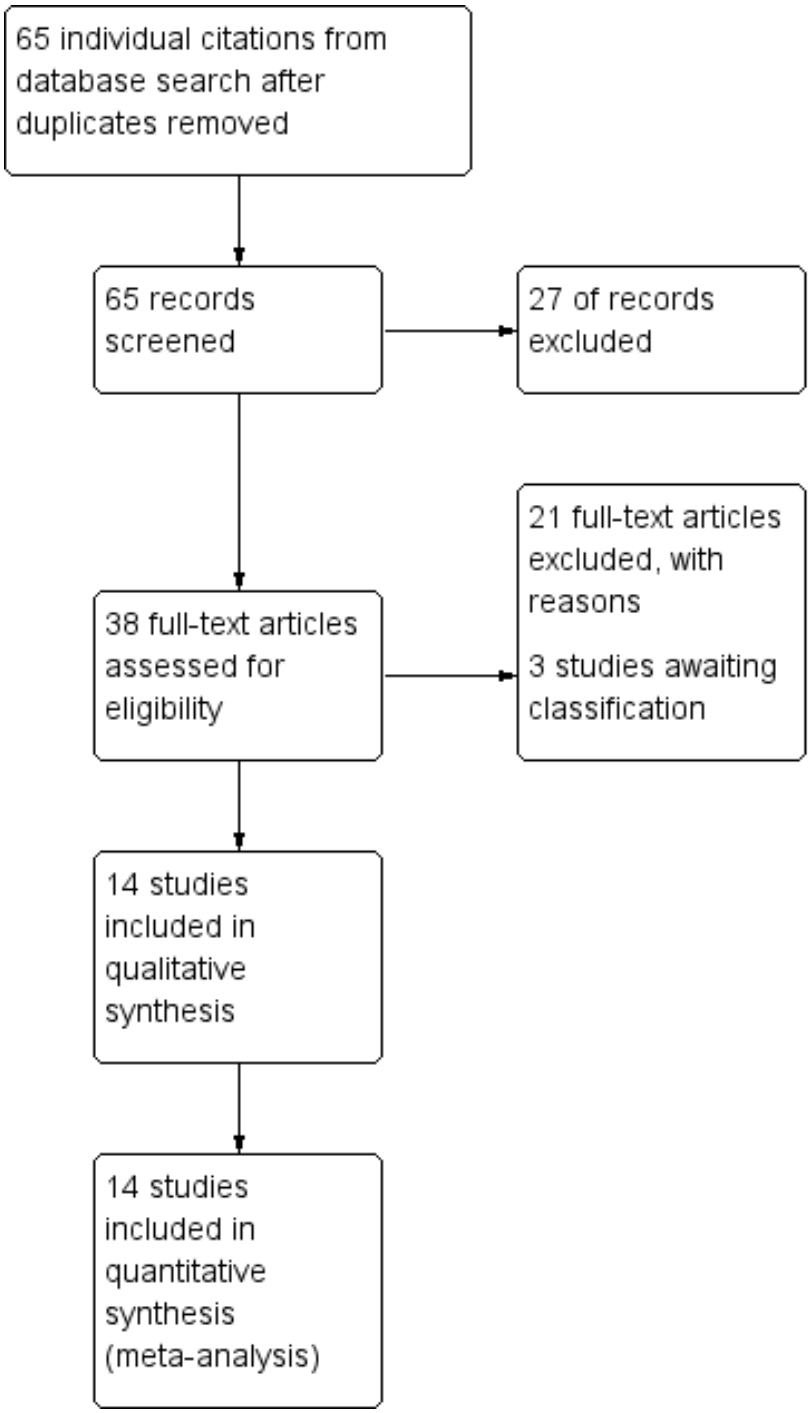
RESULTS

Description of studies

Results of the search

The search was conducted in December 2008 and repeated in November 2009, March 2011 and up to 28 March 2013. In total 65 trials were identified as being potentially relevant to this review, of which 27 were excluded on abstract screening. Thirty-eight full text articles were assessed for eligibility of which 14 are included, 21 are excluded with reasons, and three await classification pending further information from the trial authors (in two studies it is unclear whether any participants had *P. vivax* infection at baseline (van Vugt 2002; Janssens 2007), and in one only a conference abstract is available (Shin 2011). See Figure 1.

Figure 1. Study flow diagram.



Included studies

Fourteen studies are included, all conducted in Asia and Oceania between 2002 and 2011; five from Thailand (Ashley 2004 THA; Ashley 2005 THA; Hutagalung 2005 THA; Krudsood 2007 THA; Phyo 2011 THA), three from Indonesia (Hasugian 2007 IDN; Ratcliff 2007 IDN; Sutanto 2013 IDN), two from Myanmar (Smithuis 2006 MMR; Smithuis 2010 MMR), two from Afghanistan (Kolaczinski 2007 AFG; Awab 2010 AFG), one from Papua New Guinea (Karunajeewa 2008 PNG), and one multicentre trial from Cambodia, Thailand, India, and Indonesia (Poravuth 2010 ASIA). (We have added a country code to the study ID to aid interpretation).

The trial sites in Indonesia and Papua New Guinea are described as having high transmission and high levels of chloroquine resistance amongst *P. vivax* species (Hasugian 2007 IDN; Ratcliff 2007 IDN; Karunajeewa 2008 PNG). The studies sites in Thailand, Myanmar and Afghanistan are described as having low transmission. Chloroquine resistance amongst *P. vivax* is also likely to be low in these settings but not all trial authors stated this specifically. The multicentre trial (Poravuth 2010 ASIA) is likely to have included sites with variable levels of transmission and resistance.

The 14 studies included a total of 2636 participants. Of these, 67.5% were diagnosed with *P. vivax* mono-infection at baseline, 9.7% had co-infections with *P. vivax* and *P. falciparum,* and for 22.8% it was unclear how many had mixed infections. Only five studies co-administered primaquine at the recommended dose to clear the liver stage of the parasite (Hasugian 2007 IDN; Krudsood 2007 THA; Ratcliff 2007 IDN; Poravuth 2010 ASIA; Sutanto 2013 IDN).

One trial followed participants for 28 days after enrolment (Krudsood 2007 THA). This period is informative on the ability of the ACT to clear the blood stage of *P. vivax* but is not long enough to adequately assess recurrent parasitaemias due to spontaneous relapses or re-infections. Seven studies conducted a 42 day follow-up (Hutagalung 2005 THA; Smithuis 2006 MMR; Hasugian 2007 IDN; Kolaczinski 2007 AFG; Ratcliff 2007 IDN; Karunajeewa 2008 PNG; Poravuth 2010 ASIA), one continued until day 56 (Awab 2010 AFG), and four continued until day 63 (Ashley 2004 THA; Ashley 2005 THA; Smithuis 2010 MMR; Phyo 2011 THA). One trial continued an extended follow-up for one year (Sutanto 2013 IDN).

Further characteristics of the included studies are in the 'Characteristics of included studies' table.

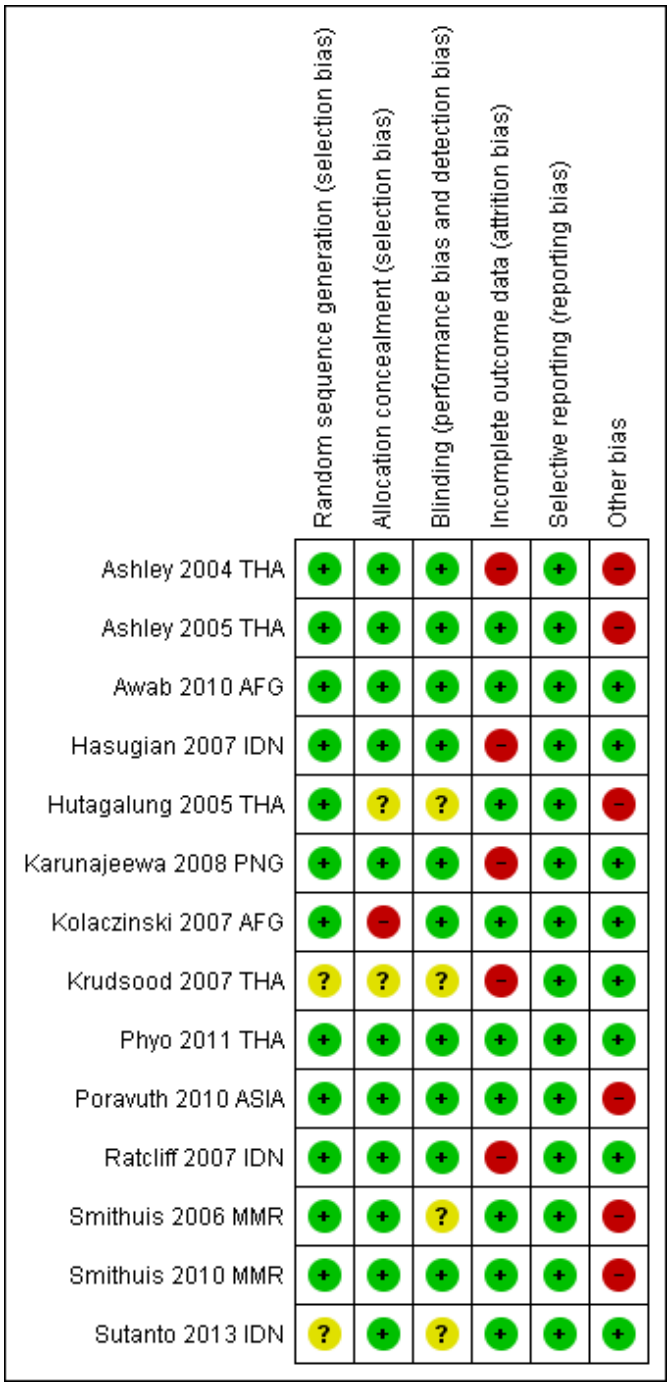
Excluded studies

The studies and reasons for their exclusion are given in the 'Characteristics of excluded studies' table.

Risk of bias in included studies

The risk of bias assessments are summarised in Figure 2, and the reasons for these judgements given in the 'Characteristics of included studies' tables.

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



Allocation

Eleven studies adequately concealed allocation to be considered at low risk of bias. In two studies the description was not clear enough to make a judgement (Hutagalung 2005 THA; Krudsood 2007 THA) and one trial did not conceal allocation (Kolaczinski 2007 AFG).

Blinding

Ten studies adequately blinded the outcome assessors (the laboratory staff) to be at low risk of bias for the primary outcome. In four studies it was unclear whether this was done (Hutagalung 2005 THA; Smithuis 2006 MMR; Krudsood 2007 THA; Sutanto 2013 IDN).

Incomplete outcome data

Five studies had high levels of attrition which could have introduced some bias into their results (Ashley 2004 THA; Hasugian 2007 IDN; Krudsood 2007 THA; Ratcliff 2007 IDN; Karunajeewa 2008 PNG).

Selective reporting

We found no evidence of selective reporting.

Other potential sources of bias

We have incorporated data from five trials which were primarily focused on the treatment of *P. falciparum* (Ashley 2004 THA; Ashley 2005 THA; Hutagalung 2005 THA; Smithuis 2006 MMR; Smithuis 2010 MMR). From these trials we have included only the very small subgroups of patients who had mixed *P. falciparum* and *P. vivax* at baseline. As such, these samples cannot be considered to be truly randomized, and prognostic balance is unlikely to have been achieved due to the low sample size.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings: ACT versus CQ; **Summary of findings 2** Summary of findings: DHA-P versus alternative ACTs in high transmission settings with known CQ resistance

Comparison 1. ACT versus chloroquine monotherapy

Four trials compared WHO recommended ACTs with chloroquine monotherapy (CQ); dihydroartemisinin-piperaquine (DHA-P) (Awab 2010 AFG; Phyo 2011 THA), artesunate plus sulphadoxine-pyrimethamine (AS+SP) (Kolaczinski 2007 AFG), and artemether-lumefantrine (AL6) (Krudsood 2007 THA).

