Cochrane Library

Cochrane Database of Systematic Reviews

Atovaquone-proguanil for treating uncomplicated Plasmodium falciparum malaria (Review)

Blanshard A, Hine P

Blanshard A, Hine P.
Atovaquone-proguanil for treating uncomplicated Plasmodium falciparum malaria.
Cochrane Database of Systematic Reviews 2021, Issue 1. Art. No.: CD004529.
DOI: 10.1002/14651858.CD004529.pub3.

www.cochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Atovaquone-proguanil for treating uncomplicated Plasmodium falciparum malaria

Andrew Blanshard[1], Paul Hine[2]

[1]Department of Medicine, Norfolk and Norwich University Hospital, Norwich, UK. [2]Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK

Contact address: Paul Hine, doc.p.hine@gmail.com.

Editorial group: Cochrane Infectious Diseases Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 1, 2021.

Citation: Blanshard A, Hine P. Atovaquone-proguanil for treating uncomplicated Plasmodium falciparum malaria. *Cochrane Database of Systematic Reviews* 2021, Issue 1. Art. No.: CD004529. DOI: 10.1002/14651858.CD004529.pub3.

ABSTRACT

Background

The World Health Organization (WHO) in 2015 stated atovaquone-proguanil can be used in travellers, and is an option in malaria-endemic areas in combination with artesunate, as an alternative treatment where first-line artemisinin-based combination therapy (ACT) is not available or effective. This review is an update of a Cochrane Review undertaken in 2005.

Objectives

To assess the efficacy and safety of atovaquone-proguanil (alone and in combination with artemisinin drugs) versus other antimalarial drugs for treating uncomplicated *Plasmodium falciparum* malaria in adults and children.

Search methods

The date of the last trial search was 30 January 2020. Search locations for published trials included the Cochrane Infectious Diseases Group Specialized Register, CENTRAL, MEDLINE, Embase, and LILACS. To include recently published and unpublished trials, we also searched ClinicalTrials.gov, the *meta*Register of Controlled Trials and the WHO International Clinical Trials Registry Platform Search Portal.

Selection criteria

Randomized controlled trials (RCTs) reporting efficacy and safety data for atovaquone-proguanil or atovaquone-proguanil with a partner drug compared with at least one other antimalarial drug for treating uncomplicated *Plasmodium falciparum* infection.

Data collection and analysis

For this update, two review authors re-extracted data and assessed certainty of evidence. We meta-analyzed data to calculate risk ratios (RRs) with 95% confidence intervals (CI) for treatment failures between comparisons, and for safety outcomes between and across comparisons. Outcome measures include unadjusted treatment failures and polymerase chain reaction (PCR)-adjusted treatment failures. PCR adjustment differentiates new infection from recrudescent infection.

Main results

Seventeen RCTs met our inclusion criteria providing 4763 adults and children from Africa, South-America, and South-East Asia. Eight trials reported PCR-adjusted data to distinguish between new and recrudescent infection during the follow-up period. In this abstract, we report only the comparisons against the three WHO-recommended antimalarials which were included within these trials.

There were two comparisons with artemether-lumefantrine, one trial from 2008 in Ethiopia with 60 participants had two failures with atovaquone-proguanil compared to none with artemether-lumefantrine (PCR-adjusted treatment failures at day 28). A second trial from 2012 in Colombia with 208 participants had one failure in each arm (PCR-adjusted treatment failures at day 42).

There was only one comparison with artesunate-amodiaquine from a 2014 trial conducted in Cameroon. There were six failures with atovaquone-proguanil at day 28 and two with artesunate-amodiaquine (PCR-adjusted treatment failures at day 28: 9.4% with atovaquone-proguanil compared to 2.9% with artesunate-amodiaquine; RR 3.19, 95% CI 0.67 to 15.22; 1 RCT, 132 participants; low-certainty evidence), although there was a similar number of PCR-unadjusted treatment failures (9 (14.1%) with atovaquone-proguanil and 8 (11.8%) with artesunate-amodiaquine; RR 1.20, 95% CI 0.49 to 2.91; 1 RCT, 132 participants; low-certainty evidence).

There were two comparisons with artesunate-mefloquine from a 2012 trial in Colombia and a 2002 trial in Thailand where there are high levels of multi-resistant malaria. There were similar numbers of PCR-adjusted treatment failures between groups at day 42 (2.7% with atovaquone-proguanil compared to 2.4% with artesunate-mefloquine; RR 1.15, 95% CI 0.57 to 2.34; 2 RCTs, 1168 participants; high-certainty evidence). There were also similar PCR-unadjusted treatment failures between groups (5.3% with atovaquone-proguanil compared to 6.6% with artesunate-mefloquine; RR 0.8, 95% CI 0.5 to 1.3; 1 RCT, 1063 participants; low-certainty evidence).

When atovaquone-proguanil was combined with artesunate, there were fewer treatment failures with and without PCR-adjustment at day 28 (PCR-adjusted treatment failures at day 28: 2.16% with atovaquone-proguanil compared to no failures with artesunate-atovaquone-proguanil; RR 5.14, 95% CI 0.61 to 43.52; 2 RCTs, 375 participants, low-certainty evidence) and day 42 (PCR-adjusted treatment failures at day 42: 3.82% with atovaquone-proguanil compared to 2.05% with artesunate-atovaquone-proguanil (RR 1.84, 95% CI 0.95 to 3.56; 2 RCTs, 1258 participants, moderate-certainty evidence). In the 2002 trial in Thailand, there were fewer treatment failures in the artesunate-atovaquone-proguanil group compared to the atovaquone-proguanil group at day 42 with PCR-adjustment.

Whilst there were some small differences in which adverse events were more frequent in the atovaquone-proguanil groups compared to comparator drugs, there were no recurrent associations to suggest that atovaquone-proguanil is strongly associated with any specific adverse event.

Authors' conclusions

Atovaquone-proguanil was effective against uncomplicated *P falciparum* malaria, although in some instances treatment failure rates were between 5% and 10%. The addition of artesunate to atovaquone-proguanil may reduce treatment failure rates. Artesunate-atovaquone-proguanil and the development of parasite resistance may represent an area for further research.

PLAIN LANGUAGE SUMMARY

What are the benefits and risks of atovaquone-proguanil for treating uncomplicated malaria caused by the *Plasmodium falciparum* parasite?

What is the aim of this review?

The most common, and most serious, type of malaria is caused by *Plasmodium falciparum*. In its mild (uncomplicated) form, the symptoms are fever, headaches, muscle pain, and vomiting. The disease can become severe and life-threatening if it is not treated soon enough or with the right medicines.

This review aimed to find out whether atovaquone-proguanil is effective and safe for treating uncomplicated cases of *P falciparum* malaria. We aimed to achieve this by comparing the results of studies that had compared atovaquone-proguanil to other malaria treatments.

Key messages

Atovaquone-proguanil is as effective for treating uncomplicated *Plasmodium falciparum* malaria as artesunate-mefloquine. It may be less effective than artemether-lumefantrine, artesunate-amodiaquine, and artesunate-atovaquone-proguanil, though more robust evidence is needed to confirm this. Side effects seem similar with atovaquone-proguanil.

What was studied in this review?

The World Health Organization (WHO) recommends treating uncomplicated malaria with oral (by mouth) artemisinin-based combination medicines (called ACTs).

ACTs are not always available worldwide and, in some places, *Plasmodium falciparum* is becoming resistant to recommended treatments (the medicines stop working). We looked at the evidence about the benefits and harms of combinations of medicines that are not artemisinin-based, but contain atovaquone-proguanil. This is an oral treatment commonly used by people from non-malaria areas to prevent them catching malaria when they travel to malaria areas. We wanted to find out whether it works as well for treating uncomplicated *Plasmodium falciparum* malaria as ACTs and other malaria treatments.

We searched for randomized controlled trials (clinical studies where people are randomly put into one of two or more treatment groups) that compared atovaquone-proguanil against other malaria treatments. These studies provide the most robust evidence about the effects of a treatment. We compared results, summarized the evidence, and rated our confidence in the evidence.

What are the main results of the review?

We found 17 studies involving 4763 adults and children in Africa, South America, and South East Asia. People were followed for 28 days to one year.

Fifteen studies compared atovaquone-proguanil against 12 different antimalarial treatments (ACTs in five studies; other therapies that combined several medicines in two studies; single medicines in nine studies).

Five studies compared atovaquone-proguanil plus another medicine (artesunate or chloroquine) against atovaquone-proguanil alone (three studies); atovaquone-proguanil plus a different medicine (one study); a combination of therapies that did not include atovaquone-proguanil (one study); or single medicines (two studies).

In 15 studies, the researchers and people who were treated knew which medicines participants received. Pharmaceutical companies funded 10 studies.

Atovaquone-proguanil against ACTs recommended by the WHO

Atovaquone-proguanil may work less well to clear *Plasmodium falciparum* parasites from the blood or prevent them from returning (treatment success) than artemether-lumefantrine (rates of success compared 28 and 42 days after treatment; one study). However this evidence was based on one small study.

Atovaquone-proguanil may work as well as, or less well than, artesunate-amodiaquine depending on whether new infections appearing after the start of treatment were counted or not (rates of success compared three and 28 days after treatment; one study). However this evidence was based on one small study of children aged under five years.

When new infections after the start of treatment were excluded, there is strong evidence of little to no difference in treatment success between atovaquone-proguanil and artesunate-mefloquine after 42 days (two studies). When new infections were counted, atovaquone-proguanil may be better than artesunate-mefloquine, but this evidence was based on the imprecise results of one study.

Atovaquone-proguanil against atovaquone-proguanil plus artesunate

Compared to atovaquone-proguanil plus artesunate, atovaquone-proguanil may be less successful at treating uncomplicated malaria after three and 28 days, however this evidence is based on the results of two small studies. It is probably less successful at treating uncomplicated malaria after 42 days (two studies).

Side effects

Studies reported several side effects, such as nausea and vomiting, or headaches. Overall, they were similar between groups.

How-up-to date is this review?

The evidence is current to 30 January 2020.

SUMMARY OF FINDINGS

Summary of findings 1. Atovaquone-proguanil compared to artemether-lumefantrine for treating uncomplicated *Plasmodium falciparum* malaria

Atovaquone-proguanil compared to artemether-lumefantrine for treating uncomplicated *Plasmodium falciparum* malaria

Patient or population: children and adults
Setting: Colombia and Ethiopia
Intervention: AV+PG
Comparison: AL

Outcomes	Study event rates*		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	With AL	With AV+PG				
Total failure day 28 PCR-adjusted	0/30 (0%)	2/30 (6.7%)	**RR 5.00** (0.25 to 99.95)	60 (1 RCT)	⊕⊕⊖⊖ **Low** [a,b]	Compared to AL, AV+PG may have more PCR-adjusted treatment failures at day 28.
Total failure day 42 PCR-unadjusted	0/30 (0%)	2/30 (6.7%)	**RR 5.00** (0.25 to 99.95)	60 (1 RCT)	⊕⊕⊖⊖ **Low** [a,b]	Compared to AL, AV+PG may have more PCR-unadjusted treatment failures at day 28.
Total failure day 42 PCR-adjusted	**Anticipated absolute effects† (95% CI)**		**RR 3.00** (0.19 to 47.12)	208 (1 RCT)	⊕⊕⊖⊖ **Low** [a,b]	Compared to AL, AV+PG may have more PCR-adjusted treatment failures at day 42.
	Risk with AL	**Risk with AV+PG**				
	6 per 1000	19 per 1000 (1 to 302)				

***We presented study event rates rather than anticipated absolute effects as there were no events in the AL group.

† **The risk in the intervention group** (and its 95% confidence interval) was based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

AL: artemether-lumefantrine; **AV+PG:** atovaquone-proguanil; **CI:** confidence interval; **PCR:** polymerase chain reaction; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded two levels for serious imprecision. Small number of participants and wide confidence intervals.
[b]We noted that indirectness was present as only one study contributed to each outcome. However, as there were higher treatment failures consistently with atovaquone-proguanil compared to artemether-lumefantrine between the two studies, we did not downgrade to beyond low certainty.

Summary of findings 2. Atovaquone-proguanil compared to artesunate-amodiaquine for treating uncomplicated *Plasmodium falciparum* malaria

Atovaquone-proguanil compared to artesunate-amodiaquine for treating uncomplicated *Plasmodium falciparum* malaria

Patient or population: children under the age of 5 years
Setting: Cameroon
Intervention: AV+PG
Comparison: AS+AQ

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with AS+AQ	Risk with AV+PG				
Total failure day 28 PCR-adjusted	29 per 1000	**94 per 1000** (20 to 448)	**RR 3.19** (0.67 to 15.22)	132 (1 RCT)	⊕⊕⊖⊖ **Low** [a,b]	Compared to AS+AQ, AV+PG may have more PCR-adjusted failures at day 28.
Total failure day 28 PCR-unadjusted	118 per 1000	**141 per 1000** (58 to 342)	**RR 1.20** (0.49 to 2.91)	132 (1 RCT)	⊕⊕⊖⊖ **Low** [a,b]	There may be little or no difference in PCR-adjusted failures at day 28 between AS+AQ and AV+PG.
Early treatment failure	**Study event rates**[†]		**RR 13.80** (0.79 to 240.11)	132 (1 RCT)	⊕⊕⊖⊖ **Low** [a,b]	Compared to AS+AQ, AV+PG may have more early treatment failures.
	With AS+AQ	**With AV+PG**				
	0/68 (0%)	6/64 (9.4%)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
[†]We presented study event rates rather than anticipated absolute effects as there were no events in the AL group for two of the outcomes.

AS+AQ: artesunate-amodiaquine; **AV+PG:** atovaquone-proguanil; **CI:** confidence interval; **PCR:** polymerase chain reaction; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for indirectness. Trial of children aged under five years only.
[b]Downgraded one level for imprecision. Low numbers of events.

Summary of findings 3. Atovaquone-proguanil compared to artesunate-mefloquine for treating uncomplicated *Plasmodium falciparum* malaria

Atovaquone-proguanil compared to artesunate-mefloquine for treating uncomplicated *Plasmodium falciparum* malaria

Patient or population: children and adults
Setting: Colombia and Thailand
Intervention: AV+PG
Comparison: AS+MQ

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with AS-MQ	Risk with AV-PG				
Total failure day 42 PCR-adjusted	24 per 1000	**27 per 1000** (14 to 56)	**RR 1.15** (0.57 to 2.34)	1168 (2 RCTs)	⊕⊕⊕⊕ **High**	There was little to no difference in PCR-adjusted failures at day 42 between AS+MQ and AV+PG.
Total failure day 42 PCR-unadjusted	66 per 1000	**53 per 1000** (33 to 85)	**RR 0.8** (0.5 to 1.3)	1063 (1 RCT)	⊕⊕⊖⊖ **Low** [a]	Compared to AS+MQ, AV+PG may have fewer PCR-unadjusted treatments at day 42.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

AS+MQ: artesunate-mefloquine; **AV+PG:** atovaquone-proguanil; **CI:** confidence interval; **PCR:** polymerase chain reaction; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded two levels for imprecision. The confidence interval crossed the line of no effect, and the effect size was small.

Summary of findings 4. Atovaquone-proguanil compared to artesunate-atovaquone-proguanil for treating uncomplicated *Plasmodium falciparum* malaria

Atovaquone-proguanil compared to artesunate-atovaquone-proguanil for health problem or population

Patient or population: children and adults
Setting: Cameroon and Thailand
Intervention: AV+PG
Comparison: AS+AV+PG

Outcomes	Study event rates*		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	With AS+AV+PG	With AV+PG				
Total failure day 28 PCR-adjusted	0/190 (0%)	4/185 (3.3%)	**RR 5.143** (0.61 to 43.52)	375 (2 RCTs)	⊕⊕⊖⊖ **Low** [a]	Compared to AS+AV+PG, AV+PG may have more PCR-adjusted treatment failures at day 28.
Total failure day 28 PCR-unadjusted	0/95 (0%)	7/92 (7.6%)	**RR 15.48** (0.90 to 267.27)	187 (1 RCT)	⊕⊕⊖⊖ **Low** [a,b]	Compared to AS+AV+PG, AV+PG may have more PCR-unadjusted treatment failures at day 28.
Total failure [day 42 PCR-adjusted	**Anticipated absolute effects† (95% CI)**		**RR 1.84** (0.95 to 3.56)	1258 (2 RCTs)	⊕⊕⊕⊖ **Moderate** [c]	Compared to AS+AV+PG, AV+PG probably leads to more PCR-adjusted treatment failures at day 42.
	Risk with AS+AV+PG	**Risk with AV+PG**				
	21 per 1000	37 per 1000 (10 to 77)				
Total failure day 42 PCR-unadjusted	34 per 1000	53 per 1000 (30 to 94)	**RR 1.56** (0.88 to 2.79)	1063 (1 RCT)	⊕⊕⊕⊖ **Moderate** [c]	Compared to AS+AV+PG, AV+PG probably leads to more PCR-unadjusted treatment failures at day 42.
Early treatment failure	0/198 (2.1%)	2/197 (1.0%)	**RR 5.11** (0.25 to 104.94)	395 (2 RCTs)	⊕⊕⊖⊖ **Low** [a]	Compared to AS+AV+PG, AV+PG may have more early treatment failures.

***** We presented study event rates rather than anticipated absolute effects as there were no events in the AL group.

† **The risk in the intervention group** (and its 95% confidence interval) was based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

AS+AV+PG: artesunate-atovaquone-proguanil; **AV+PG:** atovaquone-proguanil; **CI:** confidence interval; **PCR:** polymerase chain reaction; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

---

[a]Downgraded two levels for imprecision. Wide confidence interval that crossed the line of no effect.
[b]Downgraded one level for indirectness. Evidence came from one study in children only.
[c]Downgraded one level for imprecision. Confidence interval crossed the line of no effect.

BACKGROUND

Description of the condition

Plasmodium falciparum is the most important of all species of malaria. In 2016, it was responsible for 99% of malaria cases in the World Health Organization (WHO) African region, and 66% in the South-East Asia region (WHO 2017).

Uncomplicated malaria is defined by the absence of clinical features that define severe malaria in the presence of an asexual *P falciparum* parasitaemia (WHO 2015). Severe malaria is defined as a *P falciparum* parasitaemia with one or more of: impaired consciousness, prostration, multiple convulsions, acidosis, hypoglycaemia, severe malarial anaemia, renal impairment, jaundice, pulmonary oedema, significant bleeding, shock, or a parasitaemia greater than 10%.

The first-line treatment for uncomplicated *P falciparum* malaria is artemisinin-based combination therapy (ACT) (WHO 2015). The artemisinin component rapidly clears parasites from the blood. It is active against some sexual stages of the parasite, particularly immature gametocytes. This property helps reduce post-treatment malaria transmission. The partner drug is longer acting and protects the artemisinin component from resistance. Those with longer half-lives also provide post-treatment prophylaxis against reinfection.

Artemisinin resistance has emerged in South East Asia; initially in Western Cambodia (Noedl 2008), but has since become prevalent in Laos, Myanmar, Thailand, and Vietnam (the Greater Mekong subregion). Genetic mutations associated with artemisinin resistance in these areas have also been detected at significant prevalence (greater than 5%) in Guyana, Papua New Guinea, and Rwanda, although the clinical significance is uncertain (WHO 2019). Historically, chloroquine-resistant malaria emerged in the Greater Mekong subregion, an area of low transmission. It has since spread through Asia and Africa. Further spread of artemisinin resistance could lead to higher mortality from malaria (Lubell 2014).

Description of the intervention

Atovaquone-proguanil is commonly used to prevent malaria when travelling (ACMP 2017). It is a 'causal' prophylactic agent, meaning that it inhibits liver stage development of malaria. This means that it needs to be taken only for one week after travel to endemic areas (rather than four weeks, as for doxycycline or mefloquine).

The WHO also supports use of atovaquone-proguanil outside malaria-endemic areas and in combination with artesunate and primaquine as an alternative treatment where first-line ACT is not available or effective (WHO 2015). It has been used in areas where there are high rates of treatment failure associated with artemisinins (WHO 2012), and as such it is important to understand how it compares to ACTs and other antimalarials. The high cost of atovaquone-proguanil has limited its use for treatment, and a public-private partnership to provide the drug for free was short-lived due to concerns about poor use of resources (Oyediran 2002). While atovaquone-proguanil was previously only available as Malarone, it is now available off-licence in generic formulations.

How the intervention might work

Atovaquone selectively inhibits electron transport in the malarial cytochrome b complex. Proguanil hydrochloride mainly acts via the metabolite cycloguanil, a dihydrofolate reductase inhibitor. Proguanil's main effect is to potentiate atovaquone, rather than having direct antimalarial activity. As such, although it has two components, atovaquone-proguanil is not a combination equivalent to ACT, in which two antimalarial drugs with different modes of action, are combined.

Resistance to atovaquone is a potential barrier to its widespread use. Resistance predominantly emerges rapidly via single point mutations in the malarial cytochrome b gene (Blasco 2017). Animal studies suggest that resistance may be non-transmissible as the mutation significantly reduces parasite fitness (Goodman 2016). Therefore, it is likely that resistance usually originates in the parasite from de novo mutations, rather than being spread between mosquitoes and humans.

Atovaquone is poorly absorbed, though proguanil is rapidly absorbed from the gastrointestinal tract. The elimination half-life of atovaquone is about two days to three days in adults, and of proguanil is 12 hours to 15 hours in adults (WHO 2015). These elimination half-lives are longer than artemisinins, similar to lumefantrine and sulfadoxine-pyrimethamine, but shorter than mefloquine or piperaquine.

Why it is important to do this review

This review is an update of a Cochrane Review first published in 2005 (Osei-Akoto 2005). The previous review included 10 randomized controlled trials (RCTs) and concluded that there was some evidence that atovaquone-proguanil was superior to chloroquine, mefloquine, and amodiaquine, but that there was insufficient data for other comparisons. The authors recommended larger trials comparing atovaquone-proguanil with new combination therapies.

A 2017 non-Cochrane systematic review aimed to estimate efficacy of atovaquone-proguanil for treatment of uncomplicated malaria (including, but not limited to *P falciparum*) (Staines 2017). This included one study (Bustos 1999), which the original authors of this Cochrane Review excluded due to protocol amendments. Staines 2017 also excluded one study included in the previous Cochrane Review (Van Vugt 2002), but the reason for this was unclear. The analysis combined RCTs and observational studies, and used single-arm weighted means to estimate atovaquone-proguanil treatment efficacy. The authors used the outcome of 'treatment success at day 28', but it was unclear how this outcome was defined. Within their discussion, the authors state that "meta-analysis suggests that atovaquone-proguanil treatment success is equivalent to the use of ACT". Given the strength of this conclusion, we considered it would be useful to re-evaluate the evidence using updated Cochrane methodology.

Since the last update in 2005, the Cochrane Review process has evolved. An updated review will benefit from GRADE methodology, which will allow greater clarity for the assessment of the certainty of evidence. Inclusion of 'Summary of findings' tables will help to frame conclusions with clear indications to the reader regarding the certainty of evidence presented.

This remains an important and relevant area, particularly in the context of evolving antimalarial drug resistance.

OBJECTIVES

To assess the efficacy and safety of atovaquone-proguanil (alone and in combination with artemisinin drugs) versus other antimalarial drugs for treating uncomplicated *Plasmodium falciparum* malaria in adults and children.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs.

Types of participants

Children and adults with uncomplicated *P falciparum* malaria confirmed by microscopy or rapid diagnostic tests in all geographical locations.

Types of interventions

Intervention

Atovaquone-proguanil, alone or in combination with other antimalarials.

Control

Other antimalarial drugs, alone or in combination with other antimalarials.

Types of outcome measures

We collected data on both primary and secondary outcome measures.

Primary outcomes

- Total treatment failure at day 28 (polymerase chain reaction (PCR)-adjusted and unadjusted).
- Total treatment failure at day 42 (PCR-adjusted and unadjusted).

We based these primary outcome measures on WHO recommendations (WHO 2003; WHO 2009), which advise a 28-day follow-up to capture most failures, and 42-day follow-up to capture failures for drugs with a longer elimination half-life (mefloquine and piperaquine). PCR adjustment differentiates recrudescent infections from new infections during follow-up but may misclassify. Unadjusted treatment failure helps indicate the post-treatment prophylactic effect of partner drugs. Including both measures helps inform policy makers, and these outcomes are also consistent with previous Cochrane Reviews.

We did not use adequate clinical and parasitological response (ACPR) as this is defined as absence of failure and is, therefore, duplication.

Secondary outcomes

- Early treatment failure (WHO 2009):
  - danger signs or severe malaria on days one, two, or three in the presence of parasitaemia;
  - parasitaemia on day two higher than on day zero, irrespective of axillary temperature;
  - parasitaemia on day three with axillary temperature 37.5 °C or greater; and
  - parasitaemia on day three 25% or greater of count on day 0.

It is important to include data for parasitaemia on day three as this is both part of the standardized definition for treatment response used for all levels of malaria transmission, and it is regarded as an indirect marker of artemisinin resistance (WHO 2009; WHO 2011).

Adverse events

- Serious adverse events (including death, life-threatening events, hospitalization, and disability).
- Adverse events leading to withdrawal from the trial.
- Other adverse events.

Search methods for identification of studies

We aimed to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress). We searched for relevant trials on 10 January 2018, 14 January 2019 and 30 January 2020.

Electronic searches

The authors of the review and the Cochrane Infectious Disease Group information specialist Vittoria Lutje (VL) attempted to identify all relevant trials. We searched the following databases using the search terms and strategy described in Appendix 1:

- Cochrane Infectious Diseases Group (CIDG) Specialized Register;
- Cochrane Central Register of Controlled Trials (CENTRAL);
- MEDLINE;
- Embase;
- LILACS.

We searched ClinicalTrials.gov, the *meta*Register of Controlled Trials and the WHO International Clinical Trials Registry Platform Search Portal for ongoing or recently completed trials. The date of the last search was 30 January 2020.

Searching other resources

To identify additional published, unpublished, and ongoing studies, we checked the reference lists of all studies identified.

The original authors of this review circulated a list of identified studies to individual researchers working in the field and to the drug manufacturer to help identify additional trials and provide information on ongoing trials (Osei-Akoto 2005). We did not do this and did not search conference abstracts or proceedings because improved trial methods and search methodology means that relevant trials are more readily found through electronic databases.

Data collection and analysis

Selection of studies

For this update, two review authors (AB and PH) independently screened newly identified articles by title and abstract to assess if they met the inclusion criteria. There were no disagreements. We documented the reason for excluding trials in the Characteristics of excluded studies table. We presented an adapted PRISMA flow diagram for review updates, following standard guidance (Mohor 2009; Stovold 2014).

Data extraction and management

Due to changes in the primary and secondary outcomes of the review compared to the previous version and to ensure consistency, two review authors (AB and PH) independently re-extracted all data using a standardized form.

Unadjusted total failure rate day 28 and day 42

We extracted the following data and summed it to form the numerator.

- Early treatment failure.
- Late clinical failure.
- Late parasitological failure.

We extracted the following data and subtracted it from the number of participants randomized. This formed the denominator.

- Those found not to be fulfilling inclusion criteria after randomization.
- Those voluntarily withdrawing consent.
- Those lost to follow-up.
- Those violating protocol, including (but not limited to) missed or vomited doses, those failing to complete treatment, and those taking additional antimalarials.

Polymerase chain reaction-adjusted total failure rate day 28 and day 42

We extracted the following data and summed it to form the numerator.

- Early treatment failure due to PCR-confirmed recrudescence.
- Late clinical failure due to PCR-confirmed recrudescence.
- Late parasitological failure due to PCR-confirmed recrudescence.

We extracted the following data and subtracted it from the number of participants randomized. This formed the denominator.

- Those with indeterminate PCR results.
- Those with missing PCR results.
- Those with PCR-confirmed new infections.
- Those found not to be fulfilling inclusion criteria after randomization.
- Those voluntarily withdrawing consent.
- Those lost to follow-up.
- Those violating protocol, including (but not limited to) missed or vomited doses, those failing to complete treatment, and those taking additional antimalarials.

Adverse events

We extracted the number of people who had been reported as experiencing an adverse event to form the numerator. The denominator was formed from the number of people who had received at least one dose of the study drug, unless otherwise stated. We used the Medical Dictionary for Regulatory Activities to search for a 'higher level term' to group adverse events together and allow comparison between studies using different descriptors for similar and related symptoms (MedDRA 2018). Where a study reported multiple adverse events that had a common MedDRA term, we only included the most common adverse event to avoid double counting. Where more than one 'higher level term' was given for a symptom, we consistently applied the term that we considered most appropriate, and used footnotes in the forest plots to describe original terms where a 'higher level term' might be considered ambiguous.

Comment on efficacy denominators

This approach was based on standard WHO approaches for assessing and monitoring antimalarial drug efficacy (WHO 2003; WHO 2009). We adopted this approach within our review to ensure consistency with the WHO approach, and the analysis method used in previous Cochrane systematic reviews of malaria treatment. We recognize that this method excludes a high number of randomized participants from the denominator for the final efficacy outcome. In order to restore integrity of randomization, we had planned to conduct a series of sensitivity analyses (as described in Table 1), but, given the small number of trials included for each comparison, we did not pursue this as it was unlikely to alter conclusions.

Assessment of risk of bias in included studies

Two review authors (AB and PH) independently used the 'Risk of bias' tool developed by Cochrane to assess and identify bias in included studies (Higgins 2017). We categorized six domains as being high risk, low risk, or unclear risk, which are displayed in the Characteristics of included studies table.

Measures of treatment effect

We calculated risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous data.

Unit of analysis issues

There were no unit of analysis issues.

Dealing with missing data

We contacted trial authors to clarify ambiguous data and to add missing data that would be helpful for this review. We excluded some data because it was not interpretable. In particular, we encountered difficulties interpreting participant dropout rates to form the denominator for treatment failures. We explained any deviations from our protocol in footnotes presented with the forest plots.

Assessment of heterogeneity

We visually inspected forest plots for overlapping CIs as an indicator of clinical heterogeneity. We also used a Chi^2 test with a significance level of $P < 0.1$ or an I^2 statistic greater than 75% (or both) as an indication of substantial heterogeneity.

Assessment of reporting biases

We did not produce a funnel plot to investigate publication bias because this review contained a large number of comparator drugs rather than reviews that have compared AV+PG against the same control drug.

Data synthesis

We analyzed the data using Review Manager 5 (Review Manager 2014). We planned to use a fixed-effect model for meta-analysis if we deemed there to be no substantial heterogeneity, and a random-effects model if we identified substantial heterogeneity. Because we found no substantial heterogeneity, we used fixed-effect modelling throughout.

Subgroup analysis and investigation of heterogeneity

Within our protocol, we intended to explore heterogeneity using subgroup analysis, but there were too few trials in each comparison to yield meaningful results.

Sensitivity analysis

Within our protocol, we intended to conduct a sensitivity analysis adding excluded groups back into the analysis using stepwise methods. Given the small number of trials included for each comparison, we did not pursue this, but the planned analysis is presented in Table 1 for reference.

Summary of findings and assessment of the certainty of the evidence

We assessed the certainty of the evidence using the GRADE approach (Schünemann 2013). We appraised the certainty of evidence in relation to the following criteria.

- Study design.
- Risk of bias.
- Inconsistency.
- Indirectness.
- Imprecision.
- Other considerations (including publication bias).

We used GRADEpro 2015 to create 'Summary of findings' tables for outcomes related to treatment failure.

RESULTS

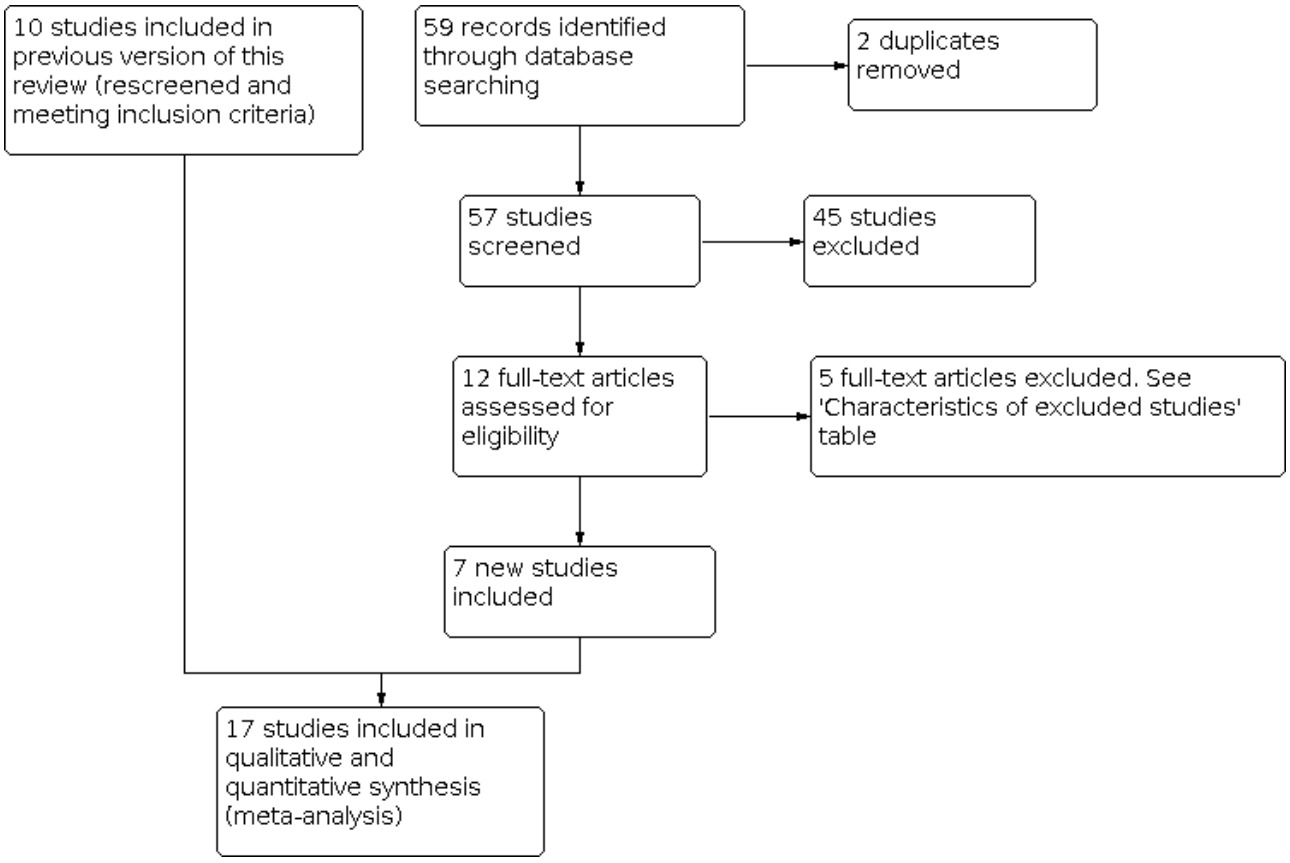
Description of studies

See Characteristics of included studies and Characteristics of excluded studies tables.

Results of the search

The updated literature search on 30 January 2020 identified 59 references. Two studies were duplicates and we excluded a further 45 studies after title and abstract screening. We assessed 12 full-text articles for eligibility of which seven met the inclusion criteria. We screened the 10 trials included in a previous review; all met the inclusion criteria giving a total of 17 studies (see Characteristics of included studies and Characteristics of excluded studies tables; and the PRISMA study flow diagram (Figure 1)). Our search initially identified Wojnarski 2019 as an abstract report, but the full results have since been published.

Figure 1. PRISMA diagram.



We contacted authors of 15 studies to request additional information. Eight authors replied (De Alencar 1997; Llanos-Cuentas 2001; Borrmann 2003; McGready 2005; Gurkov 2008; Carrasquilla 2012; Laufer 2012; Wojnarski 2019). We did not receive replies from the authors of seven studies (Radloff 1996; Anabwani 1999; Looareesuwan 1999; Mulenga 1999; Van Vugt 2002; Mulenga 2006; Tahar 2014). We did not need to contact the remaining authors.

Included studies

We identified 17 studies with 4763 participants; 2839 from trials included in the original review (Radloff 1996; De Alencar 1997; Anabwani 1999; Looareesuwan 1999; Mulenga 1999; Bouchaud 2000; Llanos-Cuentas 2001; Van Vugt 2002; Borrmann 2003; Giao 2004), and 1924 participants from newly included trials (McGready 2005; Mulenga 2006; Gurkov 2008; Carrasquilla 2012; Laufer 2012; Tahar 2014; Wojnarski 2019).

The studies compared atovaquone-proguanil to 12 different antimalarial drugs, including ACTs and non-combination therapies. Table 2 gives a summary of the comparisons made between studies. Table 3 summarizes the outcomes reported by the different studies.

We presented the trials with the dates of data collection, global region, and a range of failure rates for atovaquone-proguanil and comparator drugs in Table 4 so that it is easy to compare the overall findings between publication date, trial dates, and global regions.

Studies comparing atovaquone-proguanil to WHO-recommended artemisinin-based combination therapy

Four studies compared atovaquone-proguanil to WHO-recommended ACTs (Van Vugt 2002; Gurkov 2008; Carrasquilla 2012; Tahar 2014). These studies included 2296 participants. Carrasquilla 2012 included adults and children older than 12 years in South America. Gurkov 2008 included adults and children older than five years in Africa. Tahar 2014 included children aged six months to five years in Africa. Van Vugt 2002 included adults and children older than two years in Thailand. The four studies used weight-based dosing for atovaquone-proguanil.

Other comparisons

Studies comparing atovaquone-proguanil to artesunate-atovaquone-proguanil

Three studies compared atovaquone-proguanil to artesunate-atovaquone-proguanil (Van Vugt 2002; Tahar 2014; Wojnarski 2019). These studies included 2139 participants. Tahar 2014 included children aged six months to five years in Africa. Van Vugt 2002 included adults and children older than two years in Thailand. Wojnarski 2019 included adults in Cambodia.

Studies comparing atovaquone-proguanil to other combinations or to monotherapy

Three studies compared atovaquone-proguanil to combination therapies that are not recommended by WHO (De Alencar 1997; Giao 2004; Laufer 2012). One study compared artesunate-atovaquone-proguanil to quinine (McGready 2005). Ten studies

compared atovaquone-proguanil to monotherapies (Radloff 1996; Looareesuwan 1999; Mulenga 1999; Bouchaud 2000; Llanos-Cuentas 2001; Borrmann 2003; McGready 2005; Mulenga 2006; Gurkov 2008; Laufer 2012).

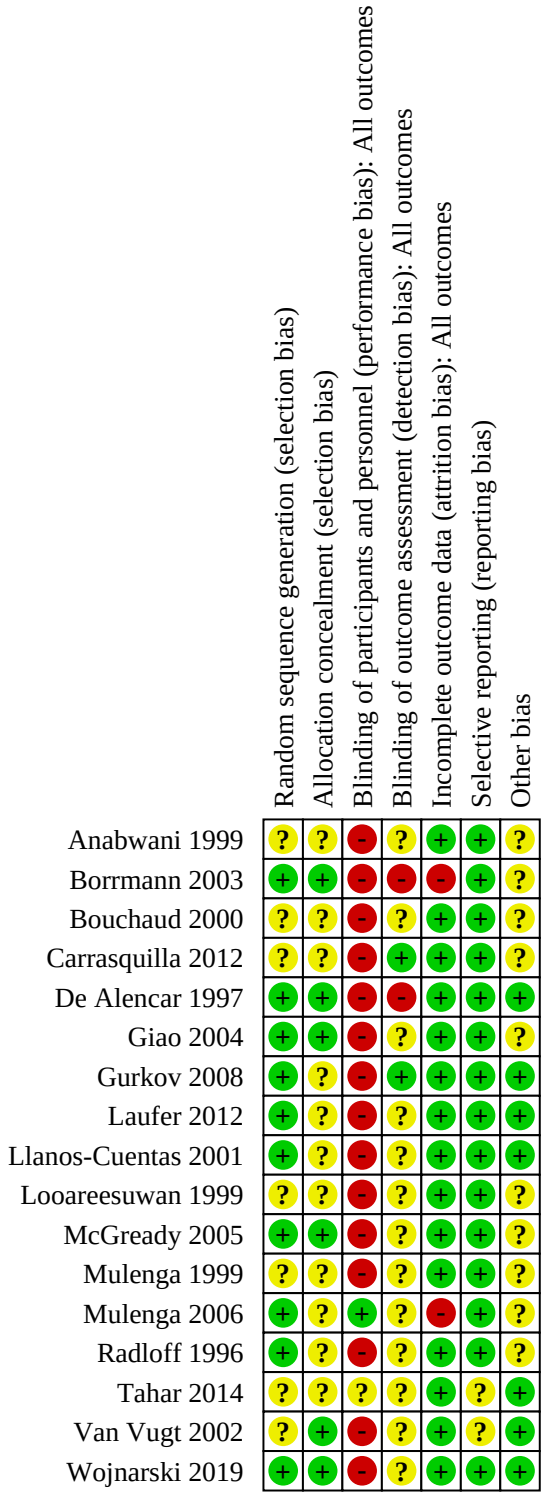
Excluded studies

We excluded five studies. The reasons for their exclusion are listed in the Characteristics of excluded studies table.

Risk of bias in included studies

See Figure 2 for 'Risk of bias' summary and Characteristics of included studies table.

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



Allocation

Nine trials described adequate sequence generation (Radloff 1996; De Alencar 1997; Borrmann 2003; Giao 2004; McGready 2005; Mulenga 2006; Gurkov 2008; Laufer 2012; Wojnarski 2019). Correspondence with a study author confirmed the use of a computer-generated randomization code for a further study (Llanos-Cuentas 2001). It was unclear how the allocation sequence had been generated in the remaining seven studies.

Five trials described methodology for allocation concealment (Van Vugt 2002; Borrmann 2003; Giao 2004; McGready 2005; Wojnarski 2019); one further study was confirmed through correspondence to have used sealed envelopes (De Alencar 1997). The remaining trials were at unclear risk.

Blinding

Only one trial blinded participants and personnel (Mulenga 2006). Tahar 2014 mentioned the use of blinding in the trial registration, but did not describe how this was performed. The remaining 15 trials were described as 'open-label', and, as such, we regarded them at high risk of performance bias, and of unclear risk of detection bias; we considered that the laboratory staff assessing the primary outcomes were unlikely to have been aware of treatment allocations.