One additional multicentre trial (with study sites in Cambodia, Thailand, India, and Indonesia), compared a new combination; artesunate-pyronaridine (AS-Py) with chloroquine (Poravuth 2010 ASIA). This combination is not yet recommended by the WHO.

Early clinical response to treatment

ACTs appear to consistently clear parasites faster than chloroquine (relative risk of remaining parasitaemic on Day 1: RR 0.42, 95% CI 0.36 to 0.50; Day 2: RR 0.18, 95% CI 0.05 to 0.74; Day 3: RR 0.08, 95% CI 0.01 to 0.43, four trials, 1652 participants, Analysis 1.1). In addition, two trials report a statistically significant reduction in median parasite clearance time with an ACT (Krudsood 2007 THA; Poravuth 2010 ASIA; see Table 2).

ACTs also appear to clear fever faster than chloroquine, with a lower risk of remaining febrile with ACT at the end of day 1 and day 2 (relative risk of remaining febrile on Day 1: RR 0.55, 95% CI 0.43 to 0.70, two trials, 990 participants; Day 2: RR 0.53, 95% CI 0.31 to 0.91, three trials, 1390 participants, Analysis 1.2). In addition, Krudsood 2007 THA found a trend towards a reduced mean fever clearance time with AL6 although this did not reach statistical significance (see Table 3). Kolaczinski 2007 AFG reported no significant difference in fever clearance times between AS+SP and CQ but only presented the data graphically.

Recurrent parasitaemia before day 28

Overall, ACTs have not been shown to reduce recurrent parasitaemias before day 28 compared to chloroquine (RR 0.58, 95% CI 0.18 to 1.90, five trials, 1622 participants, Analysis 1.3).

However, in four of these trials resistance to chloroquine appeared to be very low with very few recurrent parasitaemias before day 28 (Analysis 1.3). In this scenario, the four ACTs tested (DHA-P, AS+SP, AL6 and AS-Py) were at least as effective as chloroquine at treating the initial infection.

In the fifth trial (conducted in Thailand), DHA-P reduced recurrent parasitaemias compared to chloroquine (RR 0.25, 95% CI 0.09 to 0.66, one trial, 437 participants, (Analysis 1.3). This benefit appears to be due to an increased failure rate with CQ in this study setting (9% of participants had recurrent parasitaemias before day 28 following CQ).

Recurrent parasitaemia after day 28

Four trials followed up beyond day 28, but only one trial gave additional primaquine to achieve radical cure (Poravuth 2010 ASIA).

Compared to CQ, Poravuth 2010 ASIA found that AS-Py reduced the risk of recurrent parasitaemia between Day 28 and 42 (RR 0.27, 95% CI 0.08 to 0.94, one trial, 376 participants, Analysis 1.3). The primaquine given in this trial was delayed until Day 28 and so the course will not have been completed until Day 42.
In the absence of primaquine, recurrent parasitaemias after day 28 were more common, but AS+SP, AL6, and DHA-P were still shown to have an advantage over CQ (RR 0.57, 95% CI 0.40 to 0.82, three trials, 1066 participants, Analysis 1.3). The longest follow-up was 63 days in a trial evaluating DHA-P (Phyo 2011 THA). In this trial, 55% of participants experienced recurrent parasitaemia after day 28 following treatment with DHA-P, compared to 80% following CQ.

Secondary outcomes

Only one trial (Kolaczinski 2007 AFG) reported on gametocyte clearance. By Day 3, only one patient had gametocytes still present on a blood film, although gametocytes were cleared quicker in the group treated with AS+SP (one trial, 190 participants, Analysis 1.4).
Kolaczinski 2007 AFG also reported the mean packed cell volume on day 28 (a measure of anaemia) as not significantly different between groups.
Severe adverse events were rare in these trials and no difference has been shown (five trials, 1775 participants, Analysis 1.5).

Comparison 2. ACT versus chloroquine plus sulphadoxine-pyrimethamine

One four-arm trial from Papua New Guinea (Karunajeewa 2008 PNG), compared three ACTs (DHA-P, AL6, AS+SP) with a CQ+SP combination. *P. vivax* transmission in this region is described as high, and chloroquine resistance among *P. vivax* strains has been rising since the late 1980s.

Early response to treatment

In this trial all three ACTs cleared parasites faster than CQ+SP (relative risk of remaining parasitaemic on Day 1: RR 0.22, 95% CI 0.15 to 0.34; Day 2: RR 0.09, 95% CI 0.03 to 0.27; Day 3: RR 0.17, 95 %CI 0.03 to 0.81, one trial, 195 participants, Analysis 2.1), but there was no significant difference in fever clearance (one trial, 195 participants, Analysis 2.2).

Recurrent parasitaemia before day 28

The high recurrence rate during the first 28 days after treatment with CQ+SP confirms the presence of high levels of CQ and SP resistance at this trial site. Only DHA-P was significantly better than CQ+SP but the trial is underpowered to rule out superiority of AL6 or AS+SP (DHA-P versus CQ+SP; RR 0.35, 95% CI 0.16 to 0.77, one trial, 96 participants, Analysis 2.3). Of note, recurrences occurred within 14 days of treatment with all three ACTs, suggesting failure to clear the initial blood stage, and at day 28 the number of recurrences was 15% even with DHA-P (the best performing ACT).

Recurrent parasitaemia after day 28

DHA-P remained superior to CQ+SP during the period 28 to 42 days (RR 0.26, 95% CI 0.09 to 0.69, one trial, 53 participants, Analysis 2.3), but 27.8% of participants treated with DHA-P who completed 42 days follow-up experienced a recurrence. The differences between AL6, AS+SP and CQ+SP remained non-significant. The trial did not give primaquine to achieve radical cure.

Secondary outcomes

This trial did not report on *P. vivax* gametocytaemia. Trial authors did not report any serious adverse events.

Comparison 3. ACT versus quinine

One trial, in Indonesian soldiers diagnosed with *P. vivax* parasitaemia when returning from an endemic area, compared DHA-P against quinine (Sutanto 2013 IDN). Primaquine was offered to patients in the quinine group for 14 days from day 0, while patients in the DHA-P group commenced primaquine for 14 days from day 28. The trial participants were followed up for 12 months and all recurrences were presumed to be relapses as the area was free of endemic malaria.

Early response to treatment

All but three participants were clear of parasites by day three (two in the DHA-P group and one in the quinine group), with no significant difference between groups (one trial, 72 participants, Analysis 3.1). Trial authors did not report fever clearance.

Recurrent parasitaemia before day 28

None of the trial participants had a recurrence of parasitaemia before day 28 (one trial, 72 participants, Analysis 3.2).

Recurrent parasitaemia after day 28

Seven participants in the quinine + primaquine arm had recurrent parasitaemia between days 36 and 194, compared to two with DHA-P (one at day 82 and the second at day 126). The difference was not statistically significant (one trial, 72 participants, Analysis 3.2).

Secondary outcomes

This trial did not report *P. vivax* gametocytaemia.
Trial authors reported four serious adverse events (appendicitis, colitis, and two trauma), but they did not consider any to be related to the medication.

Comparison 4. ACT versus an alternative ACT

Eight studies directly compared ACTs in the treatment of *P. vivax*. Five studies are from low transmission settings and mainly focused on the treatment of *P. falciparum* (Ashley 2004 THA; Ashley 2005 THA; Hutagalung 2005 THA; Smithuis 2006 MMR; Smithuis 2010 MMR). We present unpublished data for only those participants who had a *P. vivax* co-infection at baseline. The numbers included are very small and should be interpreted with caution.
The three studies from high transmission areas also included participants with *P. vivax* mono-infection (Hasugian 2007 IDN; Ratcliff 2007 IDN; Karunajeewa 2008 PNG).

Early clinical response to treatment

There is no evidence that any one ACT clears parasites or fever faster than another (five trials, 278 participants, Analysis 4.1; Analysis 4.2; Analysis 4.3; Analysis 4.4).
An additional two trials comment that 99% of all participants treated with ACTs were afebrile after 48 hours (Hasugian 2007 IDN; Ratcliff 2007 IDN).

Recurrent parasitaemia before day 28

DHA-P versus AS+MQ

Recurrent parasitaemia before day 28 was rare with both these ACTs in the small subgroups of participants with *P. vivax* co-infections, from trials in Thailand and Myanmar, and no statistically significant difference was apparent (four trials, 186 participants, Analysis 4.5).

DHA-P versus AL6

Treatment with DHA-P was superior to AL6, resulting in fewer recurrent parasitaemias before day 28 in three small trials from Papua New Guinea, Indonesia, and Myanmar (RR 0.15, 95% CI 0.04 to 0.58, three trials, 237 participants, Analysis 4.5)

DHA-P versus AS+AQ

Treatment with DHA-P was superior to AS+AQ; resulting in significantly fewer recurrent parasitaemias before day 28 in one small trial from Indonesia (RR 0.04, 95% CI 0.00 to 0.73, one trial, 85 participants, Analysis 4.5).

DHA-P versus AS+SP

Treatment with DHA-P was superior to AS+SP; resulting in significantly fewer recurrent parasitaemias before day 28 in one trial from Papua New Guinea (RR 0.32, 95% CI 0.15 to 0.72, one trial, 77 participants, Analysis 4.5)

AS+MQ versus AL6

In two trials with small subgroups of patients with *P. vivax* co-infections, those treated with AS+MQ had fewer recurrent parasitaemias before day 28 than those treated with AL6 (RR 0.06, 95% CI 0.01 to 0.40, two trials, 56 participants, Analysis 4.5).

Other comparisons

No other significant differences have been shown but only very limited data are available.

Recurrent parasitaemia after day 28

DHA-P versus AS+MQ

No difference has been shown between DHA-P and AS+MQ in preventing recurrent parasitaemias after Day 28 (four trials, 169 participants, Analysis 4.6). All of the data presented represent small subgroups of patients recruited into trials of ACTs in the treatment of *P. falciparum* who were found to have co-infections at baseline.

DHA-P versus AL6

In a high transmission setting in Indonesia, Ratcliff 2007 IDN found treatment with DHA-P to result in significantly fewer recurrent parasitaemias between Day 28 and 42 (RR 0.18, 95% CI 0.07 to 0.50, one trial, 106 participants, Analysis 4.6). The primaquine given in this trial was delayed until Day 28 and so the course will not have been completed until Day 42.
In Papua New Guinea Karunajeewa 2008 PNG did not give primaquine, and found no statistically significant difference in recurrent parasitaemias between Day 28 and 42 (one trial, 46 participants, Analysis 4.6). There were however significantly fewer recurrent parasitaemias over the full 42 day period (Analysis 4.7).

DHA-P versus AS+AQ

Hasugian 2007 IDN offered an unsupervised course of primaquine to all participants on completion of their ACT regimen in this trial from a high transmission setting in Indonesia. Despite this, treatment with DHA-P still resulted in significantly fewer recurrent parasitaemias between Day 28 and 42 (RR 0.26, 95% CI 0.08 to 0.88, one trial, 73 participants, Analysis 4.6).

Other comparisons

In Papua New Guinea Karunajeewa 2008 PNG did not show a significant difference between DHA-P and AS+SP (one trial, 50 participants, Analysis 4.6), or AL6 and AS+SP (one trial, 38 participants, Analysis 4.6).
The remaining data are very limited and underpowered to detect differences.

Secondary outcomes

All of these trials included participants with *P. falciparum* mono-infection and secondary outcomes were unavailable for just the participants who had a *P. vivax* mono- or co-infection. We were given access to the data sets from three of the trials, however the numbers of participants were too low to meaningfully compare secondary measures.

Comparison 5. DHA-P versus alternative ACTs

Of the eight studies which directly compared ACTs, seven included a treatment arm which received DHA-P. It is therefore the most studied ACT for the treatment of *P. vivax*.
We have summarized the relative effects of DHA-P in two additional forest plots. We have stratified this analysis by the level of *P. vivax* transmission, as reported by the trial authors. This analysis was pre-planned as transmission intensity influences the risk of a patient experiencing a new infection, an important factor in assessing post-treatment prophylaxis.

In low transmission settings

The data from low transmission settings are all from small subgroups of patients in trials whose primary objective was to investigate ACTs in the treatment of *P. falciparum*. There is a trend towards benefit with DHA-P but this is not statistically significant and is at high risk of bias due to the very small sample sizes (Analysis 5.1).

In high transmission settings

In high transmission settings DHA-P appears superior to alternative ACTs (AL6, AS+AQ, and AS+SP) at preventing recurrent parasitaemia before Day 28 (RR 0.20, 95% CI 0.08 to 0.49, three trials, 344 participants, Analysis 5.2). It also appears superior at preventing recurrences between days 28 and 42 although this was only statistically significant in the two trials from Indonesia (RR 0.21, 95% CI 0.10 to 0.46, two trials, 179 participants, Analysis 5.2). Due to the way these two trials administered primaquine, some doubt remains about whether this effect is present when an adequate course of primaquine is given; Ratcliff 2007 IDN delayed the course of primaquine until Day 28 so the course will not have been completed until the last day of the trial, and Hasugian 2007 IDN 'offered an unsupervised course of primaquine to all participants on completion of their ACT'.

Sensitivity analysis

We conducted a series of sensitivity analyses, as described in the methods section, to restore the integrity of the randomization process and evaluate the robustness of our results. These changes did not have a significant impact on the results.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Dihydroartemisinin-piperaquine compared with alternative artemisinin-based combination treatments for uncomplicated *P. vivax* malaria

Patient or population: Adults and children with uncomplicated *P. vivax* malaria
Settings: Settings with high transmission of *P. vivax* (chloroquine resistance is also reported as high)
Intervention: Dihydroartemisinin-piperaquine
Comparison: Alternative ACTs

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Alternative ACT	DHA-P			
Effective treatment of the blood stage parasite As assessed by: Recurrent parasitaemia before day 28	**35 per 100**	**7 per 100** (3 to 17)	**RR 0.20** (0.08 to 0.49)	334 (3 studies[1,2])	**moderate**[3,4,5,6]
Post-treatment prophylaxis As assessed by: Recurrent parasitaemia between day 28 and 42	**With primaquine**		**RR 0.21** (0.1 to 0.46)	179 (2 studies[2])	**low**[6,7,8,9]
	34 per 100	**7 per 100** (3 to 16)			
	Without primaquine		**RR 0.40** (0.14 to 1.10)	66 (1 study[1])	**very low**[10,11,12]
	33 per 100	**13 per 100** (5 to 37)			

*The basis for the **assumed risk** (for example, the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; DHA-P: dihydroartemisinin-piperaquine; ACT: Artemisinin-based combination therapy

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Karunajeewa 2008 PNG (Papua New Guinea).
[2] Hasugian 2007 IDN and Ratcliff 2007 IDN (Indonesia).
[3] No serious risk of bias: Allocation was adequately concealed in these studies to be considered at low risk of bias.
[4] Downgraded by 1 for serious inconsistency: There was some clinical heterogeneity between trials. DHA-P did not perform as well in Papua New Guinea as it has elsewhere, however it was still superior to AL6 and AS+SP.
[5] No serious indirectness: Studies include adults and children and were conducted in areas where transmission is high and chloroquine resistance is well documented.
[6] No serious imprecision: Both limits of the 95% CI suggest an appreciable clinical benefit with DHA-P.
[7] Downgraded by 1 for serious risk of bias: Losses to follow-up were high (> 20% at this time-point).
[8] No serious inconsistency: Statistical heterogeneity was low.
[9] Downgraded by 1 for serious indirectness: Ratcliff 2007 IDN delayed the administration of Primaquine until day 28 and so the course will not have been completed until the last day of the trial. Hasugian 2007 IDN offered unsupervised primaquine to all participants on completion of their ACT, this reflects normal practice but it is not clear how many participants completed their course. The period of follow-up is also not long enough to fully assess this effect, the inevitable relapse may simply be delayed, rather than a reduction in clinical episodes.
[10] Downgraded by 1 for serious risk of bias: Losses to follow-up were high (>20% at this time-point).
[11] Downgraded by 1 for serious indirectness: Only one study has assessed this outcome. Recurrent parasitaemia was higher with all three ACTs than seen elsewhere. This trial is therefore not easily extrapolated to other sites.
[12] Downgraded by 1 for serious imprecision: The 95% CI of the effect estimate is wide and includes an important clinical benefit and no difference between the treatments.

DISCUSSION

Summary of main results

ACTs versus chloroquine

ACTs clear parasites from the peripheral blood quicker than chloroquine monotherapy (*high quality evidence*).

In settings where chloroquine remains effective, ACTs are as effective as chloroquine at preventing recurrent parasitaemias before day 28 (*high quality evidence*). In four of these trials, recurrent parasitaemias before day 28 were very low following treatment with both chloroquine and ACTs. The fifth trial, from Thailand in 2011, found increased recurrent parasitaemias following treatment with chloroquine (9%), while they remained low following ACT (2%).

ACT combinations with long half-lives probably also provide a longer prophylactic effect after treatment, with significantly fewer recurrent parasitaemias between day 28 and day 42 or day 63 (*moderate quality evidence*). One trial, from Cambodia, Thailand, India, and Indonesia, gave additional primaquine to both treatment groups to reduce the risk of spontaneous relapses. Recurrent parasitaemias after day 28 were lower than seen in the trials not giving primaquine, but the ACT still appeared to have an advantage (*low quality evidence*).

ACTs versus alternative ACTs

No individual ACT has been shown to clear parasites or fever quicker than an alternative.

Dihydroartemisinin-piperaquine is the most studied ACT, and in high transmission settings it is probably superior to artemether-lumefantrine, artesunate plus sulphadoxine-pyrimethamine, and artesunate plus amodiaquine at preventing recurrent parasitaemias before day 28 (*moderate quality evidence*).

Dihydroartemisinin-piperaquine may also have an improved post-treatment prophylactic effect lasting for up to six weeks, and this effect may be present even when primaquine is also given to achieve radical cure (*low quality evidence*).

The data available from low transmission settings is too limited to reliably assess the relative effectiveness of ACTs.

Overall completeness and applicability of evidence

The included trials were from a variety of settings in Asia and included both adults and children with uncomplicated *P. vivax* malaria. The findings can therefore be reasonably applied to areas within Asia, but we advise caution in extrapolation to other regions. Of note, there are no trials from South America.

The epidemiology of *P. vivax* is such that interpretation of the results is difficult. In this review we have taken parasitaemia before day 28 as a proxy for failure to clear the blood stage parasite. This is not entirely correct and this outcome may include some early relapses. When drugs with long half-lives are used this may also exclude some true recrudescences which occur beyond this time-point.

Similarly we have taken parasitaemia at time-points beyond say 28 as a proxy for an effect on relapses or new infections. In order to adequately assess this effect, the duration of follow-up needs to be considerably longer than was used in these trials. Follow-up of 42 days is only likely to include one relapse cycle and it is therefore not possible to say whether this relapse is prevented or simply delayed. In the trial with the longest follow-up (63 days) there is some evidence that the advantage with ACTs may even out over time (Phyo 2011 THA). In this trial over 50% of participants treated with dihydroartemisinin-piperaquine had developed recurrent parasitaemia by day 63, compared to 80% following chloroquine.

Quality of the evidence

We assessed the quality of the evidence using the GRADE approach and we presented the basis for the judgements in two 'Summary of findings' tables (Summary of findings for the main comparison; Summary of findings 2).

The evidence that ACTs are as effective as chloroquine (in settings without substantial chloroquine resistance), is judged to be of high quality; meaning we can have good confidence in this result and further trials assessing this may be unnecessary. As chloroquine resistance emerges, it is likely that ACTs will become superior.

The evidence that dihydroartemisinin-piperaquine has advantages over other ACTs is judged to be of low or moderate quality, meaning we can have some confidence in this result but further trials will help to clarify this. We downgraded the evidence due to concerns about the risk of bias of the trials (with high attrition rates beyond day 28), and some inconsistency in the performance of dihydroartemisinin-piperaquine (with high levels of recurrent parasitaemias before day 28 seen in Papua New Guinea).

Potential biases in the review process

As we anticipated a lack of data, we decided to include participants with *P. vivax* co-infections from trials of ACTs in *P. falciparum*. These data are, however, very limited and they may be excluded from future updates.

Agreements and disagreements with other studies or reviews

A recent review published in the Lancet Infectious Diseases (Douglas 2010) included data from the same trials published here. The authors concluded that:

'Several ACTs have high efficacy against asexual and sexual stages of P. vivax both sensitive and resistant to chloroquine. Where chloroquine resistance has emerged, long acting ACTs such as dihydroartemisinin plus piperaquine and artesunate plus mefloquine will provide greater postexposure prophylaxis against early recurrence of infection. This advantage will become more pronounced as chloroquine resistance increases.'

The findings of our review are consistent with this. However, it should be noted that artesunate plus mefloquine has not been directly compared to other ACTs in adequately powered trials. The long half-life of mefloquine suggests that it may have similar effectiveness to dihydroartemisinin-piperaquine but this has not been shown.

Additionally, in the light of the findings from Papua New Guinea, we suggest caution in assuming the effectiveness of ACTs in the presence of chloroquine resistance.

AUTHORS' CONCLUSIONS

Implications for practice

ACTs appear at least equivalent to chloroquine at effectively treating the blood stage of *P. vivax* infection. Even where chloroquine remains effective this finding may allow for simplified protocols for treating all forms of malaria with ACTs. In settings where chloroquine is no longer effective, they offer an effective alternative.

Dihydroartemisinin-piperaquine is the most studied ACT and may provide a longer period of post-treatment prophylaxis than artemether-lumefantrine or artesunate plus amodiaquine. This effect may be clinically important in high transmission settings whether primaquine is also given or not.

Implications for research

There is now sufficient evidence to support the use of ACTs as an alternative to chloroquine for effectively treating the blood stage of *P. vivax*.

Further studies, with a longer duration of follow-up (six months to one year), are required to adequately assess the nature of the post-treatment prophylactic effect with dihydroartemisinin-piperaquine, artesunate plus mefloquine, artesunate plus sulphadoxine-pyrimethamine and artesunate-pyronaridine. It is not clear from the current studies whether the longer prophylactic effect persists if participants are adequately treated with primaquine, whether the relapse is simply delayed rather than prevented, or whether this effect is associated with significant health benefits, such as a reduction in clinical episodes or anaemia.