Incomplete outcome data

We judged Mulenga 2006 at high risk of attrition bias given a relatively high attrition rate that may be sufficient to introduce clinically relevant bias (approximately 75% followed up at day 28). Similarly, we concluded that Borrmann 2003 was at high risk of attrition bias as there was differential attrition between study arms; in one arm there was 22% loss to follow-up, but only 8% loss to follow-up in the other. The remaining trials had either low rates of attrition, or moderate rates of attrition which were distributed evenly between arms; therefore, we judged these to have low risk of bias.

Selective reporting

One trial was retrospectively registered (Tahar 2014), another trial reported on an outcome (gametocyte carriage) not listed in the methodology (Van Vugt 2002). The authors of Wojnarski 2019 initially declined to share unpublished data, though their trial was later published in June 2019. There was no evidence of reporting bias in the other trials.

Other potential sources of bias

Ten studies were directly funded by pharmaceutical companies; for seven of these studies, we were unable to identify assurances of author independence from conflicts of interest and have, therefore, listed the risk of bias as unclear. Two studies received tablet donations from pharmaceutical companies but gave assurance of author independence. Of the 10 studies funded by pharmaceutical companies, five had the same senior author. Other sources of funding were national and charitable foundations, as well as the armed forces.

Effects of interventions

See: **Summary of findings 1** Atovaquone-proguanil compared to artemether-lumefantrine for treating uncomplicated *Plasmodium falciparum* malaria; **Summary of findings 2** Atovaquone-proguanil compared to artesunate-amodiaquine for treating uncomplicated *Plasmodium falciparum* malaria; **Summary of findings 3** Atovaquone-proguanil compared to artesunate-mefloquine for treating uncomplicated *Plasmodium falciparum* malaria; **Summary of findings 4** Atovaquone-proguanil compared to artesunate-atovaquone-proguanil for treating uncomplicated *Plasmodium falciparum* malaria

Abbreviations

In this analysis section, we used standard abbreviations for the antimalarial drugs (Appendix 2).

Crude treatment failure rates

Table 5 reports treatment failure rates at day 28 and day 42. We have not weighted or pooled these, but presented them for completeness. Three studies reported PCR-adjusted treatment failure rates at day 28, and, in two of these, the treatment failure rate for AV+PG was greater than 5% (Gurkov 2008; Tahar 2014). Three studies reported PCR-adjusted treatment failure rates at day 42, and, in one of these, the treatment failure rate for AV+PG was greater than 5% (Wojnarski 2019). In none of the studies did PCR-adjusted treatment failure rate at day 28 or day 42 for AV+PG exceed 10%.

Studies comparing atovaquone-proguanil to WHO-recommended artemisinin-based combination therapy

Comparison 1. Atovaquone-proguanil versus artemether-lumefantrine

Two studies compared AV+PG versus AL (Gurkov 2008; Carrasquilla 2012). See Summary of findings 1.

We were only able to reliably extract data for one study reporting PCR-adjusted treatment failures at day 28 (Gurkov 2008). There were fewer PCR-adjusted treatment failures at day 28 following treatment with AL compared to AV+PG, but the CIs were very wide and crossed the line of no effect (RR 5.00, 95% CI 0.25 to 99.95; 1 RCT, 60 participants; Analysis 1.1).

Only one study reported PCR-adjusted treatment failures at day 42 (Carrasquilla 2012). There was one PCR-adjusted treatment failure at day 42 following treatment with both AL and AV+PG. The CIs crossed the line of no effect (RR 3.00, 95% CI 0.19 to 47.12; 1 RCT, 208 participants, Analysis 1.2).

There were fewer PCR-unadjusted treatment failures at day 42 following treatment with AL compared to AV+PG, but the CIs were wide and crossed the line of no effect (RR 5.00, 95% CI 0.25 to 99.95; 1 RCT, 60 participants, Analysis 1.3). Neither trial report early treatment failure, nor PCR-unadjusted failures at day 28.

Adverse events

There were no serious adverse events or adverse events leading to withdrawal in either study contributing to this comparison. Headaches and nausea and vomiting were reported more frequently in participants receiving AV+PG compared to AL (headaches: RR 2.54, 95% CI 1.17 to 5.51; nausea and vomiting: RR 10.00, 95% CI 2.73 to 36.60; 2 RCTs, 272 participants; Analysis 1.4).

Comparison 2. Atovaquone-proguanil versus artesunate-amodiaquine

One study contributed data to this comparison (Tahar 2014). See Summary of findings 2.

There were more PCR-adjusted treatment failures at day 28 following treatment with AV+PG compared to AS+AQ, but the CIs crossed the line of no effect (RR 3.19, 95% CI 0.67 to 15.22; 1 RCT, 132 participants; Analysis 2.1).

There were similar numbers of PCR-unadjusted treatment failures at day 28 between treatments (RR 1.20, 95% CI 0.49 to 2.91; 1 RCT; 132 participants; Analysis 2.2).

The study did not report outcomes beyond day 28.

There were more early treatment failures following treatment with AV+PG compared to AS+AQ, but the CIs were wide and crossed the line of no effect (RR 13.80, 95% CI 0.79 to 240.11; 1 RCT, 132 participants; Analysis 2.3).

Adverse events

There were no serious adverse events. The authors reported one adverse event leading to withdrawal in the AV+PG group, but it is not clear what this event was (RR 3.04, 95% CI 0.13 to 73.43; 1 RCT, 139 participants; Analysis 2.4). They report that other adverse events occurred but did not report these individually or by study group.

Comparison 3. Atovaquone-proguanil versus artesunate-mefloquine

Two studies contributed data to this comparison (Van Vugt 2002; Carrasquilla 2012). See Summary of findings 3.

There were similar numbers of PCR-adjusted treatment failure at day 42 between treatments (RR 1.15, 95% CI 0.57 to 2.34; 2 RCTs, 1168 participants; Analysis 3.1).

We were only able to reliably extract data for one study reporting PCR-unadjusted treatment failures at day 42 (Van Vugt 2002). In this study, there were fewer PCR-unadjusted treatment failures in the AV+PG group compared to the AS+MQ group, but the confidence intervals crossed the line of no effect (RR 0.80, 95% CI 0.50 to 1.30; 1 RCT, 1063 participants; Analysis 3.2).

Adverse events

There were three serious adverse events in groups receiving AS+MQ, compared to one serious adverse event in groups receiving AV+PG. The CIs crossed the line of no effect (RR 0.64, 95% CI 0.10 to 4.22; 2 RCTs, 1275 participants; Analysis 3.3).

Some adverse events were more common in the AS+MQ arm. Significant adverse events included febrile disorders (RR 6.00, 95% CI 1.13 to 31.83; 1 RCT, 212 participants; Analysis 3.3) and headaches (RR 3.00, 95% CI 1.10 to 8.16; 1 RCT, 212 participants; Analysis 3.3). Nausea and vomiting was more common in the AV+PG group (RR 0.63, 95% CI 0.44 to 0.89; 2 RCTs, 896 participants, Analysis 3.3). The RR for other adverse events had wide CIs that crossed the line of no effect.

Other comparisons

Studies comparing atovaquone-proguanil to artesunate-atovaquone-proguanil

Three studies compared AV+PG versus AS+AV+PG (Van Vugt 2002; Tahar 2014; Wojnarski 2019). Tahar 2014 reported early treatment failures and day 28 data, but not day 42 data. Van Vugt 2002 reported day 42 data, but we could not extract day 28 treatment failures from the study, although the authors showed these on a figure. Wojnarski 2019 reported early treatment failures as well as day 28 and day 42 data with PCR adjustment, though we could not reliably extract PCR-unadjusted data. See Summary of findings 4.

Both PCR-adjusted treatment failures and PCR-unadjusted treatment failures occurred more frequently at day 28 with AV+PG compared to AS+AV+PG, but the CIs were wide and crossed the line of no effect (PCR-adjusted: RR 5.14, 95% CI 0.61 to 43.52; 2 RCTs, 375 participants; Analysis 4.1; PCR-unadjusted: RR 15.48, 95% CI 0.90 to 267.27; 1 RCT, 187 participants; Analysis 4.2).

There were more PCR-adjusted treatment failures at day 42 following treatment with AV+PG compared to AS+AV+PG (RR 1.84, 95% CI 0.95 to 3.56; 2 RCTs, 1258 participants; Analysis 4.3). There were more PCR-unadjusted treatment failures at day 42 following treatment with AS+AV compared to AS+AV+PG, although the CIs crossed the line of no effect (RR 1.56, 95% CI 0.88 to 2.79; 1 RCT, 1063 participants; Analysis 4.4).

There were more early treatment failures with AV+PG compared to AS+AV+PG, but the CIs crossed the line of no effect (RR 5.11, 95% CI 0.25 to 104.94; 2 RCTs, 395 participants; Analysis 4.5).

Adverse events

Van Vugt 2002 presented combined adverse events for two interventions and we were unable to obtain the separate data. We were able to extract some data showing that nausea and vomiting occurred more often in the AS+AV+PG group compared to the AV+PG group. This was significant at the 95% confidence level (RR 0.52, 95% CI 0.34 to 0.80; 1 RCT, 664 participants; Analysis 4.6). Tahar 2014 did not report on adverse events and Wojnarski 2019 reported one serious adverse event in each arm, neither of which the study authors considered was likely related to treatment.

Studies comparing atovaquone-proguanil to other combinations or to monotherapy

We presented these comparisons in a narrative summary table (Table 6).

Other comparisons

McGready 2005 compared AS+AV+PG to quinine. There were more PCR-adjusted and unadjusted treatment failures in the QN group at all time points (Analysis 13.1; Analysis 13.2; Analysis 13.3; Analysis 13.4; Analysis 13.5). There were more hearing problems in the QN group (Analysis 13.6).

Laufer 2012 compared CQ+AV+PG to CQ monotherapy; there were no treatment failures in either arm (Analysis 14.1; Analysis 14.2).

Laufer 2012 also compared CQ+AV+PG to CQ+AS. There was one PCR-adjusted treatment failure, and one PCR-unadjusted treatment failure at day 28 in the CQ+AS arm compared to no

treatment failures in the CQ+AV+PG arm. CIs crossed the line of no effect (Analysis 15.1; Analysis 15.2).

Laufer 2012 also compared CQ+AV+PG to CQ+AZ. There was one PCR-unadjusted failure in the CQ-AZ arm. CIs crossed the line of no effect (Analysis 16.1; Analysis 16.2).

None of the studies in which a drug was combined with AV+PG to form an intervention reported on drug-drug interactions between AP and the partner drug.

Atovaquone-proguanil versus WHO-recommended artemisinin-based combination therapies

We performed a supplementary analysis comparing AV+PG to pooled results for WHO-recommended ACTs to allow for easier comparison with the findings of another systematic review (Analysis 18.1; Analysis 18.3) (Staines 2017).

Atovaquone-proguanil versus all other antimalarials for adverse events

We compared adverse events across all studies. Adverse events leading to withdrawal from the studies occurred more commonly in the AV+PG groups. The only other adverse event that appeared to be observed more frequently in AV+PG compared to other antimalarials was abnormal liver function tests, but data for this came from a single study (Looareesuwan 1999; RR 2.50, 95% CI 1.02 to 6.16; 1 RCT, 182 participants; Analysis 17.23).

DISCUSSION

Summary of main results

For most studies, failure rates were less than 5%. However, two studies reported crude PCR-adjusted failure rates greater than 5% at day 28 for atovaquone-proguanil (Gurkov 2008; Tahar 2014), and one study reported crude PCR-adjusted failure rates greater than 5% at day 42 (Wojnarski 2019).

Compared to artemether-lumefantrine, atovaquone-proguanil may have more PCR-adjusted treatment failures at day 28 and 42 (day 28: RR 5.0, 95% CI 0.25 to 99.95; 1 RCT, 60 participants; low-certainty evidence; day 42: RR 3.0, 95% CI 0.19 to 47.12; 1 RCT, 208 participants; low-certainty evidence). Compared to artemether-lumefantrine, atovaquone-proguanil may also have more PCR-unadjusted treatment failures at day 28 (RR 5.00, 95% CI 0.25 to 99.95; 1 RCT, 60 participants; low-certainty evidence). See Summary of findings 1.

Compared to artesunate-amodiaquine, atovaquone-proguanil may have more PCR-adjusted failures at day 28 (RR 3.19, 95% CI 0.67 to 15.22; 1 RCT, 132 participants; low-certainty evidence), but there may be little or no difference in PCR-unadjusted failures at day 28 (RR 1.20, 95% CI 0.49 to 2.91; 1 RCT, 132 participants; low-certainty evidence). Of concern, the study that assessed this comparison reported a high number of early treatment failures (Tahar 2014). Of note, this study included only at children aged six months to five years. See Summary of findings 2.

Compared to artesunate-mefloquine, there was little or no difference in PCR-adjusted failures at day 42 (RR 1.15, 95% CI 0.57 to 2.34; 2 RCTs, 1168 participants; high-certainty evidence). Compared to artesunate-mefloquine, atovaquone-proguanil may have fewer PCR-unadjusted treatments at day 42 (RR 0.8, 95% CI 0.5 to 1.3; 1 RCT, 1063 participants; low-certainty evidence). See Summary of findings 3.

Addition of artesunate to atovaquone-proguanil appears to yield lower failure rates compared to atovaquone-proguanil alone at all time points, although certainty of evidence was low to moderate. See Summary of findings 4.

Compared to monotherapies, atovaquone-proguanil performed better than quinine, mefloquine, amodiaquine, and chloroquine. For comparisons to other combination therapies, the performance of atovaquone-proguanil was similar to that of dihydroartemisinin-piperaquine-trimethoprim-primaquine, quinine-tetracycline, sulfadoxine-pyrimethamine, and halofantrine.

When atovaquone-proguanil was compared against all other antimalarials, there were more participants with serious adverse events that led to their withdrawal from the study in the atovaquone-proguanil groups. One study that contributed to this difference was Mulenga 2006, in which there were six deaths in the atovaquone-proguanil group. These included three children who deteriorated within 24 hours of receiving atovaquone-proguanil; their deaths were likely to have been from malaria, as well as three children who died of causes likely to be unrelated to malaria, according to the authors. The only other adverse event that appeared to be observed more frequently with atovaquone-proguanil compared to other antimalarials was abnormal liver function tests, but data for this came from a single study (Looareesuwan 1999; RR 2.50, 95% CI 1.02 to 6.16; 1 RCT, 182 participants; Analysis 17.23), and was not found across other studies. Therefore, this can be regarded as low certainty. The addition of artesunate to atovaquone-proguanil led to increased nausea and vomiting in the trial that included adults (Van Vugt 2002).

Overall completeness and applicability of evidence

This review included 4250 participants of varying ages and genders across a wide geographical reach including Africa, South America, and South East Asia. However, the number of comparisons and outcomes reported were broad and include antimalarials that are not currently recommended by the WHO. This limited the extent to which we could meaningfully pool and compare the data in this review.

Only seven of the included trials reported PCR-adjusted failure rates. Of those trials comparing atovaquone-proguanil to WHO-recommended ACTs, the trials did not consistently report early treatment failures or outcomes at day 28 and day 42. Day 42 failure rates are important in capturing treatment failures that may occur when treating people with antimalarials with a long half-life (Stepniewska 2004), and because some mutations are specifically associated with late parasite recrudescence (Staines 2017).

There was extensive heterogeneity in the reporting of adverse events across trials; in some instances, adverse events were mentioned as being 'not present'.

Evidence of drug efficacy and related adverse events are important factors in determining the role of antimalarial agents, but they must be considered in a wider context when contemplating whether atovaquone-proguanil can be adopted more readily on a large scale. One of the greatest barriers to antimalarial

use is undoubtedly the development of drug resistance; this has been well documented in atovaquone-proguanil. Several strategies for delaying the emergence of resistance to atovaquone-proguanil have been suggested and include increasing the dose of atovaquone-proguanil to maintain higher blood concentrations, particularly early in infection, combining atovaquone-proguanil with other antimalarials, and targeting treatment at areas where there are low levels of mutant genes (Cottrell 2014). As suggested by our findings, the addition of artesunate to atovaquone-proguanil may result in greater efficacy, but the evidence is low certainty and the effect of this on the development of resistance has not been studied.

Certainty of the evidence

We assessed the certainty of the evidence in this review using the GRADE approach and presented it in Summary of findings 1, Summary of findings 2, Summary of findings 3, and Summary of findings 4. In almost all outcomes, we downgraded the certainty of evidence due to imprecision. This was because trials were small and there were few events. For most outcomes, we also downgraded the certainty of evidence due to indirectness, as each outcome was often informed by a single trial in a single population.

Potential biases in the review process

As we did not encounter standardized outcome reporting, in some instances we made inferences during the data extraction process which we reported in footnotes in the analysis tables. Where there was doubt, we were conservative in our decisions so as not to overestimate the effect size. In some trials, authors reported failure rates as percentages or represented them graphically in figures but did not report numbers of events or totals. This meant that it was not possible to extract data from these studies. To attempt to mitigate this, we contacted authors for clarification, but did not receive a reply in all instances.

We chose to use MedDRA 2018 to standardize adverse events terminology to allow comparison across trials. This has led to some reduction in detail, and subjectivity of their interpretation may lead to misclassification. However, we feel that standardization of these terms allows for a more meaningful overview and comparison of the adverse events between the different treatments. For the comparison of adverse events with atovaquone-proguanil to all other antimalarials (Analysis 17.1 to Analysis 17.35), where a trial had more than one comparator drug, we chose the comparator drug that was associated with the most number of events for the specific symptom experienced so as not to include participants in the atovaquone-proguanil arm more than once in the analysis (indicated in individual footnotes).

Agreements and disagreements with other studies or reviews

Staines 2017 expressed the overall efficacy rate of atovaquone-proguanil at day 28 based on study sizes and heterogeneity, and reported efficacy of 89% in 'intention-to-treat' analyses of RCTs. They concluded that this is a "reassuringly acceptable level of efficacy". We did not pool treatment failure rates across studies, but have presented a narrative overview in Table 5, including day 42 PCR-adjusted results.

Staines 2017 presented a forest plot in which compared atovaquone-proguanil to other ACTs at day 28. However, this analysis included a combination treatment which is not WHO-recommended (from Giao 2004), and did not refer to PCR-adjusted results. On the basis of this, the authors concluded, "treatment success is equivalent to the use of ACT". To reconcile this difference, we performed supplementary analyses (Analysis 18.1; Analysis 18.2; Analysis 18.3; Analysis 18.4). For each outcome, atovaquone-proguanil performed less well than WHO-recommended ACT, except at day 48 for PCR-unadjusted failure rates. The CIs crossed the line of no effect in each of these, except for PCR-adjusted failures at day 42.

The overall conclusion of Staines 2017 is that atovaquone-proguanil therapy is comparable in efficacy to ACT when treating uncomplicated malaria. Given the uncertainty of evidence, our analysis cannot support this conclusion.

In the previous version of this review (Osei-Akoto 2005), the original authors pooled the participants randomized to atovaquone-proguanil from Llanos-Cuentas 2001. We felt it was more appropriate to split the participants into two groups as was done in the trial. This has led to a different reported RR, but has not altered the conclusion.

AUTHORS' CONCLUSIONS

Implications for practice

Atovaquone-proguanil is efficacious against uncomplicated *Plasmodium falciparum* malaria, but treatment failure exceeded 5% in two studies, the level at which the WHO recommends avoiding adoption of antimalarial medicines in country programmes. Although it is efficacious, we cannot conclude with certainty that it has comparable clinical efficacy to WHO-recommended ACTs.

The addition of artesunate to atovaquone-proguanil may reduce the treatment failure rates. Artesunate-atovaquone-proguanil is not currently available in coformulation, therefore it is unlikely that this combination could be readily adopted in clinical settings. Potential resistance to atovaquone-proguanil is likely to be a barrier to its widespread uptake, but there may be strategies to delay the emergence of resistance that require further exploration.

Implications for research

There remains uncertainty about the efficacy of atovaquone-proguanil compared to WHO-recommended artemisinin-based combination therapies (ACT). However, given the strength of expert opinion favouring the importance of ACT therapy, and a risk of emerging resistance, it is unlikely there is sufficient uncertainty to justify further primary research comparing atovaquone-proguanil to WHO-recommended ACTs.

The combination of artesunate with atovaquone-proguanil may represent a promising treatment strategy, and should be compared directly to first-line ACTs, particularly in geographical areas of resistance.

ACKNOWLEDGEMENTS

The Academic Editor is Dr Hellen Gelband.

The editorial base of the Cochrane Infectious Diseases Group is funded by UK aid from the UK government for the benefit of low- and middle-income countries (project number 300342-104). The

views expressed do not necessarily reflect the UK government's official policies. We thank Paul Garner who commented on drafts of this review update. Paul Garner is a member of the Expert Committee on Malaria Chemotherapy at the WHO and is Co-ordinating Editor of the Cochrane Infectious Diseases Group (CIDG).

We thank the authors of the previously published version of this review (Osei-Akoto 2005); Alex Osei-Akoto, Shirley Owusu-Ofori, and Lois Orton.

We acknowledge the following trial authors who kindly provided further information about their studies: Professor Alejandro Llanos-Cuentas, Professor Filomena EC de Alencar, Dr Nicole Berens-Riha, Professor Thomas Löscher, Professor Rose McGready, Dr Steffan Borrmann, and Dr Miriam Laufer.

REFERENCES

References to studies included in this review

Anabwani 1999 *{published data only}*

Anabwani G, Canfield CJ, Hutchinson DB. Combination atovaquone and proguanil hydrochloride vs. halofantrine for treatment of acute Plasmodium falciparum malaria in children. *Pediatric Infectious Disease Journal* 1999;**18**(5):456-61.

Borrmann 2003 *{published data only}*

Borrmann S, Faucher JF, Bagaphou T, Missinou MA, Binder RK, Pabisch S, et al. Atovaquone and proguanil versus amodiaquine for the treatment of Plasmodium falciparum malaria in African infants and young children. *Clinical Infectious Diseases* 2003;**37**(11):1441-7.

Bouchaud 2000 *{published data only}*

Bouchaud O, Monlun E, Muanza K, Fontanet A, Scott T, Goetschel A, et al. Atovaquone plus proguanil versus halofantrine for the treatment of imported acute uncomplicated Plasmodium falciparum malaria in non-immune adults: a randomized comparative trial. *American Journal of Tropical Medicine and Hygiene* 2000;**63**(5-6):274-9.

Carrasquilla 2012 *{published data only}*

Carrasquilla G, Baron C, Monsell EM, Cousin M, Walter V, Lefevre G, et al. Randomized, prospective, three-arm study to confirm the auditory safety and efficacy of artemether-lumefantrine in Colombian patients with uncomplicated Plasmodium falciparum malaria. *American Journal of Tropical Medicine and Hygiene* 2012;**86**(1):75-83.

De Alencar 1997 *{published data only}*

De Alencar FE, Cerutti C Jr, Durlacher RR, Boulos M, Alves FP, Milhous W, et al. Atovaquone and proguanil for the treatment of malaria in Brazil. *Journal of Infectious Diseases* 1997;**175**(6):1544-7.

Giao 2004 *{published data only}*

Giao PT, de Vries PJ, Hung le Q, Binh TQ, Nam NV, Kager PA. CV8, a new combination of dihydroartemisinin, piperaquine, trimethoprim and primaquine, compared with atovaquone-proguanil against falciparum malaria in Vietnam. *Tropical Medicine and International Health* 2004;**9**(2):209-16.

Gurkov 2008 *{published data only}*

Gurkov R, Eshetu T, Miranda IB, Berens-Riha N, Mamo Y, Girma T, et al. Ototoxicity of artemether/lumefantrine in the treatment of falciparum malaria: a randomized trial. *Malaria Journal* 2008;**7**:179.

Laufer 2012 *{published data only}*

Laufer MK, Thesing PC, Dzinjalamala FK, Nyirenda OM, Masonga R, Laurens MB, et al. A longitudinal trial comparing chloroquine as monotherapy or in combination with artesunate, azithromycin or atovaquone-proguanil to treat malaria. *PloS One* 2012;**7**(8):e42284.

Llanos-Cuentas 2001 *{published data only}*

Llanos-Cuentas A, Campos P, Clendenes M, Canfield CJ, Hutchinson DB. Atovaquone and proguanil hydrochloride compared with chloroquine or pyrimethamine/sulfadoxine for treatment of acute Plasmodium falciparum malaria in Peru. *Brazilian Journal of Infectious Diseases* 2001;**5**(2):67-72.

Looareesuwan 1999 *{published data only}*

Looareesuwan S, Wilairatana P, Chalermarut K, Rattanapong Y, Canfield CJ, Hutchinson DB. Efficacy and safety of atovaquone/proguanil compared with mefloquine for treatment of acute Plasmodium falciparum malaria in Thailand. *American Journal of Tropical Medicine and Hygiene* 1999;**60**(4):526-32.

McGready 2005 *{published data only}*

McGready R, Ashley EA, Moo E, Cho T, Barends M, Hutagalung R, et al. A randomized comparison of artesunate-atovaquone-proguanil versus quinine in treatment for uncomplicated falciparum malaria during pregnancy. *Journal of Infectious Diseases* 2005;**192**(5):846-53.

Mulenga 1999 *{published data only}*

Mulenga M, Sukwa TY, Canfield CJ, Hutchinson DB. Atovaquone and proguanil versus pyrimethamine/sulfadoxine for the treatment of acute falciparum malaria in Zambia. *Clinical Therapeutics* 1999;**21**(5):841-52.

Mulenga 2006 *{published data only}*

Mulenga M, Malunga F, Bennett S, Thuma PE, Shulman C, Fielding K, et al. A randomised, double-blind, placebo-controlled trial of atovaquone-proguanil vs. sulphadoxine-pyrimethamine in the treatment of malarial anaemia in Zambian children. *Tropical Medicine & International Health* 2006;**11**(11):1643-52.

Radloff 1996 *{published data only}*

Radloff PD, Philipps J, Nkeyi M, Hutchinson D, Kremsner PG. Atovaquone and proguanil for Plasmodium falciparum malaria. *Lancet* 1996;**347**(9014):1511-4.

Tahar 2014 *{published data only}*

Tahar R, Almelli T, Debue C, Foumane Ngane V, Djaman Allico J, Whegang Youdom S, et al. Randomized trial of artesunate-amodiaquine, atovaquone-proguanil, and artesunate-atovaquone-proguanil for the treatment of uncomplicated falciparum malaria in children. *Journal of Infectious Diseases* 2014;**210**(12):1962-71.

Van Vugt 2002 *{published data only}*

Gupta RK, Van Vugt M, Paiphun L, Slight T, Looareesuwan S, White NJ, et al. Short report: no evidence of cardiotoxicity of atovaquone-proguanil alone or in combination with artesunate. *American Journal of Tropical Medicine and Hygiene* 2005;**73**(2):267-8.

* Van Vugt M, Leonardi E, Phaipun L, Slight T, Thway KL, McGready R, et al. Treatment of uncomplicated multidrug-resistant falciparum malaria with artesunate-atovaquone-proguanil. *Clinical Infectious Diseases* 2002;**35**(12):1498-504.

Wojnarski 2019 *{published data only}*

Lon C, Ittiverakul M, Somethy S, Chann S, Kuntawunginn W, Kong N, et al. Therapeutic efficacy of atovaquone-proguanil and artesunate atovaquone-proguanil for the treatment of uncomplicated Plasmodium falciparum malaria in areas of multidrug resistance in Cambodia. *American Journal of Tropical Medicine and Hygiene* 2015;**93**(4 Suppl):459.

NCT02297477. The ASAP study – therapeutic efficacy of atovaquone-proguanil vs. artesunate-atovaquone-proguanil in Cambodia (ASAP). clinicaltrials.gov/ct2/show/record/NCT02297477 (first received 21 November 2014).

Wojnarski M, Lon C, Gosi P, Vanachayangkul P, Harrison D, Berjohn C, et al. Update on the asexual and sexual stage-efficacy of atovaquone-proguanil and single low dose primaquine with or without artesunate in Cambodia. *American Journal of Tropical Medicine and Hygiene* 2016;**95 (5 Suppl 1)**:466-7.

Wojnarski M, Lon C, Vanachayangkul P, Gosi P, Sok S, Rachmat A, et al. Atovaquone-proguanil in combination with artesunate to treat multidrug-resistant *P. falciparum* malaria in Cambodia: an open-label randomized trial. *Open Forum Infect Diseases* 2019;**6**(9):ofz314.

References to studies excluded from this review

Bustos 1999 *{published data only}*

Bustos DG, Canfield CJ, Canete-Miguel E, Hutchinson DB. Atovaquone-proguanil compared with chloroquine-sulfadoxine-pyrimethamine for treatment of acute Plasmodium falciparum malaria in the Philippines. *Journal of Infectious Diseases* 1999;**179**(6):1587-90.

Gupta 2005 *{published data only}*

Gupta RK, Van Vugt M, Paiphun L, Slight T, Looareesuwan S, White NJ, et al. Short report: no evidence of cardiotoxicity of atovaquone-proguanil alone or in combination with artesunate. *American Journal of Tropical Medicine and Hygiene* 2005;**73**(2):267-8.

Hitani 2006 *{published data only}*

Hitani A, Nakamura T, Ohtomo H, Nawa Y, Kimura M. Efficacy and safety of atovaquone-proguanil compared with mefloquine in the treatment of nonimmune patients with uncomplicated P. falciparum malaria in Japan. *Journal of Infection and Chemotherapy* 2006;**12**(5):277-82.

Krudsood 2007 *{published data only}*

Krudsood S, Patel SN, Tangpukdee N, Thanachartwet W, Leowattana W, Pornpininworakij K, et al. Efficacy of atovaquone-proguanil for treatment of acute multidrug-resistant Plasmodium falciparum malaria in Thailand. *American Journal of Tropical Medicine and Hygiene* 2007;**76**(4):655-8.

Looareesuwan 1996 *{published data only}*

Looareesuwan S, Viravan C, Webster HK, Kyle DE, Hutchinson DB, Canfield CJ. Clinical studies of atovaquone, alone or in combination with other antimalarial drugs, for treatment of acute uncomplicated malaria in Thailand. *American Journal of Tropical Medicine and Hygiene* 1996;**54**(1):62-6.

Additional references

ACMP 2017

Advisory Committee on Malaria Prevention. Guidelines for malaria prevention in travellers from the UK. PHE Advisory Committee for Malaria Prevention for UK Travellers (ACMP) 2017.

Blasco 2017

Blasco B, Leroy D, Fidock DA. Antimalarial drug resistance: linking Plasmodium falciparum parasite biology to the clinic. *Nature Medicine* 2017;**23**(8):917-28.

Cottrell 2014

Cottrell G, Musset L, Hubert V, Le Bras J, Clain J. Emergence of resistance to atovaquone-proguanil in malaria parasites: insights from computational modeling and clinical case reports. *Antimicrobial Agents and Chemotherapy* 2014;**58**(8):4504-14.

Esu 2014

Esu E, Effa EE, Opie ON, Uwaoma A, Meremikwu MM. Artemether for severe malaria. *Cochrane Database of Systematic Reviews* 2014, Issue 9. Art. No: CD010678. [DOI: 10.1002/14651858.CD010678.pub2]

Flegg 2011

Flegg JA, Guerin PJ, White NJ, Stepniewska K. Standardizing the measurement of parasite clearance in falciparum malaria: the parasite clearance estimator. *Malaria Journal* 2011;**10**(10):339.

Goodman 2016

Goodman CD, Siregar JE, Mollard V, Vega-Rodriguez J, Syafruddin D, Matsuoka H, et al. Parasites resistant to the antimalarial atovaquone fail to transmit by mosquitoes. *Science* 2016;**352**(6283):349-53.

GRADEpro 2015 [Computer program]

McMaster University GRADEpro GDT. Version accessed prior to 26 November 2020. Hamilton (ON): McMaster University, 2015. (developed by Evidence Prime, Inc.). Available from gradepro.org.

Higgins 2017

Higgins JP, Altman DG, Sterne JA. Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Churchill R, Chandler J, Cumpston MS, editor(s), Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017), Cochrane, 2017 Available from www.training.cochrane.org/handbook.

Lubell 2014

Lubell Y, Dondorp A, Guerin PJ, Drake T, Meek S, Ashley E, et al. Artemisinin resistance – modelling the potential human and economic costs. *Malaria Journal* 2014;**13**:452.

MedDRA 2018 [Computer program]

Medical Dictionary for Regulatory Activities MedDRA Browser. Version 2.0. Medical Dictionary for Regulatory Activities, January 2016.

Mohor 2009

Mohor D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA Statement. *PLoS Medicine* 2009;**6**(7):e10000097.

Noedl 2008

Noedl H, Se Y, Schaecher K, Smith BL, Socheat D, Fukuda MM. Evidence of artemisinin-resistant malaria in western Cambodia. *New England Journal of Medicine* 2008;**359**(24):2619-20.

Oyediran 2002

Oyediran AB, Ddumba EM, Ochola SA, Lucas AO, Koporc K, Dowdle WR. A public-private partnership for malaria control: lessons from the Malarone Donation Programme. *Bulletin of the World Health Organization* 2002;**80**(10):817-21.

Review Manager 2014 [Computer program]

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

Schünemann 2013

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

Staines 2017

Staines HM, Burrow R, Teo BH, Chis Ster I, Kremsner PG, Krishna S. Clinical implications of Plasmodium resistance to atovaquone/proguanil: a systematic review and meta-analysis. *Journal of Antimicrobial Chemotherapy* 2017;**73**(3):581-95.

Stepniewska 2004

Stepniewska K, Taylor WR, Mayxay M, Price R, Smithuis F, Guthmann JP, et al. In vivo assessment of drug efficacy against Plasmodium falciparum malaria: duration of follow-up. *Antimicrobial Agents and Chemotherapy* 2004;**48**(11):4271-80.

Stovold 2014

Stovold E, Beecher D, Foxlee R, Noel-Storr A. Study flow diagrams in Cochrane systematic review updates: an adapted PRISMA flow diagram. *Systematic Reviews* 2014;**3**:54.

WHO 2003

World Health Organization. Assessment and monitoring of antimalarial drug efficacy for the treatment of uncomplicated falciparum malaria, 2003. www.who.int/malaria/publications/atoz/whohtmrbm200350/en/ (accessed prior to 26 November 2020).

WHO 2009

World Health Organization. Methods for surveillance of antimalarial drug efficacy, 2009. www.who.int/malaria/publications/atoz/9789241597531/en/ (accessed prior to 26 November 2020).

WHO 2011

World Health Organization. Global plan for artemisinin resistance containment (GPARC), 2011. www.who.int/malaria/publications/atoz/9789241500838/en/ (accessed prior to 26 November 2020).

WHO 2012

World Health Organization. Update of artemisinin resistance – April 2012. www.who.int/malaria/publications/atoz/updateartemsininresistanceapr2012/en/ (accessed prior to 26 November 2020).

WHO 2015

World Health Organization. Guidelines for the treatment of malaria – 3rd edition, 2015. www.who.int/publications/i/item/9789241549127 (accessed prior to 26 November 2020).

WHO 2017

World Health Organization. World malaria report, 2017. www.who.int/malaria/publications/world-malaria-report-2017/en/ (accessed prior to 26 November 2020).

WHO 2019

WHO Global Malaria Programme. Artemisinin resistance and artemisinin-based combination therapy efficacy, 2019. www.who.int/docs/default-source/documents/publications/gmp/who-cds-gmp-2019-17-eng.pdf?ua=1 (accessed prior to 26 November 2020).

References to other published versions of this review

Osei-Akoto 2005

Osei-Akoto A, Orton L, Owusu-Ofori SP. Atovaquone-proguanil for treating uncomplicated malaria. *Cochrane Database of Systematic Reviews* 2005, Issue 4. Art. No: CD004529. [DOI: 10.1002/14651858.CD004529.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Anabwani 1999

Study characteristics

Anabwani 1999 *(Continued)*

Methods	Randomized controlled trial Duration: 6 months; June 1994 to November 1994
Participants	Children with uncomplicated *P falciparum* malaria Number: 168 Inclusion criteria: aged 3–12 years; fever; tolerate oral therapy; weight > 10 kg Exclusion criteria: severe malaria; QTc interval > 0.44 seconds; mixed infections Diagnosis: parasitaemia 1000–200,000 parasites/µL
Interventions	• Atovaquone-proguanil (atovaquone 60 mg/kg + proguanil 24 mg/kg for 3 days) • Halofantrine (24 mg/kg for 12 hours)
Outcomes	• 28-day cure rate (parasite clearance within 7 days without recrudescence during the 28-day follow-up period) • Parasite clearance time (initiation of treatment to smear negative for asexual parasites)[a] • Fever clearance time (initiation of treatment until temperature < 37.2 °C and remained < 37.2 °C for 24 hours)[a] • Adverse events [a]Not assessed in quantitative synthesis in this review.
Notes	Follow-up: 28 days Countries (codes): Kenya (KEN) Setting: district hospital Malaria endemicity: high transmission (> 1 case per 1000 population) Source of funding: grant from Glaxo Wellcome Additional correspondence: we emailed the authors on 11 July 2018 but did not receive a reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Random assignment of study number".
Allocation concealment (selection bias)	Unclear risk	No allocation concealment described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Open label.
Incomplete outcome data (attrition bias)	Low risk	164/168 (97%) participants evaluable.

Anabwani 1999 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	No reporting bias detected.
Other bias	Unclear risk	No assurance given regarding independence of authors.

Borrmann 2003

Study characteristics

Methods	Randomized controlled trial Duration: 2 years; January 1999 to December 2000
Participants	Children with uncomplicated *P falciparum malaria* Number: 200 Inclusion criteria: weight 5–11 kg (age not in inclusion criteria) Exclusion criteria: antimalarials within previous 7 days; underlying severe disease; concomitant infection; mixed infection; allergy to study drugs; severe malaria Diagnosis: parasitaemia 1000–200,000 parasites/µL
Interventions	• Atovaquone-proguanil (atovaquone 62.5 mg + proguanil 25 mg for 3 days) • Amodiaquine (amodiaquine chlorohydrate 10 mg/kg of a 1% suspension once daily for 3 days)
Outcomes	• 28-day cure rate (absence of early or late treatment failure, no PCR adjustment) • Parasite clearance time (treatment initiation until temperature < 37.5 °C and remained at 37.5 °C for > 24 hour)[a] • Fever clearance time (treatment initiation until first negative blood smear)[a] • Adverse events (including haematological/biochemical) [a]Not assessed in quantitative synthesis in this review.
Notes	Follow-up: 28 days Countries (codes): Gabon (GAB) Setting: hospital Malaria endemicity: high transmission (> 1 case per 1000 population) Source of funding: GlaxoSmithKline Additional correspondence: we received email correspondence from S Borrmann on 18 January 2019.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocks of 10 and sequentially assigned to groups.

Borrmann 2003 *(Continued)*

Allocation concealment (selection bias)	Low risk	Sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label; no reported blinding of outcome assessors (confirmed by S Borrmann in email correspondence).
Incomplete outcome data (attrition bias) All outcomes	High risk	92/100 participants in atovaquone/proguanil group with day 28 data; 78/100 participants in amodiaquine group with day 28 data.
Selective reporting (reporting bias)	Low risk	No reporting bias detected.
Other bias	Unclear risk	Email correspondence from S Borrmann: GlaxoSmithKline sponsored the flights and accommodation for presentation of the study results. 1 author was an employee of GlaxoSmithKline.

Bouchaud 2000

Study characteristics	
Methods	Randomized controlled trial Duration: 1 year; October 1994 to September 1995
Participants	Adults and adolescents with imported uncomplicated *P falciparum* malaria Number: 48 Inclusion criteria: aged > 16 years; imported malaria from short stay; non-immune Exclusion criteria: severe malaria; QTc > 0.44 seconds; mixed infection; concomitant disease; inability to take oral treatment; syncope; pregnancy/breastfeeding; weight < 40 kg; resided in an endemic area for the previous year Diagnosis: parasitaemia 1000–100,000 parasites/µL
Interventions	• Atovaquone-proguanil (atovaquone 1 g + proguanil 400 mg as single daily dose for 3 days) • Halofantrine (3 doses of 500 mg 6 hours apart)
Outcomes	• Cure rate (defined as clinical and parasitological cure at day 7 without recrudescence at day 35) • Parasite clearance time (treatment initiation until no asexual forms on thick films)[a] • Fever clearance (treatment initiation until temperature of 37.2 °C maintained for > 24 hours)[a] • Adverse events (including QT elongation) [a]Not assessed in quantitative synthesis in this review
Notes	Follow-up: 35 days Countries (codes): France (FRA)

Bouchaud 2000 *(Continued)*

	Setting: not specified
	Malaria endemicity: imported
	Source of funding: Glaxo Wellcome Research and Development
	Additional correspondence: we did not contact the authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Open-label; no blinding of outcome assessors described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	85% of participants assessable.
Selective reporting (reporting bias)	Low risk	No reporting bias detected.
Other bias	Unclear risk	No assurance given regarding independence of authors.

Carrasquilla 2012

Study characteristics

Methods	Randomized controlled trial
	Duration: 1 year, 6 months; May 2007 to November 2008
Participants	Adults and adolescents with *P falciparum* malaria or mixed infection
	Number: 265
	Inclusion criteria: aged > 12 year; history of fever
	Exclusion criteria: severe malaria; multiple audiological exclusion criteria; pregnancy/breastfeeding; abnormal cardiac function; prolonged QTc; taking drugs affecting cardiac function; serious underlying disease; had received the following drugs within the previous 2 months: mefloquine, aminoglycoside antibiotics, halofantrine, artemether-lumefantrine; received the following drugs within the previous 2 weeks: quinine, chloroquine, any other antimalarial drug, aspirin, loop diuretics, macrolide antibiotics
	Diagnosis: parasite density 1000–100,000 parasites/µL blood

Carrasquilla 2012 *(Continued)*

Interventions	Assigned in a 3:1:1 ratio • Artemether-lumefantrine: 40 mg/240 mg (15–24 kg), 60 mg/360 mg (25–34 kg), or 80 mg/480 mg (≥ 35 kg) at 0, 8, 24, 36, 48, and 60 hours • Atovaquone-proguanil: 250 mg/100 mg (11–20 kg), 500 mg/200 mg (21–30 kg) or 750 mg/300 mg (31–40 kg), or 1000 mg/400 mg (> 40 kg) once daily • Artesunate-mefloquine: artesunate 4 mg/kg/day + mefloquine 25 mg/kg (15 mg/kg on day 2 and 10 mg/kg on day 3)
Outcomes	• Audiological outcomes: auditory brainstem response; pure-tone air conduction threshold[a] • Adverse events • PCR-corrected cure rates (reported at days 14, 28, and 42) [a]Not assessed in quantitative synthesis in this review.
Notes	Follow-up: 42 days Countries (codes): Colombia (COL) Setting: not specified Malaria endemicity: low transmission (< 1 case per 1000 population-years). Colombia was entering control phase at time of the study Source of funding: Novartis Pharma Ltd, Basel, Switzerland Additional correspondence: we emailed 3 of the authors on 11 July 2018 for further information. We received an initial reply but were unable to obtain the information needed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Key personnel involved in assessments of the primary objective were blinded".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "1.5% patients discontinued the study prematurely".
Selective reporting (reporting bias)	Low risk	No evidence to suggest selective reporting of efficacy outcomes.
Other bias	Unclear risk	4 authors declared as employees of Novartis who funded the study; no assurances given of independence in reporting.