The evidence from Papua New Guinea (where chloroquine resistance is common) is concerning in that treatment failures occurred before day 14, even with the best performing ACT (dihydroartemisinin-piperaquine). This is a one-off finding, and the same trial also found failure rates in *P. falciparum* that were higher than seen anywhere else in the world. Further trials are needed to confirm these data. In light of this, the efficacy of ACTs should not be assumed in chloroquine-resistant areas but rather monitored before and after any policy change.

The high proportion of recurrent parasitaemias in trials which gave primaquine is surprising, and raises questions about the effectiveness of the current regimen. The primaquine in the trials was given unsupervised (as in real life) and it may be that these failures are due to non-compliance rather than resistance. Further studies of primaquine, and the newer tafenoquine, would be helpful.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Ashley 2004 THA

Methods	Trial design: A 3-arm randomized controlled trial (RCT) Follow-up: Temperature and blood smears daily until clearance of fever and parasites, then weekly attendance until day 63 Adverse event monitoring: Adverse events defined as signs or symptoms that occurred or became more severe after treatment started
Participants	Number: 32 participants had *P. vivax* parasitaemia at baseline in treatment groups included in this review, all were co-infections with *P. falciparum* (530 randomized in total) Inclusion criteria: Age 1 to 65 yrs, symptomatic *P. falciparum* parasitaemia, informed consent Exclusion criteria: Pregnancy or lactation, signs or symptoms of severe malaria, > 4% of red blood cells parasitized, contraindication to mefloquine, treatment with mefloquine in the previous 60 days
Interventions	1. Dihydroartemisinin-piperaquine, fixed-dose combination: 40 mg/320 mg (Artekin: Holleykin) • Total dose: 6.4 mg/kg DHA and 51.2 mg/kg P in 4 divided doses at 0, 8, 24, and 48 hours 2. Artesunate plus mefloquine, loose combination (Artesunate: Guilin, Mequin: Atlantic) • AS 4 mg/kg once daily for 3 days • MQ 8 mg/kg once daily for 3 days All doses supervised Primaquine was not given
Outcomes	1. Recurrent *P. vivax* parasitaemia at 14, 28, 42 and 63 days Not included in this review: 1. Fever clearance time (not available for *P. vivax* patients only) 2. Parasite clearance time (not available for *P. vivax* patients only) 3. *P. falciparum* cure rate at day 63 4. *P. falciparum* gametocyte development during follow-up 5. Mean hematocrit at days 0 and 7 (not available for *P. vivax* patients only) 6. Adverse events (not available for *P. vivax* patients only)
Notes	Country: Thailand Setting: 4 rural clinics on the Thai-Myanmar border Transmission: Low and unstable Resistance: CQ resistance amongst *P. vivax* has not been widely reported in Thailand Dates: Jul 2002 to Apr 2003 Funding: Wellcome Trust of Great Britain. DHA-P supplied by Holleykin Pharmaceutical

Risk of bias

Bias	Authors' judgement	Support for judgement

Ashley 2004 THA (*Continued*)

Random sequence generation (selection bias)	Low risk	'The randomisation was computer generated (STATA; version 7; Statacorp)'. Randomized in blocks of 9
Allocation concealment (selection bias)	Low risk	'The treatment allocation was concealed in sealed envelopes labelled with the study code'
Blinding (performance bias and detection bias) All outcomes	Low risk	'Laboratory staff reading the blood smears had no knowledge of the treatment received'. No other blinding described
Incomplete outcome data (attrition bias) All outcomes	High risk	The included sample size was very low. Although attrition was low in absolute numbers they represent up to 50% of the *P. vivax* patients.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	High risk	For the purpose of this review we are including only a small subset of the original randomized patients. This sample may not therefore be truly randomized and the small sample size means that prognostic balance between groups is unlikely

Ashley 2005 THA

Methods	Trial design: A 3-arm RCT Follow-up: Temperature and blood smears daily until clearance of fever and parasites, then weekly attendance for examination, symptom enquiry, malaria smear and hematocrit until day 63 Adverse event monitoring: Adverse events defined as signs or symptoms that occurred or became more severe after treatment started. Symptoms were screened at each visit
Participants	Number: 47 participants had *P. vivax* parasitaemia at baseline and are included in this review (499 randomized in total) Inclusion criteria: Age 1 to 65 yrs, symptomatic *P. falciparum* infection (only mixed infections included in this review), informed consent Exclusion criteria: Pregnancy or lactation, signs or symptoms of severe malaria, > 4% of red blood cells parasitized, treatment with mefloquine in the previous 60 days
Interventions	1. Dihydroartemisinin-piperaquine, fixed-dose combination: 40 mg/320 mg (Artekin: Holleykin) • Total dose: 6.4 mg/kg DHA and 51.2 mg/kg P in 4 divided doses at 0, 8, 24, and 48 hours 2. Dihydroartemisinin-piperaquine, fixed-dose combination: 40 mg/320 mg (Artekin: Holleykin)

Ashley 2005 THA (*Continued*)

	• Total dose: 6.4 mg/kg DHA and 51.2 mg/kg P in 3 divided doses at 0, 24, and 48 hours 3. Artesunate plus mefloquine, loose combination (Artesunate: Guilin, Mequin: Atlantic) • AS 4 mg/kg once daily for 3 days • MQ 8 mg/kg once daily for 3 days All doses supervised Primaquine was not given
Outcomes	1. Recurrence of P. *vivax* during follow-up at day 14, 28, 42, 63 Not included in this review: 1. Fever clearance (not available for *P. vivax* patients only) 2. Parasite clearance (not available for *P. vivax* patients only) 3. *P. falciparum* cure rate at days 63, 42, and 28, PCR adjusted and unadjusted 4. *P. falciparum* gametocyte development during follow-up 5. Mean hematocrit during follow-up (not available for *P. vivax* patients only) 6. Adverse events (not available for *P. vivax* patients only)
Notes	Country: Thailand Setting: 4 clinics on the Thai-Myanmar border Transmission: Low and unstable Resistance: CQ resistance amongst *P. vivax* has not been widely reported in Thailand Dates: Apr 2003 to Apr 2004 Funding: Medicines for Malaria Venture, Wellcome Trust of Great Britain

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'The randomisation list was generated using STATA; version 7 (Stata)'. Randomized in blocks of 9
Allocation concealment (selection bias)	Low risk	'The treatment allocation was concealed in sealed envelopes labelled with the study code'
Blinding (performance bias and detection bias) All outcomes	Low risk	'Laboratory staff reading the blood smears had no knowledge of the treatment received'. No other blinding described
Incomplete outcome data (attrition bias) All outcomes	Low risk	The included sample size is very low. Attrition is low in absolute numbers and unlikely to have introduced significant bias
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	High risk	For the purpose of this review we are including only a small subset of the original randomized patients. This sample may not

		therefore be truly randomized and the small sample size means that prognostic balance between groups is unlikely

Awab 2010 AFG

Methods	Trial design: An open-label RCT Follow-up: Clinical assessment, blood smears and haemoglobin on days 0 to 3 then weekly until day 56 Adverse event monitoring: Astandard symptom questionnaire at each visit
Participants	Number: 536 randomized Inclusion criteria: Febrile patients aged > 3 months, slide confirmed *P. vivax* mono-infection, a negative pregnancy test, informed consent Exclusion criteria: Pregnancy or lactation, clinical or laboratory features of severe malaria, haemoglobin < 7 g/dL, concomitant disease that would mask treatment responses, known allergy to study drugs, antimalarial treatment in the past month, anticipated inability or unwillingness to complete the 56 day follow-up
Interventions	1. Dihydroartemisinin-piperaquine, fixed-dose combination: 40 mg/320 mg (Artekin: Holleypharm) • Total dose: 6 mg/kg DHA and 48 mg/kg P in 3 divided doses over 3 days 2. Chloroquine (IDA) • Total dose:25 mg base/kg in divided doses over 3 days All doses supervised Primaquine was not given
Outcomes	1. Recurrence of *P. vivax* during follow-up at day 14, 28, and 56 2. Fever clearance day 0 to 3 3. Parasite clearance day 0 to 3 4. Adverse events Not included in this review: 1. Predictors of treatment failure 2. Gametocytemia at time of relapse
Notes	Country: Afghanistan Setting: 3 provincial malaria control centres, one in the east and two in the north Transmission: Seasonal Resistance: CQ resistance amongst *P. vivax* has not been widely reported in Afghanistan Dates: Jul 2007 to Feb 2009 Funding: Mahidol-Oxford Research Unit, Thailand International Development and Cooperation Agnecy, UK MRC Clinical Science Fellowship, Wellcome Trust of Great Britain

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Awab 2010 AFG (*Continued*)

Random sequence generation (selection bias)	Low risk	'a pre-generated randomization list made in blocks of 20 that was produced and held independently of the field teams by a statistician'
Allocation concealment (selection bias)	Low risk	'The individual allocations were kept in sealed opaque envelopes and opened only after enrolment'
Blinding (performance bias and detection bias) All outcomes	Low risk	'Patients and clinical field workers were not blinded to the treatment arm after allocation. Microscopists were blinded to treatment allocation at follow-up examinations'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up were low: 25/268 (9.3%) DHA-P versus 13/268 (4.9%) CQ
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No other bias detected.

Hasugian 2007 IDN

Methods	Trial design: An open label RCT Follow-up: Daily until fever and parasites cleared then weekly until day 42, for a physical examination, a symptom questionnaire and malaria film. Haemoglobin measured on days 0, 7, 28 and day of failure Adverse event monitoring: Assessed at each follow-up visit
Participants	Number: 114 had *P. vivax* parasitaemia at baseline (340 randomized in total) Inclusion criteria: Age > 1 yr, weight > 5 kg, slide confirmed malaria (*P. falciparum*, *P. vivax* or both), fever or history of fever in the preceding 48 hours Exclusion criteria: Pregnancy or lactation, danger signs or signs of severe malaria, > 4% red blood cells parasitized, concomitant disease that required hospital admission
Interventions	1. Dihydroartemisinin-piperaquine, fixed-dose combination:40 mg/320 mg (Artekin: Holley) • Total dose: 6.75 mg/kg DHA and 54 mg/kg PQP in 3 divided doses given once daily for 3 days 2. Artesunate plus amodiaquine, loose combination (Arsumax: Guilin, Flavoquine: Aventis) • AS 4 mg/kg once daily for 3 days • AQ 10 mg/kg once daily for 3 days All doses supervised Both groups were offered an unsupervised course of Primaquine 0.3mg base/kg for 14 days, on completion of the study regimen

Hasugian 2007 IDN (*Continued*)

Outcomes	1. Parasitological failure with *P. vivax* on days 14, 28 and 42 Not included in the review: 1. Fever clearance (not available for *P. vivax* patients only) 2. Parasite clearance (not available for *P. vivax* patients only) 3. Parasitological failure due to *P. falciparum* 4. *P. falciparum* gametocyte carriage after treatment 5. Anaemia at day 0, 7, 28 (not available for *P. vivax* patients only) 6. Adverse events (not available for *P. vivax* patients only)
Notes	Country: Indonesia Setting: Rural clinics Transmission: High Resistance: CQ resistance among *P. vivax* is high at this study site Dates: Jul 2005 to Dec 2005 Funding: Wellcome Trust - National Health and Medical Research Council

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'A randomisation list was generated in blocks of 20 by an independent statistician'
Allocation concealment (selection bias)	Low risk	'Treatment allocation concealed in an opaque, sealed envelope that was opened once the patient had been enrolled'
Blinding (performance bias and detection bias) All outcomes	Low risk	'All slides were read by a certified microscopist who was blinded to treatment allocation'. An open label trial
Incomplete outcome data (attrition bias) All outcomes	High risk	The primary outcome data are unpublished data including only participants with *P. vivax* mono-infection at baseline. Attrition although balanced between groups was > 15% at day 28 and > 20% at day 42
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No other bias detected.

Hutagalung 2005 THA

Methods	Trial design: An open-label RCT Follow-up: Examination and malaria film daily until fever and parasites cleared then weekly to day 42 or any other day they became unwell Adverse event monitoring: At each visit a questionnaire on adverse events was completed
Participants	Number: 24 participants had *P. vivax* co-infections at baseline (490 randomized) Inclusion criteria: Weight > 10 kg, slide confirmed *P. falciparum* +/- *P. vivax,* informed consent Exclusion criteria: Pregnancy, clinical or laboratory signs of severe illness and/or severe and complicated malaria severe malaria, treatment with mefloquine in previous 63 days
Interventions	1. Artemether-lumefantrine, fixed dose combination, 20 mg/120 mg tablets (Coartem: Novartis) • < 15 kg 1 tablet twice daily for 3 days • 15 to 24 kg 2 tablets twice daily for 3 days • 25 to 34 kg 3 tablets twice daily for 3 days • > 35 kg 4 tablets twice daily for 3 days • Plus glass of chocolate milk with each dose 2. Artesunate plus mefloquine, loose combination (Artesunate: Guilan, Lariam: Hoffman-La Roche) • AS 4 mg/kg once daily for 3 days • MQ 15 mg/kg on day 1 and 10 mg/kg on day 2 All doses supervised Primaquine not given
Outcomes	1. *P. vivax* parasitaemia on days 0 to 3 2. *P. vivax* recurrence at days 14 and 28 Not included in the review: 1. Fever clearance (*P. falciparum*) 2. Parasite clearance (*P. falciparum*) 3. Gametocyte clearance (data only for *P. falciparum*) 4. Failure due to *P. falciparum* 5. Adverse events
Notes	Country: Thailand Setting: Malaria clinics of the Shoklo Malaria Research Unit Transmission: Low and unstable Resistance: CQ resistance amongst *P. vivax* has not been widely reported in Thailand Dates: July 2001 to June 2002 Funding: Wellcome Trust of Great Britain

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'Computerized randomisation was in blocks of ten'.
Allocation concealment (selection bias)	Unclear risk	None described.

Hutagalung 2005 THA (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	An open label trial. No comment on blinding of laboratory staff
Incomplete outcome data (attrition bias) All outcomes	Low risk	The included sample size is very low. Attrition was low in absolute numbers and unlikely to have significantly biased the result
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	High risk	For the purpose of this review we are including only a small subset of the original randomized patients. This sample may not therefore be truly randomized and the small sample size means that prognostic balance between groups is unlikely

Karunajeewa 2008 PNG

Methods	Trial design: A 4-arm open label RCT Follow-up: Standardized follow-up including temperature and malaria film on days 0, 1, 2, 3, 7, 14, 28, and 42. Drug levels assayed on day 7 Adverse event monitoring: None described
Participants	Number: 195 had *P. vivax* parasitaemia at baseline (372 randomized in total) Inclusion criteria: Age 0.5 to 5 years, axillary temp > 37.5 ºC or history of fever in the preceding 24 hours, > 1000/µL asexual *P. falciparum* or > 250/µL asexual *P. vivax, P. ovale* or *P. malariae*, informed consent Exclusion criteria: Features of severe malaria, evidence of another infection or coexisting condition including malnutrition, intake of study drug in previous 14 days
Interventions	1. Artesunate plus sulphadoxine-pyrimethamine, loose combination (Sanofi-Aventis, Roche) • AS 4 mg/kg once daily for 3 days • SP 25/1.25 mg/kg once on the first day 2. Dihydroartemisinin-piperaquine, fixed dose combination: 40 mg/320 mg (Beijing Holley-Cotec) • DHA 2.5 mg/kg once daily for 3 days • P 20 mg/kg once daily for 3 days 3. Artemether-lumefantrine, fixed dose combination, 20 mg/120 mg (Novartis), given with milk • A 1.7 mg/kg twice daily for 3 days • L 10 mg/kg twice daily for 3 day 4. Chloroquine plus sulphadoxine-pyrimethamine, loose combination (Aspen Healthcare, Roche) • CQ 10 mg base/kg once daily for 3 days • SP 25/1.25 mg/kg once on the first day

Karunajeewa 2008 PNG (*Continued*)

	All doses supervised except the evening dose of AL6 Primaquine was not given
Outcomes	1. Recurrence of *P. vivax* at day 14, 28, and 42 2. Fever clearance 3. Parasite clearance Not included in this review: 1. Drug levels day 7 2. ACPR (*P. falciparum*) at days 28 and 42, PCR adjusted and unadjusted 3. *P. falciparum* gametocyte prevalence during follow-up 4. Adverse events (not available for *P. vivax* patients only)
Notes	Country: Papua New Guinea Setting: Health centres Transmission: High Resistance: CQ resistance among *P. vivax* rising since 1980s Dates: Apr 2005 to Jul 2007 Funding: WHO Western Pacific Region, Rotary against Malaria in Papua New Guinea, National Health and Medical Research Council of Australia

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'Computer-generated randomised assignment with blocks of 24 for each site'
Allocation concealment (selection bias)	Low risk	Information from authors - allocation was concealed in sealed opaque envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	'All blood smears were subsequently reexamined independently by two skilled microscopists who were unaware of the treatment assignments'. An open label trial
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition was high (> 10%) in all groups and could have introduced bias into the result
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No other bias detected.

Kolaczinski 2007 AFG

Methods	Trial design: An open label RCT Follow-up: Clinical symptoms, temperature and malaria film recorded on days 0, 1, 2, 3, 7, 14, 28, 42 and when ill. PCV recorded on Day 0, and day 28 or day of failure Adverse event monitoring: None described
Participants	Number: 190 randomized Inclusion criteria: Age > 2 years, Weight > 5 kg, microscopically confirmed *P. vivax* mono-infection > 1 asexual parasite per 10 fields, informed consent Exclusion criteria: Pregnancy, severe malaria, evidence of concomitant infection or serious disease, recent use of antimalarial drugs, known allergy to study drugs
Interventions	1. Artesunate plus sulphadoxine-pyrimethamine, loose combination (Plasmotrim, Mepha: Fansidar, Roche) • AS 4 mg/kg once daily for 3 days • SP 25/1.25 mg/kg once on the first day 2. Chloroquine (Nivaquine; Beacon) • CQ 25 mg/kg given over 3 days All doses supervised Primaquine was not given
Outcomes	1. Recurrence of *P. vivax* at day 14, 28, and 42 2. PCV on day 0 and 28 or day of failure 3. Fever clearance 4. Parasite clearance 5. Gametocytemia 6. Adverse events
Notes	Country: Afghanistan - Jalalabad, Nangahar Province Setting: Malaria reference centre Transmission: Seasonal and unstable Resistance: Substantial CQ resistance has not been reported from Afghanistan (Author communication) Dates: Mar 2004 to Aug 2004 Funding: UNDP, World Bank, WHO Special Programme for Research on Tropical Disease

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'A computer-generated randomisation list (generated using Microsoft Excel; Microsoft Corp., Redmond, WA, USA) was used to randomly assign vivax cases within gender and age groups to one of two treatment regimens'
Allocation concealment (selection bias)	High risk	'After determining suitability for inclusion, the study clinician enrolled each patient

Kolaczinski 2007 AFG (*Continued*)

		and allocated them to the treatment arm next indicated in the randomisation list. The allocation sequence was not concealed from the study clinician'
Blinding (performance bias and detection bias) All outcomes	Low risk	'The clinical assistants responsible for directly observed treatment and clinical assessment during follow-up were blind to the nature of the treatment arms but were aware of the arm code to which patients were allocated (e.g. 'arm 1', 'arm 2'; differences in dosages and tablet appearance would not have allowed complete concealment). The microscopists and laboratory technicians were blind to treatment allocations'
Incomplete outcome data (attrition bias) All outcomes	Low risk	10 participants were lost to follow-up with similar numbers in each group. This is unlikely to have a major effect on the result
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No other bias detected.

Krudsood 2007 THA

Methods	Trial design: An open label RCT Follow-up: Admitted to hospital for 28 days. Temperature and malaria film recorded every 12 hours until parasite and fever clearance then on days 3, 7, 14, 21, and 28 Adverse event monitoring: None described
Participants	Number: 98 randomized Inclusion criteria: Age > 15 years, Weight > 40 kg, microscopically confirmed *P. vivax* mono-infection, informed consent Exclusion criteria: Pregnancy or lactation, severe malaria, concomitant febrile illness, severe malnutrition, ingestion of antimalarial drugs in the past 14 days, known allergy or intolerance to study drugs
Interventions	1. Artemether-lumefantrine, fixed-dose combination: 120/20 mg (Coartem, Novartis) • AL 4 tablets at 0, 8, 24, 32, 48, and 60 hours 2. Chloroquine (Government Pharmaceutical Organisation) • CQ 25mg/kg given over 3 days All doses supervised Both regimens received additional primaquine (Government Pharmaceutical Organization) • PQ 15 mg daily for 14 days

Krudsood 2007 THA (*Continued*)

Outcomes	1. Recurrence of *P. vivax* at day 14 and 28 2. Fever clearance 3. Parasite clearance 4. Serious adverse events 5. Other adverse events (text summary only)
Notes	Country: Thailand Setting: Bangkok Hospital for Tropical Diseases Transmission: Low endemicity Resistance: CQ resistance amongst *P. vivax* has not been widely reported in Thailand Dates: Jun 2004 to May 2005 Funding: WHO, Ministry of Health, Labor, and Welfare of Japan, and Mahidol University Research Grants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'The patients were randomly assigned', no further description
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	High risk	Participants lost to follow-up were high in both groups 18%
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No other bias detected.

Phyo 2011 THA

Methods	Trial design: Assessor blind RCT Follow-up: daily until afebrile and aparasitaemic and then weekly until day 63. Temperature, malaria film, hematocrit, and chloroquine plasma concentration at every visit Adverse event monitoring: At each visit a symptom questionnaire was completed
Participants	Number: 500 randomized Incusion criteria: Age > 1 yr; Body weight > 5 kg; Microscopically confirmed monoinfection of P. vivax parasitaemia (> 5/500 WBC); Febrile (axillary temperature, > 37.5 °C) or had history of fever Exclusion criteria: Known hypersensitivity to the study drugs; intercurrent illness; pregnant, lactating; severely anaemic (hematocrit < 20%); received mefloquine in the past

Phyo 2011 THA (*Continued*)

	60 days; received dihydroartemisinin piperaquine in the past 3 months
Interventions	1. Dihydroartemisinin-piperaquine, fixed-dose combination: 40 mg/320 mg (Duocotexin: Holley) • Total target dose: DHA 7 mg/kg + P 55 mg/kg in 3 divided doses, given once daily for 3 days with milk. 2. Chloroquine (Government Pharmaceutical Organization, Thailand) • Target dose: 25 mg base/kg in three divided doses, given once daily for 3 days All patients with normal G6PD were administered Primaquine at the target dose of 0.5 mg/kg/day for a period of 14 days at the end of the follow-up period
Outcomes	1. Recurrence of *P. vivax* on day 28, 63 2. Fever clearance 3. Parasite clearance within 24, 48, 72, and 96 hours 4. Adverse events
Notes	Country: Thailand-Myanmar border Setting: Malaria Research Unit Clinic Transmission: low and seasonal Resistance: Decreased susceptibility to CQ in some isolates. Dates: Jan 2007 to Dec 2008 Funding: Holley Pharm; Wellcome Trust

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'Pateints were allocated to the treatment arms on a pre generated randomization list in blocks of 20'
Allocation concealment (selection bias)	Low risk	'The individual allocations were concealed in sealed envelopes and opened only after enrollment'
Blinding (performance bias and detection bias) All outcomes	Low risk	'Patients and clinic workers were not blinded. Laboratory technicians were unaware of treatment allocation'
Incomplete outcome data (attrition bias) All outcomes	Low risk	35 lost to follow-up or excluded from analysis in the DHA-P arm (14%) and 37(14.8%) lost to follow-up or excluded from the chloroquine arm
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No evidence of other bias.