De Alencar 1997

Study characteristics	
Methods	Randomized controlled trial Duration: 10 months; April 1995 to January 1996
Participants	Adult men with *P falciparum* malaria Number: 175 Inclusion criteria: men; aged 18–65 years Exclusion criteria: grossly abnormal laboratory results; refusal to be hospitalized for 28 days; inability to tolerate study medication; missing study medication Diagnosis: smear positive with parasitaemia 1000–100,000 parasites/µL
Interventions	• Atovaquone-proguanil (atovaquone 1 g + proguanil 400 mg daily for 3 days) • Quinine-tetracycline (quinine 600 mg 3 times a day + tetracycline 250 mg 4 times a day for 7 days)
Outcomes	• 28-day cure rate (based on weekly thick smears) • Parasite clearance time (time to last positive blood smear before 3 negatives)[a] • Fever clearance time (time to last temperature of > 37.8 °C followed by 3 normal temperatures)[a] • Adverse events [a]Not assessed in quantitative synthesis in this review.
Notes	Follow-up: 28 days Countries (codes): Brazil (BRA) Setting: National Health Foundation posts Malaria endemicity: high transmission rate (as described in study) Source of funding: Wellcome Diagnostics Additional correspondence: we received email correspondence from F De Alencar on 12 July 2018.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Email correspondence: "The sequence was generated by statisticians of Wellcome Diagnostics and sent to the study sites".
Allocation concealment (selection bias)	Low risk	Email correspondence: "The sequence was kept locked in a cabin and was conferred always by the same investigator at each enrolment as to define the group in where the participant was to be allocated".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label.
Blinding of outcome assessment (detection bias)	High risk	No blinding of outcome assessors.

De Alencar 1997 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	154 analyzed/175 randomized (88%).
Selective reporting (reporting bias)	Low risk	No evidence to suggest selective reporting.
Other bias	Low risk	Financial support from Wellcome Diagnostics. Email correspondence: members of Wellcome did not have any participation in the organization, execution, data collection, or data analysis, being restricted to observe if the study was being performed in a way methodologically sound.

Giao 2004

Study characteristics	
Methods	Randomized controlled trial Duration: 1 year, 4 months; April 2001 to August 2002
Participants	Adults and adolescents with uncomplicated *P falciparum* malaria Number: 165 Inclusion criteria: fever presenting at a primary care facility, aged > 16 years Exclusion criteria: pregnancy/lactation; complicated malaria; inability to take oral medication; allergy to study drugs; artemisinin within 24 hours; quinine within 12 hours; mefloquine/tetracycline/doxycycline within 7 days Diagnosis: parasitaemia > 1000 parasites/µL
Interventions	• Atovaquone-proguanil (atovaquone 1 g + proguanil 400 mg once daily for 3 days • Dihydroartemisinin-piperaquine-trimethoprim-primaquine (2 × dihydroartemisinin 32 mg + piperaquine phosphate 320 mg + trimethoprim 90 mg + primaquine phosphate 5 mg at time 0, 8, 24, and 48 hours)
Outcomes	• 28-day cure rate (parasite clearance by day 7 without recrudescence up to day 28) • Parasite clearance time (time 0 to the first of 3 negative blood smears)[a] • Fever clearance time (time 0 to the first of 3 consecutive normal temperatures < 37.0 °C)[a] • Adverse events [a]Not assessed in quantitative synthesis in this review.
Notes	Follow-up: all followed up for 28 days; 92 participants followed up for 56 days Countries (codes): Vietnam (VNM) Setting: primary healthcare facility Malaria endemicity: high transmission (> 1 case per 1000 population) Source of funding: quote: "tablets were kindly donated by Glaxo Wellcome UK".

Giao 2004 *(Continued)*

Additional correspondence: we did not contact the authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Drawing an envelope with a computer-generated randomisation code".
Allocation concealment (selection bias)	Low risk	Sealed envelope.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of assessors described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	161 analyzed/165 randomized (98%).
Selective reporting (reporting bias)	Low risk	No evidence to suggest selective reporting.
Other bias	Unclear risk	Quote: "Tablets donated" No other source of funding declared.

Gurkov 2008

Study characteristics

Methods	Randomized controlled trial Duration: 5 months; April 2006 to August 2006
Participants	Adults and children with uncomplicated *P falciparum* malaria Number: 97 Inclusion criteria: aged > 5 years; temperature ≥ 37.5 °C or history of fever within 24 hours; tolerate oral therapy; residence in study area, suitable for complete audio-vestibular testing Exclusion criteria: known/suspected hearing deficits; antimalarials within 7 days; mixed infection; severe malaria; severe underlying disease; concomitant disease masking assessment of response; allergy to study medications; pregnancy Diagnosis: thick and thin blood smears
Interventions	• Artemether-lumefantrine (80 mg/480 mg (adults and children ≥ 35 kg bodyweight), at 0, 8, 24, 36, 48, and 60 hours; dose adjusted by weight for younger children. • Quinine (~ 8 mg/kg quinine base, 3 times daily for 7 days)

Gurkov 2008 *(Continued)*

	• Atovaquone-proguanil (20 mg/8 mg/kg (children < 40 kg bodyweight) or 1000 mg/400 mg (adults and children ≥ 40 kg bodyweight) per day for 3 days (3 doses)
Outcomes	• Day 7 treatment failure • Total treatment failure at day 28 (PCR adjusted and unadjusted) • Tolerability and ototoxicity
Notes	Follow-up: 90 days Countries (codes): Ethiopia (ETH) Setting: university hospital Malaria endemicity: high transmission (> 1 case per 1000 population) Source of funding: Friedrich-Baur-Stiftung, Munich, Germany Additional correspondence: we received email correspondence from T Löscher and N Berens-Riha on 13 July 2018.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated, stratified by gender and age.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open-label".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The microbiology examiners (parasitology, PCR testing) were blinded to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Day 28: 90 analyzed/97 randomized (92.7%).
Selective reporting (reporting bias)	Low risk	Email correspondence: trial was registered before study at Ethiopian MOH. Delayed registration at international registry due to 'communication problems'.
Other bias	Low risk	No other bias detected.

Laufer 2012

Study characteristics

Methods	Randomized controlled trial Duration: 1 year, 7 months; February 2007 to August 2009
Participants	Children with uncomplicated *P falciparum* malaria

Laufer 2012 *(Continued)*

	Number: 640 Inclusion criteria: aged ≥ 6 months to 5 years; signs and symptoms consistent with malaria; weight ≥ 5 kg Exclusion criteria: severe malaria; allergy to study drugs; medication with any antibiotic or antimalarial; previous enrolment; raised ALT (> 5 × ULN); raised creatinine (> 3 × ULN); chronic disease; severe malnutrition, known HIV Diagnosis: parasite density 2000–200,000 parasites/mL
Interventions	• Chloroquine: 10 mg/kg on day 0 and 1, 5 mg/kg/day on day 2 • Chloroquine-artesunate (chloroquine: 10 mg/kg on day 0 and 1, 5 mg/kg/day on day 2 + artesunate: 4 mg/kg once a day for 3 days) • Chloroquine-atovaquone-proguanil (chloroquine: 10 mg/kg on day 0 and 1, 5 mg/kg/day on day 2 + atovaquone 15–25 mg/kg/day + proguanil 5–10 mg/kg/day proguanil for 3 days) • Chloroquine-azithromycin (chloroquine: 10 mg/kg on day 0 and 1, 5 mg/kg/day on day 2 + azithromycin 30 mg/kg once a day for 3 days)
Outcomes	• Adequate clinical and parasitological response rate • Early treatment failures; late clinical failures; PCR classification • Adverse events (with a focus on anaemia) • Subsequent episodes of malaria per year[a] • Incidence of chloroquine resistance marker pfcrt T76[b] [a]Adequate clinical and parasitological response rate. [b]Not assessed in quantitative synthesis in this review.
Notes	Follow-up: 28 days active; 1 year passive Countries (codes): Malawi (MWI) Setting: health centre, peri-urban hillside township Malaria endemicity: high transmission (> 1 case per 1000 population) Source of funding: National Institute of Allergy and Infectious Diseases; Doris Duke Charitable Foundation; Howard Hughes Medical Institute; Azithromycin donated by Pfizer, Inc; first author received investigator-initiate grant from Pfizer Global Pharmaceuticals. Additional correspondence: we received email correspondence from M Laufer on 12 August 2018.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence.
Allocation concealment (selection bias)	Unclear risk	Quote: "Assignments were concealed using a pull-tab treatment list".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label.
Blinding of outcome assessment (detection bias)	Unclear risk	Open label except for (quote) "laboratory technicians who read the malaria smears were blinded to study drug allocation".

Laufer 2012 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	The lowest percentage of known 28-day treatment outcomes was 86.25% across the 4 groups.
Selective reporting (reporting bias)	Low risk	Protocol published; no evidence of reporting bias.
Other bias	Low risk	Quote: "The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript".

Llanos-Cuentas 2001

Study characteristics	
Methods	Randomized controlled trial Duration: 11 months; June 1995 to May 1996
Participants	Adults and adolescents with uncomplicated *P falciparum* malaria Number: 43 Inclusion criteria: aged 12–65 years; lifelong residents of study area Exclusion criteria: severe malaria; mixed infections; presence of concomitant disease; inability to take oral treatment; pregnancy/breastfeeding Diagnosis: parasitaemia 1000–200,000 parasites/µL
Interventions	• Atovaquone-proguanil (atovaquone 1000 mg + proguanil 400 mg for 3 days) • Chloroquine (600 mg followed by 300 mg at 6, 24, and 48 hours) • Sulfadoxine-pyrimethamine (sulfadoxine 1500 mg and pyrimethamine 75 mg single dose)
Outcomes	• 2-day cure rate • Parasite clearance time[a] • Fever clearance time[a] • Adverse events [a]Not assessed in quantitative synthesis in this review.
Notes	Follow-up: 28 days Countries (codes): Peru (PER) Setting: study house, Piura. Email correspondence: participants stayed in a house in an area with no transmission of malaria for the full study duration. Malaria endemicity: high transmission (> 1 case per 1000 population) Source of funding: supported by a grant from GlaxoSmithKline Additional correspondence: we received email correspondence from A Llanos-Cuentas on 16 July 2018
Risk of bias	

Llanos-Cuentas 2001 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Email correspondence: computer-generated random number table, assigned in blocks of 10.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessment described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "39 analysed/43 randomised" (91%).
Selective reporting (reporting bias)	Low risk	No evidence of reporting bias detected.
Other bias	Low risk	Email communication from Prof Alejandro Llanos-Cuentas 16 July 2018; (quote) "no conflict of interest".

Looareesuwan 1999

Study characteristics	
Methods	Randomized controlled trial Duration: 11 months; August 1993 to July 1994
Participants	Adults and adolescents with uncomplicated *P falciparum* malaria Number: 182 Inclusion criteria: aged 16–65 years; weight ≥ 40 kg Exclusion criteria: mixed infections; concomitant disease (intercurrent febrile infections); persistent vomiting; pregnancy/breastfeeding Diagnosis: parasitaemia 1000–200,000 parasites/µL
Interventions	• Atovaquone-proguanil (atovaquone 1000 mg + proguanil 400 mg daily for 3 days) • Mefloquine (1250 mg over 6 hours)
Outcomes	• 28-day cure rate (parasite clearance within 7 days without recrudescence during the 28-day follow-up period) • Parasite clearance time (from initiation of antimalarial treatment until the first time that peripheral blood films were negative for asexual parasites)[a] • Fever clearance time (from initiation of treatment until temperature < 37.2 °C, and remained < 37.2 °C for at least 24 hours)[a] • Adverse events (including haematological/biochemical).

Looareesuwan 1999 *(Continued)*

[a]Not assessed in quantitative synthesis in this review.

Notes	Follow-up: 28 days Countries (codes): Thailand (THA) Setting: Hospital for Tropical Diseases in Bangkok Malaria endemicity: low and unstable transmission Source of funding: supported by a grant from Glaxo Wellcome, Inc Additional correspondence: we emailed the authors on 10 July 2018 but did not receive a reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessment described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "87% completed the study and were evaluable".
Selective reporting (reporting bias)	Low risk	No evidence of reporting bias detected.
Other bias	Unclear risk	Quote: "no author has an undeclared conflict of interest". Comment: no assurance given regarding the nature of the financial support received from Glaxo Wellcome and independence of authors.

McGready 2005

Study characteristics

Methods	Randomized controlled trial Duration: 20 months; December 2001 to July 2003
Participants	Pregnant women with uncomplicated *P falciparum* malaria Number: 81

McGready 2005 *(Continued)*

	Inclusion criteria: first episode of uncomplicated *P falciparum* or mixed infection; second (> 13 weeks) or early third (< 32 weeks) trimester of pregnancy, haematocrit ≥ 20% Exclusion criteria: known chronic disease; alcohol abuse; imminent delivery of baby; inability to tolerate oral treatment, inability to follow the consultation Diagnosis: thick and thin blood films (no parasite density limit)
Interventions	• Quinine (quinine sulphate 3 times daily (10 mg salt/kg every 8 hours) for 7 days) • Artesunate-atovaquone-proguanil (artesunate 4 mg/kg/day + atovaquone 20 mg/kg/day + proguanil 8 mg/kg/day, for 3 days)
Outcomes	• Fever clearance time (first time fever dropped < 37.5 °C and stayed < 37.5 °C for 48 hours). Email correspondence: measured daily or before if participant complained of feeling febrile.[a] • Parasite clearance time (first negative smear (if this was supported by a second consecutive negative smear) for blood stage (trophozoites or schizonts, or both) parasites (but not including gametocytes)). Email correspondence: blood smear performed every 24 hours.[a] • PCR-adjusted cumulative cure rate over follow-up • Anaemia • Gametocyte carriage (person-gametocyte-weeks)[a] • Adverse events • Delivery outcomes[a] • Infant outcomes[a] [a]Not assessed in quantitative synthesis in this review.
Notes	Follow-up: 9 weeks in total or until delivery of baby, depending on which occurred later Countries (codes): Thailand (THA) Setting: antenatal clinics, Shoklo Malaria Research Unit Malaria endemicity: low and unstable transmission Source of funding: Wellcome Trust–Mahidol University–Oxford Tropical Medicine Research Program Additional correspondence: we received email correspondence from R McGready on 12 July 2018. Data on early treatment failure, day 28 and day 42 treatment failure (adjusted and unadjusted) supplied by authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Computer generated in blocks of 10".
Allocation concealment (selection bias)	Low risk	Quote: "Concealed in envelopes".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Laboratory technicians blinded; therefore, low risk for laboratory outcomes; clinicians not blinded; therefore, higher risk for clinical outcomes.

McGready 2005 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	From email correspondence: (quote) "zero loss to follow-up at day 28".
Selective reporting (reporting bias)	Low risk	No evidence of reporting bias detected.
Other bias	Unclear risk	Restricted sequential trial design to detect a reduction in treatment failure from 30% in the quinine group to 5% in the artesunate-atovaquone-proguanil group.

Mulenga 1999

Study characteristics	
Methods	Randomized controlled trial Duration: 5 months; December 1993 to May 1994
Participants	Adults and adolescents with uncomplicated *P falciparum* malaria Number: 163 Inclusion criteria: aged 12–65 years; weight ≥ 40 kg Exclusion criteria: mixed infection; underlying disease; pregnancy/breastfeeding; persistent vomiting; intercurrent febrile illness Diagnosis: parasitaemia 1000–200,000 parasites/µL
Interventions	• Atovaquone-proguanil (atovaquone 1000 mg + proguanil 400 mg once daily for 3 days) • Sulfadoxine-pyrimethamine (sulfadoxine 1500 mg + pyrimethamine 75 mg single dose)
Outcomes	• Cure rate day 28 (no PCR adjustment) • Parasite clearance time (from initiation of treatment until first negative blood film)[a] • Fever clearance time (from initiation of treatment until temperature < 37.5 °C and thereafter < 37.5 °C for 24 hours)[a] • Adverse events [a]Not assessed in quantitative synthesis in this review.
Notes	Follow-up: 28 days Countries (codes): Zambia (ZMB) Setting: hospital Malaria endemicity: high transmission (> 1 case per 1000 population) Source of funding: grant from Glaxo Wellcome Research and Development Additional correspondence: we emailed the authors on 16 July 2018 but did not receive a reply.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Mulenga 1999 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No details given.
Allocation concealment (selection bias)	Unclear risk	No details given.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessors described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	98% of participants randomized had 28-day follow-up.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Unclear risk	No assurance given regarding the nature of the financial support received from Glaxo Wellcome and independence of authors.

Mulenga 2006

Study characteristics	
Methods	Randomized controlled trial Duration: 8 months, November 2000 to June 2001 (phase 1); 5 months, February 2002 to June 2002 (phase 2)
Participants	Children with uncomplicated *P falciparum* malaria Number: 255 Inclusion criteria: aged 6–119 months; packed cell volume < 21%; fever; weight ≥ 5 kg Exclusion criteria: severe malaria; respiratory distress; serious concurrent illness; antimalarial drugs within 2 weeks prior, packed cell volume > 9% (for first phase of trial, increased to > 12% for second phase on ethics advice); unable to take oral medications; could not sit or stand supported Diagnosis: asexual forms of *P falciparum* at a density of 50–500,000 parasites/µL
Interventions	• Atovaquone-proguanil (atovaquone 17 mg + proguanil 7 mg/kg once daily for 3 days • Sulfadoxine-pyrimethamine (single dose, of approximately sulfadoxine 25 mg/kg)
Outcomes	• Treatment failure day 14 (need for escape medication, blood transfusion, failure to increase packed cell volume to > 21%, death) • Fever clearance time (first dose of the study medication until the axillary temperature decreased to < 37.5 °C) • Adverse events [a]Not assessed in quantitative synthesis in this review.

Mulenga 2006 *(Continued)*

Notes	Follow-up: 28 days Countries (codes): Zambia (ZMB) Setting: 500-bed hospital Malaria endemicity: high transmission (> 1 case per 1000 population) Source of funding: received financial support, atovaquone-proguanil, and matching placebo from GlaxoSmithKline. Additional correspondence: we emailed the authors on 16 July 2018 but did not receive a reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blind. Matching placebos.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as "double blind", no further details given.
Incomplete outcome data (attrition bias) All outcomes	High risk	76% had 28-day follow-up in atovaquone-proguanil group; 75% had 28-day follow-up in sulfadoxine-pyrimethamine group.
Selective reporting (reporting bias)	Low risk	No evidence of reporting bias detected.
Other bias	Unclear risk	No assurance given regarding the nature of the financial support received from GlaxoSmithKline and independence of authors.

Radloff 1996

Study characteristics

Methods	Randomized controlled trial Duration: 8 months; July 1994 to February 1995
Participants	Adults with *P falciparum* malaria Number: 142 Inclusion criteria: acute manifestation of malaria; aged 15–65 years; weight > 40 kg; urine test negative for chloroquine or sulphonamides

Radloff 1996 *(Continued)*

	Exclusion criteria: severe malaria; mixed infection; significant concomitant disease; previous antimalarials in last 2 weeks; pregnancy/breastfeeding Diagnosis: initial parasitaemia 200–100,000 parasites/µL blood
Interventions	• Atovaquone-proguanil (atovaquone 1000 mg + proguanil 400 mg once daily for 3 days) • Amodiaquine (600 mg on admission; 600 mg at 24 hours; 300 mg at 48 hours)
Outcomes	• "Cure rate" at days 14, 21, and 28 • Parasite clearance time (undefined)[a] • Fever clearance time (undefined)[a] • Adverse events [a]Not assessed in quantitative synthesis in this review.
Notes	Follow-up: 28 days Countries (codes): Gabon (GAB) Setting: hospital Malaria endemicity: high transmission (> 1 case per 1000 population) Source of funding: supported by Wellcome Research Laboratories Additional correspondence: we emailed the authors on 12 August 2018 but did not receive a reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	11% of participants lost to follow-up.
Selective reporting (reporting bias)	Low risk	No evidence of reporting bias.
Other bias	Unclear risk	No assurance given regarding the nature of the financial support received from Wellcome Research Laboratories and independence of authors.

Tahar 2014

Study characteristics	
Methods	Randomized controlled trial Duration: 2008–2009
Participants	Children with *P falciparum* malaria Number: 338 Inclusion criteria: aged 6 months to 5 years, temperature ≥ 38.0 °C Exclusion criteria: weight < 5 kg; concomitant infectious diseases; severe malnutrition; signs of severe and complicated malaria Diagnosis: parasite density ≥ 2000 asexual *P falciparum* parasites/µL of blood, without other *Plasmodium* species
Interventions	• Artesunate-amodiaquine (artesunate 4 mg/kg bodyweight for 3 days; amodiaquine 10 mg base/kg bodyweight for 3 days) • Atovaquone-proguanil (atovaquone 20 mg/kg bodyweight/day for 3 days; proguanil 8 mg/kg bodyweight/day for 3 days) • Artesunate-atovaquone-proguanil (artesunate 4 mg/kg bodyweight for 3 days; atovaquone 20 mg/kg bodyweight/day for 3 days; proguanil 8 mg/kg bodyweight/day for 3 days)
Outcomes	• Total treatment failure at day 28 (PCR adjusted and unadjusted) • Early treatment failure • Parasite clearance (proportion of participants with a positive blood film at day 3)[a] • Fever clearance (proportion of participants with fever at day 3)[a] • Adverse events • Haematocrit improvement on day 14[a] [a]Not assessed in quantitative synthesis in this review.
Notes	Follow-up: 28 days Countries (codes): Cameroon (CMR) Setting: missionary dispensary, Yaoundé Malaria endemicity: high transmission (> 1 case per 1000 population) Source of funding: French Agence Nationale de la Recherche (grant ANR-08-MIE-024) Additional correspondence: we emailed the authors on 9 July 2018 but did not receive a reply.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Trial registration document reported "central registration"; no further details.
Blinding of participants and personnel (performance bias)	Unclear risk	Trial registration document reported that participants were blinded but this was not discussed in the main report.

Tahar 2014 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessors described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	94% of participants seen at day 28.
Selective reporting (reporting bias)	Unclear risk	Trial was retrospectively registered on 23 June 2010.
Other bias	Low risk	No other source of bias detected.

Van Vugt 2002

Study characteristics	
Methods	Randomized controlled trial Duration: 2 years; June 1998 to July 2000
Participants	Adults and children with uncomplicated multiple-drug-resistant *P falciparum* malaria Number: 1596 Inclusion criteria: weight > 10 kg Exclusion criteria: pregnancy, use of mefloquine in previous 63 days, obtunded, vomiting, other clinical or laboratory signs of illness Diagnosis: slide-confirmed acute *P falciparum* malaria
Interventions	• Artesunate-mefloquine (artesunate 4 mg/kg once daily for 3 days + mefloquine 15 mg/kg on day 1 and 10 mg/kg on day 2) • Artesunate-atovaquone-proguanil (artesunate 4 mg/kg + atovaquone 15 mg/kg/day + proguanil 8 mg/kg/day, once daily for 3 days) • Atovaquone-proguanil (atovaquone 15 mg/kg/day + proguanil 8 mg/kg/day once daily for 3 days)
Outcomes	• Treatment failure day 42 unadjusted • Treatment failure day 42 PCR adjusted • Parasite clearance (proportion of participants with a positive blood film at day 3)[a] • Fever clearance (proportion of participants with fever at day 2)[a] • Gametocyte carriage (person gametocyte weeks)[a] • Degree of anaemia (mean values)[a] • Adverse events [a]Not assessed in quantitative synthesis in this review.
Notes	Follow-up: 42 days Countries (codes): Thailand (THA) Setting: Maela and Mawker Tai malaria clinics; Shoklo Malaria Research Unit Malaria endemicity: low and unstable transmission

Van Vugt 2002 *(Continued)*

	Source of funding: Wellcome-Trust Mahidol University Oxford Tropical Medicine Research Programme (funded by the Wellcome Trust of Great Britain). GlaxoSmithKline donated atovaquone-proguanil Additional correspondence: we emailed the authors on 6 October 2018 but did not receive a reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomisation was in blocks of 12". Comment: no further details given.
Allocation concealment (selection bias)	Low risk	Quote: "Sealed envelope".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessors described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "88.7% (1352 of 1524) were seen at day 42".
Selective reporting (reporting bias)	Unclear risk	Authors reported gametocyte carriage yet this outcome was not listed in the methods. Adverse events: data together for both atovaquone-proguanil and artesunate-atovaquone-proguanil.
Other bias	Low risk	No other source of bias detected.

Wojnarski 2019

Study characteristics

Methods	Randomized controlled trial Duration: 11 months, December 2014 to December 2015
Participants	Adults with *P falciparum* malaria or mixed *P falciparum* and *P vivax* infections Number: 205 Inclusion criteria: aged 18–65 years Exclusion criteria: allergic reaction/medical contraindication to study drugs; creatinine clearance < 30 mL/minute; significant acute comorbidity requiring urgent medical intervention; severe malaria; use of antimalarial in prior 7 days, or atovaquone-proguanil in prior 30 days; use of drugs with possible interactions (tetracycline, metoclopramide, rifampicin, rifabutin, zidovudine, or etoposide); pregnancy, lactation, not agreeing to contraception. Diagnosis: microscopy (asexual parasite density 100–200,000 parasites/μL)

Wojnarski 2019 *(Continued)*

Interventions	• Atovaquone-proguanil (daily fixed dose combination of 4 tablets containing atovaquone 250 mg + proguanil hydrochloride 100 mg (total 1000 mg/400 mg) for 3 days) • Artesunate-atovaquone-proguanil (daily fixed dose combination of 4 tablets containing atovaquone 250 mg + proguanil hydrochloride 100 mg (total 1000 mg/400 mg daily) + 4 tablets containing artesunate 50 mg (200 mg daily) for 3 days) Both arms received a single dose of primaquine 15 mg.
Outcomes	• ACPR[a] day 42 PCR adjusted • ACPR[a] day 42 unadjusted • ACPR[a] day 28 PCR adjusted • ACPR[a] day 28 unadjusted • Rates of gametocyte carriage at days 1, 4, 7, and 14 (based on combined light microscopy and PCR)[b] • Parasite clearance time[b] • Adverse events • Atovaquone levels [a]Adequate clinical and parasitological response rate. [b]Not assessed in quantitative synthesis in this review.
Notes	Follow-up: 42 days Countries (codes): Cambodia (KHM) Setting: 2 hospitals Malaria endemicity: high transmission (> 1 case per 1000 population) Source of funding: Naval Advanced Medical Development Program, Washington DC Additional correspondence: we emailed the authors on 4 June 2018 to determine whether trial findings had been published in full, though this was subsequently published in 2019.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Volunteers were randomly assigned to…with 1:1 allocation using time-blocked randomization with a block size of 4".
Allocation concealment (selection bias)	Low risk	Quote: "…sealed envelopes to mask allocation".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Microscopists were blinded…"
Incomplete outcome data (attrition bias) All outcomes	Low risk	95% of participants seen at day 42.

Wojnarski 2019 *(Continued)*

Selective reporting (reporting bias)	Low risk	No evidence of reporting bias.
Other bias	Low risk	The funding source had no role in the analysis or interpretation of the data, preparation of the manuscript or the decision to publish.

ALT: alanine aminotransferase; *P falciparum*: *Plasmodium falciparum*; PCR: polymerase chain reaction; ULN: upper limits of normal.

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

Study	Reason for exclusion
Bustos 1999	Participants were initially randomized to receive either atovaquone-proguanil or chloroquine. However, because of a low cure rates in the chloroquine group, future participants were additionally given sulfadoxine-pyrimethamine. The data were presented as though this was a 3-arm trial, but we considered that data for 2 atovaquone-proguanil groups (those recruited before and after the addition of sulfadoxine-pyrimethamine) would be needed to compare these separately with chloroquine and chloroquine-sulfadoxine-pyrimethamine.
Gupta 2005	This report was part of an already included trial (Van Vugt 2002).
Hitani 2006	Retrospective data; intervention arms were not randomized.
Krudsood 2007	Single arm trial.
Looareesuwan 1996	Unclear study design with non-randomized methodology.

DATA AND ANALYSES

Comparison 1. Atovaquone-proguanil (AV+PG) versus artemether-lumefantrine (AL)

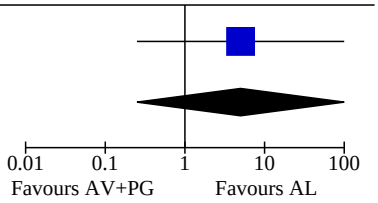
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Total failure day 28 PCR-adjusted	1	60	Risk Ratio (M-H, Fixed, 95% CI)	5.00 [0.25, 99.95]
1.2 Total failure day 42 PCR-adjusted	1	208	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.19, 47.12]
1.3 Total failure day 42 PCR-unadjusted	1	60	Risk Ratio (M-H, Fixed, 95% CI)	5.00 [0.25, 99.95]
1.4 Adverse events	2	2236	Risk Ratio (M-H, Fixed, 95% CI)	2.35 [1.57, 3.53]
1.4.1 Serious adverse events	2	272	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.4.2 Adverse events leading to withdrawal	2	272	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.4.3 Headaches	2	272	Risk Ratio (M-H, Fixed, 95% CI)	2.54 [1.17, 5.51]
1.4.4 Diarrhoea	2	272	Risk Ratio (M-H, Fixed, 95% CI)	2.25 [0.48, 10.54]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.4.5 Gastrointestinal and abdominal pains	1	212	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [0.34, 11.65]
1.4.6 Nausea and vomiting	2	272	Risk Ratio (M-H, Fixed, 95% CI)	10.00 [2.73, 36.60]
1.4.7 Dizziness	1	212	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.58, 4.75]
1.4.8 Hearing problem	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.87]
1.4.9 Inner ear signs and symptoms	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 3.03]
1.4.10 Feelings and sensations	1	60	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.33, 27.23]
1.4.11 Febrile disorders	2	272	Risk Ratio (M-H, Fixed, 95% CI)	2.25 [0.77, 6.60]

Analysis 1.1. Comparison 1: Atovaquone-proguanil (AV+PG) versus artemether-lumefantrine (AL), Outcome 1: Total failure day 28 PCR-adjusted

Study or Subgroup	AV+PG Events	AV+PG Total	AL Events	AL Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gurkov 2008	2	30	0	30	100.0%	5.00 [0.25 , 99.95]
Total (95% CI)		**30**		**30**	**100.0%**	**5.00 [0.25 , 99.95]**
Total events:	2		0			

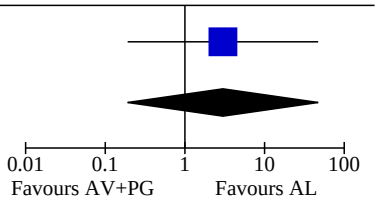
Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.29)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Atovaquone-proguanil (AV+PG) versus artemether-lumefantrine (AL), Outcome 2: Total failure day 42 PCR-adjusted

Study or Subgroup	AV+PG Events	AV+PG Total	AL Events	AL Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Carrasquilla 2012	1	52	1	156	100.0%	3.00 [0.19 , 47.12]
Total (95% CI)		**52**		**156**	**100.0%**	**3.00 [0.19 , 47.12]**
Total events:	1		1			

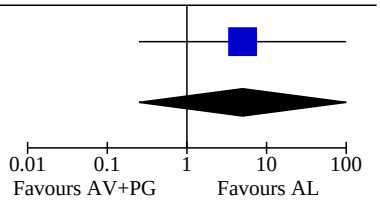
Heterogeneity: Not applicable
Test for overall effect: Z = 0.78 (P = 0.43)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Atovaquone-proguanil (AV+PG) versus artemether-lumefantrine (AL), Outcome 3: Total failure day 42 PCR-unadjusted

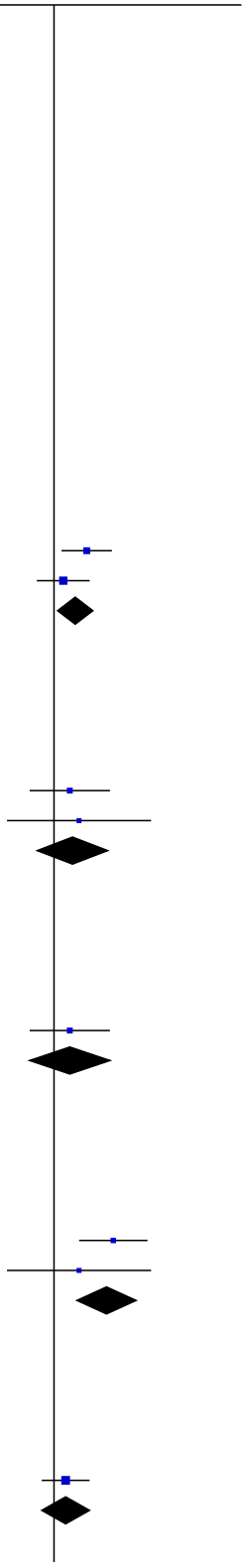
Study or Subgroup	AV+PG Events	AV+PG Total	AL Events	AL Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gurkov 2008	2	30	0	30	100.0%	5.00 [0.25 , 99.95]
Total (95% CI)		**30**		**30**	**100.0%**	**5.00 [0.25 , 99.95]**
Total events:	2		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.29)
Test for subgroup differences: Not applicable



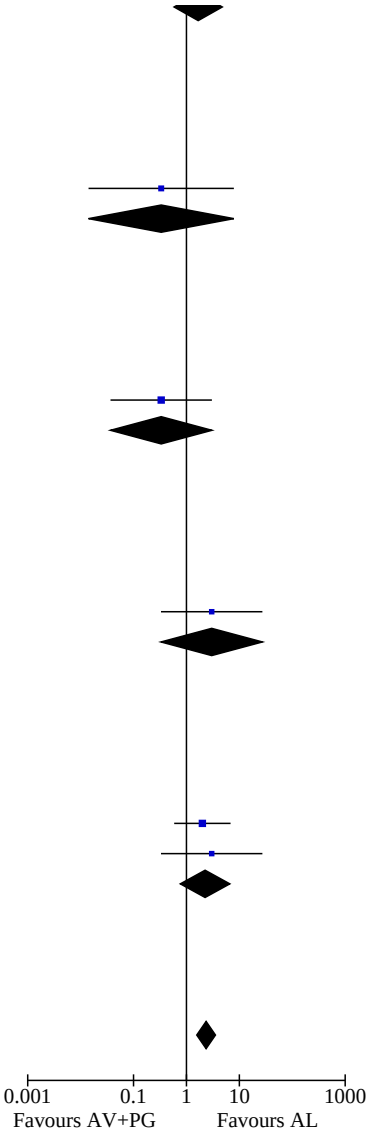
Analysis 1.4. Comparison 1: Atovaquone-proguanil (AV+PG) versus artemether-lumefantrine (AL), Outcome 4: Adverse events

Study or Subgroup	AV+PG Events	AV+PG Total	AL Events	AL Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Serious adverse events						
Carrasquilla 2012	0	53	0	159		Not estimable
Gurkov 2008	0	30	0	30		Not estimable
Subtotal (95% CI)		**83**		**189**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.4.2 Adverse events leading to withdrawal						
Carrasquilla 2012	0	53	0	159		Not estimable
Gurkov 2008	0	30	0	30		Not estimable
Subtotal (95% CI)		**83**		**189**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.4.3 Headaches						
Carrasquilla 2012	7	53	5	159	9.8%	4.20 [1.39 , 12.68]
Gurkov 2008	6	30	4	30	15.7%	1.50 [0.47 , 4.78]
Subtotal (95% CI)		**83**		**189**	**25.5%**	**2.54 [1.17 , 5.51]**
Total events:	13		9			
Heterogeneity: Chi² = 1.59, df = 1 (P = 0.21); I² = 37%						
Test for overall effect: Z = 2.36 (P = 0.02)						
1.4.4 Diarrhoea						
Carrasquilla 2012	2	53	3	159	5.9%	2.00 [0.34 , 11.65]
Gurkov 2008	1	30	0	30	2.0%	3.00 [0.13 , 70.83]
Subtotal (95% CI)		**83**		**189**	**7.8%**	**2.25 [0.48 , 10.54]**
Total events:	3		3			
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%						
Test for overall effect: Z = 1.03 (P = 0.30)						
1.4.5 Gastrointestinal and abdominal pains						
Carrasquilla 2012	2	53	3	159	5.9%	2.00 [0.34 , 11.65]
Subtotal (95% CI)		**53**		**159**	**5.9%**	**2.00 [0.34 , 11.65]**
Total events:	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.77 (P = 0.44)						
1.4.6 Nausea and vomiting						
Carrasquilla 2012	9	53	2	159	3.9%	13.50 [3.01 , 60.52]
Gurkov 2008	1	30	0	30	2.0%	3.00 [0.13 , 70.83]
Subtotal (95% CI)		**83**		**189**	**5.9%**	**10.00 [2.73 , 36.60]**
Total events:	10		2			
Heterogeneity: Chi² = 0.71, df = 1 (P = 0.40); I² = 0%						
Test for overall effect: Z = 3.48 (P = 0.0005)						
1.4.7 Dizziness						
Carrasquilla 2012	5	53	9	159	17.6%	1.67 [0.58 , 4.75]
Subtotal (95% CI)		**53**		**159**	**17.6%**	**1.67 [0.58 , 4.75]**
Total events:	5		9			



Analysis 1.4. (Continued)

Total events:	5		9				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.96 (P = 0.34)							
1.4.8 Hearing problem							
Gurkov 2008 (1)	0	30	1	30	5.9%	0.33 [0.01 , 7.87]	
Subtotal (95% CI)		**30**		**30**	**5.9%**	**0.33 [0.01 , 7.87]**	
Total events:	0		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.68 (P = 0.50)							
1.4.9 Inner ear signs and symptoms							
Gurkov 2008	1	30	3	30	11.8%	0.33 [0.04 , 3.03]	
Subtotal (95% CI)		**30**		**30**	**11.8%**	**0.33 [0.04 , 3.03]**	
Total events:	1		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.98 (P = 0.33)							
1.4.10 Feelings and sensations							
Gurkov 2008 (2)	3	30	1	30	3.9%	3.00 [0.33 , 27.23]	
Subtotal (95% CI)		**30**		**30**	**3.9%**	**3.00 [0.33 , 27.23]**	
Total events:	3		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.98 (P = 0.33)							
1.4.11 Febrile disorders							
Carrasquilla 2012	4	53	6	159	11.8%	2.00 [0.59 , 6.82]	
Gurkov 2008	3	30	1	30	3.9%	3.00 [0.33 , 27.23]	
Subtotal (95% CI)		**83**		**189**	**15.7%**	**2.25 [0.77 , 6.60]**	
Total events:	7		7				
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%							
Test for overall effect: Z = 1.48 (P = 0.14)							
Total (95% CI)		**694**		**1542**	**100.0%**	**2.35 [1.57 , 3.53]**	
Total events:	44		38				
Heterogeneity: Chi² = 12.01, df = 12 (P = 0.44); I² = 0%							
Test for overall effect: Z = 4.12 (P < 0.0001)							
Test for subgroup differences: Chi² = 9.80, df = 8 (P = 0.28), I² = 18.4%							



Footnotes

(1) No medDRA term.

(2) Original term was 'shivering'.

Comparison 2. Atovaquone-proguanil (AV+PG) versus artesunate-amodiaquine (AS+AQ)

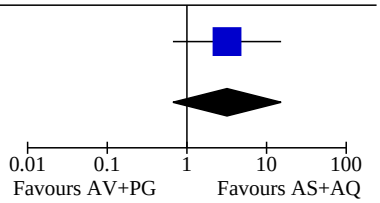
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Total failure day 28 PCR-adjusted	1	132	Risk Ratio (M-H, Fixed, 95% CI)	3.19 [0.67, 15.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Total failure day 28 PCR-unadjusted	1	132	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.49, 2.91]
2.3 Early treatment failure	1	132	Risk Ratio (M-H, Fixed, 95% CI)	13.80 [0.79, 240.11]
2.4 Adverse events	1	278	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [0.13, 73.43]
2.4.1 Serious adverse events	1	139	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.4.2 Adverse events leading to withdrawal	1	139	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [0.13, 73.43]

Analysis 2.1. Comparison 2: Atovaquone-proguanil (AV+PG) versus artesunate-amodiaquine (AS+AQ), Outcome 1: Total failure day 28 PCR-adjusted

Study or Subgroup	AV+PG Events	AV+PG Total	AS+AQ Events	AS+AQ Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tahar 2014 (1)	6	64	2	68	100.0%	3.19 [0.67 , 15.22]
Total (95% CI)		**64**		**68**	**100.0%**	**3.19 [0.67 , 15.22]**
Total events:	6		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.45 (P = 0.15)
Test for subgroup differences: Not applicable

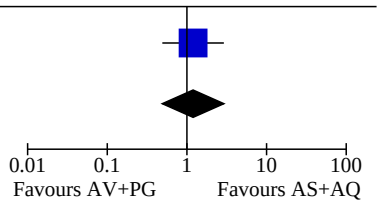


Footnotes
(1) Study described 'early treatment failures' included in total treatment failures as PCR was performed at day 7 and day 28.