Poravuth 2010 ASIA

Methods	Trial design: Double-blind RCT Follow-up: All participants were hospitalized for 3 days then seen for follow-up at day 7, 14, 21, 28, 35, and 42 Adverse event monitoring: Monitored throughout the study, 12-lead ECGs at day 0 2, 7, 14, and 42 if clinically indicated, laboratory tests at day 0, 3, 7, 28, and 42 if clinically indicated
Participants	Number: 456 randomized Inclusion criteria: Age 3 to 60 years, weight 20 to 90 kg, uncomplicated P. vivax mono-infection with a parasite density > 250 mL, fever or documented history of fever in the previous 24 hours Exclusion criteria: pregnancy or lactation, any other condition requiring hospitalisation; haemoglobin < 8 g/dL; hepatic or renal impairment; malnutrition; presence or history of clinically significant disorders; known hypersensitivity to study drugs; known active hepatitis A IgM, hepatitis B surface antigen, hepatitis C antibody or seropositive for HIV antibody; used an antimalarial within the previous two weeks; used an antibacterial with anti-malarial activity within the previous two weeks
Interventions	1. Artesunate-pyronaridine, fixed-dose combination 60 mg/180 mg (Shin Poong) • 20 kg to 25 kg 1 tablet once daily for 3 days • 26 kg to 44 kg 2 tablets once daily for 3 days • 45 kg to 64 kg 3 tablets once daily for 3 days • 65 kg to 90 kg 4 tablets once daily for 3 days • Target dose 2. Chloroquine tablets 155 mg (Shin Poong) • Adult target dose 620 mg on Days 0 and 1 and 310 mg on Day 2. • Child target dose 10 mg/kg on Days 0 and 1 and 5 mg/kg onDay 2. All doses supervised Primaquine was given for 14 days starting on day 28
Outcomes	1. Recurrence of *P. vivax* at day 14, 28, and 42 2. Median time to parasite clearance/parasitaemia on days 1, 2, and 3. 3. Median time to fever clearance/fever on days 1, 2, and 3. 4. Adverse events
Notes	Country: 5 study sites in Cambodia, Thailand, India and Indonesia Setting: Local hospitals Transmission: Not stated Resistance: Not stated Dates: Mar 2007 to Mar 2008 Funding: Shin Poong Pharmaceutical Company, Seoul, Republic of Korea, and the Medicines for Malaria Venture, Geneva, Switzerland

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'A computer-generated randomization scheme was provided by the sponsor'

Poravuth 2010 ASIA (*Continued*)

Allocation concealment (selection bias)	Low risk	'Randomization numbers were assigned in ascending order to each subject according to the order recruited. The subject was allocated an individually numbered treatment pack, which contained sufficient tablets for 3 days' therapy plus an overage bottle containing tablets in case the subject vomited the first dose'
Blinding (performance bias and detection bias) All outcomes	Low risk	'Study drugs were administered on a double-blind, double-dummy basis. The investigator calculated the appropriate dose and study drug was administered by a different member of staff, designated by the investigator. All study investigators, laboratory technicians and patients were blind to treatment assignment. Active drugs and placebos were packaged similarly'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of participants lost to follow-up was low and balanced between groups: 4% AS-Py versus 8% CQ
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	High risk	'The study sponsors were responsible for data collection, statistical analysis and interpretation'

Ratcliff 2007 IDN

Methods	Trial design: An open-label RCT Follow-up: A symptom questionnaire, physical examination, malaria film and haemoglobin measurement daily until fever and parasites cleared then weekly to day 42 Adverse event monitoring: A symptom questionnaire at each visit
Participants	Number: 175 had *P. vivax* parasitaemia at baseline (774 randomized in total) Inclusion criteria: Weight >10 kg, fever or a history of fever in the preceding 48 hrs, slide confirmed malaria (*P. falciparum, P. vivax* or mixed infections) Exclusion criteria: Pregnancy or lactation, danger signs or signs of severity, parasitaemia > 4%, concomitant disease requiring hospital admission
Interventions	1. Dihydroartemisinin-piperaquine, fixed-dose combination: 40 mg/320 mg (Artekin: Holleykin) • Total dose: DHA 6.75 mg/kg + P 54 mg/kg in 3 divided doses, given once daily for 3 days 2. Artemether-lumefantrine, fixed-dose combination: 20 mg/120 mg (Coartem: Novartis)

	• 10 kg to 15 kg 1 tablet twice daily for 3 days • 15 kg to 25 kg 2 tablets twice daily for 3 days • 25 kg to 35 kg 3 tablets twice daily for 3 days • > 35 kg 4 tablets twice daily for 3 days Only the first dose of each day was supervised. All participants advised to take each dose with a biscuit or milk All patients were also given primaquine • PQ 0·3 mg base/kg 14 days starting on day 28
Outcomes	1. *P. vivax* recurrence at day 14, 28, and 42 Not included in the review: 1. Fever clearance (not available for *P. vivax* patients only) 2. Parasite clearance (not available for *P. vivax* patients only) 3. *P. falciparum* at days 42 and 28, PCR adjusted and unadjusted 4. *P. falciparum* gametocyte carriage after treatment 5. Anaemia during follow-up (not available for *P. vivax* patients only) 6. Adverse events (not available for *P. vivax* patients only)
Notes	Country: Indonesia Setting: Rural outpatient clinics Transmission: High Resistance: CQ resistance is high at this study site Dates: Jul 2004 to Jun 2005 Funding: Wellcome Trust UK and National Health and Medical Research Council Australia

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'A randomisation list was generated in blocks of 20 patients by an independent statistician'
Allocation concealment (selection bias)	Low risk	'Treatment allocation concealed in an opaque sealed envelope that was opened once the patient had been enrolled'
Blinding (performance bias and detection bias) All outcomes	Low risk	'All slides were read by a certified microscopist with at least 10 years experience, who was blinded to treatment allocation'. No other blinding was conducted
Incomplete outcome data (attrition bias) All outcomes	High risk	The primary outcome data are unpublished data including only participants with *P. vivax* mono-infection at baseline. Attrition although balanced between groups was >10% at day 28 and >15% at day 42

Ratcliff 2007 IDN (*Continued*)

Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No other bias detected.

Smithuis 2006 MMR

Methods	Trial design: A 4-arm open-label RCT Follow-up: A symptom questionnaire, malaria film, and gametocyte count on days 0, 1, 2, 3, 7, 14, 21, 28, 35, and 42. Haemoglobin was measured on days 0 and 28 Adverse event monitoring: A symptom questionnaire at each visit
Participants	Number: 87 patients had *P. vivax* parasitaemia at baseline (652 randomized in total) Inclusion criteria: Age > 1 year, axillary temperature > 37.5 ºC or history of fever in the previous 48 hours, *P. falciparum* mono-infection 500 to 100,000 parasites/µL or co-infection with *P. vivax*, informed consent Exclusion criteria: Pregnancy, signs of severe malaria, signs or symptoms of other diseases, history of taking mefloquine in the previous 2 months or any other antimalarial in the previous 48 hours, history of psychiatric disease
Interventions	1. Dihydroartemisinin-piperaquine, fixed-dose combination: 40 mg/320 mg (Artekin: Holleykin) • Total dose: DHA 6.3 mg/kg + P 50.4 mg/kg in 3 divided doses, given once daily for 3 days • Supervised 2. Dihydroartemisinin-piperaquine, fixed-dose combination: 40 mg/320 mg (Artekin: Holleykin) • Total dose: DHA 6.3 mg/kg + P 50.4 mg/kg in 3 divided doses, given once daily for 3 days • Unsupervised 3. Artesunate plus mefloquine, loose combination (artesunate: Guilin, Lariam: Hoffman-La Roche) • AS 4 mg/kg once daily for 3 days • MQ 25 mg base/kg as a single dose on day 0 • Supervised 4. Artesunate plus mefloquine, loose combination (artesunate: Guilin, Lariam: Hoffman-La Roche) • AS 4 mg/kg once daily for 3 days • MQ 25 mg base/kg as a single dose on day 0 • Unsupervised Primaquine was not given
Outcomes	1. P. *vivax* recurrence at day 14, 28, and 42 2. Fever clearance 3. Parasite clearance 4. Mean change in haemoglobin from day 0 to day 28 Not included in the review: 1. P. *falciparum* at days 42 and 28, 42 PCR unadjusted and PCR adjusted 2. *P. falciparum* gametocyte appearance at day 7 and day 14

	3. *P. falciparum* gametocyte carriage at days 0, 7, 14, 21, and 28 4. Adverse events (not available for *P. vivax* patients only)
Notes	Country: Myanmar Setting: Rural village tracts Transmission: Low and seasonal Resistance: CQ resistance amongst *P. vivax* has not been widely reported in Myanmar Dates: Nov 2003 to Feb 2004 Funding: Médecins sans Frontières (Holland)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'At both study locations three boxes were prepared, one for each of the three age groups, by an administrator who was otherwise not connected with the study. In each box, 40 unmarked and sealed opaque envelopes were deposited. Each envelope contained a card that described the treatment assignment, and each treatment allocation had an equal number of cards (ten). Each new patient (or his or her carer) was asked to take one of the envelopes from the box for their age group. Treatment was then dispensed in accordance with the treatment allocation in the envelope. Whenever a box became empty, another 40 envelopes were put in that box'
Allocation concealment (selection bias)	Low risk	See above.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	An open label trial. No comment on blinding of laboratory staff
Incomplete outcome data (attrition bias) All outcomes	Low risk	The included sample size is low. Attrition is low in absolute numbers and unlikely to have introduced significant bias
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	High risk	For the purpose of this review we are including only a small subset of the original randomized patients. This sample may not therefore be truly randomized and the small sample size means that prognostic balance between groups is unlikely