Analysis 2.2. Comparison 2: Atovaquone-proguanil (AV+PG) versus artesunate-amodiaquine (AS+AQ), Outcome 2: Total failure day 28 PCR-unadjusted

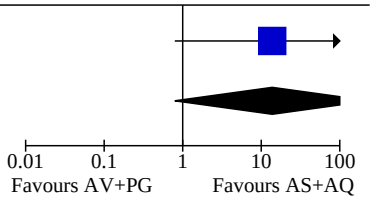
Study or Subgroup	AV+PG Events	AV+PG Total	AS+AQ Events	AS+AQ Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tahar 2014	9	64	8	68	100.0%	1.20 [0.49 , 2.91]
Total (95% CI)		**64**		**68**	**100.0%**	**1.20 [0.49 , 2.91]**
Total events:	9		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.69)
Test for subgroup differences: Not applicable



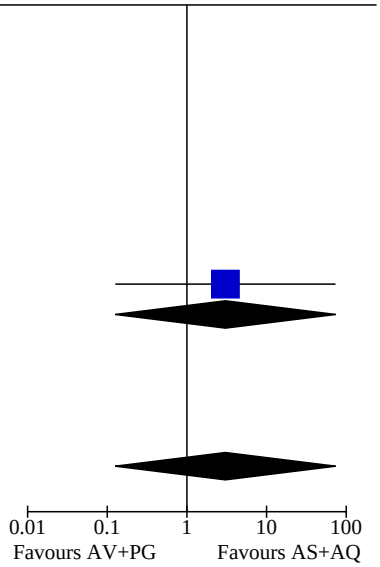
Analysis 2.3. Comparison 2: Atovaquone-proguanil (AV+PG) versus artesunate-amodiaquine (AS+AQ), Outcome 3: Early treatment failure

Study or Subgroup	AV+PG Events	AV+PG Total	AS+AQ Events	AS+AQ Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tahar 2014	6	64	0	68	100.0%	13.80 [0.79 , 240.11]
Total (95% CI)		**64**		**68**	**100.0%**	**13.80 [0.79 , 240.11]**
Total events:	6		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.80 (P = 0.07)						
Test for subgroup differences: Not applicable						



Analysis 2.4. Comparison 2: Atovaquone-proguanil (AV+PG) versus artesunate-amodiaquine (AS+AQ), Outcome 4: Adverse events

Study or Subgroup	AV+PG Events	AV+PG Total	AS+AQ Events	AS+AQ Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.4.1 Serious adverse events						
Tahar 2014	0	69	0	70		Not estimable
Subtotal (95% CI)		**69**		**70**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.4.2 Adverse events leading to withdrawal						
Tahar 2014	1	69	0	70	100.0%	3.04 [0.13 , 73.43]
Subtotal (95% CI)		**69**		**70**	**100.0%**	**3.04 [0.13 , 73.43]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
Total (95% CI)		**138**		**140**	**100.0%**	**3.04 [0.13 , 73.43]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
Test for subgroup differences: Not applicable						



Comparison 3. Atovaquone-proguanil (AV+PG) versus artesunate-mefloquine (AS+MQ)

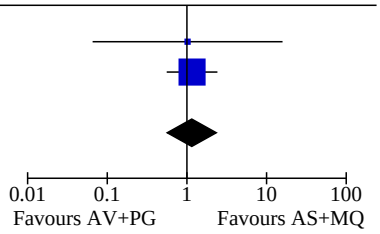
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Total failure day 42 PCR-adjusted	2	1168	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.57, 2.34]
3.2 Total failure day 42 PCR-unadjusted	1	1063	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.50, 1.30]
3.3 Adverse events	2	5312	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.60, 0.99]
3.3.1 Serious adverse events	2	1275	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.10, 4.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3.2 Adverse events leading to withdrawal	2	1275	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.04, 23.89]
3.3.3 Headaches	1	212	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [1.10, 8.16]
3.3.4 Diarrhoea	1	212	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.18, 4.00]
3.3.5 Gastrointestinal and abdominal pains	1	212	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.28, 7.96]
3.3.6 Nausea and vomiting	2	896	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.44, 0.89]
3.3.7 Disturbances in initiating and maintaining sleep	1	212	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 6.02]
3.3.8 Feelings and sensations	1	594	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.34, 1.02]
3.3.9 Dizziness	1	212	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.41, 2.83]
3.3.10 Febrile disorders	1	212	Risk Ratio (M-H, Fixed, 95% CI)	6.00 [1.13, 31.83]

Analysis 3.1. Comparison 3: Atovaquone-proguanil (AV+PG) versus artesunate-mefloquine (AS+MQ), Outcome 1: Total failure day 42 PCR-adjusted

	AV+PG		AS+MQ			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Carrasquilla 2012 (1)	1	52	1	53	7.1%	1.02 [0.07 , 15.87]	
Van Vugt 2002 (2)	15	530	13	533	92.9%	1.16 [0.56 , 2.41]	
Total (95% CI)		**582**		**586**	**100.0%**	**1.15 [0.57 , 2.34]**	
Total events:	16		14				

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.39 (P = 0.70)
Test for subgroup differences: Not applicable



Footnotes

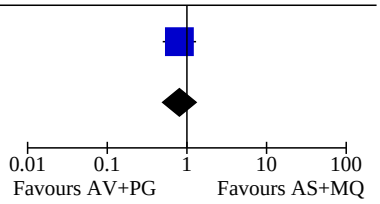
(1) Data unclear. 51/52 had PCR-adjusted cure.

(2) Authors reported missing data as treatment failures; denominator is number randomised, not evaluable population.

Analysis 3.2. Comparison 3: Atovaquone-proguanil (AV+PG) versus artesunate-mefloquine (AS+MQ), Outcome 2: Total failure day 42 PCR-unadjusted

Study or Subgroup	AV+PG Events	AV+PG Total	AS+MQ Events	AS+MQ Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Van Vugt 2002 (1)	28	530	35	533	100.0%	0.80 [0.50 , 1.30]
Total (95% CI)		**530**		**533**	**100.0%**	**0.80 [0.50 , 1.30]**
Total events:	28		35			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.88 (P = 0.38)
Test for subgroup differences: Not applicable

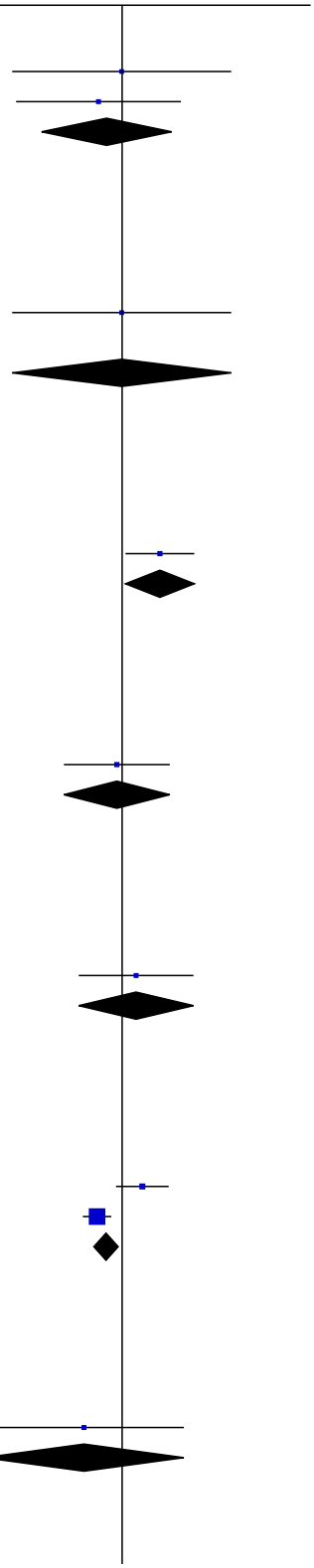


Footnotes

(1) Authors reported missing data as treatment failures; denominator is number randomised, not evaluable population.

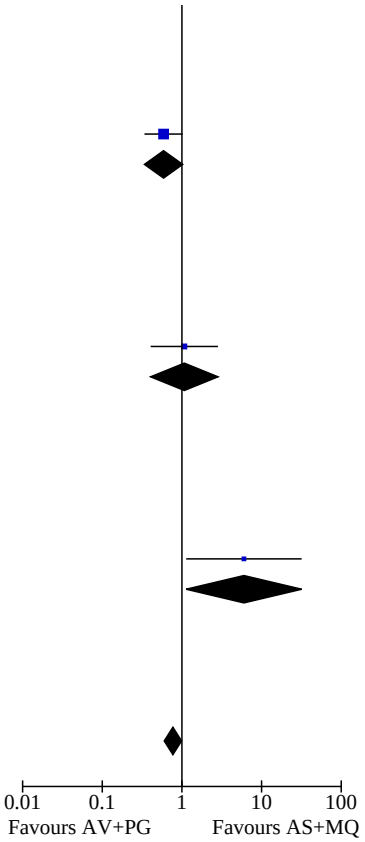
Analysis 3.3. Comparison 3: Atovaquone-proguanil (AV+PG) versus artesunate-mefloquine (AS+MQ), Outcome 3: Adverse events

Study or Subgroup	AV+PG Events	AV+PG Total	AS+MQ Events	AS+MQ Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.3.1 Serious adverse events						
Carrasquilla 2012	0	53	1	159	0.6%	0.99 [0.04 , 23.89]
Van Vugt 2002	1	530	2	533	1.6%	0.50 [0.05 , 5.53]
Subtotal (95% CI)		**583**		**692**	**2.2%**	**0.64 [0.10 , 4.22]**
Total events:	1		3			
Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%						
Test for overall effect: Z = 0.47 (P = 0.64)						
3.3.2 Adverse events leading to withdrawal						
Carrasquilla 2012	0	53	1	159	0.6%	0.99 [0.04 , 23.89]
Van Vugt 2002	0	530	0	533		Not estimable
Subtotal (95% CI)		**583**		**692**	**0.6%**	**0.99 [0.04 , 23.89]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 0.99)						
3.3.3 Headaches						
Carrasquilla 2012	7	53	7	159	2.8%	3.00 [1.10 , 8.16]
Subtotal (95% CI)		**53**		**159**	**2.8%**	**3.00 [1.10 , 8.16]**
Total events:	7		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.15 (P = 0.03)						
3.3.4 Diarrhoea						
Carrasquilla 2012	2	53	7	159	2.8%	0.86 [0.18 , 4.00]
Subtotal (95% CI)		**53**		**159**	**2.8%**	**0.86 [0.18 , 4.00]**
Total events:	2		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.20 (P = 0.84)						
3.3.5 Gastrointestinal and abdominal pains						
Carrasquilla 2012	2	53	4	159	1.6%	1.50 [0.28 , 7.96]
Subtotal (95% CI)		**53**		**159**	**1.6%**	**1.50 [0.28 , 7.96]**
Total events:	2		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.48 (P = 0.63)						
3.3.6 Nausea and vomiting						
Carrasquilla 2012	9	53	15	159	6.1%	1.80 [0.84 , 3.87]
Van Vugt 2002 (1)	29	334	63	350	50.1%	0.48 [0.32 , 0.73]
Subtotal (95% CI)		**387**		**509**	**56.2%**	**0.63 [0.44 , 0.89]**
Total events:	38		78			
Heterogeneity: Chi² = 8.84, df = 1 (P = 0.003); I² = 89%						
Test for overall effect: Z = 2.60 (P = 0.009)						
3.3.7 Disturbances in initiating and maintaining sleep						
Carrasquilla 2012	0	53	4	159	1.8%	0.33 [0.02 , 6.02]
Subtotal (95% CI)		**53**		**159**	**1.8%**	**0.33 [0.02 , 6.02]**
Total events:	0		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.75 (P = 0.45)						



Analysis 3.3. (Continued)

Heterogeneity: Not applicable						
Test for overall effect: Z = 0.75 (P = 0.45)						
3.3.8 Feelings and sensations						
Van Vugt 2002 (2)	19	308	30	286	25.3%	0.59 [0.34 , 1.02]
Subtotal (95% CI)		**308**		**286**	**25.3%**	**0.59 [0.34 , 1.02]**
Total events:	19		30			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.89 (P = 0.06)						
3.3.9 Dizziness						
Carrasquilla 2012	5	53	14	159	5.7%	1.07 [0.41 , 2.83]
Subtotal (95% CI)		**53**		**159**	**5.7%**	**1.07 [0.41 , 2.83]**
Total events:	5		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.14 (P = 0.89)						
3.3.10 Febrile disorders						
Carrasquilla 2012	4	53	2	159	0.8%	6.00 [1.13 , 31.83]
Subtotal (95% CI)		**53**		**159**	**0.8%**	**6.00 [1.13 , 31.83]**
Total events:	4		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.10 (P = 0.04)						
Total (95% CI)		**2179**		**3133**	**100.0%**	**0.77 [0.60 , 0.99]**
Total events:	78		150			
Heterogeneity: Chi^2 = 25.04, df = 11 (P = 0.009); I^2 = 56%						
Test for overall effect: Z = 2.04 (P = 0.04)						
Test for subgroup differences: Chi^2 = 16.63, df = 9 (P = 0.05), I^2 = 45.9%						



Footnotes

(1) This only included reported adverse event 'nausea' and not 'early vomiting' or 'late vomiting'.

(2) Original term was 'chills/rigours'.

Comparison 4. Atovaquone-proguanil (AV+PG) versus artesunate-atovaquone-proguanil (AS+AV+PG)

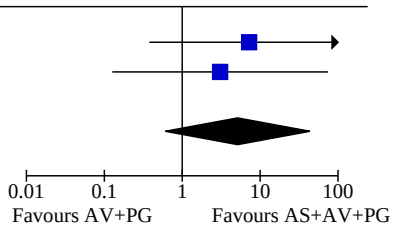
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Total failure day 28 PCR-adjusted	2	375	Risk Ratio (M-H, Fixed, 95% CI)	5.14 [0.61, 43.52]
4.2 Total failure day 28 PCR-unadjusted	1	187	Risk Ratio (M-H, Fixed, 95% CI)	15.48 [0.90, 267.27]
4.3 Total failure day 42 PCR-adjusted	2	1258	Risk Ratio (M-H, Fixed, 95% CI)	1.84 [0.95, 3.56]
4.4 Total failure day 42 PCR-unadjusted	1	1063	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.88, 2.79]
4.5 Early treatment failure	2	395	Risk Ratio (M-H, Fixed, 95% CI)	5.11 [0.25, 104.94]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.6 Adverse events	3	4732	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.43, 0.76]
4.6.1 Serious adverse events	3	1455	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [0.22, 12.49]
4.6.2 Adverse events leading to withdrawal	2	1250	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.6.3 Nausea and vomiting	1	664	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.34, 0.80]
4.6.4 Gastrointestinal and abdominal pains	1	752	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.33, 1.04]
4.6.5 Feelings and sensations	1	611	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.35, 1.04]

Analysis 4.1. Comparison 4: Atovaquone-proguanil (AV+PG) versus artesunate-atovaquone-proguanil (AS+AV+PG), Outcome 1: Total failure day 28 PCR-adjusted

Study or Subgroup	AV+PG Events	AV+PG Total	AS+AV+PG Events	AS+AV+PG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tahar 2014	3	92	0	95	49.9%	7.23 [0.38 , 137.98]
Wojnarski 2019	1	93	0	95	50.1%	3.06 [0.13 , 74.26]
Total (95% CI)		**185**		**190**	**100.0%**	**5.14 [0.61 , 43.52]**
Total events:	4		0			

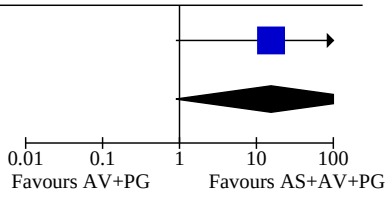
Heterogeneity: Chi² = 0.15, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 1.50 (P = 0.13)
Test for subgroup differences: Not applicable



Analysis 4.2. Comparison 4: Atovaquone-proguanil (AV+PG) versus artesunate-atovaquone-proguanil (AS+AV+PG), Outcome 2: Total failure day 28 PCR-unadjusted

Study or Subgroup	AV+PG Events	AV+PG Total	AS+AV+PG Events	AS+AV+PG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tahar 2014	7	92	0	95	100.0%	15.48 [0.90 , 267.27]
Total (95% CI)		**92**		**95**	**100.0%**	**15.48 [0.90 , 267.27]**
Total events:	7		0			

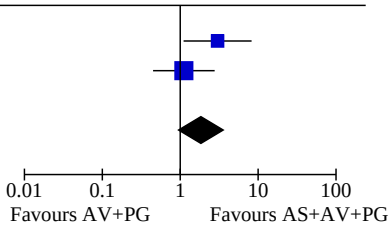
Heterogeneity: Not applicable
Test for overall effect: Z = 1.89 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 4.3. Comparison 4: Atovaquone-proguanil (AV+PG) versus artesunate-atovaquone-proguanil (AS+AV+PG), Outcome 3: Total failure day 42 PCR-adjusted

Study or Subgroup	AV+PG Events	AV+PG Total	AS+AV+PG Events	AS+AV+PG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Van Vugt 2002 (1)	15	530	5	533	38.3%	3.02 [1.10 , 8.24]
Wojnarski 2019	9	98	8	97	61.7%	1.11 [0.45 , 2.77]
Total (95% CI)		**628**		**630**	**100.0%**	**1.84 [0.95 , 3.56]**
Total events:	24		13			

Heterogeneity: Chi² = 2.10, df = 1 (P = 0.15); I² = 52%
Test for overall effect: Z = 1.82 (P = 0.07)
Test for subgroup differences: Not applicable

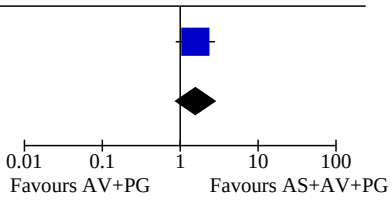


Footnotes
(1) Authors reported missing data as treatment failures; denominator is number randomised, not evaluable population.

Analysis 4.4. Comparison 4: Atovaquone-proguanil (AV+PG) versus artesunate-atovaquone-proguanil (AS+AV+PG), Outcome 4: Total failure day 42 PCR-unadjusted

Study or Subgroup	AV+PG Events	AV+PG Total	AS+AV+PG Events	AS+AV+PG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Van Vugt 2002 (1)	28	530	18	533	100.0%	1.56 [0.88 , 2.79]
Total (95% CI)		**530**		**533**	**100.0%**	**1.56 [0.88 , 2.79]**
Total events:	28		18			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.51 (P = 0.13)
Test for subgroup differences: Not applicable

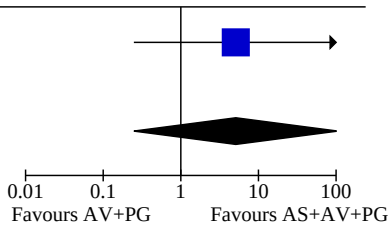


Footnotes
(1) Authors reported missing data as treatment failures; denominator is number randomised, not evaluable population.

Analysis 4.5. Comparison 4: Atovaquone-proguanil (AV+PG) versus artesunate-atovaquone-proguanil (AS+AV+PG), Outcome 5: Early treatment failure

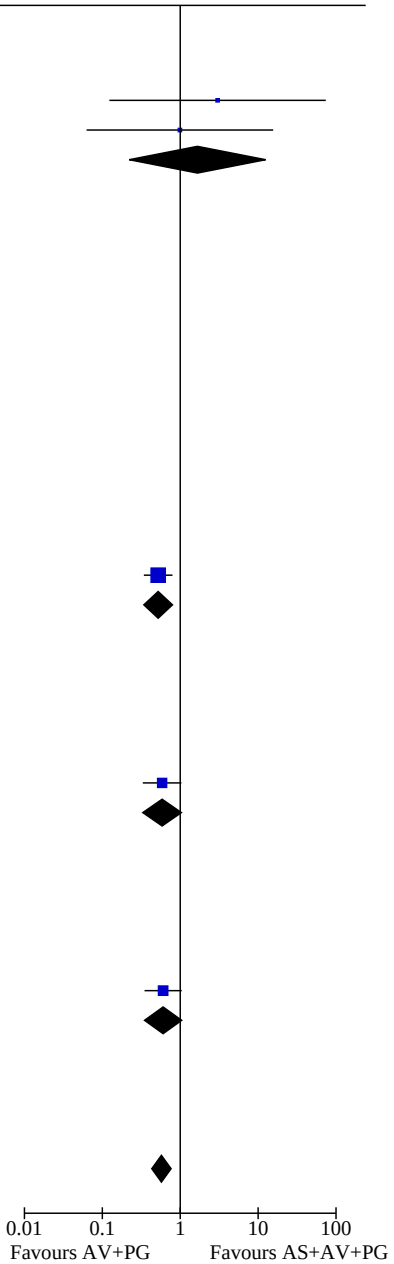
Study or Subgroup	AV+PG Events	AV+PG Total	AS+AV+PG Events	AS+AV+PG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tahar 2014	2	94	0	96	100.0%	5.11 [0.25 , 104.94]
Wojnarski 2019	0	103	0	102		Not estimable
Total (95% CI)		**197**		**198**	**100.0%**	**5.11 [0.25 , 104.94]**
Total events:	2		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.06 (P = 0.29)
Test for subgroup differences: Not applicable



Analysis 4.6. Comparison 4: Atovaquone-proguanil (AV+PG) versus artesunate-atovaquone-proguanil (AS+AV+PG), Outcome 6: Adverse events

Study or Subgroup	AV+PG Events	AV+PG Total	AS+AV+PG Events	AS+AV+PG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.6.1 Serious adverse events						
Tahar 2014	0	92	0	95		Not estimable
Van Vugt 2002	1	530	0	533	0.4%	3.02 [0.12 , 73.89]
Wojnarski 2019	1	103	1	102	0.9%	0.99 [0.06 , 15.62]
Subtotal (95% CI)		**725**		**730**	**1.3%**	**1.66 [0.22 , 12.49]**
Total events:	2		1			
Heterogeneity: Chi² = 0.27, df = 1 (P = 0.60); I² = 0%						
Test for overall effect: Z = 0.49 (P = 0.62)						
4.6.2 Adverse events leading to withdrawal						
Tahar 2014	0	92	0	95		Not estimable
Van Vugt 2002	0	530	0	533		Not estimable
Subtotal (95% CI)		**622**		**628**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.6.3 Nausea and vomiting						
Van Vugt 2002 (1)	29	334	55	330	46.9%	0.52 [0.34 , 0.80]
Subtotal (95% CI)		**334**		**330**	**46.9%**	**0.52 [0.34 , 0.80]**
Total events:	29		55			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.02 (P = 0.003)						
4.6.4 Gastrointestinal and abdominal pains						
Van Vugt 2002	18	387	29	365	25.3%	0.59 [0.33 , 1.04]
Subtotal (95% CI)		**387**		**365**	**25.3%**	**0.59 [0.33 , 1.04]**
Total events:	18		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.84 (P = 0.07)						
4.6.5 Feelings and sensations						
Van Vugt 2002	19	308	31	303	26.5%	0.60 [0.35 , 1.04]
Subtotal (95% CI)		**308**		**303**	**26.5%**	**0.60 [0.35 , 1.04]**
Total events:	19		31			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.81 (P = 0.07)						
Total (95% CI)		**2376**		**2356**	**100.0%**	**0.57 [0.43 , 0.76]**
Total events:	68		116			
Heterogeneity: Chi² = 1.42, df = 4 (P = 0.84); I² = 0%						
Test for overall effect: Z = 3.82 (P = 0.0001)						
Test for subgroup differences: Chi² = 1.30, df = 3 (P = 0.73), I² = 0%						



Footnotes

(1) Included adverse event 'nausea' only (not 'early/late vomiting').

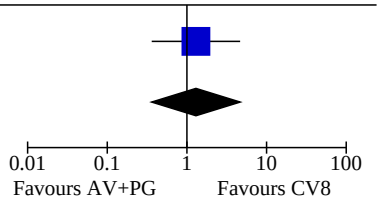
Comparison 5. Atovaquone-proguanil (AV+PG) versus dihydroartemisinin-piperaquine-trimethoprim-primaquine (CV8)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Total failure day 28 PCR-unadjusted	1	161	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.36, 4.66]
5.2 Early treatment failure	1	161	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.3 Adverse events	1	1155	Risk Ratio (M-H, Fixed, 95% CI)	1.90 [0.71, 5.11]
5.3.1 Serious adverse events	1	165	Risk Ratio (M-H, Fixed, 95% CI)	5.18 [0.25, 106.33]
5.3.2 Adverse events leading to withdrawal	1	165	Risk Ratio (M-H, Fixed, 95% CI)	5.18 [0.25, 106.33]
5.3.3 Nausea and vomiting	1	165	Risk Ratio (M-H, Fixed, 95% CI)	5.18 [0.25, 106.33]
5.3.4 Diarrhoea	1	165	Risk Ratio (M-H, Fixed, 95% CI)	3.11 [0.13, 75.24]
5.3.5 Headaches	1	165	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.36]
5.3.6 Oral dryness and saliva altered	1	165	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.36]
5.3.7 Pruritis	1	165	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.07, 16.30]

Analysis 5.1. Comparison 5: Atovaquone-proguanil (AV+PG) versus dihydroartemisinin-piperaquine-trimethoprim-primaquine (CV8), Outcome 1: Total failure day 28 PCR-unadjusted

Study or Subgroup	AV+PG Events	AV+PG Total	CV8 Events	CV8 Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Giao 2004	5	79	4	82	100.0%	1.30 [0.36 , 4.66]
Total (95% CI)		**79**		**82**	**100.0%**	**1.30 [0.36 , 4.66]**
Total events:	5		4			

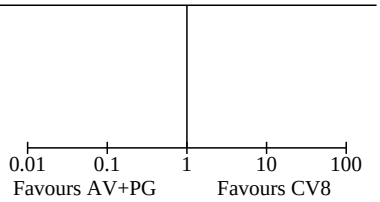
Heterogeneity: Not applicable
Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Not applicable



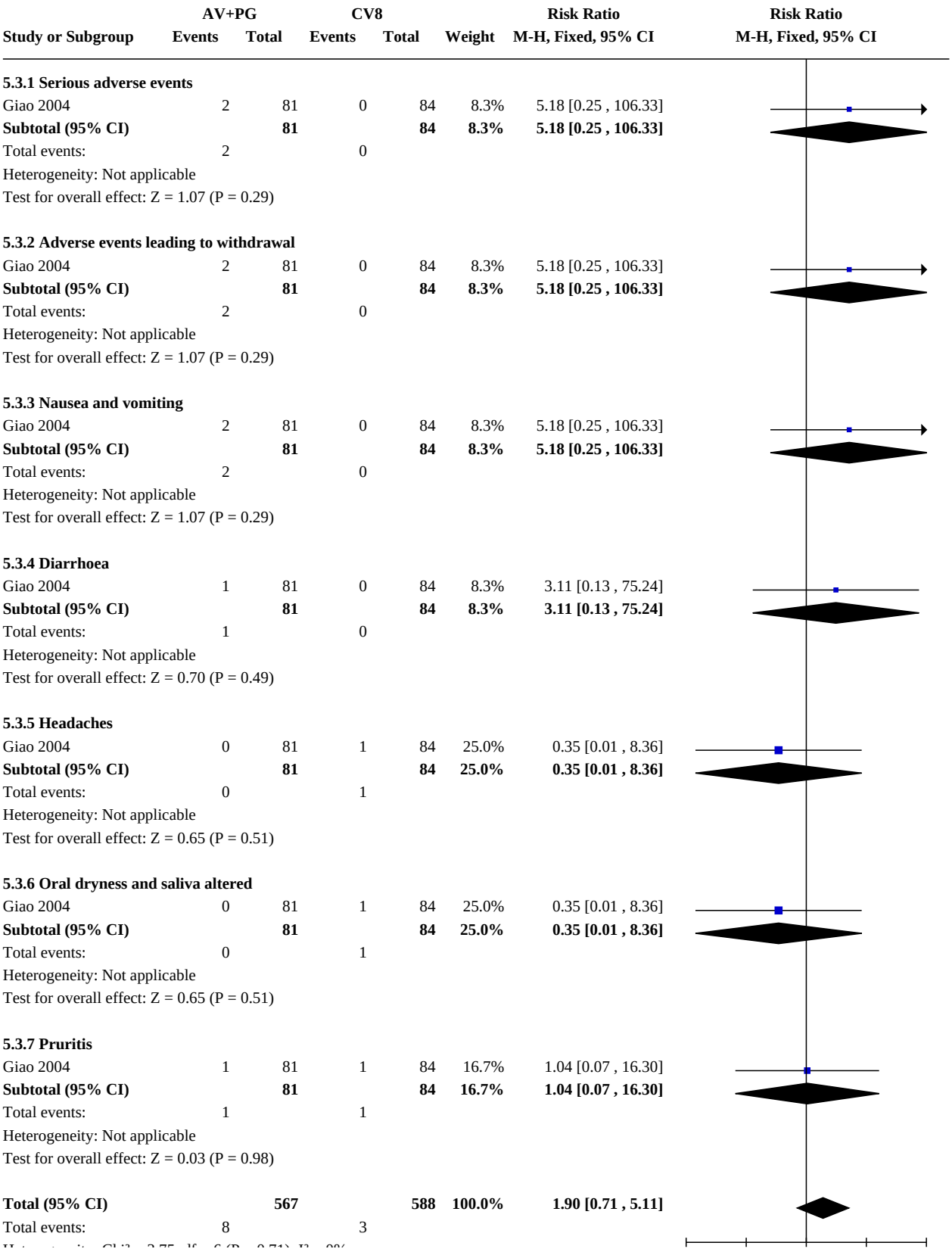
Analysis 5.2. Comparison 5: Atovaquone-proguanil (AV+PG) versus dihydroartemisinin-piperaquine-trimethoprim-primaquine (CV8), Outcome 2: Early treatment failure

Study or Subgroup	AV+PG Events	AV+PG Total	CV8 Events	CV8 Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Giao 2004	0	79	0	82		Not estimable
Total (95% CI)		**79**		**82**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 5.3. Comparison 5: Atovaquone-proguanil (AV+PG) versus dihydroartemisinin-piperaquine-trimethoprim-primaquine (CV8), Outcome 3: Adverse events



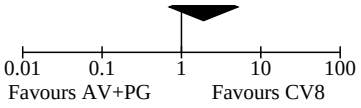
Analysis 5.3. (Continued)

Total events: 8 3

Heterogeneity: Chi² = 3.75, df = 6 (P = 0.71); I² = 0%

Test for overall effect: Z = 1.27 (P = 0.20)

Test for subgroup differences: Chi² = 3.74, df = 6 (P = 0.71), I² = 0%



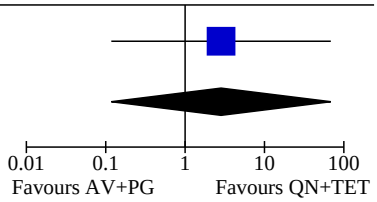
Comparison 6. Atovaquone-proguanil (AV+PG) versus quinine-tetracycline (QN+TET)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Total failure day 28 PCR-unadjusted	1	142	Risk Ratio (M-H, Fixed, 95% CI)	2.84 [0.12, 68.51]
6.2 Early treatment failure	1	142	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.3 Adverse events	1	1694	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.37, 0.60]
6.3.1 Serious adverse events	1	154	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.3.2 Adverse events leading to withdrawal	1	154	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.3.3 Gastrointestinal and abdominal pains	1	154	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.64, 1.93]
6.3.4 Nausea and vomiting	1	154	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.29, 1.02]
6.3.5 Asthenic conditions	1	154	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.28, 1.29]
6.3.6 Diarrhoea	1	154	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.20, 1.58]
6.3.7 Headaches	1	154	Risk Ratio (M-H, Fixed, 95% CI)	1.89 [0.90, 3.97]
6.3.8 Dizziness	1	154	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.14, 0.48]
6.3.9 Pruritis	1	154	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.44, 5.11]
6.3.10 Auditory nerve disorders	1	154	Risk Ratio (M-H, Fixed, 95% CI)	0.05 [0.02, 0.17]
6.3.11 Appetite disorders	1	154	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.14, 1.03]

Analysis 6.1. Comparison 6: Atovaquone-proguanil (AV+PG) versus quinine-tetracycline (QN+TET), Outcome 1: Total failure day 28 PCR-unadjusted

Study or Subgroup	AV+PG Events	AV+PG Total	QN+TET Events	QN+TET Total	Weight	Risk Ratio M-H, Fixed, 95% CI
De Alencar 1997	1	73	0	69	100.0%	2.84 [0.12 , 68.51]
Total (95% CI)		**73**		**69**	**100.0%**	**2.84 [0.12 , 68.51]**
Total events:	1		0			

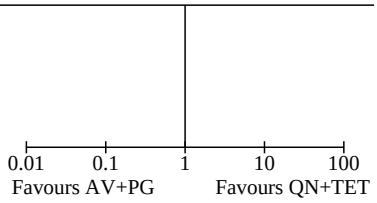
Heterogeneity: Not applicable
Test for overall effect: Z = 0.64 (P = 0.52)
Test for subgroup differences: Not applicable



Analysis 6.2. Comparison 6: Atovaquone-proguanil (AV+PG) versus quinine-tetracycline (QN+TET), Outcome 2: Early treatment failure

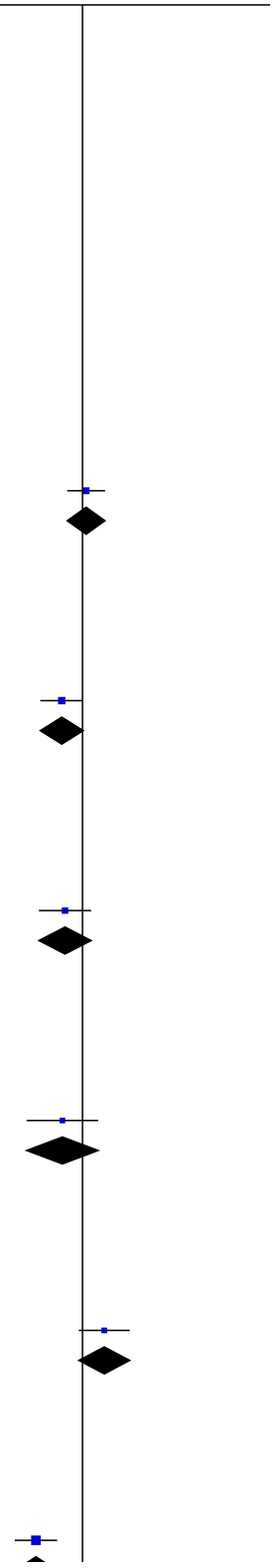
Study or Subgroup	AV+PG Events	AV+PG Total	QN+TET Events	QN+TET Total	Weight	Risk Ratio M-H, Fixed, 95% CI
De Alencar 1997	0	73	0	69		Not estimable
Total (95% CI)		**73**		**69**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



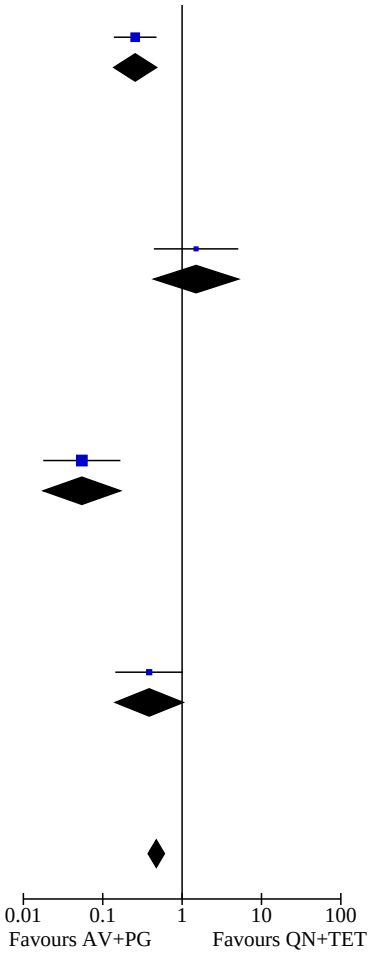
Analysis 6.3. Comparison 6: Atovaquone-proguanil (AV+PG) versus quinine-tetracycline (QN+TET), Outcome 3: Adverse events

Study or Subgroup	AV+PG Events	AV+PG Total	QN+TET Events	QN+TET Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.3.1 Serious adverse events						
De Alencar 1997 (1)	0	77	0	77		Not estimable
Subtotal (95% CI)		**77**		**77**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
6.3.2 Adverse events leading to withdrawal						
De Alencar 1997 (1)	0	77	0	77		Not estimable
Subtotal (95% CI)		**77**		**77**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
6.3.3 Gastrointestinal and abdominal pains						
De Alencar 1997 (1)	20	77	18	77	9.8%	1.11 [0.64 , 1.93]
Subtotal (95% CI)		**77**		**77**	**9.8%**	**1.11 [0.64 , 1.93]**
Total events:	20		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.37 (P = 0.71)						
6.3.4 Nausea and vomiting						
De Alencar 1997 (2)	12	77	22	77	12.0%	0.55 [0.29 , 1.02]
Subtotal (95% CI)		**77**		**77**	**12.0%**	**0.55 [0.29 , 1.02]**
Total events:	12		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.89 (P = 0.06)						
6.3.5 Asthenic conditions						
De Alencar 1997 (1)	9	77	15	77	8.2%	0.60 [0.28 , 1.29]
Subtotal (95% CI)		**77**		**77**	**8.2%**	**0.60 [0.28 , 1.29]**
Total events:	9		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.31 (P = 0.19)						
6.3.6 Diarrhoea						
De Alencar 1997 (1)	5	77	9	77	4.9%	0.56 [0.20 , 1.58]
Subtotal (95% CI)		**77**		**77**	**4.9%**	**0.56 [0.20 , 1.58]**
Total events:	5		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.10 (P = 0.27)						
6.3.7 Headaches						
De Alencar 1997 (1)	17	77	9	77	4.9%	1.89 [0.90 , 3.97]
Subtotal (95% CI)		**77**		**77**	**4.9%**	**1.89 [0.90 , 3.97]**
Total events:	17		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.68 (P = 0.09)						
6.3.8 Dizziness						
De Alencar 1997 (1)	10	77	39	77	21.2%	0.26 [0.14 , 0.48]



Analysis 6.3. (Continued)

De Alencar 1997 (1)	10	77	39	77	21.2%	0.26 [0.14 , 0.48]
Subtotal (95% CI)		**77**		**77**	**21.2%**	**0.26 [0.14 , 0.48]**
Total events:	10		39			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.31 (P < 0.0001)						
6.3.9 Pruritis						
De Alencar 1997 (1)	6	77	4	77	2.2%	1.50 [0.44 , 5.11]
Subtotal (95% CI)		**77**		**77**	**2.2%**	**1.50 [0.44 , 5.11]**
Total events:	6		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
6.3.10 Auditory nerve disorders						
De Alencar 1997 (1)	3	77	55	77	29.9%	0.05 [0.02 , 0.17]
Subtotal (95% CI)		**77**		**77**	**29.9%**	**0.05 [0.02 , 0.17]**
Total events:	3		55			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.10 (P < 0.00001)						
6.3.11 Appetite disorders						
De Alencar 1997 (1)	5	77	13	77	7.1%	0.38 [0.14 , 1.03]
Subtotal (95% CI)		**77**		**77**	**7.1%**	**0.38 [0.14 , 1.03]**
Total events:	5		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.91 (P = 0.06)						
Total (95% CI)		**847**		**847**	**100.0%**	**0.47 [0.37 , 0.60]**
Total events:	87		184			
Heterogeneity: Chi² = 44.83, df = 8 (P < 0.00001); I² = 82%						
Test for overall effect: Z = 6.26 (P < 0.00001)						
Test for subgroup differences: Chi² = 41.86, df = 8 (P < 0.00001), I² = 80.9%						



Footnotes

(1) Denominator formed from participants completing treatment.

(2) Denominator formed from participants completing treatment. Included adverse event 'nausea' only (not 'vomiting').