Smithuis 2010 MMR

Methods	Trial design: A 10-arm RCT Follow-up: Patients were asked to return weekly for 9 weeks for assessment and at any other time they were unwell. Haemoglobin was measured on days 0 and 63 Adverse event monitoring: Not described
Participants	Number: 66 participants had *P. vivax* co-infections at baseline and are included in this review. The participants who received the one-off dose of primaquine are excluded from this review Inclusion criteria: Age > 6 months, weight > 5 kg, *P. falciparum* mono-infection 500 to 200,000 parasites/μL or co-infection with *P. vivax*, informed consent Exclusion criteria: Pregnancy, signs of severe malaria, severe malnutrition, history of hypersensitivity to any of the study drugs, severe malnutrition, concomitant febrile illness, history of psychiatric disorder, a full course of mefloquine in the previous 9 weeks or any other antimalarial in the previous 48 hours
Interventions	Each of the five study arms were also divided into two where one half also received a one-off dose of 0.75 mg/kg primaquine 1. Dihydroartemisinin-piperaquine, fixed-dose combination: 40 mg/320 mg or 20 mg/160 mg tablets (Artekin: Holleykin) • DHA 2.5 mg/kg once daily for 3 days • P 20 mg/kg once daily for 3 days 2. Artesunate plus amodiaquine, fixed dose combination: 25 mg/67.5 mg or 50 mg/135 mg or 100 mg/270 mg tablets • AS 4 mg/kg once daily for 3 days • AQ 10.8 mg base/kg once daily for 3 days 3. Artemether-lumefantrine, fixed dose combination: 20 mg/120 mg tablets • A 3.3 mg/kg in two divided doses each day for 3 days • L 19.8 mg/kg in two divided doses each day for 3 days • Plus advised to consume fatty food or breast feed before each dose 4. Artesunate plus mefloquine, fixed dose combination: 25 mg/55 mg or 100 mg/220 mg tablets (artesunate: Guilin, Lariam: Hoffman-La Roche) • AS 4 mg/kg once daily for 3 days • MQ 8.8 mg/kg once daily for 3 days 5. Artesunate plus mefloquine, loose combination (artesunate: Guilin, Lariam: Hoffman-La Roche) • AS 4 mg/kg once daily for 3 days • MQ 25 mg base/kg as a single dose on day 0 First dose supervised, all others unsupervised. Primaquine was not given
Outcomes	1. Recurrent parasitaemia at day 14, 28, 42, and 63 Not included in the review: 1. Failure due to *P. falciparum* 2. Gametocytemia (not available for *P. vivax* patients only) 3. Haemoglobin (not available for*P. vivax* patients only) 4. Adverse events

Notes	Country: Myanmar Setting: Clinics Transmission: Not described Resistance: CQ resistance amongst *P. vivax* has not been widely reported in Myanmar Dates: Dec 2008 to March 2009 Funding: Médecins sans Frontières (Holland)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'They were stratified prospectively into three age groups...patients were randomly assigned in equal numbers to receive one of the five different treatments'
Allocation concealment (selection bias)	Low risk	'Treatment allocations were put in sealed envelopes in blocks of 50 for each age-group...patients drawing an envelope from a box after enrolment'
Blinding (performance bias and detection bias) All outcomes	Low risk	An open label trial. 'Microscopists examining blood films were unaware of treatment allocation'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition is low in absolute numbers and unlikely to have introduced significant bias
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	High risk	For the purpose of this review we are including only a small subset of the original randomized patients. This sample may not therefore be truly randomized and the small sample size means that prognostic balance between groups is unlikely

Sutanto 2013 IDN

Methods	Trial design: An open-label RCT Follow-up: Routine blood films were taken on days 3, 7, 14, 21, 28, 35, 41, 56, 63, 70, 84, 126, 140, 180, and 365, plus other visits to the clinic with illness Adverse event monitoring: Symptom questionnaire and hematology and biochemistry investigations (WBC, RBC, MCV, MCHC, LFT, RFT, gamma glutathione hydroxylase, pyruvic transaminase, creatine kinase, serum electrolytes, G6PD) were performed on days 3, 7, 14, 28, 41, and 84
Participants	Number: 116 randomized (41, 39, and 36 in each of the three arms) Inclusion criteria: Indonesian soldiers after a year of duty in malarious Papua, Indonesia diagnosed with *P. Vivax* malaria by microscopy Exclusion criteria: Refusal to consent; any condition requiring hospitalization; G6PD deficiency; SGOT, SGPT > 2.5 times upper limit of normal; QTcF > 450ms; anaemia (haemoglobin < 8 g/dL); definite plans for absence from the site in 28 days
Interventions	1. Quinine 200mg tablets (Quinine: Kimia Pharma) • 10 mg/kg three times daily for 7 days • Plus primaquine 30 mg daily for 14 days, starting from day 0 (45 mg if weight > 70 kg) 2. Dihydroartemisinin-piperaquine, fixed-dose combination: 40 mg/320 mg (Eurartemisim: Sigma Tau) • Three tablets once daily for three days • Plus primaquine 30 mg daily for 14 days, starting from day 28 (45 mg if weight > 70 kg) The third study arm received artesunate alone and was excluded from this review
Outcomes	1. Recurrence of *P. vivax* at day 28 2. Recurrence of *P. vivax* between days 29 to 163 3. Parasite clearance at 72 hours 4. Anaemia 5. Adverse events
Notes	Country: Indonesia Setting: Army base Transmission: Soldiers had returned from endemic Papua, Indomesia to East Java, Indonesia where there is no endemic *P. vivax*. Resistance: CQ resistance amongst *P. vivax* is prevalent in Papua Dates: Enrolment Nov 2010 to Apr 2011 Funding: Medicines for Malaria Venture, Wellcome Trust. Sigma Tau provided the DHA-P

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'A randomized list of study numbers that were block allocated was generated by varying the blocking number at random'

Sutanto 2013 IDN (*Continued*)

Allocation concealment (selection bias)	Low risk	'An envelope revealing the assigned therapy was opened after informed consent'
Blinding (performance bias and detection bias) All outcomes	Unclear risk	An open label trial. No comment on blinding of laboratory staff
Incomplete outcome data (attrition bias) All outcomes	Low risk	Three were lost to follow-up in the quinine + primaquine arm (8%) and none in the other two arms
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No evidence of any other bias.

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

Study	Reason for exclusion
Batty 1998	No ACT given. A pharmacokinetic study of artesunate monotherapy
Betuela 2012	There was no arm that has received ACT.
Dao 2007	Not randomized. A single arm study of artesunate plus primaquine
Davis 2011	This study is a cost-effectiveness study already published in NEJM in 2008. We included the data from this study in the previous review
Douglas 2010	A review article, not a RCT.
Hamedi 2004	No ACT given. An RCT of artesunate plus primaquine versus chloroquine plus primaquine
Hombhanje 2009	Participants did not have uncomplicated *P. vivax* at baseline. An RCT of artesunate-naphthoquine versus chloroquine plus sulfadoxine-pyrimethamine in *P. falciparum* malaria.
Leang 2013	Although the study reports outcome measures for different arms including one with ACT, there is no mention on whether the study is randomized
Luxemburger 1996	Not randomized. Trial authors gave all participants with *P. vivax* a single dose of mefloquine.
Naing 2010	Review article.
Price 2007a	Uses data from Hasugian 2007 IDN and Ratcliff 2007 IDN. No new efficacy or safety data.
Pukrittayakamee 2000	No ACT given. A RCT of eight different monotherapies.

(*Continued*)

Rueangweerayut 2012	The participants of this study had only *P. falciparum* infection.
Senn 2013	This study is on intermittent preventive treatment in infants (IPTi)
Thimasarn 1997	Participants did not have uncomplicated *P. vivax* malaria. RCT of different treatment combinations for *P. falciparum*.
Tjitra 2002	Not randomized. Two separate trials are reported: a quasi-RCT of chloroquine versus chloroquine plus sulfadoxine-pyrimethamine, followed by a single arm study of artesunate plus sulfadoxine-pyrimethamine
Tjitra 2012	Trial authors only gave the comparator artemisinin-napthoquine as a single dose ACT
van Vugt 1998	Artesunate plus mefloquine versus a four-dose course of artemther-lumefantrine. This regimen is no longer recommended as it was shown to be inferior to six doses for treating *P. falciparum*.
Yeshiwondim 2010	No participants received ACT.
Yohannes 2011	Quasi-RCT: alternate allocation.
Zwang 2009	An individual patient data meta-analysis of six clinical trials including Ashley 2004 THA, Ashley 2005 THA, Janssens 2007a, Smithuis 2010 MMR and two other trials which did not include patients with *P. vivax* at baseline. No new efficacy data.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Janssens 2007

Methods	Trial design: Open label RCT Follow-up: Monitored daily until fever and parasites cleared then weekly to day 63. Temperature, symptom questionnaire, malaria film, and hematocrit at each visit Adverse event monitoring: An adverse event defined as any new sign or symptom appearing after treatment started. At each visit a symptom questionnaire was completed
Participants	Number: It is unclear whether any participants had *P. vivax* infection at baseline (464 randomized in total) Inclusion criteria: Age > 1 yr, axillary temp > 37.5 ºC or history of fever, signs and symptoms of uncomplicated malaria, *P. falciparum* mono or mixed infections, written informed consent Exclusion criteria: Pregnancy or lactation, signs or symptoms of severe malaria, > 4% red blood cells parasitized, a history of convulsions or neuropsychiatric disorder, treatment with mefloquine in the past 60 days
Interventions	1. Dihydroartemisinin-piperaquine, fixed-dose combination, 40 mg/320 mg tablets (Artekin: Holleykin) • Adult total dose: 6 mg/kg DHA and 48 mg/kg P in 4 divided doses, given at 0, 8, 24, and 48 hours • Children total dose: 6.4 mg/kg DHA + 51.2 mg/kg P in 4 divided doses, given at 0, 8, 24, 48 hours 2. Artesunate plus mefloquine, loose combination (Artesunate: Guilin, Mefloquine: Mepha) • Adults: 100 mg AS plus 500 mg MQ twice daily on day 0, then 200 mg AS once daily on day 1 and day 2 • Children: AS 4 mg/kg once daily for 3 days plus 25 mg/kg MQ split into 2 doses on day 0 All doses supervised

Janssens 2007 (*Continued*)

	Primaquine was not given
Outcomes	1. *P. vivax* recurrence at day 14, 28, 42 and 63 Not included in the review: 1. Fever clearance (not available for *P. vivax* patients only) 2. Parasite clearance (not available for *P. vivax* patients only) 3. *P. falciparum* at days 63, 42, and 28, PCR adjusted and unadjusted 4. Mean hematocrit at day 0 and 63 (not available for *P. vivax* patients only) 5. Adverse effects (not available for *P. vivax* patients only)
Notes	Country: Cambodia Setting: Rural health centres and outreach malaria clinics Transmission: Low and seasonal Resistance: Not stated Dates: Oct 2002 to March 2003 Funding: Médecins sans Frontières

Shin 2011

Methods	Trial design: Randomized, double-blind, double-dummy, comparative study Inclusion criteria: Age between 3 and 60 years; body weight between 20 and 90 kg; acute uncomplicated *P. vivax* mono-infection confirmed with fever and positive microscopy of *P. vivax* with parasite density = 250/µL of blood and a rapid negative test for *P. falciparum.*
Participants	Number: 30
Interventions	Pyronaridine (180 mg) + artesunate (60 mg) once a day for 3 days Chloroquine (155 mg) once a day for 3 days
Outcomes	1. Cure rate at Day 14 2. Proportion of patients cured at day 28 and day 42 3. Parasite clearance time 4. Fever clearance time 5. Proportion of patients aparasitaemic on days 1, 2 and 3 6. Adverse events
Notes	This is a conference abstract and no details of either the study or the contact information of the authors are available

van Vugt 2002

Methods	Trial design: Open label RCT Follow-up: Monitored daily until fever and parasites cleared then weekly to day 42. Clinical examination, symptom questionnaire, malaria film, and hematocrit at each visit Adverse event monitoring: At each visit a symptom questionnaire was completed
Participants	Number: It is unclear whether any participants had *P. vivax* infection at baseline (1596 were randomized in total) Inclusion criteria: Weight >10 kg, slide confirmed acute *P. falciparum* malaria, written informed consent

van Vugt 2002 (*Continued*)

	Exclusion criteria: Pregnancy, not obtunded or vomiting, no other clinical or laboratory signs of severe illness, treatment with mefloquine in the past 63 days
Interventions	1. Artesunate plus mefloquine, loose combination • AS 4mg/kg once daily for 3 days • MQ 15 mg/kg on day 1 and 10 mg/kg on day 2 2. Artesunate plus atavoquone-proguanil • AS 4 mg/kg once daily for 3 days • Atavoquine 15 mg/kg once daily for 3 days • Proguanil 8 mg/kg once daily for 3 days 3. Atavoquone-proguanil • Atavoquine 15 mg/kg once daily for 3 days • Proguanil 8 mg/kg once daily for 3 days All doses supervised Primaquine was not given
Outcomes	1. *P. vivax* recurrence by day 42 Not included in the review: 1. Parasite clearance 2. *P. falciparum* at days 42, and 28, PCR adjusted and unadjusted 3. Gametocyte carriage 4. Adverse effects (not available for *P. vivax* patients only)
Notes	Country: Thailand Setting: Malaria clinics of the Shoklo Malaria Research Unit Transmission: Low transmission Resistance: Not stated Dates: July 1998 to July 2000 Funding: Atavoquine-proguanil was donated by Glaxo-SmithKline. The Wellcome Trust of Great Britain

DATA AND ANALYSES

Comparison 1. ACT versus Chloroquine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasite clearance	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Remaining parasitaemic after 24 hours	4	1652	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.36, 0.50]
1.2 Remaining parasitaemic after 48 hours	4	1648	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.05, 0.74]
1.3 Remaining parasitaemic after 72 hours	4	1648	Risk Ratio (M-H, Random, 95% CI)	0.08 [0.01, 0.43]
2 Fever clearance	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Remaining febrile after 24 hours	2	990	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.43, 0.70]
2.2 Remaining febrile after 48 hours	3	1390	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.31, 0.91]
2.3 Remaining febrile after 72 hours	2	985	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.27, 1.36]
3 Recurrence of parasitaemia	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Before day 14	1	427	Risk Ratio (M-H, Random, 95% CI)	2.88 [0.12, 70.22]
3.2 Before day 28	5	1622	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.18, 1.90]
3.3 After day 28 (primaquine not given)	3	1066	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.40, 0.82]
3.4 After day 28 (primaquine given)	1	376	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.08, 0.94]
3.5 During full follow-up period (42 or 56 days)	4	1460	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.44, 0.78]
4 Gametocytemia	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 On Day 0	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 On Day 1	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 On Day 2	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.4 On Day 3	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Serious adverse events	5	1775	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.14, 7.04]

Comparison 2. ACT versus Chloroquine plus Sulfadoxine-pyrimethamine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasite clearance	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Remaining parasitaemic after 24 hours	1	195	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.15, 0.34]
1.2 Remaining parasitaemic after 48 hours	1	195	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.03, 0.27]

1.3 Remaining parasitaemic after 72 hours	1	195	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.03, 0.81]
2 Fever clearance	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Remaining febrile after 24 hours	1	195	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.75, 1.48]
2.2 Remaining febrile after 48 hours	1	195	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.31, 1.23]
2.3 Remaining febrile after 72 hours	1	195	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.29, 2.02]
3 Recurrence of parasitaemia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Before day 14	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Before day 28	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 After day 28	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.4 During full follow-up period (42 days)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Serious adverse events	1	209	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 3. ACT versus Quinine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasite clearance	1	72	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.19, 21.09]
1.1 Remaining parasitaemia after 72 hours	1	72	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.19, 21.09]
2 Recurrence of parasitaemia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Before day 14	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Before day 28	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 After day 28	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 During full follow-up period (42 days)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 4. ACT versus ACT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Remaining parasitemic after 24 hours	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 DHA-P versus AS+MQ	3	120	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.28, 4.92]
1.2 DHA-P versus AL6	1	83	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.31, 1.94]
1.3 AS+MQ versus AL6	1	24	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.60, 1.72]
1.4 DHA-P versus AS+SP	1	95	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.49, 3.72]
2 Remaining parasitemic after 48 hours	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 DHA-P versus AS+MQ	3	120	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 DHA-P versus AL6	1	83	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.04, 4.70]

2.3 AS+MQ versus AL6	1	24	Risk Ratio (M-H, Random, 95% CI)	5.13 [0.29, 89.57]
2.4 DHA-P versus AS+SP	1	95	Risk Ratio (M-H, Random, 95% CI)	3.47 [0.14, 83.00]
3 Remaining febrile after 24 hours	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 DHA-P versus AL6	1	83	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.83, 2.33]
3.2 DHA-P versus AS+SP	1	95	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.64, 1.40]
4 Remaining febrile after 48 hours	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 DHA-P versus AL6	1	83	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.22, 1.83]
4.2 DHA-P versus AS+SP	1	95	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.41, 5.06]
5 Recurrent parasitaemia before day 28	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 DHA-P versus AS+MQ	4	186	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.02, 1.45]
5.2 DHA-P versus AL6	3	237	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.04, 0.58]
5.3 DHA-P versus AS+AQ	2	108	Risk Ratio (M-H, Random, 95% CI)	0.04 [0.00, 0.73]
5.4 DHA-P versus AS+SP	1	77	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.15, 0.72]
5.5 AS+MQ versus AL6	2	56	Risk Ratio (M-H, Random, 95% CI)	0.06 [0.01, 0.40]
5.6 AS+MQ versus AS+AQ	1	34	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.7 AL6 versus AS+AQ	1	28	Risk Ratio (M-H, Random, 95% CI)	16.06 [1.03, 249.60]
5.8 AL6 versus AS+SP	1	72	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.67, 1.68]
6 Recurrent parasitaemia after day 28	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 DHA-P versus AS+MQ	4	169	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.58, 1.09]
6.2 DHA-P versus AL6	3	168	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.11, 1.38]
6.3 DHA-P versus AS+AQ	2	95	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.12, 2.40]
6.4 DHA-P versus AS+SP	1	50	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.14, 1.38]
6.5 AS+MQ versus AL6	2	45	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.61, 1.37]
6.6 AS+MQ versus AS+AQ	1	36	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.72, 1.55]
6.7 AL6 versus AS+AQ	1	18	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.68, 1.80]
6.8 AL6 versus AS+SP	1	38	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.29, 1.84]
7 Recurrent parasitaemia during full follow-up period (0 to 42 or 63 days)	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 DHA-P versus AS+MQ	4	186	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.02, 1.45]
7.2 DHA-P versus AL6	3	237	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.04, 0.58]
7.3 DHA-P versus AS+AQ	2	108	Risk Ratio (M-H, Random, 95% CI)	0.04 [0.00, 0.73]
7.4 DHA-P versus AS+SP	1	77	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.15, 0.72]
7.5 AS+MQ versus AL6	2	56	Risk Ratio (M-H, Random, 95% CI)	0.06 [0.01, 0.40]
7.6 AS+MQ versus AS+AQ	1	34	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.7 AL6 versus AS+AQ	1	28	Risk Ratio (M-H, Random, 95% CI)	16.06 [1.03, 249.60]
7.8 AL6 versus AS+SP	1	72	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.67, 1.68]

Comparison 5. DHA-P versus alternative ACTs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrent parasitaemia - settings described as low transmission	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Before day 28	4	239	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.02, 0.63]
1.2 After day 28 - without primaquine	4	187	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.59, 1.09]

1.3 During full follow-up period (42 to 63 days) - without primaquine	4	201	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.56, 1.02]
2 Recurrent parasitaemia - settings described as high transmission	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Before day 28	3	334	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.08, 0.49]
2.2 After day 28 - with primaquine	2	179	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.10, 0.46]
2.3 After day 28 - without primaquine	1	66	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.14, 1.10]
2.4 During full follow-up period (42 days) - with primaquine	2	210	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.08, 0.32]
2.5 During full follow-up period (42 days) - without primaquine	1	108	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.24, 0.72]

ADDITIONAL TABLES

Table 1. Detailed search strategy

Search set	Search terms used for all databases[1]
1	vivax
2	Arte*
3	Dihydroarte*
4	2 or 3
5	1 and 4
6	(search terms for RCTs)
7	5 and 6
8	Limit 7 to Human

[1] Cochrane Infectious Disease Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library*; MEDLINE; EMBASE; and LILACS.

Table 2. Median parasite clearance times

Study ID	Comparison	Median parasite clearance time (range)		P value
		ACT	CQ	
Krudsood 2007 THA	AL6 versus CQ	41.6 hrs	55.8 hrs	< 0.01

Table 2. Median parasite clearance times (*Continued*)

Poravuth 2010 ASIA	AS-Py versus CQ	23.0 hrs (7.0 to 55.9)	32.0 hrs (7.5 to 63.9)	< 0.0001

Table 3. Fever clearance times

Study ID	Comparison	Median fever clearance time (range)		P value
		ACT	CQ	
Krudsood 2007 THA	AL6 versus CQ	21.8 hrs	25.3 hrs	0.12
Poravuth 2010 ASIA	AS-Py versus CQ	15.9 hrs	23.8 hrs	0.0017

WHAT'S NEW

Last assessed as up-to-date: 28 March 2013.

Date	Event	Description
30 September 2013	New search has been performed	We performed a new search in March 2013 and we included two new trials. New authors joined the team and one author stood down
30 September 2013	New citation required but conclusions have not changed	We performed a new search and included two new trials. There is no substantial change to the conclusions

HISTORY

Protocol first published: Issue 4, 2010

Review first published: Issue 7, 2011

Date	Event	Description
3 August 2011	Amended	We amended figures and tables to improve readability.

CONTRIBUTIONS OF AUTHORS

David Sinclair, Felicity Brand, and Piero Olliaro conceived and designed the protocol. For the original review David Sinclair, Felicity Brand, and Nithya Gogtay extracted the data, and David Sinclair analysed the data and wrote the first draft with Nithya Gogtay. For this update. Nithya Gogtay, Kannan Sridharan, and Urmila Thatte screened the search articles, extracted data, and analysed the data. David Sinclair and Piero Olliaro assisted with revising subsequent drafts and preparing the final draft for publication.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Department for International Development (DFID), UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following adjustments:

The protocol stated: *'For the primary outcome 'Recurrence of P. vivax by day 14 or 28' we will subgroup trials according to those which also gave primaquine and those which did not'*. In conducting the review we found that there were too few trials to make this subgroup analysis informative.

The protocol stated: *'For the secondary outcome with prolonged follow-up 'Recurrence of P. vivax parasitaemia at 1 to 12 months' we will only include trials which also give the WHO recommended dose of primaquine to both treatment arms'*. We chose to include the trials where primaquine was not given as this is informative for settings where primaquine is not administered routinely due to either a high local prevalence of G6PD or very high transmission intensity.

When analysing the data for *'Recurrent parasitemias after day 28'* we excluded the participants who had experienced a recurrence before day 28 from both the numerator and the denominator. This was not explicitly stated in the protocol. The reasoning for this change was to prevent a drug which was superior in the first 28 days (more indicative of treatment of the blood stage) appearing superior at 42 days or longer (more indicative of an effect on relapse or re-infection) even if there was no difference during the second period.

INDEX TERMS

Medical Subject Headings (MeSH)

Antimalarials [*therapeutic use]; Artemisinins [*therapeutic use]; Drug Combinations; Drug Resistance; Drug Therapy, Combination [methods]; Ethanolamines [therapeutic use]; Fluorenes [therapeutic use]; Malaria, Vivax [*drug therapy; prevention & control]; Parasitemia [*drug therapy]; Primaquine [therapeutic use]; Pyrimethamine [therapeutic use]; Quinolines [therapeutic use]; Randomized Controlled Trials as Topic; Secondary Prevention; Sulfadoxine [therapeutic use]

MeSH check words

Humans