Comparison 7. Atovaquone-proguanil (AV+PG) versus sulfadoxine-pyrimethamine (SP)

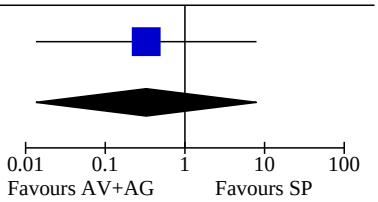
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
7.1 Total failure day 28 PCR-adjusted	1	192	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.92]
7.2 Total failure day 28 PCR-unadjusted	3	364	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.10, 0.59]
7.3 Early treatment failure	2	172	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.06]
7.4 Adverse events	3	5569	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.84, 1.23]
7.4.1 Serious adverse events	3	447	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.35, 1.41]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.4.2 Adverse events leading to withdrawal	3	447	Risk Ratio (M-H, Fixed, 95% CI)	5.95 [0.73, 48.75]
7.4.3 Gastrointestinal and abdominal pains	2	192	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.78, 2.18]
7.4.4 Diarrhoea	2	418	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.65, 2.96]
7.4.5 Nausea and vomiting	2	192	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.47, 1.74]
7.4.6 Headaches	2	192	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.56, 1.42]
7.4.7 Hypotensive disorders	1	163	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.17, 1.05]
7.4.8 Seizure and seizure disorders	2	284	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.08, 5.43]
7.4.9 Appetite disorders	2	192	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [0.52, 5.00]
7.4.10 Hepatobiliary signs and symptoms	1	163	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.30, 3.28]
7.4.11 Pruritis	2	192	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.35, 5.67]
7.4.12 Spleen disorders	1	163	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.25, 8.64]
7.4.13 Cardiac signs and symptoms	1	163	Risk Ratio (M-H, Fixed, 95% CI)	6.92 [0.36, 131.79]
7.4.14 Disturbances in initiating and maintaining sleep	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.09, 1.21]
7.4.15 Feelings and sensations	1	29	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.06, 32.05]
7.4.16 Rubeola viral infections	1	255	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.11, 3.89]
7.4.17 Hypoglycaemic conditions	1	255	Risk Ratio (M-H, Fixed, 95% CI)	4.96 [0.24, 102.33]
7.4.18 Lower respiratory tract and lung infections	1	255	Risk Ratio (M-H, Fixed, 95% CI)	2.48 [0.49, 12.55]
7.4.19 Anaemias	1	255	Risk Ratio (M-H, Fixed, 95% CI)	2.98 [0.12, 72.39]
7.4.20 Sepsis, bacteraemia, viraemia, fungaemia	1	255	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.14]
7.4.21 Breathing abnormalities	1	255	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 1.61]
7.4.22 Muscle pains	1	163	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.54, 4.63]
7.4.23 Asthenic conditions	2	418	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.68, 2.28]
7.4.24 Dizziness	2	192	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.28, 1.81]

Analysis 7.1. Comparison 7: Atovaquone-proguanil (AV+PG) versus sulfadoxine-pyrimethamine (SP), Outcome 1: Total failure day 28 PCR-adjusted

Study or Subgroup	AV+PG Events	AV+PG Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mulenga 2006	0	97	1	95	100.0%	0.33 [0.01 , 7.92]
Total (95% CI)		**97**		**95**	**100.0%**	**0.33 [0.01 , 7.92]**
Total events:	0		1			

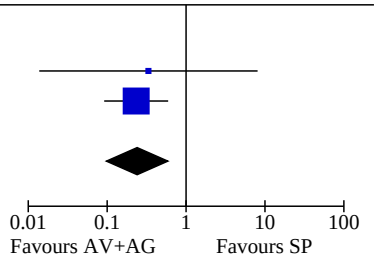
Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable



Analysis 7.2. Comparison 7: Atovaquone-proguanil (AV+PG) versus sulfadoxine-pyrimethamine (SP), Outcome 2: Total failure day 28 PCR-unadjusted

Study or Subgroup	AV+PG Events	AV+PG Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Llanos-Cuentas 2001	0	5	0	7		Not estimable
Mulenga 1999	0	80	1	80	6.6%	0.33 [0.01 , 8.06]
Mulenga 2006	5	97	21	95	93.4%	0.23 [0.09 , 0.59]
Total (95% CI)		**182**		**182**	**100.0%**	**0.24 [0.10 , 0.59]**
Total events:	5		22			

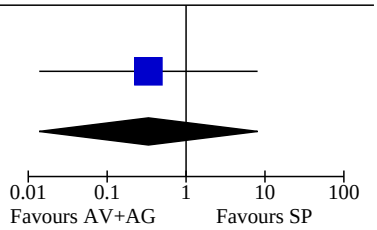
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 3.13 (P = 0.002)
Test for subgroup differences: Not applicable



Analysis 7.3. Comparison 7: Atovaquone-proguanil (AV+PG) versus sulfadoxine-pyrimethamine (SP), Outcome 3: Early treatment failure

Study or Subgroup	AV+PG Events	AV+PG Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Llanos-Cuentas 2001 (1)	0	5	0	7		Not estimable
Mulenga 1999	0	80	1	80	100.0%	0.33 [0.01 , 8.06]
Total (95% CI)		**85**		**87**	**100.0%**	**0.33 [0.01 , 8.06]**
Total events:	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable

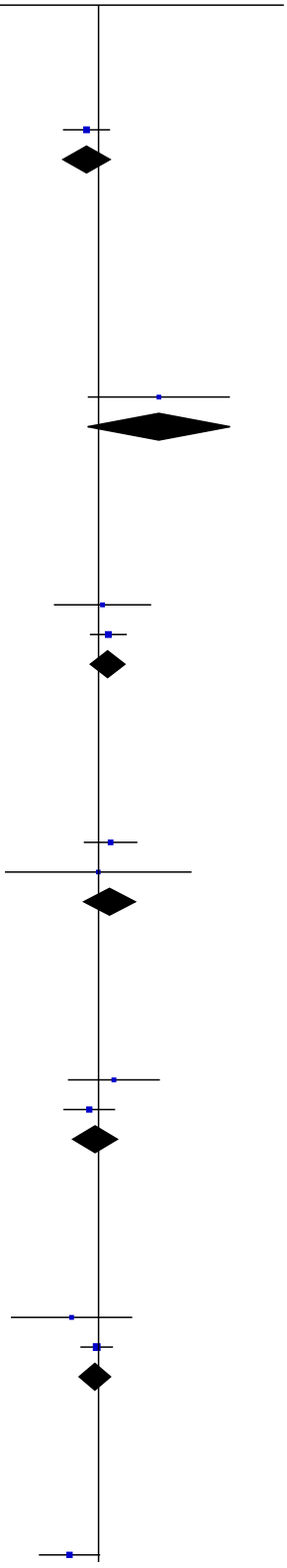


Footnotes

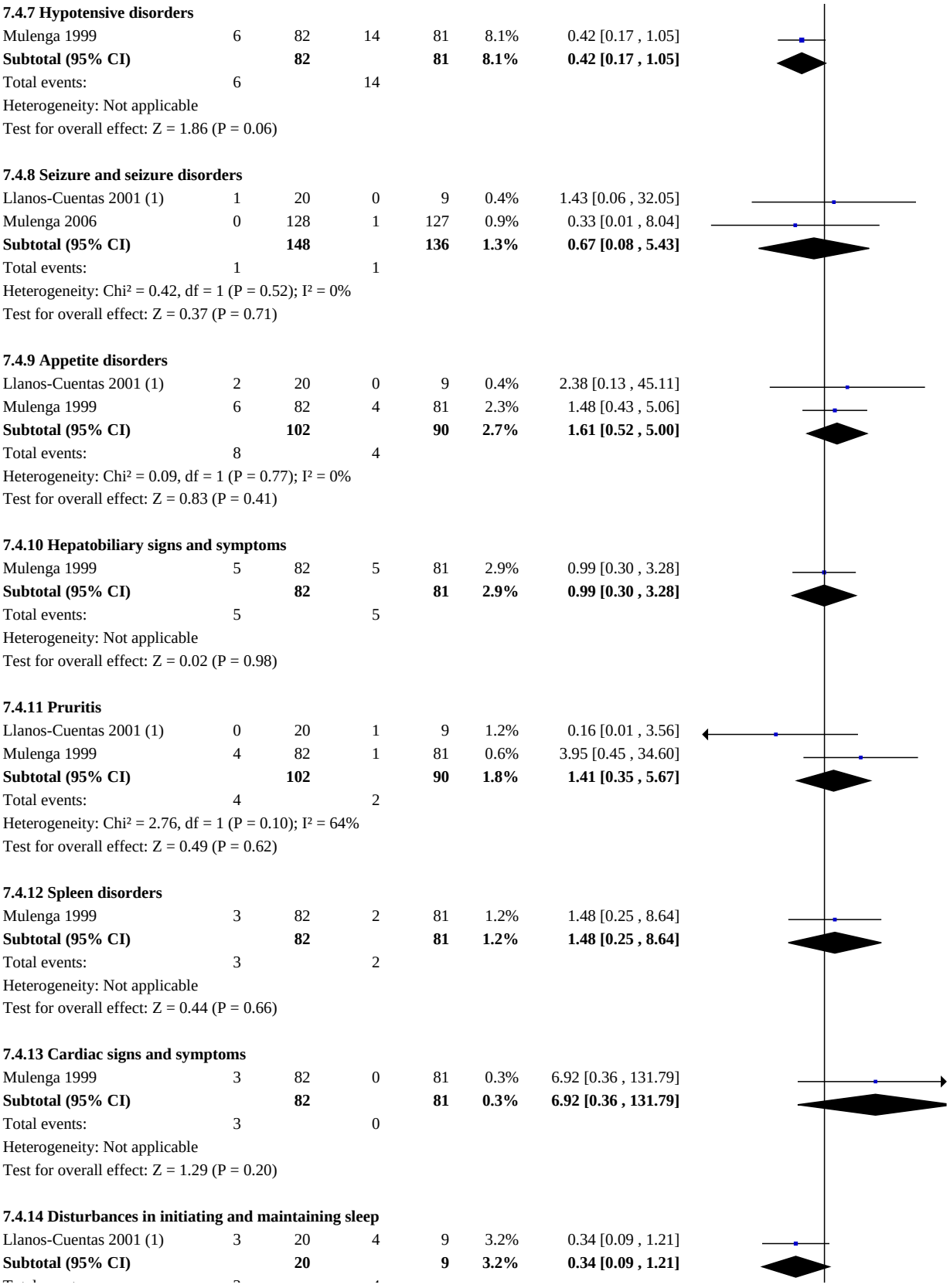
(1) Denominator for AV+PG formed from addition of 'phase 1' and 'phase 2' trial data.

Analysis 7.4. Comparison 7: Atovaquone-proguanil (AV+PG) versus sulfadoxine-pyrimethamine (SP), Outcome 4: Adverse events

Study or Subgroup	AV+PG Events	AV+PG Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.4.1 Serious adverse events						
Llanos-Cuentas 2001 (1)	0	20	0	9		Not estimable
Mulenga 1999	0	82	0	81		Not estimable
Mulenga 2006 (2)	12	128	17	127	9.8%	0.70 [0.35 , 1.41]
Subtotal (95% CI)		**230**		**217**	**9.8%**	**0.70 [0.35 , 1.41]**
Total events:	12		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.00 (P = 0.32)						
7.4.2 Adverse events leading to withdrawal						
Llanos-Cuentas 2001 (1)	0	20	0	9		Not estimable
Mulenga 1999	0	82	0	81		Not estimable
Mulenga 2006	6	128	1	127	0.6%	5.95 [0.73 , 48.75]
Subtotal (95% CI)		**230**		**217**	**0.6%**	**5.95 [0.73 , 48.75]**
Total events:	6		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.66 (P = 0.10)						
7.4.3 Gastrointestinal and abdominal pains						
Llanos-Cuentas 2001 (1)	5	20	2	9	1.6%	1.13 [0.27 , 4.74]
Mulenga 1999	23	82	17	81	9.9%	1.34 [0.77 , 2.31]
Subtotal (95% CI)		**102**		**90**	**11.5%**	**1.31 [0.78 , 2.18]**
Total events:	28		19			
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.83); I² = 0%						
Test for overall effect: Z = 1.03 (P = 0.30)						
7.4.4 Diarrhoea						
Mulenga 1999	13	82	9	81	5.2%	1.43 [0.65 , 3.15]
Mulenga 2006	1	128	1	127	0.6%	0.99 [0.06 , 15.69]
Subtotal (95% CI)		**210**		**208**	**5.8%**	**1.38 [0.65 , 2.96]**
Total events:	14		10			
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 0.84 (P = 0.40)						
7.4.5 Nausea and vomiting						
Llanos-Cuentas 2001 (3)	7	20	2	9	1.6%	1.57 [0.40 , 6.14]
Mulenga 1999 (4)	10	82	13	81	7.5%	0.76 [0.35 , 1.63]
Subtotal (95% CI)		**102**		**90**	**9.1%**	**0.90 [0.47 , 1.74]**
Total events:	17		15			
Heterogeneity: Chi² = 0.84, df = 1 (P = 0.36); I² = 0%						
Test for overall effect: Z = 0.31 (P = 0.76)						
7.4.6 Headaches						
Llanos-Cuentas 2001 (1)	2	20	2	9	1.6%	0.45 [0.07 , 2.71]
Mulenga 1999	23	82	24	81	13.9%	0.95 [0.58 , 1.53]
Subtotal (95% CI)		**102**		**90**	**15.5%**	**0.90 [0.56 , 1.42]**
Total events:	25		26			
Heterogeneity: Chi² = 0.62, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.47 (P = 0.64)						
7.4.7 Hypotensive disorders						
Mulenga 1999	6	82	14	81	8.1%	0.42 [0.17 , 1.05]



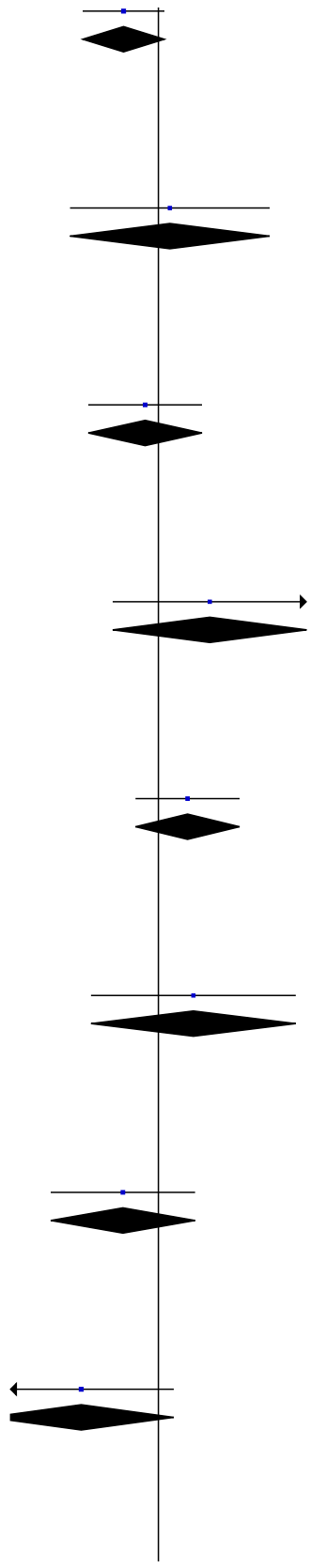
Analysis 7.4. (Continued)



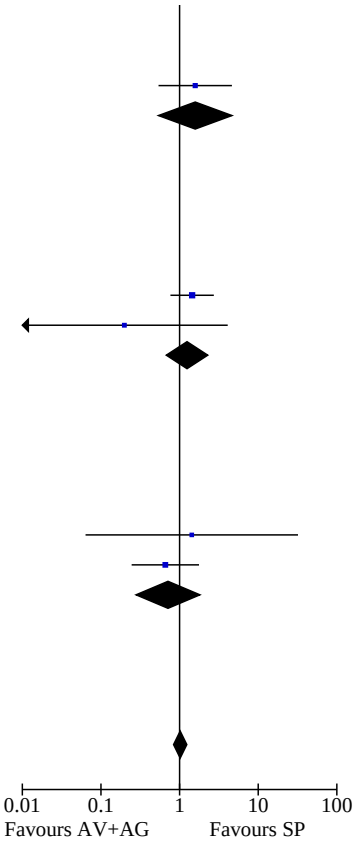
7.4.7 Hypotensive disorders						
Mulenga 1999	6	82	14	81	8.1%	0.42 [0.17 , 1.05]
Subtotal (95% CI)		**82**		**81**	**8.1%**	**0.42 [0.17 , 1.05]**
Total events:	6		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.86 (P = 0.06)						
7.4.8 Seizure and seizure disorders						
Llanos-Cuentas 2001 (1)	1	20	0	9	0.4%	1.43 [0.06 , 32.05]
Mulenga 2006	0	128	1	127	0.9%	0.33 [0.01 , 8.04]
Subtotal (95% CI)		**148**		**136**	**1.3%**	**0.67 [0.08 , 5.43]**
Total events:	1		1			
Heterogeneity: Chi² = 0.42, df = 1 (P = 0.52); I² = 0%						
Test for overall effect: Z = 0.37 (P = 0.71)						
7.4.9 Appetite disorders						
Llanos-Cuentas 2001 (1)	2	20	0	9	0.4%	2.38 [0.13 , 45.11]
Mulenga 1999	6	82	4	81	2.3%	1.48 [0.43 , 5.06]
Subtotal (95% CI)		**102**		**90**	**2.7%**	**1.61 [0.52 , 5.00]**
Total events:	8		4			
Heterogeneity: Chi² = 0.09, df = 1 (P = 0.77); I² = 0%						
Test for overall effect: Z = 0.83 (P = 0.41)						
7.4.10 Hepatobiliary signs and symptoms						
Mulenga 1999	5	82	5	81	2.9%	0.99 [0.30 , 3.28]
Subtotal (95% CI)		**82**		**81**	**2.9%**	**0.99 [0.30 , 3.28]**
Total events:	5		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.98)						
7.4.11 Pruritis						
Llanos-Cuentas 2001 (1)	0	20	1	9	1.2%	0.16 [0.01 , 3.56]
Mulenga 1999	4	82	1	81	0.6%	3.95 [0.45 , 34.60]
Subtotal (95% CI)		**102**		**90**	**1.8%**	**1.41 [0.35 , 5.67]**
Total events:	4		2			
Heterogeneity: Chi² = 2.76, df = 1 (P = 0.10); I² = 64%						
Test for overall effect: Z = 0.49 (P = 0.62)						
7.4.12 Spleen disorders						
Mulenga 1999	3	82	2	81	1.2%	1.48 [0.25 , 8.64]
Subtotal (95% CI)		**82**		**81**	**1.2%**	**1.48 [0.25 , 8.64]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.44 (P = 0.66)						
7.4.13 Cardiac signs and symptoms						
Mulenga 1999	3	82	0	81	0.3%	6.92 [0.36 , 131.79]
Subtotal (95% CI)		**82**		**81**	**0.3%**	**6.92 [0.36 , 131.79]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.29 (P = 0.20)						
7.4.14 Disturbances in initiating and maintaining sleep						
Llanos-Cuentas 2001 (1)	3	20	4	9	3.2%	0.34 [0.09 , 1.21]
Subtotal (95% CI)		**20**		**9**	**3.2%**	**0.34 [0.09 , 1.21]**

Analysis 7.4. (Continued)

Llanos-Cuentas 2001 (1)	3	20	4	9	3.2%	0.34 [0.09 , 1.21]
Subtotal (95% CI)		**20**		**9**	**3.2%**	**0.34 [0.09 , 1.21]**
Total events:	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.67 (P = 0.09)						
7.4.15 Feelings and sensations						
Llanos-Cuentas 2001 (1)	1	20	0	9	0.4%	1.43 [0.06 , 32.05]
Subtotal (95% CI)		**20**		**9**	**0.4%**	**1.43 [0.06 , 32.05]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.22 (P = 0.82)						
7.4.16 Rubeola viral infections						
Mulenga 2006	2	128	3	127	1.7%	0.66 [0.11 , 3.89]
Subtotal (95% CI)		**128**		**127**	**1.7%**	**0.66 [0.11 , 3.89]**
Total events:	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						
7.4.17 Hypoglycaemic conditions						
Mulenga 2006	2	128	0	127	0.3%	4.96 [0.24 , 102.33]
Subtotal (95% CI)		**128**		**127**	**0.3%**	**4.96 [0.24 , 102.33]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						
7.4.18 Lower respiratory tract and lung infections						
Mulenga 2006	5	128	2	127	1.2%	2.48 [0.49 , 12.55]
Subtotal (95% CI)		**128**		**127**	**1.2%**	**2.48 [0.49 , 12.55]**
Total events:	5		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.10 (P = 0.27)						
7.4.19 Anaemias						
Mulenga 2006	1	128	0	127	0.3%	2.98 [0.12 , 72.39]
Subtotal (95% CI)		**128**		**127**	**0.3%**	**2.98 [0.12 , 72.39]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
7.4.20 Sepsis, bacteraemia, viraemia, fungaemia						
Mulenga 2006	1	128	3	127	1.7%	0.33 [0.03 , 3.14]
Subtotal (95% CI)		**128**		**127**	**1.7%**	**0.33 [0.03 , 3.14]**
Total events:	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.96 (P = 0.34)						
7.4.21 Breathing abnormalities						
Mulenga 2006	0	128	5	127	3.2%	0.09 [0.01 , 1.61]
Subtotal (95% CI)		**128**		**127**	**3.2%**	**0.09 [0.01 , 1.61]**
Total events:	0		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.63 (P = 0.10)						
7.4.22 Muscle pains						



Analysis 7.4. (Continued)



7.4.22 Muscle pains						
Mulenga 1999	8	82	5	81	2.9%	1.58 [0.54 , 4.63]
Subtotal (95% CI)		**82**		**81**	**2.9%**	**1.58 [0.54 , 4.63]**
Total events:	8		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.84 (P = 0.40)						
7.4.23 Asthenic conditions						
Mulenga 1999 (5)	19	82	13	81	7.5%	1.44 [0.76 , 2.72]
Mulenga 2006 (5)	0	128	2	127	1.4%	0.20 [0.01 , 4.09]
Subtotal (95% CI)		**210**		**208**	**9.0%**	**1.24 [0.68 , 2.28]**
Total events:	19		15			
Heterogeneity: Chi² = 1.62, df = 1 (P = 0.20); I² = 38%						
Test for overall effect: Z = 0.70 (P = 0.48)						
7.4.24 Dizziness						
Llanos-Cuentas 2001 (1)	1	20	0	9	0.4%	1.43 [0.06 , 32.05]
Mulenga 1999	6	82	9	81	5.2%	0.66 [0.25 , 1.77]
Subtotal (95% CI)		**102**		**90**	**5.6%**	**0.71 [0.28 , 1.81]**
Total events:	7		9			
Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.71 (P = 0.48)						
Total (95% CI)		**2858**		**2711**	**100.0%**	**1.02 [0.84 , 1.23]**
Total events:	181		162			
Heterogeneity: Chi² = 30.00, df = 32 (P = 0.57); I² = 0%						
Test for overall effect: Z = 0.18 (P = 0.86)						
Test for subgroup differences: Chi² = 23.28, df = 23 (P = 0.44), I² = 1.2%						

Footnotes

(1) Denominator for AV+PG formed from addition of 'phase 1' and 'phase 2' trial data.
(2) AV+PG group: 6 deaths. SP group: 1 death.
(3) Denominator for AV+PG formed from addition of 'phase 1' and 'phase 2' trial data. Included adverse event 'vomiting' only (not 'nausea').
(4) Included adverse event 'vomiting' only (not 'nausea').
(5) Original reported symptom 'lethargy'.

Comparison 8. Atovaquone-proguanil (AV+PG) versus quinine (QN)

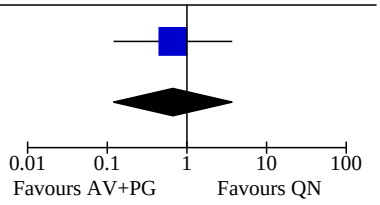
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
8.1 Total failure day 28 PCR-adjusted	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.12, 3.71]
8.2 Total failure day 42 PCR-unadjusted	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.06, 1.26]
8.3 Early treatment failure	1	66	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8.4 Adverse events	1	660	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.44, 1.49]
8.4.1 Serious adverse events	1	60	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.4.2 Adverse events leading to withdrawal	1	60	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8.4.3 Inner ear signs and symptoms	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.87]
8.4.4 Febrile disorders	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.16, 2.29]
8.4.5 Feelings and sensations	1	60	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.33, 27.23]
8.4.6 Headaches	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.41, 3.51]
8.4.7 Nausea and vomiting	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.05, 5.22]
8.4.8 Diarrhoea	1	60	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.13, 70.83]
8.4.9 Appetite disorders	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.87]
8.4.10 Hearing problem	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.87]
8.4.11 Auditory nerve disorders	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 3.03]

Analysis 8.1. Comparison 8: Atovaquone-proguanil (AV+PG) versus quinine (QN), Outcome 1: Total failure day 28 PCR-adjusted

Study or Subgroup	AV+PG Events	AV+PG Total	QN Events	QN Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gurkov 2008	2	30	3	30	100.0%	0.67 [0.12 , 3.71]
Total (95% CI)		**30**		**30**	**100.0%**	**0.67 [0.12 , 3.71]**
Total events:	2		3			

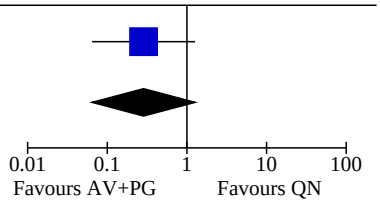
Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.64)
Test for subgroup differences: Not applicable



Analysis 8.2. Comparison 8: Atovaquone-proguanil (AV+PG) versus quinine (QN), Outcome 2: Total failure day 42 PCR-unadjusted

Study or Subgroup	AV+PG Events	AV+PG Total	QN Events	QN Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gurkov 2008 (1)	2	30	7	30	100.0%	0.29 [0.06 , 1.26]
Total (95% CI)		**30**		**30**	**100.0%**	**0.29 [0.06 , 1.26]**
Total events:	2		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.65 (P = 0.10)
Test for subgroup differences: Not applicable

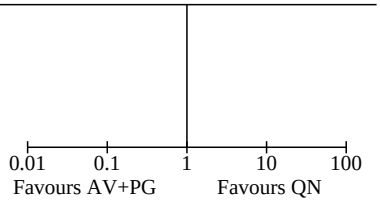


Footnotes
(1) Denominator formed from number of participants at day 28 (unclear rate of drop out by day 42).

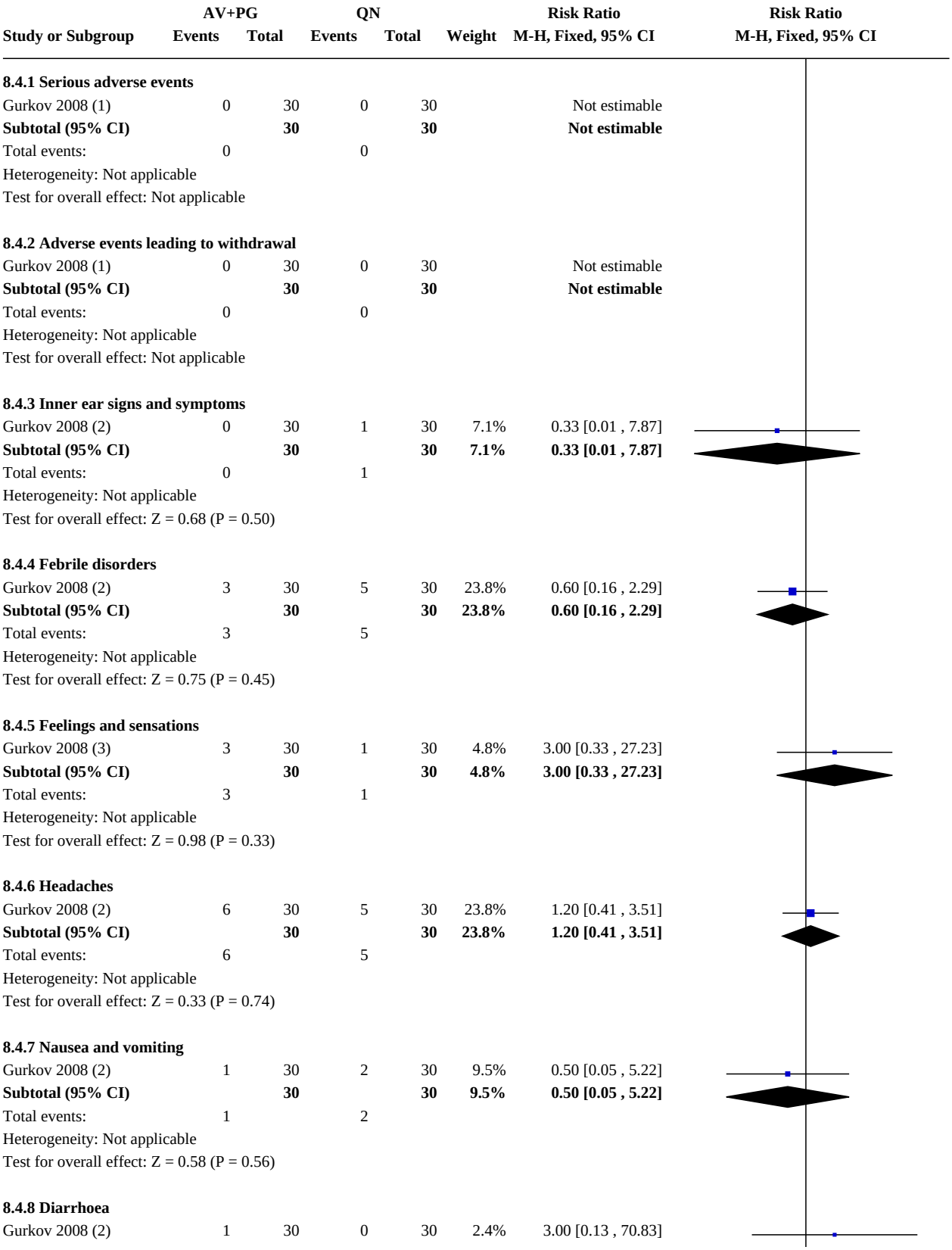
Analysis 8.3. Comparison 8: Atovaquone-proguanil (AV+PG) versus quinine (QN), Outcome 3: Early treatment failure

Study or Subgroup	AV+PG Events	AV+PG Total	QN Events	QN Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gurkov 2008	0	32	0	34		Not estimable
Total (95% CI)		**32**		**34**		**Not estimable**
Total events:	0		0			

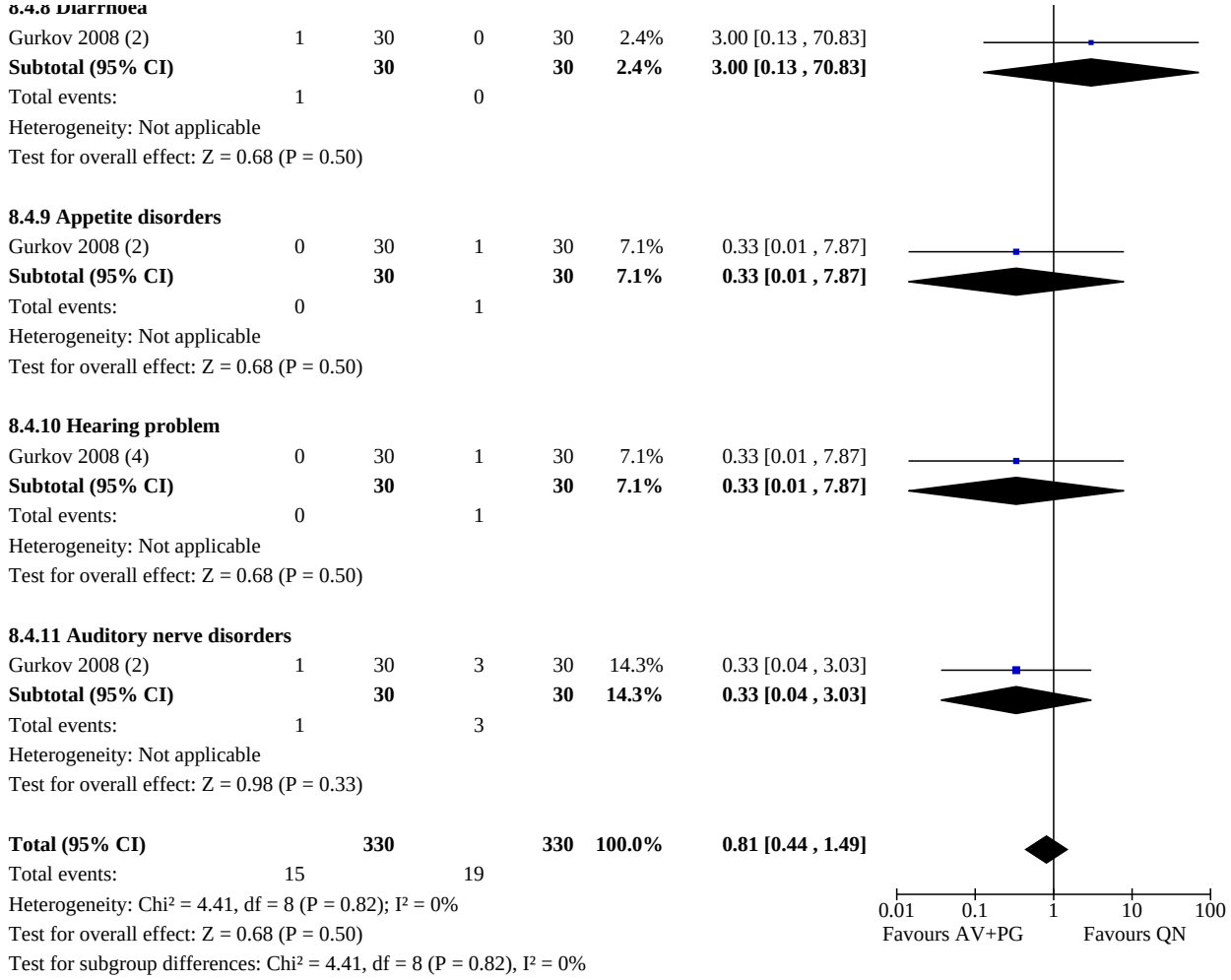
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 8.4. Comparison 8: Atovaquone-proguanil (AV+PG) versus quinine (QN), Outcome 4: Adverse events



Analysis 8.4. (Continued)



Footnotes

(1) Denominator formed from number of participants with adverse events at day 28.
(2) Denominator formed from number of participants with adverse event at day 28.
(3) Denominator formed from number of participants with adverse event at day 28. Original symptom term 'shivering'.
(4) Denominator formed from number of participants with adverse event at day 28. No medDRA term.

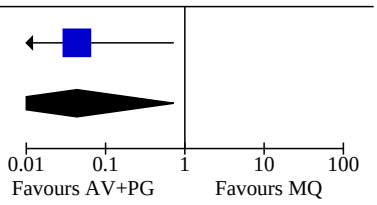
Comparison 9. Atovaquone-proguanil (AV+PG) versus mefloquine (MQ)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Total failure day 28 PCR-unadjusted	1	158	Risk Ratio (M-H, Fixed, 95% CI)	0.04 [0.00, 0.73]
9.2 Early treatment failure	1	158	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.3 Adverse events	1	2184	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.75, 1.66]
9.3.1 Serious adverse events	1	182	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.3.2 Adverse events leading to withdrawal	1	182	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.08]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
9.3.3 Diarrhoea	1	182	Risk Ratio (M-H, Fixed, 95% CI)	2.50 [0.50, 12.56]
9.3.4 Gastrointestinal and abdominal pains	1	182	Risk Ratio (M-H, Fixed, 95% CI)	5.00 [0.24, 102.72]
9.3.5 Nausea and vomiting	1	182	Risk Ratio (M-H, Fixed, 95% CI)	4.50 [1.00, 20.26]
9.3.6 Appetite disorders	1	182	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 4.11]
9.3.7 Headaches	1	182	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 4.11]
9.3.8 Dizziness	1	182	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 4.11]
9.3.9 Anaemias	1	182	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.23, 1.29]
9.3.10 Abnormal liver function tests	1	182	Risk Ratio (M-H, Fixed, 95% CI)	2.50 [1.02, 6.16]
9.3.11 Disturbances in initiating and main-taining sleep	1	182	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.73]
9.3.12 Oral soft tissue signs and symptoms	1	182	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.37, 2.74]

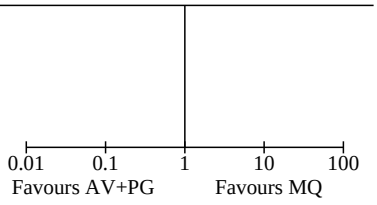
Analysis 9.1. Comparison 9: Atovaquone-proguanil (AV+PG) versus mefloquine (MQ), Outcome 1: Total failure day 28 PCR-unadjusted

	AV+PG		MQ			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Looareesuwan 1999	0	79	11	79	100.0%	0.04 [0.00 , 0.73]	
Total (95% CI)		**79**		**79**	**100.0%**	**0.04 [0.00 , 0.73]**	
Total events:	0		11				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.18 (P = 0.03)							
Test for subgroup differences: Not applicable							



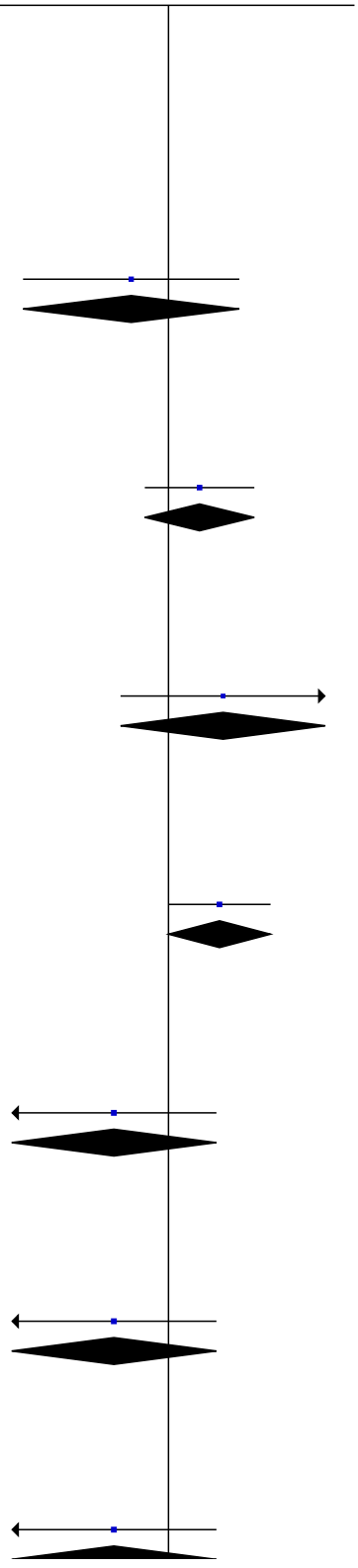
Analysis 9.2. Comparison 9: Atovaquone-proguanil (AV+PG) versus mefloquine (MQ), Outcome 2: Early treatment failure

	AV+PG		MQ			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Looareesuwan 1999	0	79	0	79		Not estimable	
Total (95% CI)		**79**		**79**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							



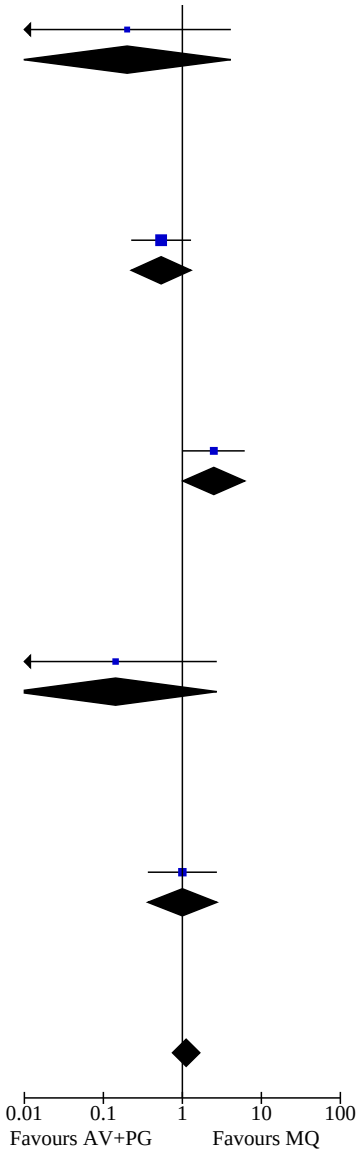
Analysis 9.3. Comparison 9: Atovaquone-proguanil (AV+PG) versus mefloquine (MQ), Outcome 3: Adverse events

Study or Subgroup	AV+PG Events	AV+PG Total	MQ Events	MQ Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.3.1 Serious adverse events						
Looareesuwan 1999	0	91	0	91		Not estimable
Subtotal (95% CI)		**91**		**91**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.3.2 Adverse events leading to withdrawal						
Looareesuwan 1999	0	91	1	91	3.5%	0.33 [0.01 , 8.08]
Subtotal (95% CI)		**91**		**91**	**3.5%**	**0.33 [0.01 , 8.08]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
9.3.3 Diarrhoea						
Looareesuwan 1999	5	91	2	91	4.7%	2.50 [0.50 , 12.56]
Subtotal (95% CI)		**91**		**91**	**4.7%**	**2.50 [0.50 , 12.56]**
Total events:	5		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.11 (P = 0.27)						
9.3.4 Gastrointestinal and abdominal pains						
Looareesuwan 1999	2	91	0	91	1.2%	5.00 [0.24 , 102.72]
Subtotal (95% CI)		**91**		**91**	**1.2%**	**5.00 [0.24 , 102.72]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						
9.3.5 Nausea and vomiting						
Looareesuwan 1999 (1)	9	91	2	91	4.7%	4.50 [1.00 , 20.26]
Subtotal (95% CI)		**91**		**91**	**4.7%**	**4.50 [1.00 , 20.26]**
Total events:	9		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.96 (P = 0.05)						
9.3.6 Appetite disorders						
Looareesuwan 1999	0	91	2	91	5.8%	0.20 [0.01 , 4.11]
Subtotal (95% CI)		**91**		**91**	**5.8%**	**0.20 [0.01 , 4.11]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						
9.3.7 Headaches						
Looareesuwan 1999	0	91	2	91	5.8%	0.20 [0.01 , 4.11]
Subtotal (95% CI)		**91**		**91**	**5.8%**	**0.20 [0.01 , 4.11]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						
9.3.8 Dizziness						
Looareesuwan 1999	0	91	2	91	5.8%	0.20 [0.01 , 4.11]
Subtotal (95% CI)		**91**		**91**	**5.8%**	**0.20 [0.01 , 4.11]**



Analysis 9.3. (Continued)

Looareesuwan 1999	0	91	2	91	5.8%	0.20 [0.01 , 4.11]
Subtotal (95% CI)		**91**		**91**	**5.8%**	**0.20 [0.01 , 4.11]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						
9.3.9 Anaemias						
Looareesuwan 1999	7	91	13	91	30.2%	0.54 [0.23 , 1.29]
Subtotal (95% CI)		**91**		**91**	**30.2%**	**0.54 [0.23 , 1.29]**
Total events:	7		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.39 (P = 0.16)						
9.3.10 Abnormal liver function tests						
Looareesuwan 1999	15	91	6	91	14.0%	2.50 [1.02 , 6.16]
Subtotal (95% CI)		**91**		**91**	**14.0%**	**2.50 [1.02 , 6.16]**
Total events:	15		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.99 (P = 0.05)						
9.3.11 Disturbances in initiating and maintaining sleep						
Looareesuwan 1999	0	91	3	91	8.1%	0.14 [0.01 , 2.73]
Subtotal (95% CI)		**91**		**91**	**8.1%**	**0.14 [0.01 , 2.73]**
Total events:	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.29 (P = 0.20)						
9.3.12 Oral soft tissue signs and symptoms						
Looareesuwan 1999	7	91	7	91	16.3%	1.00 [0.37 , 2.74]
Subtotal (95% CI)		**91**		**91**	**16.3%**	**1.00 [0.37 , 2.74]**
Total events:	7		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**1092**		**1092**	**100.0%**	**1.12 [0.75 , 1.66]**
Total events:	45		40			
Heterogeneity: Chi² = 17.16, df = 10 (P = 0.07); I² = 42%						
Test for overall effect: Z = 0.54 (P = 0.59)						
Test for subgroup differences: Chi² = 17.15, df = 10 (P = 0.07), I² = 41.7%						



Footnotes

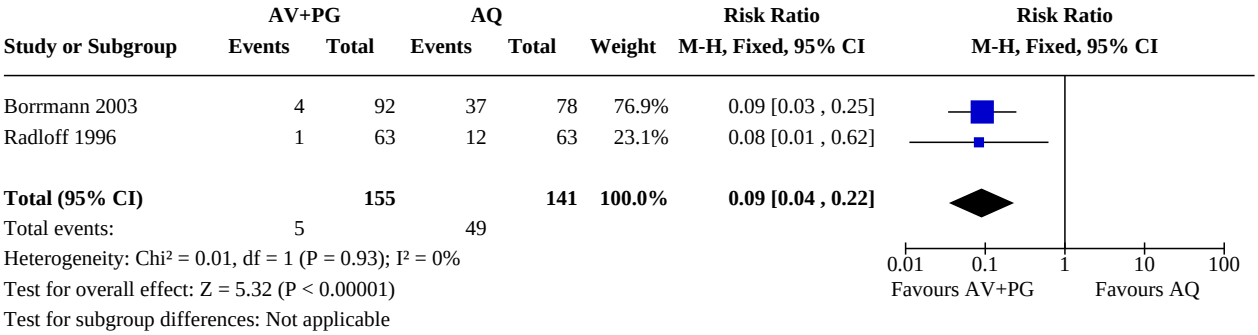
(1) Included adverse event 'vomiting' only (not 'nausea').

Comparison 10. Atovaquone-proguanil (AV+PG) versus amodiaquine (AQ)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Total failure day 28 PCR-unadjusted	2	296	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.04, 0.22]
10.2 Early treatment failure	1	170	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.03, 2.66]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.3 Adverse events	2	2860	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.59, 0.96]
10.3.1 Serious adverse events	2	326	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.73]
10.3.2 Adverse events leading to withdrawal	2	326	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.12, 72.77]
10.3.3 Diarrhoea	2	326	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.57, 1.61]
10.3.4 Nausea and vomiting	2	326	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [1.05, 3.33]
10.3.5 Asthenic conditions	2	326	Risk Ratio (M-H, Fixed, 95% CI)	0.12 [0.02, 0.64]
10.3.6 Respiratory tract infections	1	200	Risk Ratio (M-H, Fixed, 95% CI)	9.00 [0.49, 165.00]
10.3.7 Pruritis	1	126	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.04, 0.35]
10.3.8 Disturbances in initiating and maintaining sleep	1	126	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.12, 0.75]
10.3.9 Gastrointestinal and abdominal pains	1	126	Risk Ratio (M-H, Fixed, 95% CI)	2.80 [1.07, 7.31]
10.3.10 Appetite disorders	1	126	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.30, 3.29]
10.3.11 Coughing and associated symptoms	1	200	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.53, 2.17]
10.3.12 Upper respiratory tract infections	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.20]
10.3.13 Dizziness	1	126	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.08, 0.93]

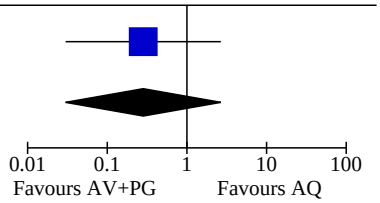
Analysis 10.1. Comparison 10: Atovaquone-proguanil (AV+PG) versus amodiaquine (AQ), Outcome 1: Total failure day 28 PCR-unadjusted



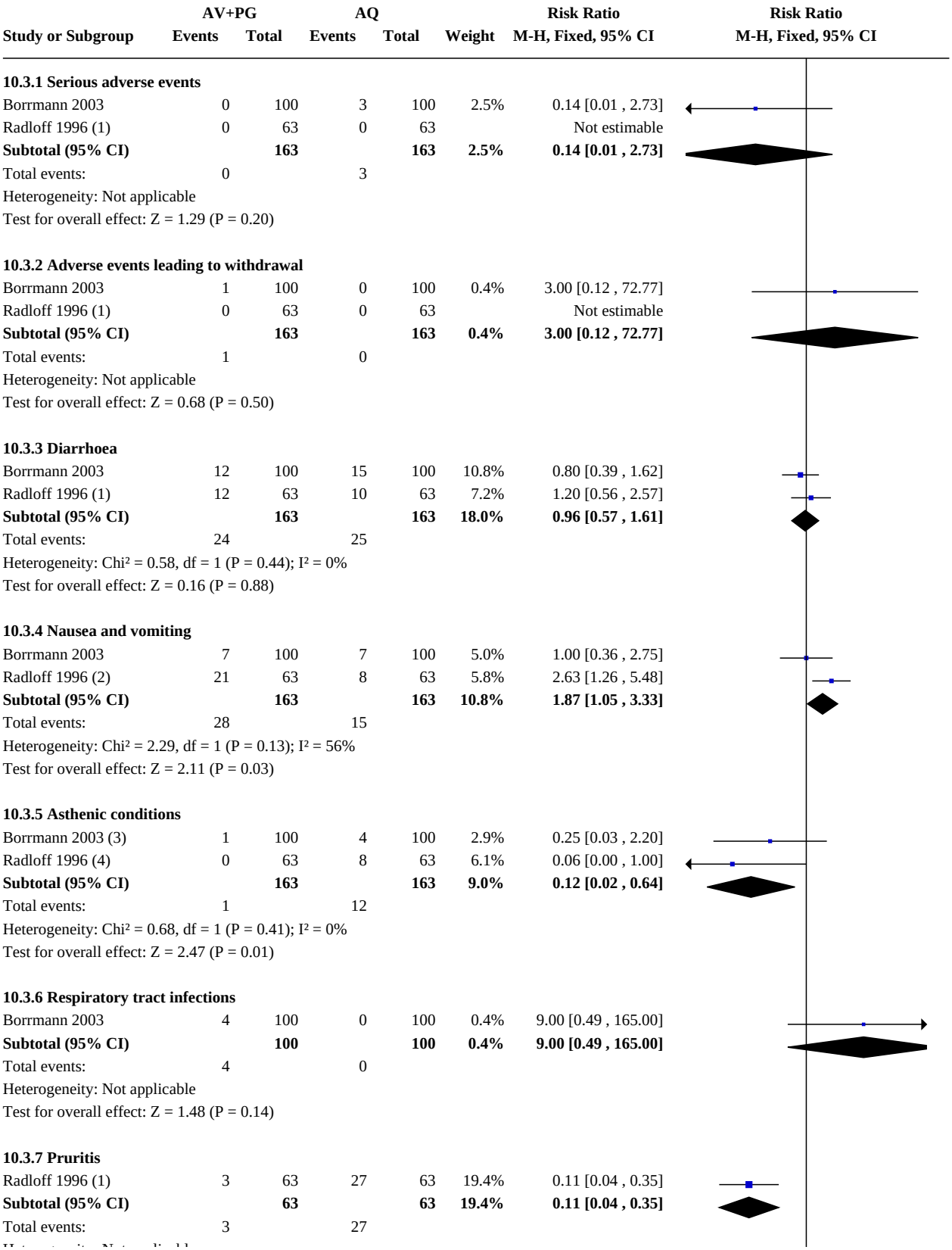
Analysis 10.2. Comparison 10: Atovaquone-proguanil (AV+PG) versus amodiaquine (AQ), Outcome 2: Early treatment failure

Study or Subgroup	AV+PG Events	AV+PG Total	AQ Events	AQ Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Borrmann 2003	1	92	3	78	100.0%	0.28 [0.03 , 2.66]
Total (95% CI)		**92**		**78**	**100.0%**	**0.28 [0.03 , 2.66]**
Total events:	1		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.10 (P = 0.27)
Test for subgroup differences: Not applicable

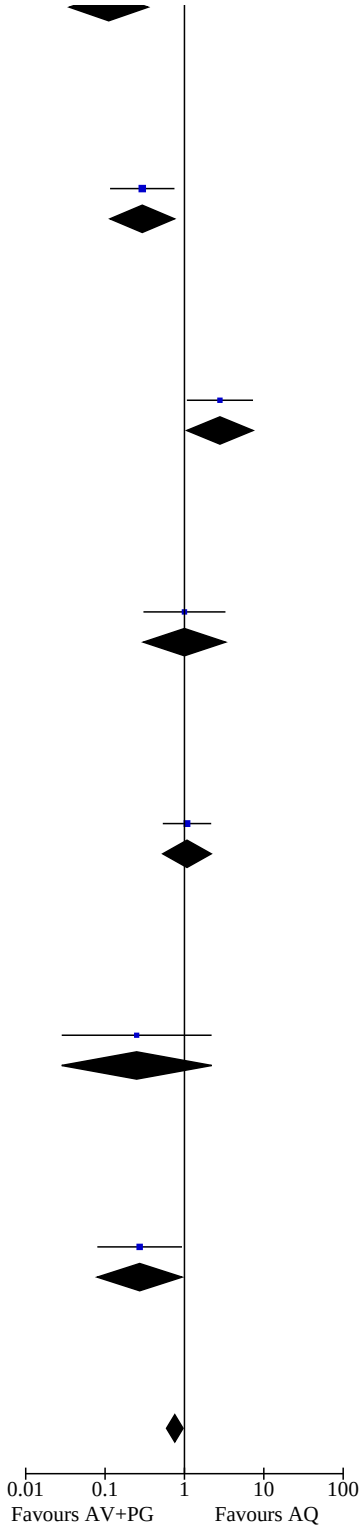


Analysis 10.3. Comparison 10: Atovaquone-proguanil (AV+PG) versus amodiaquine (AQ), Outcome 3: Adverse events



Analysis 10.3. (Continued)

Total events:	3		27				
Heterogeneity: Not applicable							
Test for overall effect: Z = 3.78 (P = 0.0002)							
10.3.8 Disturbances in initiating and maintaining sleep							
Radloff 1996 (1)	5	63	17	63	12.2%	0.29 [0.12 , 0.75]	
Subtotal (95% CI)		**63**		**63**	**12.2%**	**0.29 [0.12 , 0.75]**	
Total events:	5		17				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.57 (P = 0.01)							
10.3.9 Gastrointestinal and abdominal pains							
Radloff 1996 (1)	14	63	5	63	3.6%	2.80 [1.07 , 7.31]	
Subtotal (95% CI)		**63**		**63**	**3.6%**	**2.80 [1.07 , 7.31]**	
Total events:	14		5				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.10 (P = 0.04)							
10.3.10 Appetite disorders							
Radloff 1996 (1)	5	63	5	63	3.6%	1.00 [0.30 , 3.29]	
Subtotal (95% CI)		**63**		**63**	**3.6%**	**1.00 [0.30 , 3.29]**	
Total events:	5		5				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.00 (P = 1.00)							
10.3.11 Coughing and associated symptoms							
Borrmann 2003	14	100	13	100	9.4%	1.08 [0.53 , 2.17]	
Subtotal (95% CI)		**100**		**100**	**9.4%**	**1.08 [0.53 , 2.17]**	
Total events:	14		13				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.21 (P = 0.84)							
10.3.12 Upper respiratory tract infections							
Borrmann 2003 (5)	1	100	4	100	2.9%	0.25 [0.03 , 2.20]	
Subtotal (95% CI)		**100**		**100**	**2.9%**	**0.25 [0.03 , 2.20]**	
Total events:	1		4				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.25 (P = 0.21)							
10.3.13 Dizziness							
Radloff 1996 (6)	3	63	11	63	7.9%	0.27 [0.08 , 0.93]	
Subtotal (95% CI)		**63**		**63**	**7.9%**	**0.27 [0.08 , 0.93]**	
Total events:	3		11				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.07 (P = 0.04)							
Total (95% CI)		**1430**		**1430**	**100.0%**	**0.76 [0.59 , 0.96]**	
Total events:	103		137				
Heterogeneity: Chi² = 48.36, df = 15 (P < 0.0001); I² = 69%							
Test for overall effect: Z = 2.30 (P = 0.02)							
Test for subgroup differences: Chi² = 45.13, df = 12 (P < 0.00001), I² = 73.4%							



Footnotes

(1) Denominator formed from participants completing treatment.

Analysis 10.3. (Continued)

Footnotes

(1) Denominator formed from participants completing treatment.
(2) Denominator formed from participants completing treatment. Includes adverse event 'nausea' only (not 'vomiting').
(3) Originally reported symptom 'weakness'.
(4) Denominator formed from participants completing treatment. Originally reported symptom 'weakness'.
(5) Included adverse event 'common cold' only (not 'respiratory tract infection').
(6) Denominator formed from patients completing treatment.

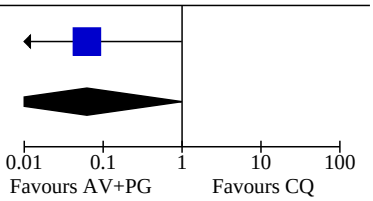
Comparison 11. Atovaquone-proguanil (AV+PG) versus chloroquine (CQ)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Total failure day 28 PCR-unadjusted	1	27	Risk Ratio (M-H, Fixed, 95% CI)	0.06 [0.00, 0.99]
11.2 Early treatment failure	1	27	Risk Ratio (M-H, Fixed, 95% CI)	0.08 [0.01, 1.40]
11.3 Adverse events	1	442	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.36, 0.96]
11.3.1 Serious adverse events	1	34	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.3.2 Adverse events leading to withdrawal	1	34	Risk Ratio (M-H, Fixed, 95% CI)	2.14 [0.09, 49.08]
11.3.3 Gastrointestinal and abdominal pains	1	34	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [0.39, 7.77]
11.3.4 Nausea and vomiting	1	34	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.44, 3.40]
11.3.5 Dizziness	1	34	Risk Ratio (M-H, Fixed, 95% CI)	2.14 [0.09, 49.08]
11.3.6 Asthenic conditions	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.06 [0.00, 1.09]
11.3.7 Appetite disorders	1	34	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.14, 13.98]
11.3.8 Pruritis	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.01, 1.83]
11.3.9 Cardiac signs and symptoms	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.01, 1.83]
11.3.10 Feelings and sensations	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.04, 3.50]
11.3.11 Seizures and seizure disorders	1	34	Risk Ratio (M-H, Fixed, 95% CI)	2.14 [0.09, 49.08]
11.3.12 Headaches	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.05, 0.99]
11.3.13 Disturbances in initiating and maintaining sleep	1	34	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.20, 5.49]

Analysis 11.1. Comparison 11: Atovaquone-proguanil (AV+PG) versus chloroquine (CQ), Outcome 1: Total failure day 28 PCR-unadjusted

Study or Subgroup	AV+PG Events	AV+PG Total	CQ Events	CQ Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Llanos-Cuentas 2001	0	14	7	13	100.0%	0.06 [0.00 , 0.99]
Total (95% CI)		**14**		**13**	**100.0%**	**0.06 [0.00 , 0.99]**
Total events:	0		7			

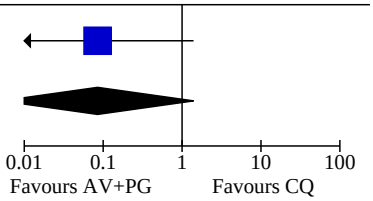
Heterogeneity: Not applicable
Test for overall effect: Z = 1.97 (P = 0.05)
Test for subgroup differences: Not applicable



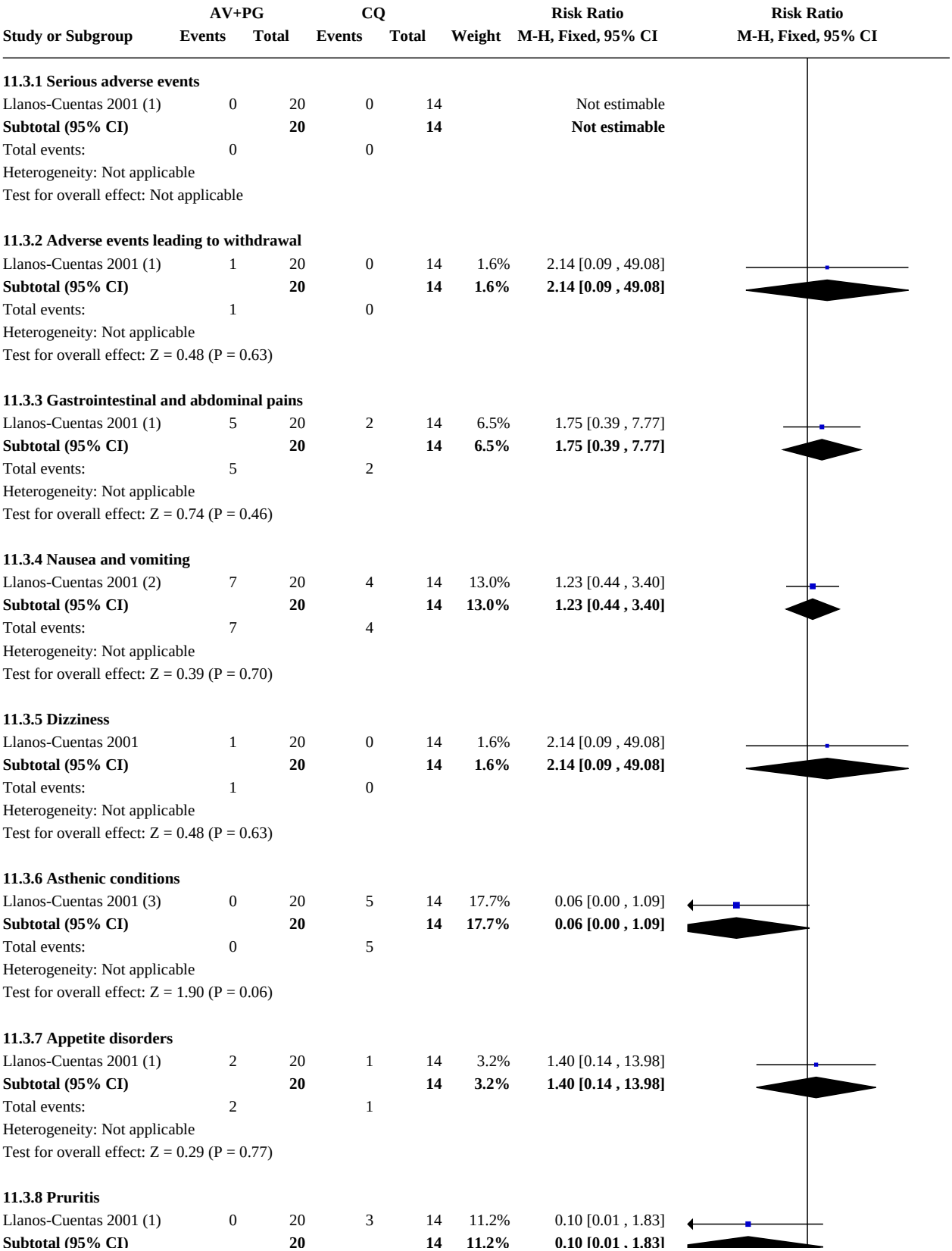
Analysis 11.2. Comparison 11: Atovaquone-proguanil (AV +PG) versus chloroquine (CQ), Outcome 2: Early treatment failure

Study or Subgroup	AV+PG Events	AV+PG Total	CQ Events	CQ Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Llanos-Cuentas 2001	0	14	5	13	100.0%	0.08 [0.01 , 1.40]
Total (95% CI)		**14**		**13**	**100.0%**	**0.08 [0.01 , 1.40]**
Total events:	0		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.73 (P = 0.08)
Test for subgroup differences: Not applicable



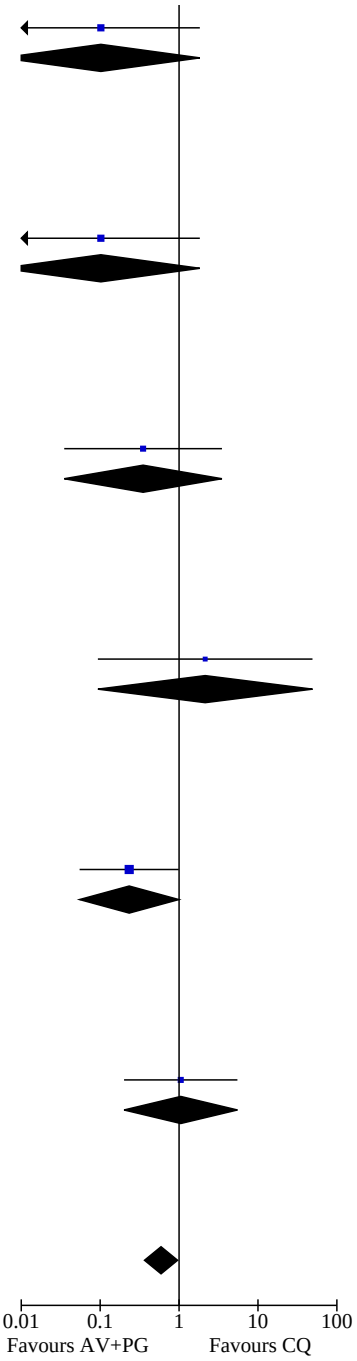
Analysis 11.3. Comparison 11: Atovaquone-proguanil (AV+PG) versus chloroquine (CQ), Outcome 3: Adverse events



Study or Subgroup	AV+PG Events	AV+PG Total	CQ Events	CQ Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.3.1 Serious adverse events						
Llanos-Cuentas 2001 (1)	0	20	0	14		Not estimable
Subtotal (95% CI)		**20**		**14**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
11.3.2 Adverse events leading to withdrawal						
Llanos-Cuentas 2001 (1)	1	20	0	14	1.6%	2.14 [0.09 , 49.08]
Subtotal (95% CI)		**20**		**14**	**1.6%**	**2.14 [0.09 , 49.08]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.48 (P = 0.63)						
11.3.3 Gastrointestinal and abdominal pains						
Llanos-Cuentas 2001 (1)	5	20	2	14	6.5%	1.75 [0.39 , 7.77]
Subtotal (95% CI)		**20**		**14**	**6.5%**	**1.75 [0.39 , 7.77]**
Total events:	5		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.74 (P = 0.46)						
11.3.4 Nausea and vomiting						
Llanos-Cuentas 2001 (2)	7	20	4	14	13.0%	1.23 [0.44 , 3.40]
Subtotal (95% CI)		**20**		**14**	**13.0%**	**1.23 [0.44 , 3.40]**
Total events:	7		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.70)						
11.3.5 Dizziness						
Llanos-Cuentas 2001	1	20	0	14	1.6%	2.14 [0.09 , 49.08]
Subtotal (95% CI)		**20**		**14**	**1.6%**	**2.14 [0.09 , 49.08]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.48 (P = 0.63)						
11.3.6 Asthenic conditions						
Llanos-Cuentas 2001 (3)	0	20	5	14	17.7%	0.06 [0.00 , 1.09]
Subtotal (95% CI)		**20**		**14**	**17.7%**	**0.06 [0.00 , 1.09]**
Total events:	0		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.90 (P = 0.06)						
11.3.7 Appetite disorders						
Llanos-Cuentas 2001 (1)	2	20	1	14	3.2%	1.40 [0.14 , 13.98]
Subtotal (95% CI)		**20**		**14**	**3.2%**	**1.40 [0.14 , 13.98]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.29 (P = 0.77)						
11.3.8 Pruritis						
Llanos-Cuentas 2001 (1)	0	20	3	14	11.2%	0.10 [0.01 , 1.83]
Subtotal (95% CI)		**20**		**14**	**11.2%**	**0.10 [0.01 , 1.83]**

Analysis 11.3. (Continued)

Llanos-Cuentas 2001 (1)	0	20	3	14	11.2%	0.10 [0.01 , 1.83]
Subtotal (95% CI)		**20**		**14**	**11.2%**	**0.10 [0.01 , 1.83]**
Total events:	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.55 (P = 0.12)						
11.3.9 Cardiac signs and symptoms						
Llanos-Cuentas 2001 (1)	0	20	3	14	11.2%	0.10 [0.01 , 1.83]
Subtotal (95% CI)		**20**		**14**	**11.2%**	**0.10 [0.01 , 1.83]**
Total events:	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.55 (P = 0.12)						
11.3.10 Feelings and sensations						
Llanos-Cuentas 2001 (4)	1	20	2	14	6.5%	0.35 [0.04 , 3.50]
Subtotal (95% CI)		**20**		**14**	**6.5%**	**0.35 [0.04 , 3.50]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.89 (P = 0.37)						
11.3.11 Seizures and seizure disorders						
Llanos-Cuentas 2001 (1)	1	20	0	14	1.6%	2.14 [0.09 , 49.08]
Subtotal (95% CI)		**20**		**14**	**1.6%**	**2.14 [0.09 , 49.08]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.48 (P = 0.63)						
11.3.12 Headaches						
Llanos-Cuentas 2001 (1)	2	20	6	14	19.4%	0.23 [0.05 , 0.99]
Subtotal (95% CI)		**20**		**14**	**19.4%**	**0.23 [0.05 , 0.99]**
Total events:	2		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.97 (P = 0.05)						
11.3.13 Disturbances in initiating and maintaining sleep						
Llanos-Cuentas 2001 (1)	3	20	2	14	6.5%	1.05 [0.20 , 5.49]
Subtotal (95% CI)		**20**		**14**	**6.5%**	**1.05 [0.20 , 5.49]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.06 (P = 0.95)						
Total (95% CI)		**260**		**182**	**100.0%**	**0.59 [0.36 , 0.96]**
Total events:	23		28			
Heterogeneity: Chi² = 13.93, df = 11 (P = 0.24); I² = 21%						
Test for overall effect: Z = 2.14 (P = 0.03)						
Test for subgroup differences: Chi² = 13.34, df = 11 (P = 0.27), I² = 17.5%						



Footnotes

(1) Denominator for AV+PG formed from addition of 'phase 1' and 'phase 2' trial data.
(2) Denominator for AV+PG formed from addition of 'phase 1' and 'phase 2' trial data. Included reported adverse event 'vomiting' only (not 'nausea').
(3) Denominator for AV+PG formed from addition of 'phase 1' and 'phase 2' trial data. Originally reported symptom 'weakness'.
(4) Denominator for AV+PG formed from addition of 'phase 1' and 'phase 2' trial data. Originally reported symptom 'chills/rigours'.

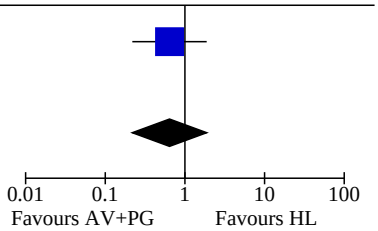
Comparison 12. Atovaquone-proguanil (AV+PG) versus halofantrine (HL)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Total failure day 28 PCR-unadjusted	2	205	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.22, 1.88]
12.2 Early treatment failure	2	54	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12.3 Adverse events	2	3072	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.62, 1.04]
12.3.1 Serious adverse events	2	216	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12.3.2 Adverse events leading to withdrawal	2	216	Risk Ratio (M-H, Fixed, 95% CI)	5.75 [0.71, 46.65]
12.3.3 Headaches	2	216	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.36, 1.50]
12.3.4 Nausea and vomiting	2	216	Risk Ratio (M-H, Fixed, 95% CI)	2.93 [1.36, 6.30]
12.3.5 Gastrointestinal and abdominal pains	2	216	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.27, 1.08]
12.3.6 Diarrhoea	2	216	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.23, 1.38]
12.3.7 Appetite disorders	1	168	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.10, 1.36]
12.3.8 Disturbances in initiating and maintaining sleep	2	216	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.22, 1.53]
12.3.9 Rashes, eruptions and exanthems	1	168	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.15, 2.43]
12.3.10 Feelings and sensations	1	168	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.11, 3.89]
12.3.11 Haemorrhages	1	168	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.02, 1.68]
12.3.12 Asthenic conditions	1	168	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.19]
12.3.13 Muscle pains	1	168	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.72]
12.3.14 Cardiac signs and symptoms	1	168	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.05, 5.41]
12.3.15 Pruritis	2	216	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.52, 2.90]
12.3.16 Coughing and associated symptoms	1	168	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.34, 1.52]

Analysis 12.1. Comparison 12: Atovaquone-proguanil (AV+PG) versus halofantrine (HL), Outcome 1: Total failure day 28 PCR-unadjusted

Study or Subgroup	AV+PG Events	AV+PG Total	HL Events	HL Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anabwani 1999	5	81	8	83	100.0%	0.64 [0.22 , 1.88]
Bouchaud 2000	0	21	0	20		Not estimable
Total (95% CI)		**102**		**103**	**100.0%**	**0.64 [0.22 , 1.88]**
Total events:	5		8			

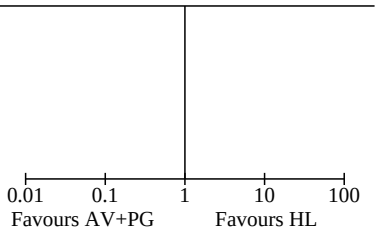
Heterogeneity: Not applicable
Test for overall effect: Z = 0.81 (P = 0.42)
Test for subgroup differences: Not applicable



Analysis 12.2. Comparison 12: Atovaquone-proguanil (AV +PG) versus halofantrine (HL), Outcome 2: Early treatment failure

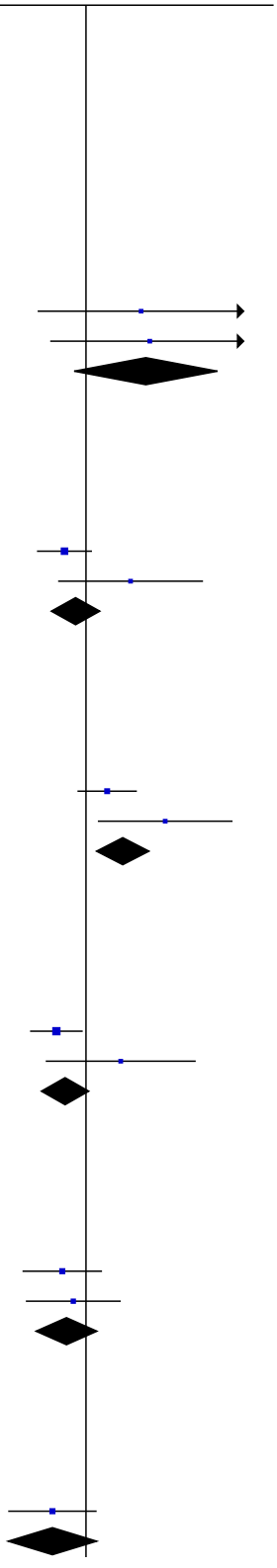
Study or Subgroup	AV+PG Events	AV+PG Total	HL Events	HL Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anabwani 1999	0	5	0	8		Not estimable
Bouchaud 2000	0	21	0	20		Not estimable
Total (95% CI)		**26**		**28**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



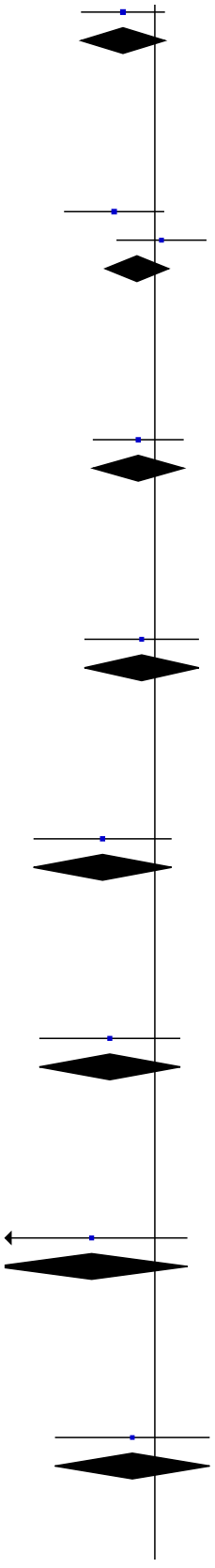
Analysis 12.3. Comparison 12: Atovaquone-proguanil (AV+PG) versus halofantrine (HL), Outcome 3: Adverse events

Study or Subgroup	AV+PG Events	AV+PG Total	HL Events	HL Total	Weight	Risk Ratio M-H, Fixed, 95% CI
12.3.1 Serious adverse events						
Anabwani 1999	0	84	0	84		Not estimable
Bouchaud 2000	0	25	0	23		Not estimable
Subtotal (95% CI)		**109**		**107**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
12.3.2 Adverse events leading to withdrawal						
Anabwani 1999	2	84	0	84	0.4%	5.00 [0.24 , 102.60]
Bouchaud 2000	3	25	0	23	0.4%	6.46 [0.35 , 118.71]
Subtotal (95% CI)		**109**		**107**	**0.8%**	**5.75 [0.71 , 46.65]**
Total events:	5		0			
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.90); I² = 0%						
Test for overall effect: Z = 1.64 (P = 0.10)						
12.3.3 Headaches						
Anabwani 1999	8	84	15	84	12.5%	0.53 [0.24 , 1.19]
Bouchaud 2000	4	25	1	23	0.9%	3.68 [0.44 , 30.56]
Subtotal (95% CI)		**109**		**107**	**13.3%**	**0.74 [0.36 , 1.50]**
Total events:	12		16			
Heterogeneity: Chi² = 2.84, df = 1 (P = 0.09); I² = 65%						
Test for overall effect: Z = 0.84 (P = 0.40)						
12.3.4 Nausea and vomiting						
Anabwani 1999	13	84	7	84	5.8%	1.86 [0.78 , 4.42]
Bouchaud 2000 (1)	11	25	1	23	0.9%	10.12 [1.42 , 72.37]
Subtotal (95% CI)		**109**		**107**	**6.7%**	**2.93 [1.36 , 6.30]**
Total events:	24		8			
Heterogeneity: Chi² = 2.58, df = 1 (P = 0.11); I² = 61%						
Test for overall effect: Z = 2.75 (P = 0.006)						
12.3.5 Gastrointestinal and abdominal pains						
Anabwani 1999	8	84	19	84	15.8%	0.42 [0.20 , 0.91]
Bouchaud 2000	3	25	1	23	0.9%	2.76 [0.31 , 24.69]
Subtotal (95% CI)		**109**		**107**	**16.6%**	**0.54 [0.27 , 1.08]**
Total events:	11		20			
Heterogeneity: Chi² = 2.54, df = 1 (P = 0.11); I² = 61%						
Test for overall effect: Z = 1.73 (P = 0.08)						
12.3.6 Diarrhoea						
Anabwani 1999	4	84	8	84	6.6%	0.50 [0.16 , 1.60]
Bouchaud 2000	3	25	4	23	3.5%	0.69 [0.17 , 2.76]
Subtotal (95% CI)		**109**		**107**	**10.1%**	**0.57 [0.23 , 1.38]**
Total events:	7		12			
Heterogeneity: Chi² = 0.12, df = 1 (P = 0.73); I² = 0%						
Test for overall effect: Z = 1.26 (P = 0.21)						
12.3.7 Appetite disorders						
Anabwani 1999	3	84	8	84	6.6%	0.38 [0.10 , 1.36]
Subtotal (95% CI)		**84**		**84**	**6.6%**	**0.38 [0.10 , 1.36]**



Analysis 12.3. (Continued)

Anabwani 1999	3	84	8	84	6.6%	0.38 [0.10 , 1.36]
Subtotal (95% CI)		**84**		**84**	**6.6%**	**0.38 [0.10 , 1.36]**
Total events:	3		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.49 (P = 0.14)						
12.3.8 Disturbances in initiating and maintaining sleep						
Anabwani 1999	2	84	7	84	5.8%	0.29 [0.06 , 1.34]
Bouchaud 2000	4	25	3	23	2.6%	1.23 [0.31 , 4.90]
Subtotal (95% CI)		**109**		**107**	**8.4%**	**0.58 [0.22 , 1.53]**
Total events:	6		10			
Heterogeneity: $Chi^2 = 1.94$, df = 1 (P = 0.16); $I^2 = 48\%$						
Test for overall effect: Z = 1.11 (P = 0.27)						
12.3.9 Rashes, eruptions and exanthems						
Anabwani 1999	3	84	5	84	4.2%	0.60 [0.15 , 2.43]
Subtotal (95% CI)		**84**		**84**	**4.2%**	**0.60 [0.15 , 2.43]**
Total events:	3		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
12.3.10 Feelings and sensations						
Anabwani 1999 (2)	2	84	3	84	2.5%	0.67 [0.11 , 3.89]
Subtotal (95% CI)		**84**		**84**	**2.5%**	**0.67 [0.11 , 3.89]**
Total events:	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.65)						
12.3.11 Haemorrhages						
Anabwani 1999 (3)	1	84	5	84	4.2%	0.20 [0.02 , 1.68]
Subtotal (95% CI)		**84**		**84**	**4.2%**	**0.20 [0.02 , 1.68]**
Total events:	1		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.48 (P = 0.14)						
12.3.12 Asthenic conditions						
Anabwani 1999 (4)	1	84	4	84	3.3%	0.25 [0.03 , 2.19]
Subtotal (95% CI)		**84**		**84**	**3.3%**	**0.25 [0.03 , 2.19]**
Total events:	1		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.25 (P = 0.21)						
12.3.13 Muscle pains						
Anabwani 1999	0	84	3	84	2.9%	0.14 [0.01 , 2.72]
Subtotal (95% CI)		**84**		**84**	**2.9%**	**0.14 [0.01 , 2.72]**
Total events:	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.29 (P = 0.20)						
12.3.14 Cardiac signs and symptoms						
Anabwani 1999	1	84	2	84	1.7%	0.50 [0.05 , 5.41]
Subtotal (95% CI)		**84**		**84**	**1.7%**	**0.50 [0.05 , 5.41]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						



Analysis 12.3. (Continued)

Heterogeneity: Not applicable
Test for overall effect: Z = 0.57 (P = 0.57)

12.3.15 Pruritis

Anabwani 1999	9	84	8	84	6.6%	1.13 [0.46 , 2.78]
Bouchaud 2000	1	25	0	23	0.4%	2.77 [0.12 , 64.76]
Subtotal (95% CI)		**109**		**107**	**7.1%**	**1.23 [0.52 , 2.90]**
Total events:	10		8			

Heterogeneity: Chi² = 0.29, df = 1 (P = 0.59); I² = 0%
Test for overall effect: Z = 0.46 (P = 0.64)

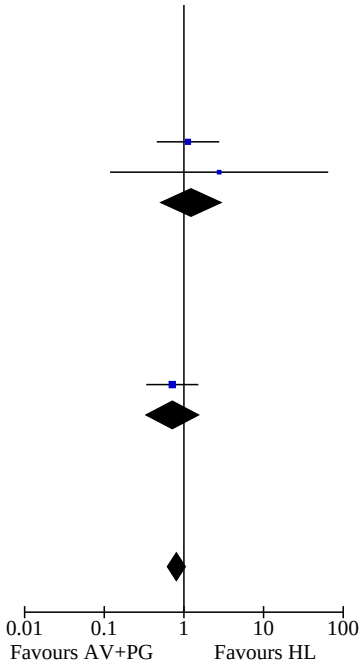
12.3.16 Coughing and associated symptoms

Anabwani 1999	10	84	14	84	11.6%	0.71 [0.34 , 1.52]
Subtotal (95% CI)		**84**		**84**	**11.6%**	**0.71 [0.34 , 1.52]**
Total events:	10		14			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.88 (P = 0.38)

Total (95% CI)		**1544**		**1528**	**100.0%**	**0.80 [0.62 , 1.04]**
Total events:	96		118			

Heterogeneity: Chi² = 30.01, df = 21 (P = 0.09); I² = 30%
Test for overall effect: Z = 1.68 (P = 0.09)
Test for subgroup differences: Chi² = 23.45, df = 14 (P = 0.05), I² = 40.3%



Footnotes

(1) Includes adverse event 'vomiting' only (not 'nausea').
(2) Original symptom 'chills/rigours'.
(3) Originally reported as 'epistaxis'.
(4) Original symptom 'weakness'.

Comparison 13. Artesunate-atovaquone-proguanil (AS+AV+PG) versus quinine (QN)

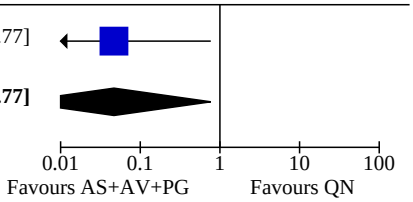
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Total failure day 28 PCR-adjusted	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.05 [0.00, 0.77]
13.2 Total failure day 42 PCR-adjusted	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.08 [0.01, 0.56]
13.3 Total failure day 28 PCR-unadjusted	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.03 [0.00, 0.56]
13.4 Total failure day 42 PCR-unadjusted	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.06 [0.01, 0.40]
13.5 Early treatment failure	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.34]
13.6 Adverse events	1	301	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.62, 0.90]
13.6.1 Serious adverse events	1	81	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
13.6.2 Adverse events leading to withdrawal	1	81	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13.6.3 Auditory nerve disorders	1	58	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.16, 0.60]
13.6.4 Anaemias	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.91, 1.14]

Analysis 13.1. Comparison 13: Artesunate-atovaquone-proguanil (AS+AV+PG) versus quinine (QN), Outcome 1: Total failure day 28 PCR-adjusted

Study or Subgroup	AS+AV+PG Events	AS+AV+PG Total	QN Events	QN Total	Weight	Risk Ratio M-H, Fixed, 95% CI
McGready 2005	0	39	11	42	100.0%	0.05 [0.00 , 0.77]
Total (95% CI)		**39**		**42**	**100.0%**	**0.05 [0.00 , 0.77]**
Total events:	0		11			

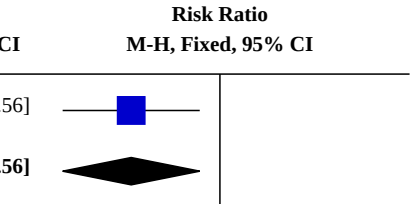
Heterogeneity: Not applicable
Test for overall effect: Z = 2.15 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 13.2. Comparison 13: Artesunate-atovaquone-proguanil (AS+AV+PG) versus quinine (QN), Outcome 2: Total failure day 42 PCR-adjusted

Study or Subgroup	AS+AV+PG Events	AS+AV+PG Total	QN Events	QN Total	Weight	Risk Ratio M-H, Fixed, 95% CI
McGready 2005	1	39	14	42	100.0%	0.08 [0.01 , 0.56]
Total (95% CI)		**39**		**42**	**100.0%**	**0.08 [0.01 , 0.56]**
Total events:	1		14			

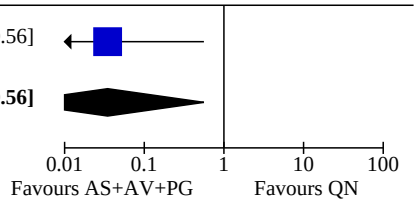
Heterogeneity: Not applicable
Test for overall effect: Z = 2.54 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 13.3. Comparison 13: Artesunate-atovaquone-proguanil (AS+AV +PG) versus quinine (QN), Outcome 3: Total failure day 28 PCR-unadjusted

Study or Subgroup	AS+AV+PG Events	AS+AV+PG Total	QN Events	QN Total	Weight	Risk Ratio M-H, Fixed, 95% CI
McGready 2005	0	39	15	42	100.0%	0.03 [0.00 , 0.56]
Total (95% CI)		**39**		**42**	**100.0%**	**0.03 [0.00 , 0.56]**
Total events:	0		15			

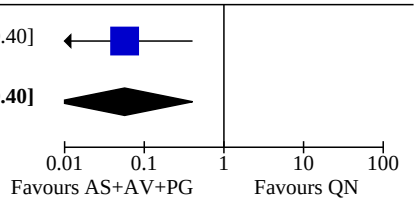
Heterogeneity: Not applicable
Test for overall effect: Z = 2.37 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 13.4. Comparison 13: Artesunate-atovaquone-proguanil (AS+AV +PG) versus quinine (QN), Outcome 4: Total failure day 42 PCR-unadjusted

Study or Subgroup	AS+AV+PG Events	AS+AV+PG Total	QN Events	QN Total	Weight	Risk Ratio M-H, Fixed, 95% CI
McGready 2005	1	39	19	42	100.0%	0.06 [0.01 , 0.40]
Total (95% CI)		**39**		**42**	**100.0%**	**0.06 [0.01 , 0.40]**
Total events:	1		19			

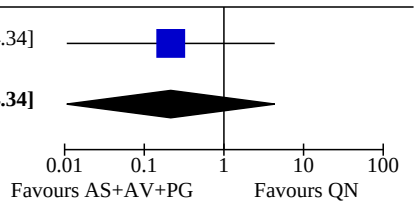
Heterogeneity: Not applicable
Test for overall effect: Z = 2.87 (P = 0.004)
Test for subgroup differences: Not applicable



Analysis 13.5. Comparison 13: Artesunate-atovaquone-proguanil (AS +AV+PG) versus quinine (QN), Outcome 5: Early treatment failure

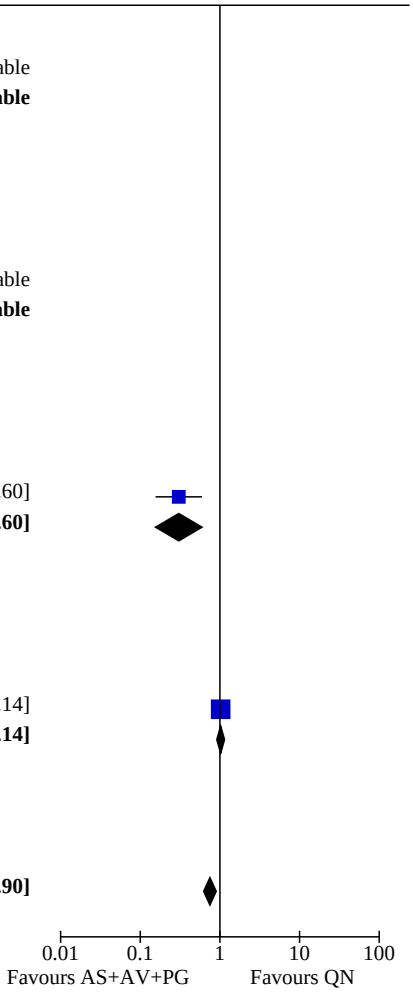
Study or Subgroup	AS+AV+PG Events	AS+AV+PG Total	QN Events	QN Total	Weight	Risk Ratio M-H, Fixed, 95% CI
McGready 2005	0	39	2	42	100.0%	0.21 [0.01 , 4.34]
Total (95% CI)		**39**		**42**	**100.0%**	**0.21 [0.01 , 4.34]**
Total events:	0		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.00 (P = 0.32)
Test for subgroup differences: Not applicable



Analysis 13.6. Comparison 13: Artesunate-atovaquone-proguanil (AS+AV+PG) versus quinine (QN), Outcome 6: Adverse events

Study or Subgroup	AS+AV+PG Events	AS+AV+PG Total	QN Events	QN Total	Weight	Risk Ratio M-H, Fixed, 95% CI
13.6.1 Serious adverse events						
McGready 2005	0	39	0	42		Not estimable
Subtotal (95% CI)		**39**		**42**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
13.6.2 Adverse events leading to withdrawal						
McGready 2005	0	39	0	42		Not estimable
Subtotal (95% CI)		**39**		**42**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
13.6.3 Auditory nerve disorders						
McGready 2005 (1)	7	29	23	29	38.0%	0.30 [0.16 , 0.60]
Subtotal (95% CI)		**29**		**29**	**38.0%**	**0.30 [0.16 , 0.60]**
Total events:	7		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.47 (P = 0.0005)						
13.6.4 Anaemias						
McGready 2005	37	39	39	42	62.0%	1.02 [0.91 , 1.14]
Subtotal (95% CI)		**39**		**42**	**62.0%**	**1.02 [0.91 , 1.14]**
Total events:	37		39			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.38 (P = 0.71)						
Total (95% CI)		**146**		**155**	**100.0%**	**0.75 [0.62 , 0.90]**
Total events:	44		62			
Heterogeneity: Chi² = 36.81, df = 1 (P < 0.00001); I² = 97%						
Test for overall effect: Z = 3.12 (P = 0.002)						
Test for subgroup differences: Chi² = 12.16, df = 1 (P = 0.0005), I² = 91.8%						



Footnotes

(1) Denominator for specific adverse event reported by study authors.

Comparison 14. Chloroquine-atovaquone-proguanil (CQ+AV+PG) versus chloroquine (CQ)

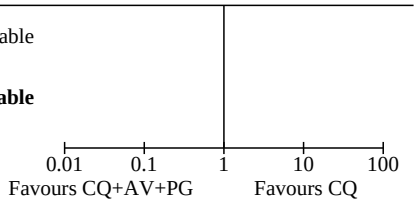
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 Total failure day 28 PCR-unadjusted	1	268	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14.2 Early treatment failure	1	268	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14.3 Adverse events	1	640	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.06, 1.35]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.3.1 Serious adverse events	1	320	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.06, 1.35]
14.3.2 Adverse events leading to withdrawal	1	320	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 14.1. Comparison 14: Chloroquine-atovaquone-proguanil (CQ+AV+PG) versus chloroquine (CQ), Outcome 1: Total failure day 28 PCR-unadjusted

Study or Subgroup	CQ+AV+PG Events	CQ+AV+PG Total	CQ Events	CQ Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Laufer 2012	0	133	0	135		Not estimable
Total (95% CI)		**133**		**135**		**Not estimable**
Total events:	0		0			

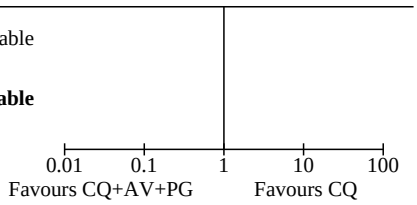
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 14.2. Comparison 14: Chloroquine-atovaquone-proguanil (CQ+AV+PG) versus chloroquine (CQ), Outcome 2: Early treatment failure

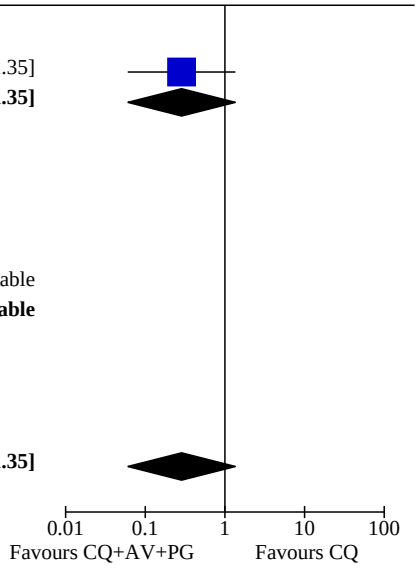
Study or Subgroup	CQ+AV+PG Events	CQ+AV+PG Total	CQ Events	CQ Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Laufer 2012	0	133	0	135		Not estimable
Total (95% CI)		**133**		**135**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 14.3. Comparison 14: Chloroquine-atovaquone-proguanil (CQ+AV+PG) versus chloroquine (CQ), Outcome 3: Adverse events

Study or Subgroup	CQ+AV+PG Events	CQ+AV+PG Total	CQ Events	CQ Total	Weight	Risk Ratio M-H, Fixed, 95% CI
14.3.1 Serious adverse events						
Laufer 2012 (1)	2	160	7	160	100.0%	0.29 [0.06 , 1.35]
Subtotal (95% CI)		**160**		**160**	**100.0%**	**0.29 [0.06 , 1.35]**
Total events:	2		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.58 (P = 0.11)						
14.3.2 Adverse events leading to withdrawal						
Laufer 2012	0	160	0	160		Not estimable
Subtotal (95% CI)		**160**		**160**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**320**		**320**	**100.0%**	**0.29 [0.06 , 1.35]**
Total events:	2		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.58 (P = 0.11)						
Test for subgroup differences: Not applicable						



Footnotes

(1) Includes two deaths in CQ group. Others were 'severe malaria'.

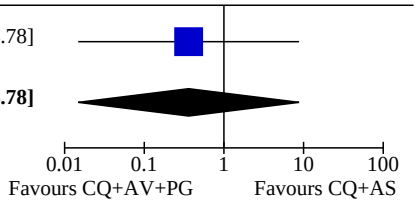
Comparison 15. Chloroquine-atovaquone-proguanil (CQ+AV+PG) versus chloroquine-artesunate (CQ+AS)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 Total failure day 28 PCR-adjusted	1	277	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.01, 8.78]
15.2 Total failure day 28 PCR-unadjusted	1	277	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.01, 8.78]
15.3 Early treatment failure	1	277	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15.4 Adverse events	1	640	Risk Ratio (M-H, Fixed, 95% CI)	5.00 [0.24, 103.33]
15.4.1 Serious adverse events	1	320	Risk Ratio (M-H, Fixed, 95% CI)	5.00 [0.24, 103.33]
15.4.2 Adverse events leading to withdrawal	1	320	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 15.1. Comparison 15: Chloroquine-atovaquone-proguanil (CQ+AV+PG) versus chloroquine-artesunate (CQ+AS), Outcome 1: Total failure day 28 PCR-adjusted

Study or Subgroup	CQ+AV+PG Events	CQ+AV+PG Total	CQ+AS Events	CQ+AS Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Laufer 2012	0	133	1	144	100.0%	0.36 [0.01 , 8.78]
Total (95% CI)		**133**		**144**	**100.0%**	**0.36 [0.01 , 8.78]**
Total events:	0		1			

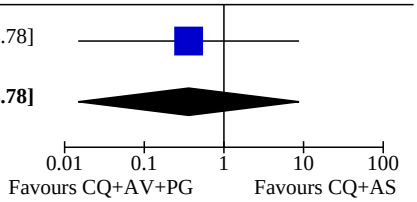
Heterogeneity: Not applicable
Test for overall effect: Z = 0.63 (P = 0.53)
Test for subgroup differences: Not applicable



Analysis 15.2. Comparison 15: Chloroquine-atovaquone-proguanil (CQ+AV+PG) versus chloroquine-artesunate (CQ+AS), Outcome 2: Total failure day 28 PCR-unadjusted

Study or Subgroup	CQ+AV+PG Events	CQ+AV+PG Total	CQ+AS Events	CQ+AS Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Laufer 2012	0	133	1	144	100.0%	0.36 [0.01 , 8.78]
Total (95% CI)		**133**		**144**	**100.0%**	**0.36 [0.01 , 8.78]**
Total events:	0		1			

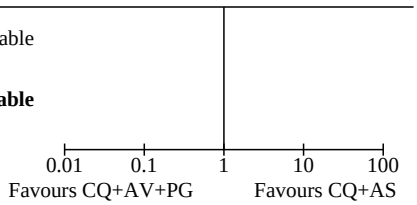
Heterogeneity: Not applicable
Test for overall effect: Z = 0.63 (P = 0.53)
Test for subgroup differences: Not applicable



Analysis 15.3. Comparison 15: Chloroquine-atovaquone-proguanil (CQ+AV +PG) versus chloroquine-artesunate (CQ+AS), Outcome 3: Early treatment failure

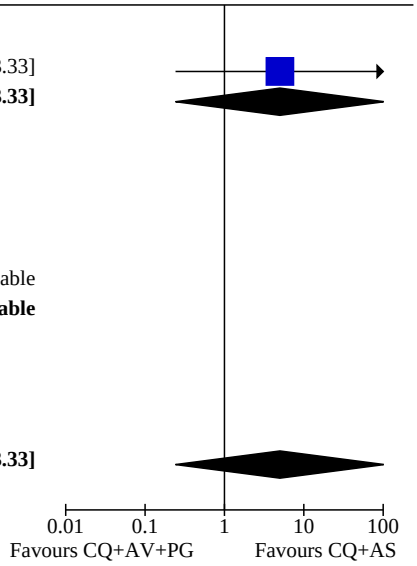
Study or Subgroup	CQ+AV+PG Events	CQ+AV+PG Total	CQ+AS Events	CQ+AS Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Laufer 2012	0	133	0	144		Not estimable
Total (95% CI)		**133**		**144**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 15.4. Comparison 15: Chloroquine-atovaquone-proguanil (CQ+AV+PG) versus chloroquine-artesunate (CQ+AS), Outcome 4: Adverse events

Study or Subgroup	CQ+AV+PG Events	CQ+AV+PG Total	CQ+AS Events	CQ+AS Total	Weight	Risk Ratio M-H, Fixed, 95% CI
15.4.1 Serious adverse events						
Laufer 2012	2	160	0	160	100.0%	5.00 [0.24 , 103.33]
Subtotal (95% CI)		**160**		**160**	**100.0%**	**5.00 [0.24 , 103.33]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						
15.4.2 Adverse events leading to withdrawal						
Laufer 2012	0	160	0	160		Not estimable
Subtotal (95% CI)		**160**		**160**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**320**		**320**	**100.0%**	**5.00 [0.24 , 103.33]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						
Test for subgroup differences: Not applicable						



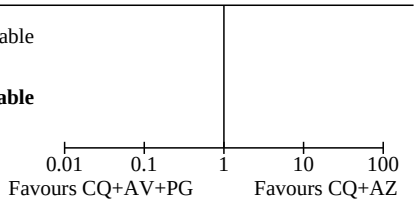
Comparison 16. Chloroquine-atovaquone-proguanil (CQ+AV+PG) versus chloroquine-azithromycin (CQ+AZ)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.1 Total failure day 28 PCR-adjusted	1	271	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16.2 Total failure day 28 PCR-unadjusted	1	271	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.41]
16.3 Early treatment failure	1	271	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16.4 Adverse events	1	640	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.14, 7.01]
16.4.1 Serious adverse events	1	320	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.14, 7.01]
16.4.2 Adverse events leading to withdrawal	1	320	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 16.1. Comparison 16: Chloroquine-atovaquone-proguanil (CQ+AV+PG) versus chloroquine-azithromycin (CQ+AZ), Outcome 1: Total failure day 28 PCR-adjusted

Study or Subgroup	CQ+AV+PG Events	CQ+AV+PG Total	CQ+AZ Events	CQ+AZ Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Laufer 2012	0	133	0	138		Not estimable
Total (95% CI)		**133**		**138**		**Not estimable**
Total events:	0		0			

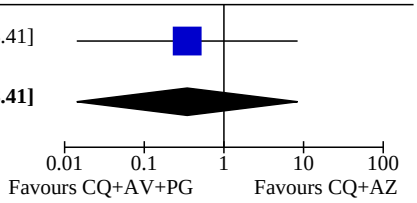
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 16.2. Comparison 16: Chloroquine-atovaquone-proguanil (CQ+AV+PG) versus chloroquine-azithromycin (CQ+AZ), Outcome 2: Total failure day 28 PCR-unadjusted

Study or Subgroup	CQ+AV+PG Events	CQ+AV+PG Total	CQ+AZ Events	CQ+AZ Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Laufer 2012	0	133	1	138	100.0%	0.35 [0.01 , 8.41]
Total (95% CI)		**133**		**138**	**100.0%**	**0.35 [0.01 , 8.41]**
Total events:	0		1			

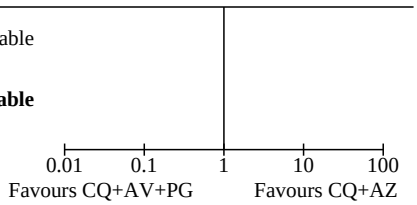
Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.51)
Test for subgroup differences: Not applicable



Analysis 16.3. Comparison 16: Chloroquine-atovaquone-proguanil (CQ+AV+PG) versus chloroquine-azithromycin (CQ+AZ), Outcome 3: Early treatment failure

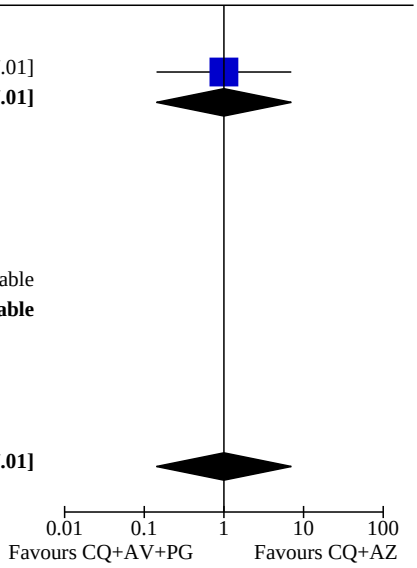
Study or Subgroup	CQ+AV+PG Events	CQ+AV+PG Total	CQ+AZ Events	CQ+AZ Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Laufer 2012	0	133	0	138		Not estimable
Total (95% CI)		**133**		**138**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 16.4. Comparison 16: Chloroquine-atovaquone-proguanil (CQ+AV+PG) versus chloroquine-azithromycin (CQ+AZ), Outcome 4: Adverse events

Study or Subgroup	CQ+AV+PG Events	CQ+AV+PG Total	CQ+AZ Events	CQ+AZ Total	Weight	Risk Ratio M-H, Fixed, 95% CI
16.4.1 Serious adverse events						
Laufer 2012 (1)	2	160	2	160	100.0%	1.00 [0.14 , 7.01]
Subtotal (95% CI)		**160**		**160**	**100.0%**	**1.00 [0.14 , 7.01]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
16.4.2 Adverse events leading to withdrawal						
Laufer 2012	0	160	0	160		Not estimable
Subtotal (95% CI)		**160**		**160**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**320**		**320**	**100.0%**	**1.00 [0.14 , 7.01]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Test for subgroup differences: Not applicable						



Footnotes

(1) Includes one death in CQ group. Others were 'severe malaria'.

Comparison 17. Adverse events: atovaquone-proguanil (AV+PG) versus all other antimalarials

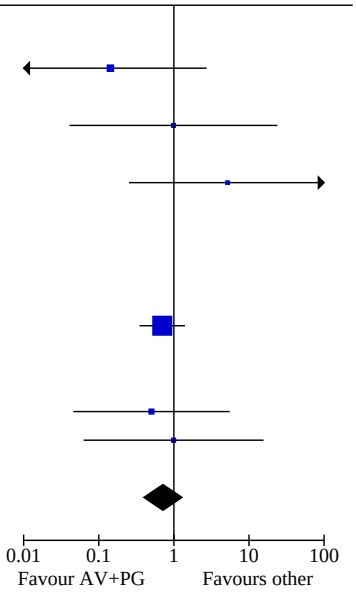
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.1 Serious adverse events	15	3222	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.40, 1.28]
17.2 Adverse events leading to withdrawal	14	2969	Risk Ratio (M-H, Fixed, 95% CI)	3.13 [1.29, 7.62]
17.3 Anaemias	2	437	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.28, 1.43]
17.4 Appetite disorders	7	887	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.37, 1.03]
17.5 Asthenic conditions	7	1100	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.39, 0.88]
17.6 Auditory nerve disorders	2	214	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.03, 0.18]
17.7 Hypotensive disorders	1	163	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.17, 1.05]
17.8 Breathing abnormalities	1	255	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 1.61]
17.9 Cardiac signs and symptoms	3	365	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.24, 2.29]
17.10 Coughing and associated symptoms	2	368	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.53, 1.48]
17.11 Diarrhoea	11	1733	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.70, 1.35]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.12 Disturbances in initiating and maintaining sleep	6	765	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.20, 0.64]
17.13 Dizziness	6	871	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.25, 0.57]
17.14 Febrile disorders	2	272	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.47, 2.67]
17.15 Feelings and sensations	4	856	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.39, 1.05]
17.16 Gastrointestinal and abdominal pains	9	1834	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.76, 1.28]
17.17 Haemorrhages	1	168	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.02, 1.68]
17.18 Headaches	9	1186	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.77, 1.38]
17.19 Hearing problems	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.87]
17.20 Hepatobiliary signs and symptoms	1	163	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.30, 3.28]
17.21 Hypoglycaemic conditions	1	255	Risk Ratio (M-H, Fixed, 95% CI)	4.96 [0.24, 102.33]
17.22 Inner ear signs and symptoms	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 3.03]
17.23 Liver function tests abnormal	1	182	Risk Ratio (M-H, Fixed, 95% CI)	2.50 [1.02, 6.16]
17.24 Lower respiratory tract and lung infections	1	255	Risk Ratio (M-H, Fixed, 95% CI)	2.48 [0.49, 12.55]
17.25 Muscle pains	2	331	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.39, 2.49]
17.26 Nausea and vomiting	12	2196	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.79, 1.23]
17.27 Oral dryness and saliva altered	1	165	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.36]
17.28 Oral soft tissue signs and symptoms	1	182	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.37, 2.74]
17.29 Pruritis	7	858	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.34, 0.87]
17.30 Rashes, eruptions, and exanthems	1	168	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.15, 2.43]
17.31 Rubeola viral infections	1	255	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.11, 3.89]
17.32 Seizures and seizure disorders	2	289	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.11, 6.26]
17.33 Spleen disorders	1	163	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.25, 8.64]
17.34 Sepsis, bacteraemia, viraemia, fungaemia	1	255	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.14]
17.35 Upper respiratory tract infections	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.20]

Analysis 17.1. Comparison 17: Adverse events: atovaquone-proguanil (AV +PG) versus all other antimalarials, Outcome 1: Serious adverse events

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anabwani 1999	0	84	0	84		Not estimable
Borrmann 2003	0	100	3	100	14.1%	0.14 [0.01 , 2.73]
Bouchaud 2000	0	25	0	23		Not estimable
Carrasquilla 2012 (1)	0	53	1	159	3.1%	0.99 [0.04 , 23.89]
De Alencar 1997	0	77	0	77		Not estimable
Giao 2004	2	81	0	84	2.0%	5.18 [0.25 , 106.33]
Gurkov 2008 (2)	0	30	0	30		Not estimable
Llanos-Cuentas 2001 (3)	0	20	0	14		Not estimable
Looareesuwan 1999	0	91	0	91		Not estimable
Mulenga 1999	0	82	0	81		Not estimable
Mulenga 2006 (4)	12	128	17	127	68.8%	0.70 [0.35 , 1.41]
Radloff 1996	0	63	0	63		Not estimable
Tahar 2014 (5)	0	92	0	95		Not estimable
Van Vugt 2002 (1)	1	530	2	533	8.0%	0.50 [0.05 , 5.53]
Wojnarski 2019	1	103	1	102	4.0%	0.99 [0.06 , 15.62]
Total (95% CI)		**1559**		**1663**	**100.0%**	**0.72 [0.40 , 1.28]**
Total events:	16		24			

Heterogeneity: Chi² = 2.98, df = 5 (P = 0.70); I² = 0%
Test for overall effect: Z = 1.12 (P = 0.26)
Test for subgroup differences: Not applicable



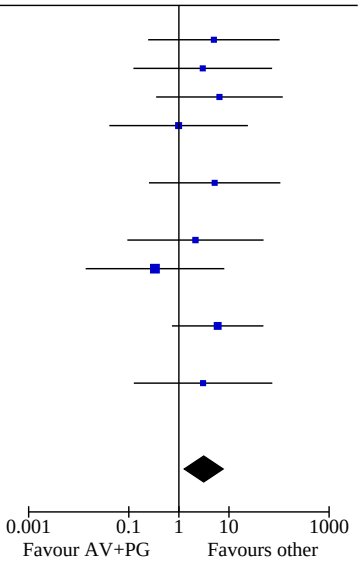
Footnotes

(1) Data from AV+PG versus AS+MQ only.
(2) Data from AV+PG versus AL only.
(3) Data from AV+PG versus CQ only.
(4) Six deaths in AV+PG group, one death in comparator group.
(5) Data from AV+PG versus AS+AV+PG only.

Analysis 17.2. Comparison 17: Adverse events: atovaquone-proguanil (AV+PG) versus all other antimalarials, Outcome 2: Adverse events leading to withdrawal

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anabwani 1999	2	84	0	84	7.9%	5.00 [0.24 , 102.60]
Borrmann 2003	1	100	0	100	7.9%	3.00 [0.12 , 72.77]
Bouchaud 2000	3	25	0	23	8.2%	6.46 [0.35 , 118.71]
Carrasquilla 2012 (1)	0	53	1	159	11.9%	0.99 [0.04 , 23.89]
De Alencar 1997	0	77	0	77		Not estimable
Giao 2004	2	81	0	84	7.7%	5.18 [0.25 , 106.33]
Gurkov 2008 (2)	0	30	0	30		Not estimable
Llanos-Cuentas 2001 (3)	1	20	0	14	9.2%	2.14 [0.09 , 49.08]
Looareesuwan 1999	0	91	1	91	23.6%	0.33 [0.01 , 8.08]
Mulenga 1999	0	82	0	81		Not estimable
Mulenga 2006	6	128	1	127	15.8%	5.95 [0.73 , 48.75]
Radloff 1996	0	63	0	63		Not estimable
Tahar 2014	1	69	0	70	7.8%	3.04 [0.13 , 73.43]
Van Vugt 2002 (4)	0	530	0	533		Not estimable
Total (95% CI)		**1433**		**1536**	**100.0%**	**3.13 [1.29 , 7.62]**
Total events:	16		3			

Heterogeneity: Chi² = 3.25, df = 8 (P = 0.92); I² = 0%
Test for overall effect: Z = 2.52 (P = 0.01)
Test for subgroup differences: Not applicable

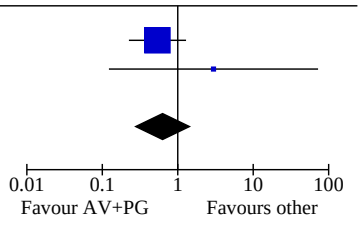


Footnotes
(1) Data from AV+PG versus AS+MQ only.
(2) Data from AV+PG versus AL only.
(3) Data from AV+PG versus CQ only.
(4) Data from AV+PG versus AM only.

Analysis 17.3. Comparison 17: Adverse events: atovaquone-proguanil (AV+PG) versus all other antimalarials, Outcome 3: Anaemias

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Looareesuwan 1999	7	91	13	91	96.3%	0.54 [0.23 , 1.29]
Mulenga 2006	1	128	0	127	3.7%	2.98 [0.12 , 72.39]
Total (95% CI)		**219**		**218**	**100.0%**	**0.63 [0.28 , 1.43]**
Total events:	8		13			

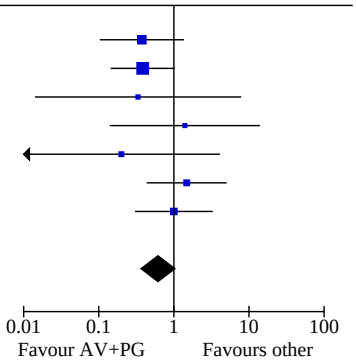
Heterogeneity: Chi² = 1.03, df = 1 (P = 0.31); I² = 3%
Test for overall effect: Z = 1.11 (P = 0.27)
Test for subgroup differences: Not applicable



Analysis 17.4. Comparison 17: Adverse events: atovaquone-proguanil (AV+PG) versus all other antimalarials, Outcome 4: Appetite disorders

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anabwani 1999	3	84	8	84	22.7%	0.38 [0.10 , 1.36]
De Alencar 1997	5	77	13	77	36.9%	0.38 [0.14 , 1.03]
Gurkov 2008	0	30	1	30	4.3%	0.33 [0.01 , 7.87]
Llanos-Cuentas 2001 (1)	2	20	1	14	3.3%	1.40 [0.14 , 13.98]
Looareesuwan 1999	0	91	2	91	7.1%	0.20 [0.01 , 4.11]
Mulenga 1999	6	82	4	81	11.4%	1.48 [0.43 , 5.06]
Radloff 1996	5	63	5	63	14.2%	1.00 [0.30 , 3.29]
Total (95% CI)		**447**		**440**	**100.0%**	**0.61 [0.37 , 1.03]**
Total events:	21		34			

Heterogeneity: Chi² = 5.22, df = 6 (P = 0.52); I² = 0%
Test for overall effect: Z = 1.85 (P = 0.06)
Test for subgroup differences: Not applicable

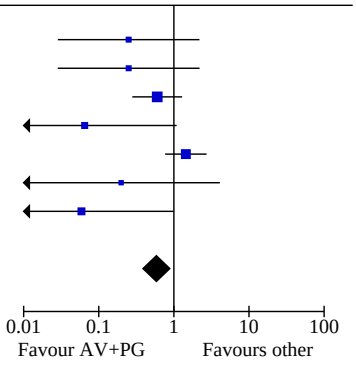


Footnotes
(1) Data from AP versus QN only.

Analysis 17.5. Comparison 17: Adverse events: atovaquone-proguanil (AV+PG) versus all other antimalarials, Outcome 5: Asthenic conditions

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anabwani 1999 (1)	1	84	4	84	7.5%	0.25 [0.03 , 2.19]
Borrmann 2003 (1)	1	100	4	100	7.5%	0.25 [0.03 , 2.20]
De Alencar 1997 (1)	9	77	15	77	28.0%	0.60 [0.28 , 1.29]
Llanos-Cuentas 2001 (1)	0	20	5	14	12.0%	0.06 [0.00 , 1.09]
Mulenga 1999 (1)	19	82	13	81	24.4%	1.44 [0.76 , 2.72]
Mulenga 2006 (2)	0	128	2	127	4.7%	0.20 [0.01 , 4.09]
Radloff 1996 (1)	0	63	8	63	15.9%	0.06 [0.00 , 1.00]
Total (95% CI)		**554**		**546**	**100.0%**	**0.58 [0.39 , 0.88]**
Total events:	30		51			

Heterogeneity: Chi² = 14.31, df = 6 (P = 0.03); I² = 58%
Test for overall effect: Z = 2.56 (P = 0.01)
Test for subgroup differences: Not applicable

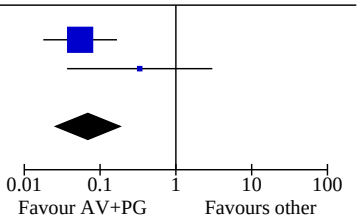


Footnotes
(1) Originally reported as 'weakness'.
(2) Originally reported as 'lethargy'.

Analysis 17.6. Comparison 17: Adverse events: atovaquone-proguanil (AV+PG) versus all other antimalarials, Outcome 6: Auditory nerve disorders

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
De Alencar 1997	3	77	55	77	94.8%	0.05 [0.02 , 0.17]
Gurkov 2008 (1)	1	30	3	30	5.2%	0.33 [0.04 , 3.03]
Total (95% CI)		**107**		**107**	**100.0%**	**0.07 [0.03 , 0.18]**
Total events:	4		58			

Heterogeneity: Chi² = 2.13, df = 1 (P = 0.14); I² = 53%
Test for overall effect: Z = 5.37 (P < 0.00001)
Test for subgroup differences: Not applicable

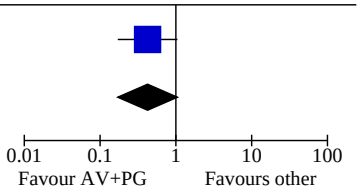


Footnotes
(1) Data from AV+PG versus QN only.

Analysis 17.7. Comparison 17: Adverse events: atovaquone-proguanil (AV+PG) versus all other antimalarials, Outcome 7: Hypotensive disorders

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mulenga 1999	6	82	14	81	100.0%	0.42 [0.17 , 1.05]
Total (95% CI)		**82**		**81**	**100.0%**	**0.42 [0.17 , 1.05]**
Total events:	6		14			

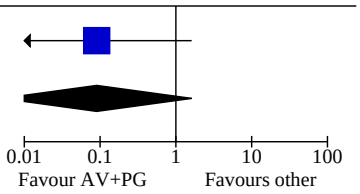
Heterogeneity: Not applicable
Test for overall effect: Z = 1.86 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 17.8. Comparison 17: Adverse events: atovaquone-proguanil (AV+PG) versus all other antimalarials, Outcome 8: Breathing abnormalities

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mulenga 2006	0	128	5	127	100.0%	0.09 [0.01 , 1.61]
Total (95% CI)		**128**		**127**	**100.0%**	**0.09 [0.01 , 1.61]**
Total events:	0		5			

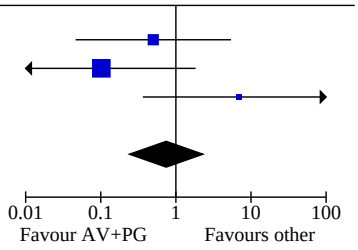
Heterogeneity: Not applicable
Test for overall effect: Z = 1.63 (P = 0.10)
Test for subgroup differences: Not applicable



Analysis 17.9. Comparison 17: Adverse events: atovaquone-proguanil (AV +PG) versus all other antimalarials, Outcome 9: Cardiac signs and symptoms

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anabwani 1999	1	84	2	84	30.4%	0.50 [0.05 , 5.41]
Llanos-Cuentas 2001	0	20	3	14	62.0%	0.10 [0.01 , 1.83]
Mulenga 1999	3	82	0	81	7.6%	6.92 [0.36 , 131.79]
Total (95% CI)		**186**		**179**	**100.0%**	**0.74 [0.24 , 2.29]**
Total events:	4		5			

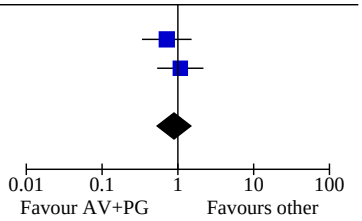
Heterogeneity: Chi² = 4.12, df = 2 (P = 0.13); I² = 51%
Test for overall effect: Z = 0.52 (P = 0.60)
Test for subgroup differences: Not applicable



Analysis 17.10. Comparison 17: Adverse events: atovaquone-proguanil (AV+PG) versus all other antimalarials, Outcome 10: Coughing and associated symptoms

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anabwani 1999	10	84	14	84	51.9%	0.71 [0.34 , 1.52]
Borrmann 2003	14	100	13	100	48.1%	1.08 [0.53 , 2.17]
Total (95% CI)		**184**		**184**	**100.0%**	**0.89 [0.53 , 1.48]**
Total events:	24		27			

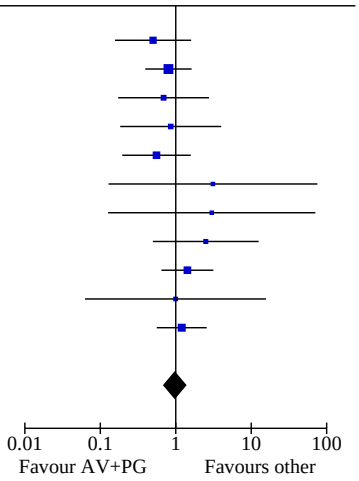
Heterogeneity: Chi² = 0.61, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.45 (P = 0.65)
Test for subgroup differences: Not applicable



Analysis 17.11. Comparison 17: Adverse events: atovaquone-proguanil (AV+PG) versus all other antimalarials, Outcome 11: Diarrhoea

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anabwani 1999	4	84	8	84	12.8%	0.50 [0.16 , 1.60]
Borrmann 2003	12	100	15	100	23.9%	0.80 [0.39 , 1.62]
Bouchaud 2000	3	25	4	23	6.6%	0.69 [0.17 , 2.76]
Carrasquilla 2012 (1)	2	53	7	159	5.6%	0.86 [0.18 , 4.00]
De Alencar 1997	5	77	9	77	14.4%	0.56 [0.20 , 1.58]
Giao 2004	1	81	0	84	0.8%	3.11 [0.13 , 75.24]
Gurkov 2008 (2)	1	30	0	30	0.8%	3.00 [0.13 , 70.83]
Looareesuwan 1999	5	91	2	91	3.2%	2.50 [0.50 , 12.56]
Mulenga 1999	13	82	9	81	14.4%	1.43 [0.65 , 3.15]
Mulenga 2006	1	128	1	127	1.6%	0.99 [0.06 , 15.69]
Radloff 1996	12	63	10	63	15.9%	1.20 [0.56 , 2.57]
Total (95% CI)		**814**		**919**	**100.0%**	**0.97 [0.70 , 1.35]**
Total events:	59		65			

Heterogeneity: Chi² = 6.42, df = 10 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.18 (P = 0.86)
Test for subgroup differences: Not applicable

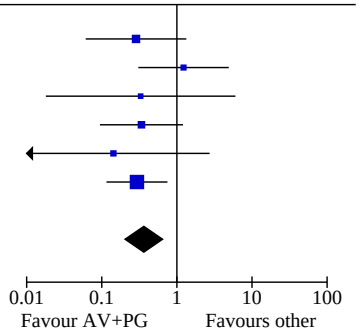


Footnotes
(1) Data from AV+PG versus AS+MQ only.
(2) Data from AV+PG versus QN only.

Analysis 17.12. Comparison 17: Adverse events: atovaquone-proguanil (AV+PG) versus all other antimalarials, Outcome 12: Disturbances in initiating and maintaining sleep

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anabwani 1999	2	84	7	84	18.2%	0.29 [0.06 , 1.34]
Bouchaud 2000	4	25	3	23	8.1%	1.23 [0.31 , 4.90]
Carrasquilla 2012 (1)	0	53	4	159	5.9%	0.33 [0.02 , 6.02]
Llanos-Cuentas 2001 (2)	3	20	4	9	14.4%	0.34 [0.09 , 1.21]
Looareesuwan 1999	0	91	3	91	9.1%	0.14 [0.01 , 2.73]
Radloff 1996	5	63	17	63	44.3%	0.29 [0.12 , 0.75]
Total (95% CI)		**336**		**429**	**100.0%**	**0.36 [0.20 , 0.64]**
Total events:	14		38			

Heterogeneity: Chi² = 3.65, df = 5 (P = 0.60); I² = 0%
Test for overall effect: Z = 3.46 (P = 0.0005)
Test for subgroup differences: Not applicable

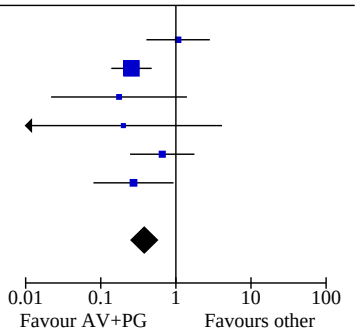


Footnotes
(1) Data from AV+PG versus AS+MQ only.
(2) Data from AV+PG versus SP only.

Analysis 17.13. Comparison 17: Adverse events: atovaquone-proguanil (AV+PG) versus all other antimalarials, Outcome 13: Dizziness

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Carrasquilla 2012 (1)	5	53	14	159	9.6%	1.07 [0.41 , 2.83]
De Alencar 1997	10	77	39	77	53.2%	0.26 [0.14 , 0.48]
Llanos-Cuentas 2001 (2)	1	20	4	14	6.4%	0.17 [0.02 , 1.40]
Looareesuwan 1999	0	91	2	91	3.4%	0.20 [0.01 , 4.11]
Mulenga 1999	6	82	9	81	12.4%	0.66 [0.25 , 1.77]
Radloff 1996 (3)	3	63	11	63	15.0%	0.27 [0.08 , 0.93]
Total (95% CI)		**386**		**485**	**100.0%**	**0.38 [0.25 , 0.57]**
Total events:	25		79			

Heterogeneity: Chi² = 8.10, df = 5 (P = 0.15); I² = 38%
Test for overall effect: Z = 4.72 (P < 0.00001)
Test for subgroup differences: Not applicable

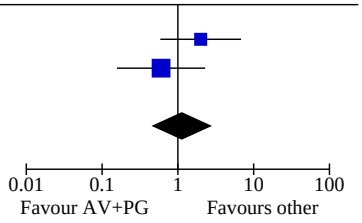


Footnotes
(1) Data from AV+PG versus AS+MQ only.
(2) Data from AV+PG versus CQ only.
(3) Denominator formed from patients completing treatment.

Analysis 17.14. Comparison 17: Adverse events: atovaquone-proguanil (AV+PG) versus all other antimalarials, Outcome 14: Febrile disorders

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Carrasquilla 2012 (1)	4	53	6	159	37.5%	2.00 [0.59 , 6.82]
Gurkov 2008 (2)	3	30	5	30	62.5%	0.60 [0.16 , 2.29]
Total (95% CI)		**83**		**189**	**100.0%**	**1.13 [0.47 , 2.67]**
Total events:	7		11			

Heterogeneity: Chi² = 1.69, df = 1 (P = 0.19); I² = 41%
Test for overall effect: Z = 0.27 (P = 0.79)
Test for subgroup differences: Not applicable

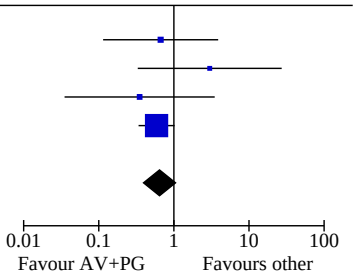


Footnotes
(1) Data only from AV+PG versus AL.
(2) Data only from AV+PG versus QN.

Analysis 17.15. Comparison 17: Adverse events: atovaquone-proguanil (AV+PG) versus all other antimalarials, Outcome 15: Feelings and sensations

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anabwani 1999	2	84	3	84	8.0%	0.67 [0.11 , 3.89]
Gurkov 2008 (1)	3	30	1	30	2.7%	3.00 [0.33 , 27.23]
Llanos-Cuentas 2001 (2)	1	20	2	14	6.3%	0.35 [0.04 , 3.50]
Van Vugt 2002 (3)	19	308	30	286	83.0%	0.59 [0.34 , 1.02]
Total (95% CI)		**442**		**414**	**100.0%**	**0.64 [0.39 , 1.05]**
Total events:	25		36			

Heterogeneity: Chi² = 2.24, df = 3 (P = 0.52); I² = 0%
Test for overall effect: Z = 1.76 (P = 0.08)
Test for subgroup differences: Not applicable



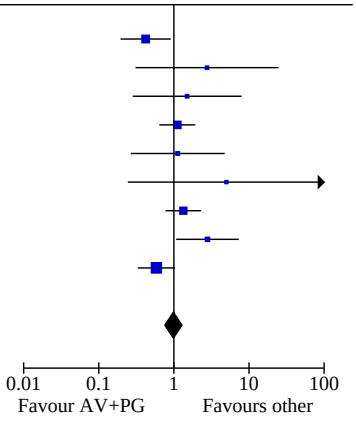
Footnotes

(1) Data only from AV+PG versus QN.
(2) Data only from AV+PG versus CQ.
(3) Data only from AV+PG versus AS+MQ.

Analysis 17.16. Comparison 17: Adverse events: atovaquone-proguanil (AV+PG) versus all other antimalarials, Outcome 16: Gastrointestinal and abdominal pains

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anabwani 1999	8	84	19	84	19.9%	0.42 [0.20 , 0.91]
Bouchaud 2000	3	25	1	23	1.1%	2.76 [0.31 , 24.69]
Carrasquilla 2012 (1)	2	53	4	159	2.1%	1.50 [0.28 , 7.96]
De Alencar 1997	20	77	18	77	18.9%	1.11 [0.64 , 1.93]
Llanos-Cuentas 2001 (2)	5	20	2	9	2.9%	1.13 [0.27 , 4.74]
Looareesuwan 1999	2	91	0	91	0.5%	5.00 [0.24 , 102.72]
Mulenga 1999	23	82	17	81	18.0%	1.34 [0.77 , 2.31]
Radloff 1996	14	63	5	63	5.2%	2.80 [1.07 , 7.31]
Van Vugt 2002	18	387	29	365	31.3%	0.59 [0.33 , 1.04]
Total (95% CI)		**882**		**952**	**100.0%**	**0.98 [0.76 , 1.28]**
Total events:	95		95			

Heterogeneity: Chi² = 16.06, df = 8 (P = 0.04); I² = 50%
Test for overall effect: Z = 0.11 (P = 0.91)
Test for subgroup differences: Not applicable



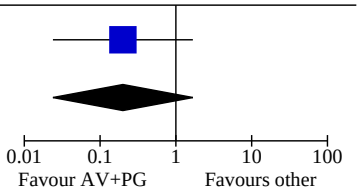
Footnotes

(1) Data only from AV+PG versus AS+MQ.
(2) Data only from AV+PG versus SP.

Analysis 17.17. Comparison 17: Adverse events: atovaquone-proguanil (AV+PG) versus all other antimalarials, Outcome 17: Haemorrhages

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anabwani 1999	1	84	5	84	100.0%	0.20 [0.02 , 1.68]
Total (95% CI)		**84**		**84**	**100.0%**	**0.20 [0.02 , 1.68]**
Total events:	1		5			

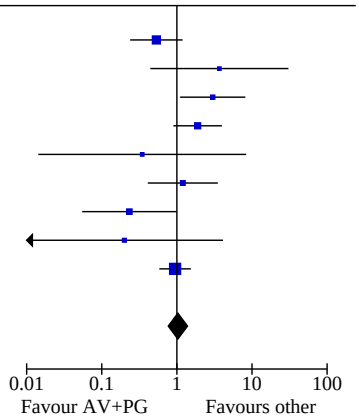
Heterogeneity: Not applicable
Test for overall effect: Z = 1.48 (P = 0.14)
Test for subgroup differences: Not applicable



Analysis 17.18. Comparison 17: Adverse events: atovaquone-proguanil (AV+PG) versus all other antimalarials, Outcome 18: Headaches

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anabwani 1999	8	84	15	84	21.8%	0.53 [0.24 , 1.19]
Bouchaud 2000	4	25	1	23	1.5%	3.68 [0.44 , 30.56]
Carrasquilla 2012 (1)	7	53	7	159	5.1%	3.00 [1.10 , 8.16]
De Alencar 1997	17	77	9	77	13.1%	1.89 [0.90 , 3.97]
Giao 2004	0	81	1	84	2.1%	0.35 [0.01 , 8.36]
Gurkov 2008 (2)	6	30	5	30	7.3%	1.20 [0.41 , 3.51]
Llanos-Cuentas 2001 (3)	2	20	6	14	10.3%	0.23 [0.05 , 0.99]
Looareesuwan 1999	0	91	2	91	3.6%	0.20 [0.01 , 4.11]
Mulenga 1999	23	82	24	81	35.1%	0.95 [0.58 , 1.53]
Total (95% CI)		**543**		**643**	**100.0%**	**1.03 [0.77 , 1.38]**
Total events:	67		70			

Heterogeneity: $Chi^2 = 16.73$, df = 8 (P = 0.03); $I^2 = 52\%$
Test for overall effect: Z = 0.20 (P = 0.84)
Test for subgroup differences: Not applicable



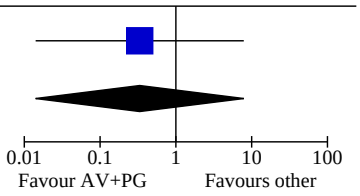
Footnotes

(1) Data only from AV+PG versus AS+MQ.
(2) Data only from AV+PG versus QN.
(3) Data only from AV+PG versus CQ.

Analysis 17.19. Comparison 17: Adverse events: atovaquone-proguanil (AV+PG) versus all other antimalarials, Outcome 19: Hearing problems

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gurkov 2008 (1)	0	30	1	30	100.0%	0.33 [0.01 , 7.87]
Total (95% CI)		**30**		**30**	**100.0%**	**0.33 [0.01 , 7.87]**
Total events:	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable

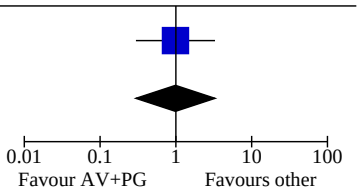


Footnotes
(1) Data only from AV+PG versus QN.

Analysis 17.20. Comparison 17: Adverse events: atovaquone-proguanil (AV+PG) versus all other antimalarials, Outcome 20: Hepatobiliary signs and symptoms

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mulenga 1999	5	82	5	81	100.0%	0.99 [0.30 , 3.28]
Total (95% CI)		**82**		**81**	**100.0%**	**0.99 [0.30 , 3.28]**
Total events:	5		5			

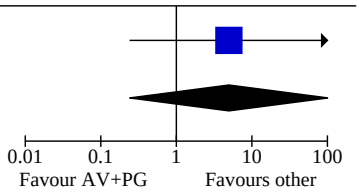
Heterogeneity: Not applicable
Test for overall effect: Z = 0.02 (P = 0.98)
Test for subgroup differences: Not applicable



Analysis 17.21. Comparison 17: Adverse events: atovaquone-proguanil (AV +PG) versus all other antimalarials, Outcome 21: Hypoglycaemic conditions

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mulenga 1999	2	128	0	127	100.0%	4.96 [0.24 , 102.33]
Total (95% CI)		**128**		**127**	**100.0%**	**4.96 [0.24 , 102.33]**
Total events:	2		0			

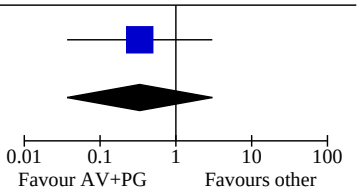
Heterogeneity: Not applicable
Test for overall effect: Z = 1.04 (P = 0.30)
Test for subgroup differences: Not applicable



Analysis 17.22. Comparison 17: Adverse events: atovaquone-proguanil (AV +PG) versus all other antimalarials, Outcome 22: Inner ear signs and symptoms

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gurkov 2008 (1)	1	30	3	30	100.0%	0.33 [0.04 , 3.03]
Total (95% CI)		**30**		**30**	**100.0%**	**0.33 [0.04 , 3.03]**
Total events:	1		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)
Test for subgroup differences: Not applicable

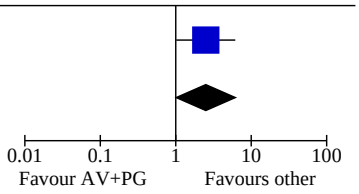


Footnotes
(1) Data only from AV+PG versus AL.

Analysis 17.23. Comparison 17: Adverse events: atovaquone-proguanil (AV +PG) versus all other antimalarials, Outcome 23: Liver function tests abnormal

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Looareesuwan 1999	15	91	6	91	100.0%	2.50 [1.02 , 6.16]
Total (95% CI)		**91**		**91**	**100.0%**	**2.50 [1.02 , 6.16]**
Total events:	15		6			

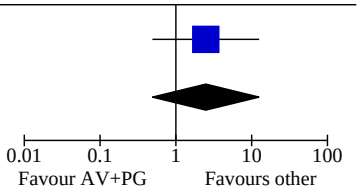
Heterogeneity: Not applicable
Test for overall effect: Z = 1.99 (P = 0.05)
Test for subgroup differences: Not applicable



Analysis 17.24. Comparison 17: Adverse events: atovaquone-proguanil (AV+PG) versus all other antimalarials, Outcome 24: Lower respiratory tract and lung infections

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mulenga 2006	5	128	2	127	100.0%	2.48 [0.49 , 12.55]
Total (95% CI)		**128**		**127**	**100.0%**	**2.48 [0.49 , 12.55]**
Total events:	5		2			

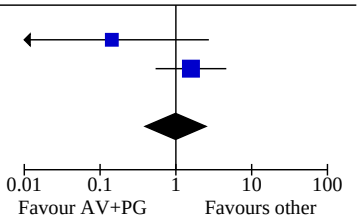
Heterogeneity: Not applicable
Test for overall effect: Z = 1.10 (P = 0.27)
Test for subgroup differences: Not applicable



Analysis 17.25. Comparison 17: Adverse events: atovaquone-proguanil (AV+PG) versus all other antimalarials, Outcome 25: Muscle pains

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anabwani 1999	0	84	3	84	41.0%	0.14 [0.01 , 2.72]
Mulenga 1999	8	82	5	81	59.0%	1.58 [0.54 , 4.63]
Total (95% CI)		**166**		**165**	**100.0%**	**0.99 [0.39 , 2.49]**
Total events:	8		8			

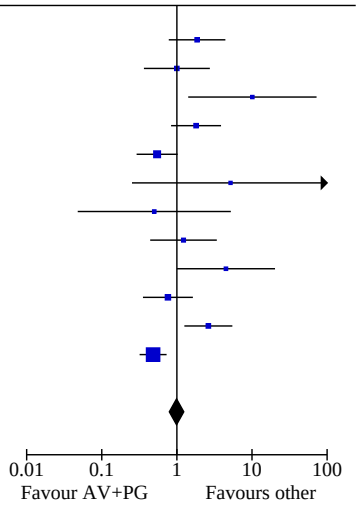
Heterogeneity: Chi² = 2.38, df = 1 (P = 0.12); I² = 58%
Test for overall effect: Z = 0.02 (P = 0.98)
Test for subgroup differences: Not applicable



Analysis 17.26. Comparison 17: Adverse events: atovaquone-proguanil (AV +PG) versus all other antimalarials, Outcome 26: Nausea and vomiting

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anabwani 1999	13	84	7	84	5.1%	1.86 [0.78 , 4.42]
Borrmann 2003	7	100	7	100	5.1%	1.00 [0.36 , 2.75]
Bouchaud 2000	11	25	1	23	0.8%	10.12 [1.42 , 72.37]
Carrasquilla 2012 (1)	9	53	15	159	5.5%	1.80 [0.84 , 3.87]
De Alencar 1997	12	77	22	77	16.1%	0.55 [0.29 , 1.02]
Giao 2004	2	81	0	84	0.4%	5.18 [0.25 , 106.33]
Gurkov 2008 (2)	1	30	2	30	1.5%	0.50 [0.05 , 5.22]
Llanos-Cuentas 2001 (3)	7	20	4	14	3.5%	1.23 [0.44 , 3.40]
Looareesuwan 1999	9	91	2	91	1.5%	4.50 [1.00 , 20.26]
Mulenga 1999	10	82	13	81	9.6%	0.76 [0.35 , 1.63]
Radloff 1996	21	63	8	63	5.9%	2.63 [1.26 , 5.48]
Van Vugt 2002 (1)	29	334	63	350	45.1%	0.48 [0.32 , 0.73]
Total (95% CI)		**1040**		**1156**	**100.0%**	**0.99 [0.79 , 1.23]**
Total events:	131		144			

Heterogeneity: Chi² = 37.54, df = 11 (P < 0.0001); I² = 71%
Test for overall effect: Z = 0.09 (P = 0.93)
Test for subgroup differences: Not applicable



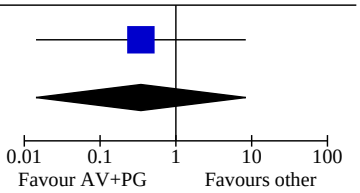
Footnotes

(1) Data only from AV+PG versus AS+MQ.
(2) Data only from AV+PG versus QN.
(3) Data only from AV+PG versus CQ.

Analysis 17.27. Comparison 17: Adverse events: atovaquone-proguanil (AV+PG) versus all other antimalarials, Outcome 27: Oral dryness and saliva altered

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Giao 2004	0	81	1	84	100.0%	0.35 [0.01 , 8.36]
Total (95% CI)		**81**		**84**	**100.0%**	**0.35 [0.01 , 8.36]**
Total events:	0		1			

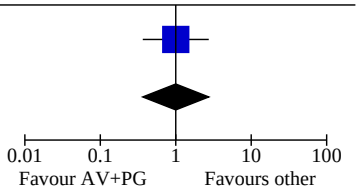
Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.51)
Test for subgroup differences: Not applicable



Analysis 17.28. Comparison 17: Adverse events: atovaquone-proguanil (AV+PG) versus all other antimalarials, Outcome 28: Oral soft tissue signs and symptoms

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Looareesuwan 1999	7	91	7	91	100.0%	1.00 [0.37 , 2.74]
Total (95% CI)		**91**		**91**	**100.0%**	**1.00 [0.37 , 2.74]**
Total events:	7		7			

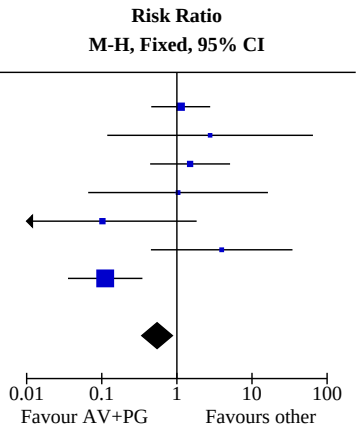
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



Analysis 17.29. Comparison 17: Adverse events: atovaquone-proguanil (AV+PG) versus all other antimalarials, Outcome 29: Pruritis

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anabwani 1999	9	84	8	84	17.5%	1.13 [0.46 , 2.78]
Bouchaud 2000	1	25	0	23	1.1%	2.77 [0.12 , 64.76]
De Alencar 1997	6	77	4	77	8.8%	1.50 [0.44 , 5.11]
Giao 2004	1	81	1	84	2.2%	1.04 [0.07 , 16.30]
Llanos-Cuentas 2001 (1)	0	20	3	14	9.0%	0.10 [0.01 , 1.83]
Mulenga 1999	4	82	1	81	2.2%	3.95 [0.45 , 34.60]
Radloff 1996	3	63	27	63	59.2%	0.11 [0.04 , 0.35]
Total (95% CI)		**432**		**426**	**100.0%**	**0.55 [0.34 , 0.87]**
Total events:	24		44			

Heterogeneity: Chi² = 18.29, df = 6 (P = 0.006); I² = 67%
Test for overall effect: Z = 2.54 (P = 0.01)
Test for subgroup differences: Not applicable



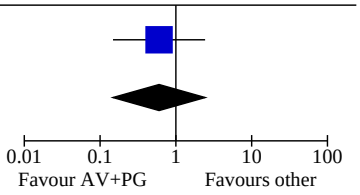
Footnotes

(1) Data only from AV+PG versus CQ.

Analysis 17.30. Comparison 17: Adverse events: atovaquone-proguanil (AV+PG) versus all other antimalarials, Outcome 30: Rashes, eruptions, and exanthems

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anabwani 1999	3	84	5	84	100.0%	0.60 [0.15 , 2.43]
Total (95% CI)		**84**		**84**	**100.0%**	**0.60 [0.15 , 2.43]**
Total events:	3		5			

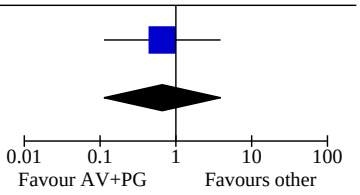
Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)
Test for subgroup differences: Not applicable



Analysis 17.31. Comparison 17: Adverse events: atovaquone-proguanil (AV +PG) versus all other antimalarials, Outcome 31: Rubeola viral infections

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mulenga 2006	2	128	3	127	100.0%	0.66 [0.11 , 3.89]
Total (95% CI)		**128**		**127**	**100.0%**	**0.66 [0.11 , 3.89]**
Total events:	2		3			

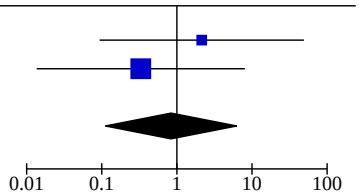
Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.65)
Test for subgroup differences: Not applicable



Analysis 17.32. Comparison 17: Adverse events: atovaquone-proguanil (AV +PG) versus all other antimalarials, Outcome 32: Seizures and seizure disorders

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Llanos-Cuentas 2001 (1)	1	20	0	14	27.9%	2.14 [0.09 , 49.08]
Mulenga 2006	0	128	1	127	72.1%	0.33 [0.01 , 8.04]
Total (95% CI)		**148**		**141**	**100.0%**	**0.84 [0.11 , 6.26]**
Total events:	1		1			

Heterogeneity: Chi² = 0.67, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 0.17 (P = 0.86)
Test for subgroup differences: Not applicable



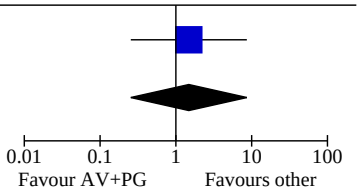
Footnotes

(1) Data only from AV+PG versus SP.

Analysis 17.33. Comparison 17: Adverse events: atovaquone-proguanil (AV+PG) versus all other antimalarials, Outcome 33: Spleen disorders

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mulenga 1999	3	82	2	81	100.0%	1.48 [0.25 , 8.64]
Total (95% CI)		**82**		**81**	**100.0%**	**1.48 [0.25 , 8.64]**
Total events:	3		2			

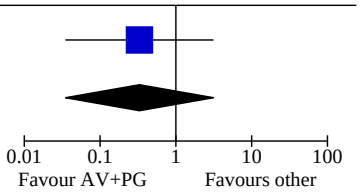
Heterogeneity: Not applicable
Test for overall effect: Z = 0.44 (P = 0.66)
Test for subgroup differences: Not applicable



Analysis 17.34. Comparison 17: Adverse events: atovaquone-proguanil (AV+PG) versus all other antimalarials, Outcome 34: Sepsis, bacteraemia, viraemia, fungaemia

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mulenga 2006	1	128	3	127	100.0%	0.33 [0.03 , 3.14]
Total (95% CI)		**128**		**127**	**100.0%**	**0.33 [0.03 , 3.14]**
Total events:	1		3			

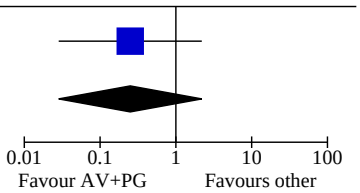
Heterogeneity: Not applicable
Test for overall effect: Z = 0.96 (P = 0.34)
Test for subgroup differences: Not applicable



Analysis 17.35. Comparison 17: Adverse events: atovaquone-proguanil (AV +PG) versus all other antimalarials, Outcome 35: Upper respiratory tract infections

Study or Subgroup	AV+PG Events	AV+PG Total	All other antimalarials Events	All other antimalarials Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Borrmann 2003	1	100	4	100	100.0%	0.25 [0.03 , 2.20]
Total (95% CI)		**100**		**100**	**100.0%**	**0.25 [0.03 , 2.20]**
Total events:	1		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.25 (P = 0.21)
Test for subgroup differences: Not applicable



Comparison 18. Supplementary: atovaquone-proguanil (AV+PG) versus WHO-recommended artemisinin-based combination therapy (ACT)

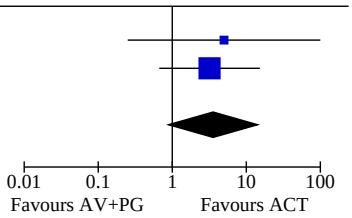
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
18.1 Total failure day 28 PCR-adjusted	2	192	Risk Ratio (M-H, Fixed, 95% CI)	3.56 [0.89, 14.19]
18.2 Total failure day 28 PCR-unadjusted	1	132	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.49, 2.91]
18.3 Total failure day 42 PCR-adjusted	2	1271	Risk Ratio (M-H, Fixed, 95% CI)	3.02 [1.17, 7.78]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
18.4 Total failure day 42 PCR-unadjusted	2	1123	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.54, 1.38]

Analysis 18.1. Comparison 18: Supplementary: atovaquone-proguanil (AV+PG) versus WHO-recommended artemisinin-based combination therapy (ACT), Outcome 1: Total failure day 28 PCR-adjusted

Study or Subgroup	AV+PG Events	AV+PG Total	WHO-recommended ACT Events	WHO-recommended ACT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gurkov 2008	2	30	0	30	20.5%	5.00 [0.25 , 99.95]
Tahar 2014 (1)	6	64	2	68	79.5%	3.19 [0.67 , 15.22]
Total (95% CI)		**94**		**98**	**100.0%**	**3.56 [0.89 , 14.19]**
Total events:	8		2			

Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 1.80 (P = 0.07)
Test for subgroup differences: Not applicable



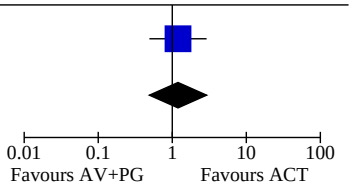
Footnotes

(1) Study described 'early treatment failures' included in total treatment failures as PCR was performed at day 7 and day 28.

Analysis 18.2. Comparison 18: Supplementary: atovaquone-proguanil (AV+PG) versus WHO-recommended artemisinin-based combination therapy (ACT), Outcome 2: Total failure day 28 PCR-unadjusted

Study or Subgroup	AV+PG Events	AV+PG Total	WHO-recommended ACT Events	WHO-recommended ACT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tahar 2014	9	64	8	68	100.0%	1.20 [0.49 , 2.91]
Total (95% CI)		**64**		**68**	**100.0%**	**1.20 [0.49 , 2.91]**
Total events:	9		8			

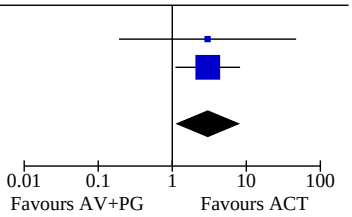
Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.69)
Test for subgroup differences: Not applicable



Analysis 18.3. Comparison 18: Supplementary: atovaquone-proguanil (AV+PG) versus WHO-recommended artemisinin-based combination therapy (ACT), Outcome 3: Total failure day 42 PCR-adjusted

Study or Subgroup	AV+PG Events	AV+PG Total	WHO-recommended ACT Events	WHO-recommended ACT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Carrasquilla 2012	1	52	1	156	9.1%	3.00 [0.19 , 47.12]
Van Vugt 2002 (1)	15	530	5	533	90.9%	3.02 [1.10 , 8.24]
Total (95% CI)		**582**		**689**	**100.0%**	**3.02 [1.17 , 7.78]**
Total events:	16		6			

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 2.28 (P = 0.02)
Test for subgroup differences: Not applicable



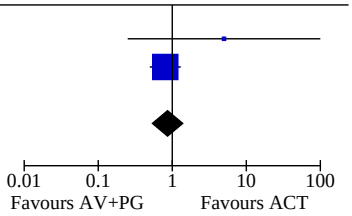
Footnotes

(1) Authors reported missing data as treatment failures; denominator was number randomized, not evaluable population.

Analysis 18.4. Comparison 18: Supplementary: atovaquone-proguanil (AV+PG) versus WHO-recommended artemisinin-based combination therapy (ACT), Outcome 4: Total failure day 42 PCR-unadjusted

Study or Subgroup	AV+PG Events	AV+PG Total	WHO-recommended ACT Events	WHO-recommended ACT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gurkov 2008	2	30	0	30	1.4%	5.00 [0.25 , 99.95]
Van Vugt 2002	28	530	35	533	98.6%	0.80 [0.50 , 1.30]
Total (95% CI)		**560**		**563**	**100.0%**	**0.86 [0.54 , 1.38]**
Total events:	30		35			

Heterogeneity: Chi² = 1.40, df = 1 (P = 0.24); I² = 29%
Test for overall effect: Z = 0.61 (P = 0.54)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Sensitivity analysis

Numerator	Analysis	Participants	Denominator	Numerator	Denominator
Primary analysis[a]	Exclusions after enrolment	Excluded[c]	Excluded	Excluded	Excluded
	Missing or indeterminate PCR[b]	Included as failures	Included	Excluded	Excluded
	New infections	Included as failures	Included	Excluded	Excluded
Sensitivity analysis 1[d]	As 'Primary analysis' except missing or indeterminate PCR	—	—	Included as failures	Included
Sensitivity analysis 2[e]	As 'Sensitivity analysis 1' except new infections	—	—	Included as successes	Included
Sensitivity analysis 3[f]	As 'Sensitivity analysis 2' except exclusions after enrolment	Included as failures	Included	Included as failures	Included

Table 1. Sensitivity analysis *(Continued)*

Sensitivity analysis 4[g]	As 'Sensitivity analysis 2' except exclusions after enrolment	Included as successes	Included	Included as successes	Included

[a]Note: participants who did not satisfy the inclusion criteria after randomization were removed from all calculations.
[b]PCR: polymerase chain reaction.
[c]'Excluded' means removed from the calculation.
[d]To reclassify all indeterminate or missing PCR results as treatment failures in the PCR-adjusted analysis.
[e]To reclassify all PCR-confirmed new infections as treatment successes in the PCR-adjusted analysis. (This analysis may overestimate efficacy as PCR is not wholly reliable and some recrudescences may be falsely classified as new infections. Also some participants may have gone on to develop a recrudescence after the new infection.)
[f]To reclassify all exclusions after enrolment (losses to follow-up, withdrawn consent, other antimalarial use, or failure to complete treatment) as treatment failures. For PCR-unadjusted total failure this represents a true worst-case scenario.
[g]To reclassify all exclusions after enrolment (losses to follow-up, withdrawn consent, other antimalarial use, or failure to complete treatment) as treatment successes.

Table 2. Comparison of Interventions

	WHO-recommended artemisinin-based combination therapy				Other antimalarials		
Study	**AV+PG**	**AL**	**AS+AQ**	**AS+MQ**	**AS+AV+PG**	**Other combinations**	**Monotherapy**
Anabwani 1999	√	—	—	—	—	—	HL
Borrmann 2003	√	—	—	—	—	—	AQ
Bouchaud 2000	√	—	—	—	—	—	HL
Carrasquilla 2012	√	√	—	√	—	—	—
De Alencar 1997	√	—	—	—	—	QN +TET	—
Giao 2004	√	—	—	—	—	CV8	—
Gurkov 2008	√	√	—	—	—	—	QN
Llanos-Cuentas 2001	√	—	—	—	—	—	CQ, SP
Looareesuwan 1999	√	—	—	—	—	—	MQ
Mulenga 1999	√	—	—	—	—	—	SP
Mulenga 2006	√	—	—	—	—	—	SP
Radloff 1996	√	—	—	—	—	—	AQ
Tahar 2014	√	—	√	—	√	—	—
Van Vugt 2002	√	—	—	√	√	—	—
Wojnarski 2019	√	—	—	—	√	—	—
McGready 2005	—	—	—	—	√	—	QN
Laufer 2012	—	—	—	—	—	CQ +AS,	CQ

Table 2. Comparison of Interventions *(Continued)*

						CQ +AV +PG, CQ +AZ	
Total number	15	2	1	2	4	3	11

AL: artemether-lumefantrine; AQ: amodiaquine; AS+AQ: artesunate-amodiaquine; AS+AV+PG: artesunate-atovaquone-proguanil; AS+MQ: artesunate-mefloquine; AV +PG: atovaquone-proguanil; CQ: chloroquine; CQ+AS: chloroquine-artesunate; CQ+AV+PG: chloroquine-atovaquone-proguanil; CQ+AZ: chloroquine-azithromycin; CV8: dihydroartemisinin-piperaquine-trimethoprim-primaquine; HL: halofantrine; MQ: mefloquine; QN: quinine; QN+TET: quinine-tetracycline; SP: sulfadoxine-pyrimethamine; WHO: World Health Organization.

Table 3. Outcome reporting

Study	Cure/failure rate	Adverse events	Parasite clearance time	Fever clearance time	Gametocyte carriage rate	Audiological outcomes	Other
Anabwani 1999	√	√	√	√	—	—	—
Borrmann 2003	√	√	√	√	—	—	—
Bouchaud 2000	√	√	√	√	—	—	—
Carrasquilla 2012	√	√	—	—	—	√	—
De Alencar 1997	√	√	√	√	—	—	—
Giao 2004	√	√	√	√	—	—	—
Gurkov 2008	√	√	—	—	—	√	—
Laufer 2012	√	√	—	—	—	—	√
Llanos-Cuentas 2001	√	√	√	√	—	—	—
Looareesuwan 1999	√	√	√	√	—	—	—
McGready 2005	√	√	√	√	√	—	√
Mulenga 1999	√	√	√	√	—	—	—

Table 3. Outcome reporting *(Continued)*

Mulenga 2006	√	√	—	√	—	—	—
Radloff 1996	√	√	√	√	—	—	—
Tahar 2014	√	√	√	√	—	—	√
Van Vugt 2002	√	√	√	√	√	—	—
Wojnarski 2019	√	√	√	√	√	—	√
Total number making comparison	17	17	13	14	3	2	4

Table 4. Trial dates, global region, and drug failure rates

Study	Trial dates	Region	Failure rate of AV+PG (+ partner drug)	Failure rate of comparators
Anabwani 1999	1994	Africa	6%	10%
Borrmann 2003	1999–2000	Africa	1–4%	4–47%
Bouchaud 2000	1994–1995	Returning travellers	0%	0%
Carrasquilla 2012	2007–2008	South America	2%	1–2%
De Alencar 1997	1995–1996	South America	0–1%	0%
Giao 2004	2001–2002	Asia	0–6%	0–5%
Gurkov 2008	2006	Africa	0–7%	0–23%
Laufer 2012	2007–2009	Africa	0% (+CQ)	0–1%
Llanos-Cuentas 2001	1995–1996	South America	0%	0–54%
Looareesuwan 1999	1993–1994	Asia	0%	0–14%
McGready 2005	2001–2003	Asia	0–3% (+AS)	0–45%
Mulenga 1999	1993–1994	Africa	0%	1%
Mulenga 2006	2000–2002	Africa	0–5%	1–22%
Radloff 1996	1994–1995	Africa	2%	19%
Tahar 2014	2008–2009	Africa	2–15%	0–12%
Van Vugt 2002	1998–2000	Asia	3–5%	1–7%
Wojnarski 2019	2014–2015	Asia	0–9%	0–8%

Failure rates presented to the nearest percentage. Shows range of failure rates reported at different outcome time points including both PCR-adjusted and PCR-unadjusted data.
AV+PG: atovaquone-proguanil; PCR: polymerase chain reaction.

Table 5. Crude PCR-adjusted failures for atovaquone-proguanil

Study	Total treatment failure day 28 PCR-adjusted		Observed rate
	Events	Total	
Gurkov 2008	2	30	6.67%
Tahar 2014	6	64	9.38%
Mulenga 2006	0	97	0%

Table 5. Crude PCR-adjusted failures for atovaquone-proguanil *(Continued)*

Wojnarski 2019	1	93	1.08%

Study	Total treatment failure day 42 PCR-adjusted		Observed rate
	Events	Total	
Carrasquilla 2012	1	152	0.66%
Van Vugt 2002	15	530	2.83%
Wojnarski 2019	9	98	9.18%

PCR: polymerase chain reaction.

Table 6. Studies comparing atovaquone-proguanil to other combinations or to monotherapy

Comparator	Studies	Efficacy findings	Adverse events
CV8	Giao 2004	Little or no difference between AV+PG and CV8 in PCR-unadjusted treatment failures day 28 (Analysis 5.1; Analysis 5.2).	Few adverse events reported.
QN+TET	De Alencar 1997	1 PCR-unadjusted treatment failure at day 28 reported (Analysis 6.1).	Auditory problems reported in QN group.
SP	Mulenga 1999; Llanos-Cuentas 2001; Mulenga 2006	3 RCTs contributed data to analysis. Little or no difference for PCR-adjusted treatment failures at day 28 (Analysis 7.1). Greater PCR-unadjusted treatment failures at day 28 for SP (Analysis 7.2).	Large numbers of adverse events reported, but little or no difference between AV+PG and SP.
QN	Gurkov 2008	Study reported PCR adjusted data at day 28, and unadjusted data at day 42. Little or no difference for PCR-adjusted treatment failures at day 28 (Analysis 8.1) or PCR-unadjusted treatment failures at day 42 (Analysis 8.2).	Small numbers of adverse events reported. Little or no difference between AV+PG and QN.
MQ	Looareesuwan 1999	Fewer PCR-unadjusted treatment failures at day 28 for AV+PG compared to MQ (Analysis 9.1).	Several adverse events reported. Both nausea and vomiting symptoms and abnormal liver function tests more frequent with AV+PG versus MQ (Analysis 9.3).
AQ	Radloff 1996; Borrmann 2003	2 RCTs contributed data to analysis. Fewer failures PCR-unadjusted failures at day 28 for AV+PG compared to AQ (Analysis 10.1).	Several adverse events reported. Asthenic conditions, pruritis, sleep disturbance, and dizziness more common in the AQ group. Nausea and vomiting more common in AV+PG group.
CQ	Llanos-Cuentas 2001	1 small RCT (27 participants). Fewer PCR-unadjusted failures at day 28 for AV-PG compared to CQ (Analysis 11.1).	Several adverse events reported with little or no difference between groups. Headaches more common in CQ group.

Table 6. Studies comparing atovaquone-proguanil to other combinations or to monotherapy *(Continued)*

HL	Anabwani 1999; Bouchaud 2000	2 RCTs contributed data to analysis. Little or no difference between AV+PG and HL in PCR-unadjusted treatment failures day 28 (Analysis 12.1).	Nausea and vomiting seen more frequently with AV+PG compared to HL.

AQ: amodiaquine; CQ: chloroquine; CV8: dihydroartemisinin-piperaquine-trimethoprim-primaquine; HL: halofantrine; MQ: mefloquine; QN: quinine; QN+TET: quinine-tetracycline; RCT: randomized controlled trial; SP: sulfadoxine-pyrimethamine.

APPENDICES

Appendix 1. Search strategy

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	Embase[b]	LILACS[b]
1	atovaquone	atovaquone	malaria	malaria	malaria
2	proguanil	proguanil	Exp MALARIA	Exp MALARIA	proguanil
3	Malarone	Malarone	1 or 2	1 or 2	atovaquone
4	malaria	malaria	atovaquone	atovaquone	Malarone
5	—	—	proguanil	proguanil	—
6	—	—	Atovaquone-proguanil	Atovaquone-proguanil	—
7	—	—	chloriguane	chloriguane	—
8	—	—	Chlorguanid*	cycloguanil	—
9	—	—	cycloguanil	7 or 8	—
10	—	—	7 or 8 or 9	5 or 9	—
11	—	—	5 or 10	4 and 10	—
12	—	—	4 and 10	6 or 11	—
13	—	—	6 or 12	Malarone	—
14	—	—	Malarone	12 or 13	—
15	—	—	13 or 14	3 and 14	—
16	—	—	3 and 15	—	—
17	—	—	—	—	—

[a]Cochrane Infectious Diseases Group Specialized Register.

[b]Search terms used in combination with the search strategy for retrieving trials developed by Cochrane; upper case: MeSH or EMTREE heading; lower case: free-text term.

Appendix 2. Abbreviations

Antimalarials

Monotherapy abbreviation	Name of antimalarial	Combination therapy abbreviation	Name of antimalarial
AQ	Amodiaquine	AL	Artemether-lumefantrine
AM	Artemether	AS+AQ	Artesunate-amodiaquine
ART	Artemisinin	AS+AV+PG	Artesunate-atovaquone-proguanil
AS	Artesunate	AS+MQ	Artesunate-mefloquine
AV	Atovaquone	AV+PG	Atovaquone-proguanil
AZ	Azithromycin	CV8	Dihydroartemisinin-piperaquine-trimethoprim-primaquine
CL	Clindamycin	SP	Sulfadoxine-Pyrimethamine
CQ	Chloroquine	QN+TET	Quinine-Tetracycline
DHA	Dihydroartemisinin	CQ+AV+PG	Chloroquine-Atovaquone-Proguanil
HL	Halofantrine	CQ+AS	Chloroquine-Artesunate
LUM	Lumefantrine	CQ+AZ	Chloroquine-Azithromycin
MQ	Mefloquine		
NQ	Naphthoquine		
PIP	Piperaquine		
PQ	Primaquine		
PG	Proguanil		
SX	Sulfadoxine		
QN	Quinine		
TET	Tetracycline		

Others

ACPR: clinical and parasitological response

ACT: artemisinin-based combination therapy

CENTRAL: Cochrane Central Register of Controlled Trials

CI: confidence interval

CIDG: Cochrane Infectious Diseases Group

GRADE: Grading of Recommendations, Assessment, Development and Evaluation

MedDRA: Medical Dictionary for Regulatory Activities

P falciparum: *Plasmodium falciparum*

PCR: polymerase chain reaction

PCV: packed cell volume

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCT: randomized controlled trial

RR: risk ratio

WHO: World Health Organization

Appendix 3. Prespecified changes for review update 2021

Protocol section	Refreshed protocol
Background	We updated the title to reflect that the review pertains to *Plasmodium falciparum* malaria, and follows Cochrane title conventions. We updated information in the background to follow the advised Cochrane/MECIR subheading structure. We updated the background to reflect the current global policy setting on malaria. The main review question has acquired a new relevance in the context of emerging artemisinin resistance; we reflected this in the updated protocol.
Research question	The existing PICO (population, intervention, comparison, outcome) remained relevant. We updated the protocol to incorporate WHO standards on reporting of malaria trials. These are in harmony with other Cochrane Reviews of malaria. Our protocol did not incorporate participant-reported outcomes. In accordance with Cochrane guidelines, we restricted the number of primary and secondary outcomes. The inclusion criteria remain limited to randomized controlled trials.
Methods	We updated the description of the 'Risk of bias' tool. We added a plan to summarize the evidence using the GRADE approach.

This table was approved by the Cochrane Infectious Diseases Group editorial team on 27 April 2018.

WHAT'S NEW

Date	Event	Description
14 January 2021	New citation required and conclusions have changed	A new author team (Andrew Blanshard and Paul Hine) prepared this review. We have rewritten the protocol, updated the back-

Date	Event	Description
		ground to reflect changes in the field, updated the outcomes of the review, and used newer Cochrane methodology.
14 January 2021	New search has been performed	We aligned the outcomes with the emerging core outcome set used by the Cochrane Infectious Diseases Group. This led us to remove the following secondary outcomes from the original protocol. • Treatment failure by day 14: we replaced this with early treatment failure. • Parasite clearance time: we omitted this as there is commonly heterogeneity in measures of parasite clearance time between studies, as encountered in previous Cochrane Reviews (see Esu 2014). The preferred measure would be parasite clearance rate using the WWARN calculator (Flegg 2011), but we did not include as the frequent sampling required may be too demanding for trials in resource-limited settings. • Fever clearance time: we omitted this as there was overlap with early treatment failure. • Progression to severe malaria: we omitted this as there was overlap with early treatment failure and treatment failure at day 28 and day 42. An updated protocol was approved by the CIDG editorial team on 27 April 2018, and the changes are described in Appendix 3. In a change to the protocol, we focused comparisons on WHO-approved ACT, and presented the other comparisons in narrative format as we consider this will be of more relevance to current clinical practice.

HISTORY

Protocol first published: Issue 4, 2003
Review first published: Issue 4, 2005

Date	Event	Description
5 August 2008	Amended	Converted to new review format with minor editing.

CONTRIBUTIONS OF AUTHORS

PH and AB updated the protocol of this review in March 2018. They both extracted data from all studies, completed the 'risk of bias' assessments, results, summary of findings, and analysis.

Both review authors read and approved the final manuscript.

DECLARATIONS OF INTEREST

AB has no known conflicts of interest. He is a doctor working full time within the UK National Health Service (NHS).

PH was previously employed full-time by the Cochrane Infectious Diseases Group (CIDG), is a CIDG Editor, and currently works full-time within the UK NHS. He received a Registration Scholarship to attend the 23rd Annual British HIV Association Conference 2017 from ViiV healthcare. ViiV had no involvement in the selection of recipients of the scholarship. In 2018, he attended a CPD certified clinical research training programme organized and funded by Gilead Sciences Europe Ltd. To the best of his knowledge, neither financial nor non-financial conflicts of interests have influenced the current submitted work.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK

External sources

- Foreign, Commonwealth and Development Office (FCDO), UK

  Project number 300342-104

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

An updated protocol was approved by the CIDG editorial team on 27 April 2018, and the changes are described in Appendix 3. In a change to the protocol, we focused comparisons on WHO-approved ACT, and presented the other comparisons in narrative format as we consider this will be of more relevance to current clinical practice.

We intended to explore heterogeneity using subgroup analysis, but there were too few trials in each comparison to yield meaningful results.

We intended to conduct a sensitivity analysis adding excluded groups back into the analysis in using stepwise methods. Given the small number of trials included for each comparison, we did not pursue this, but the planned analysis is presented in Table 1 for reference.

INDEX TERMS

Medical Subject Headings (MeSH)

Antimalarials [*therapeutic use]; Atovaquone; Drug Combinations; Malaria, Falciparum [*drug therapy]; Naphthoquinones [*therapeutic use]; Proguanil [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans