

# Amodiaquine for treating malaria (Review)

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[Intervention Review]

# Amodiaquine for treating malaria

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## ABSTRACT

### Background

Amodiaquine has been widely used to treat malaria. Fatal adverse reactions have been reported in adults taking it for prophylaxis. This has led some authorities to suggest it is withdrawn as a first line treatment for malaria.

### Objectives

To compare amodiaquine with chloroquine or sulfadoxine-pyrimethamine for treating uncomplicated *Plasmodium falciparum* malaria.

### Search strategy

We searched the Cochrane Infectious Diseases Group specialized trials register (February 2003), The Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 1, 2003), MEDLINE (1966 to February 2003), EMBASE (1980 to December 2002), LILACS (February 2003). We contacted researchers in the field and pharmaceutical companies.

### Selection criteria

Randomised and quasi-randomised trials.

### Data collection and analysis

Two reviewers independently extracted data and assessed trial quality.

### Main results

56 studies included, mostly from Africa. Treatment allocation was adequately concealed in three trials, and unclear or inadequate in the remainder. Amodiaquine was more effective than chloroquine for parasite clearance (day 7, Peto odds ratio 4.42 (95% confidence interval 3.65 to 5.35); day 14, Peto odds ratio 6.44 (95% confidence interval (CI) 5.09 to 8.15). Comparisons with sulfadoxine/pyrimethamine were more mixed, with sulfadoxine/pyrimethamine more effective on day 28 (Peto odds ratio 0.41; 95% CI 0.28 to 0.61). No significant difference for adverse events was observed between amodiaquine and chloroquine and sulfadoxine/pyrimethamine. Reported adverse effects were minor or moderate. No life threatening events were detected.

## Authors' conclusions

There is evidence to support the continued use of amodiaquine to treat uncomplicated malaria, although local drug resistance patterns need to be considered. Monitoring for adverse events should continue.

*This review summarizes trials up to 2003. For the reasons in the 'What's new' section, this review will no longer be updated.*

## PLAIN LANGUAGE SUMMARY

### Amodiaquine for treating malaria

Plain language summary pending.

## BACKGROUND

Amodiaquine (AQ) is a 4-aminoquinoline, similar to chloroquine (CQ), that has been used widely to treat and prevent malaria. AQ is a cheap alternative to CQ, and is available in several countries, some with local production facilities. It is more palatable than CQ and therefore easier to administer to children. It has also been suggested that it may be a less toxic alternative to sulphadoxine-pyrimethamine (SP) in people infected with HIV in Sub Saharan Africa (Coopman 1993). It is also used in combination with the antimalarial drugs artesunate and SP. These combinations are the subject of other Cochrane Reviews (IASG 2002; MacIntosh 2002).

Amodiaquine was first added to the World Health Organization (WHO) Essential Drugs List (EDL) in 1977. In 1979, the committee decided to delete it from the List due to its similarity with CQ. However, it was quickly reinstated in the same year (WHO 2002). In the mid 1980s, fatal adverse drug reactions were described in travellers using AQ for prophylaxis (Hatton 1986; Nefel 1986). As a result, the manufacturer (Parke-Davis) modified the labelling and withdrew prophylaxis as an indication, while, in 1988, the WHO deleted it from the EDL and prevented its use in malaria control programmes (WHO 1990).

The WHO's recommendations confused policy and practice. Several countries banned its use altogether, whilst others have continued to use the drug as first line treatment for uncomplicated malaria - either giving it alone or in combination with other drugs. In the light of this, the 19th Expert Committee on Malaria, held in 1993, modified their statement to say that "amodiaquine could be used for treatment if the risk of infection outweighs the potential for ADRs [adverse drug reactions]", but still did not recommend AQ as first line treatment (WHO 1993).

This Cochrane Review, first published in 1996, compares the effectiveness of AQ, CQ and SP for treating uncomplicated falciparum malaria. The 1996 version concluded that AQ was a valuable drug and supported its continued use for the treatment of uncomplicated malaria with the proviso that, due to the partial cross-resistance with CQ, research must continue into both its effectiveness and safety. These findings led the WHO to modify its recommendations and reinstate AQ as an option for treating falciparum malaria (WHO 1997).

## OBJECTIVES

To compare amodiaquine with chloroquine and sulphadoxine-pyrimethamine for treating uncomplicated malaria in adults and children.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomized and quasi-randomized controlled trials conducted during and after 1980.

The year restriction takes account of the changing patterns of resistance development to antimalarial drugs, which can affect the treatment outcome.

## Types of participants

Individuals with uncomplicated falciparum malaria infection. Defined as either:

- (1) fever or a history of fever, accompanied by *P. falciparum* parasitaemia (“symptomatic”) or;
- (2) *P. falciparum* parasitaemia detected through blood survey and no fever (“asymptomatic”).

## Types of interventions

### Intervention

Amodiaquine (AQ).

### Control

Chloroquine (CQ) or sulphadoxine-pyrimethamine (SP).

## Types of outcome measures

### Primary

Parasitological conversion, defined as conversion from a positive blood smear at baseline to a negative smear for *P. falciparum* at day 7, 14, or 28.

### Secondary

Time to sustained parasite clearance (restricted to days 0 through 7).

### Adverse events

Adverse events that are:

1. Fatal, life threatening, or require hospitalization;
2. Result in the discontinuation of treatment.

## Search methods for identification of studies

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

We used the following search terms for all trial registers and databases: malaria; amod\*.

We searched the Cochrane Infectious Diseases Group specialized trials register for relevant trials up to February 2003. Full details of the Cochrane Infectious Diseases Group methods and the journals hand searched are published in *The Cochrane Library* in the section on Collaborative Review Groups.

We searched the Cochrane Central Register of Controlled Trials, published in *The Cochrane Library* (Issue 1, 2003). This contains mainly reference information to randomized controlled trials and controlled clinical trials in health care.

We searched the following electronic databases using the topic search terms in combination with the search strategy developed by the Cochrane Collaboration and detailed in the Cochrane Reviewers’ Handbook (Clarke 2003); MEDLINE (1966 to February 2003); EMBASE (1980 to December 2002); and LILACS (La Literatura Latinoamericana y del Caribe de Informacion en Ciencias de Salud) [www.bireme.br](http://www.bireme.br); accessed February 2003.

We contacted organizations, individual researchers working in the field, and pharmaceutical companies for unpublished and ongoing trials.

We sought unpublished and raw data by extensive liaison with experienced researchers in the field, and by requests to the pharmaceutical companies manufacturing the product. In view of the large amount of unpublished studies known to exist on amodiaquine, we contacted key researchers known to the World Health Organization and set up meetings, during which we explained the objectives of the systematic review, sought and collected data, reviewed and discussed the results.

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

## Data collection and analysis

### Selection of studies

The main author scanned the results of the literature search for potentially relevant trials. We retrieved the full articles for all trials thought to be potentially relevant. Three people independently assessed the potentially relevant trials for inclusion in the review.

### Data extraction and management

The data were extracted by two reviewers independently, using a data extraction form. Where there were disagreements, these were resolved by discussion. The data were entered into [Review Manager 5](#) by the main reviewer, and checked by Ms Mussano for all editions of the review. We contacted the authors to obtain additional data, unpublished components of studies, and to clarify details of the methods used.

### Assessment of risk of bias in included studies

We assessed the methodological quality of each included trial with respect to the generation of allocation sequence, allocation concealment, blinding, and loss to follow up.

## Data synthesis

We analysed data using [Review Manager 5](#).

Whenever possible, we contacted authors and asked them to help in the production of this review by reanalysing their data and/or to provide individual patient data to reanalyse the data using pre-specified outcome measures. In cases where the authors provided crude data, we entered these into a statistical package for analysis. To minimize selection bias and the effect of participant attrition, we calculated the proportion of parasitological conversion from the total number of participants reportedly “evaluable” on day 7, 14, and 28. “Success” was a participant who was assessed and had a negative smear, while “failures” were participants who were either assessed and had a positive smear, or were lost to follow up. We calculated the Peto odds ratio and 95% confidence intervals (log odds, Peto) for individual studies and in meta-analysis.

We calculated the time to sustained parasitological clearance, for individual studies and the pooled data, using the Kaplan-Meier method. We created two pools of data, dependent on the time points available for analysis, for trials using chloroquine as the comparator drug. Pool A had 6 time points (days 0, 1, 2, 3, 5, and 7); and pool B had assessments only on days 0, 1, 2, and 7. For trials of comparisons of amodiaquine (AQ) and sulphadoxine-pyrimethamine, we used 5 time points (day 0, 1, 2, 3, and 7). We used the log-rank test to compare the results in the AQ and comparator arms. Parasite clearance times, reported in the individual papers, measure the time to clearance of only those participants who were eventually cured, and exclude people that are treatment failures. However, in the various analyses described above, we considered all participants with a baseline positive smear regardless of whether they achieved parasite clearance or not.

## RESULTS

### Description of studies

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

[See Appendices]

### Eligibility

Of the 101 studies identified, 56 met the inclusion criteria. Where articles or communications reported more than one study; each study has been individually referenced (Appendix 1).

### Publication status and language

The eligible studies included both published (47) and unpublished (9) reports. We also analyzed the single patient data where

this was made available by the trialists or Parke-Davis (18 studies, published and unpublished). Single patient data accounted for approximately one fourth of total amodiaquine (AQ) participants in the studies compared with chloroquine (CQ) and approximately half of those comparing AQ with sulphadoxine-pyrimethamine (SP).

The studies were written in English (34); French (20); Portuguese (1); and Spanish (1).

### Study location

The majority of studies were conducted between 1983 and 2001 in the following Africa countries (Appendix 2): Burkina Faso (1); Cameroon (12); Congo (4); Equatorial Guinea (1); Gabon (2); Gambia (1); Ivory Coast (1); Kenya (17); Madagascar (2); Malawi (1); Mozambique (1); Nigeria (3); Senegal (3); Tanzania (2); and Uganda (1). Studies were also conducted in China (1); Brazil (1); Colombia (1); and the Philippines (1).

### Participants

A total number of 2429 participants were followed up in the 56 studies (Appendix 3). Comparisons of AQ with CQ were made in 41 studies (34 involving symptomatic participants and 7 involving asymptomatic participants); and comparisons of AQ with SP were made in 19 studies (all with symptomatic malaria). Appendix 1 shows the studies included.

The number of patients followed up decreases with the length of follow up, which ranges from 7 to 28 days (Appendix 2). This is due to the combined effect of fewer studies following up participants for longer periods and increasing dropout rates. Some studies only reported results at the end of the follow-up period, that is, with no results available at intermediate times. Appendix 5 summarises the evaluable patients.

### Interventions

AQ was administered, at doses ranging from 15.6 to 35 mg/kg, over three days. It was compared to CQ administered at doses ranging from 25 to 35 mg/kg over three days and SP (fixed ratio sulphadoxine:pyrimethamine of 1:20) administered as standard single dose of 25 mg of sulfadoxine (Appendix 2).

### Outcomes

All studies reported on the outcome of parasitological conversion (Appendix 4). Eighteen of these studies sought adverse outcomes, either clinical or laboratory.

As some studies conducted multiple comparisons and varied in their reporting of results at day 7, 14 and/or 28, the breakdown for individual comparisons do not add up to these totals. Considering

all parasitological outcomes, 1538 and 1166 AQ symptomatic patients were reported for the comparisons with CQ and SP, respectively. In the comparator arms, 101 asymptomatic infections and 1538 uncomplicated malaria cases were treated with CQ, while 1158 cases were treated with SP (Appendix 4).

## Risk of bias in included studies

### Generation of allocation sequence

Six trials specified the method of generating the allocation sequence; 22 mentioned randomization but were not specific about the method used; and 28 used other methods that appeared to be unbiased.

### Allocation concealment

Allocation was adequately concealed in three trials, and was either not clearly described or unconcealed in the remaining 53.

### Blinding

With the exception of one trial in the Philippines and one in China, no study was blinded.

### Loss to follow up

Nine studies used an intention-to-treat analysis with few losses to follow up. Eight trials reported exclusion levels of less than 10%, while in the remaining 23 trials, there was either no reporting of exclusions, or exclusions were greater than 10%.

Quality of number generation and analysis was better in the three trials with adequate concealment of allocation. There were 8 trials that scored low on all three quality parameters.

Diagnostic procedures varied between centres. In most, patients were admitted on the basis of thick and thin blood film results. No quality control of slide reading was mentioned in any of the studies. In Kenya, an observer checked 10% of slides without knowledge of the first reading.

## Effects of interventions

### Parasitological outcomes

#### I. Amodiaquine versus chloroquine

In 34 studies, a total of 1538 participants receiving amodiaquine (AQ) were compared with 1166 participants receiving chloroquine

(CQ). These studies were conducted at 33 different sites, 30 of them in Africa (accounting for 96% of the AQ participants), predominantly Kenya and Cameroon.

#### a. Parasitological conversion

##### i. Symptomatic participants

Twenty seven studies reported parasitological conversion. On day 7, a total of 1230 participants received AQ while 1234 received CQ. The parasitological conversion success rate ranged from 33% to 100% for AQ and from 9 to 100% for CQ. The meta-analysis shows that, on day 7, those receiving AQ had a statistically significantly higher level of parasitological conversion than those receiving CQ (Peto odds ratio (Peto OR) 4.42; 95% confidence interval (CI) 3.65 to 5.35). In this analysis, participants with a positive smear, or no data, on day 7 were deemed 'failures'.

One thousand six hundred and ten participants (802 receiving AQ; and 808 receiving CQ) were followed up to day 14. The parasitological conversion success rate ranged from 15% to 100% for AQ and from 10 to 93% for CQ. Participants receiving AQ experienced statistically significantly higher levels of parasitological conversion (Peto OR 6.44; 95% CI 5.09 to 8.15).

Only three studies reported results on day 28. Two hundred and fifty four participants received AQ while 248 received CQ. The parasitological conversion success rate ranged from 25% to 95% for AQ and from 24% to 58% for CQ. As for day 7 and day 14, participants receiving AQ experienced statistically significantly higher levels of parasitological conversion than those receiving CQ (Peto OR 3.62; 95% CI 2.49 to 5.29).

There was significant heterogeneity in all comparisons, as may be anticipated with varying age groups and malaria endemicities.

The Peto ORs for days 7, 14, and 28 should not be compared directly for two reasons: (1) participants who were not available for follow up at day 14 were simply excluded in most cases and; (2) some studies reported results on only one of the three visits.

No variation was observed when the analysis was restricted to the African studies. The Peto OR was 4.94 (95% CI 4.06 to 6.02) at day 7; 6.86 (95% CI 5.38 to 8.75) at day 14; and 3.62 (95% CI 2.49 to 5.29) at day 28.

##### ii. Asymptomatic participants

An additional nine studies tested AQ against CQ in people who were asymptomatic but found to be parasitaemic at cross sectional blood survey. In these studies, 543 participants received AQ and were compared to 586 participants who received CQ. AQ recipients experienced statistically significantly higher levels of parasitological conversion at day 7 than CQ recipients (Peto OR 3.64; 95% CI 2.65 to 5.00).

## **b. Time to sustained parasite clearance**

### ***i. Symptomatic participants***

Time to sustained parasite clearance (day 0 through 7) was calculated for participants with 6 data points (pool A: day 0, 1, 2, 3, 5, and 7) or 4 data points (pool B: day 0, 1, 2, and 7). Pool A comprised 3 studies with 108 AQ and 109 CQ recipients, of whom 99 and 78, respectively, achieved a sustained parasitological conversion. Pool B (11 studies) included 519 AQ and 509 CQ recipients, with 478 and 307 successes, respectively. The time to parasite clearance was significantly shorter for AQ in both analyses (log to rank  $p = 0.0025$  and  $0.0001$ , respectively).

### ***ii. Asymptomatic participants***

No data.

## **c. Adverse events**

No difference in event rate was seen between the two groups (Peto OR 0.85, 95% CI 0.50 to 1.42).

## **2. Amodiaquine versus sulphadoxine-pyrimethamine**

Sulphadoxine-pyrimethamine (SP) was used as comparator in 19 studies (16 from Africa), enrolling 1166 amodiaquine (AQ) and 1158 SP recipients ("evaluable patient population").

## **a. Parasitological conversion**

### ***i. Symptomatic participants***

Parasitological outcome was reported by 14 studies on day 7 and 14; five of these studies only reported results for day 14. Seven studies reported results on day 28.

On day seven, 824 participants received AQ while 818 received SP. The parasitological conversion success rate ranged from 42% to 100% for AQ and from 67% to 100% for SP. The graphical display shows no obvious trend, and meta-analysis did not demonstrate a statistically significant difference between AQ and SP for parasitological conversion (Peto OR 0.73; 95% CI 0.53 to 1.01). On day 14, 786 participants received AQ and 821 received SP. The parasitological conversion success rate ranged from 58% to 100% for AQ and from 65% to 100% for SP. As for day 7, the graphical display showed no trend and there was no statistically significant difference between AQ and SP for parasitological conversion (Peto OR 0.86; 95% CI 0.64 to 1.14).

By day 28, 667 participants remained in the analysis (345 receiving AQ; and 322 receiving SP). The parasitological conversion success rate ranged from 48% to 92% for AQ and from 54% to 100% for CQ. SP recipients had a statistically significantly higher level of parasitological conversion than AQ recipients (Peto OR 0.41; 95% CI 0.28 to 0.61).

The Peto ORs remained almost unchanged when the analyses were restricted to studies conducted in Africa, or to Africa after 1990 (when the use of SP started, particularly in the East and the South of the continent). In this latter case, the Peto ORs on day 7, 14, and 28 were 0.81 (95% CI 0.57 to 1.15); 0.92 (95% CI 0.68 to 1.23); and 0.58 (95% CI 0.37 to 0.91), respectively.

### ***ii. Asymptomatic participants***

Two of the AQ versus CQ studies (above), on asymptomatic *P.falciparum* infected participants, also had an SP arm. They enrolled 143 participants to receive AQ and 122 to receive SP, with a success rate on day 7 of 93% and 99%, respectively.

## **b. Time to sustained parasite clearance**

### ***i. Symptomatic participants***

The time to sustained parasitological clearance (days 0 to 7) was similar in the two groups. Participants had parasitological assessments on day 0, 1, 2, 3, and 7. Overall, 385 of the 424 participants receiving AQ, and 401 of the 451 participants receiving SP, reached the endpoint and remained negative until day 7 (log to rank  $p$  value = 0.27).

### ***ii. Asymptomatic participants***

No data available.

## **c. Adverse effects**

Three studies reported on this, with no obvious difference between the two groups (Peto OR 1.68, 95% CI 0.84 to 3.38). Results are summarised in Appendix 6.

Adverse events were reported for 52 AQ recipients (8.8%), 36 CQ recipients (8.8%), and 15 SP recipients (14.3%). The most commonly reported adverse events were gastrointestinal adverse events (nausea and vomiting) and pruritus. The adverse events were reportedly minor and moderate; no serious or life-threatening adverse events were reported among AQ recipients.

No statistically significant difference was observed in the incidence of adverse events between AQ and CQ recipients (Peto OR 0.85;

95% CI 0.50 to 1.42) or AQ and SP recipients (Peto OR 1.68; 95% CI 0.84 to 3.38).

A complete biochemical and haematological evaluation was performed for the 62 AQ and 59 CQ recipients recruited to a study in Ivory Coast. No difference was observed between the two groups. Neutrophil counts on thick smear were available for 191 AQ, 22 CQ, and 116 SP recipients from Kenya. Paired observations of neutrophil counts on day 14 (compared to baseline values of Ivory Coast and Kenya patients) showed no significant change.

A systematic review of prospective observational and experimental studies of adverse events is currently under way (MacLehose H, Klaes D, Garner P. Amodiaquine: a systematic review of adverse events [2003] (unpublished document)). This review will include additional studies to those reported in this Cochrane Review. The results of this review are available on <http://archives.who.int/eml/expcom/expcom13/Amodiaquine-adv-events.pdf>. We will update the Cochrane Review with a summary derived from the systematic review of adverse events in subsequent issues of the Cochrane Library.

## DISCUSSION

Some of the methodological deficiencies of articles and trials have inevitably led to a bias in the analyses. Most articles report data only on the patients deemed “evaluable” as per the protocol, usually those who completed the scheduled study period (7, 14, or 28 days). As no details were given on the “eligible” patients, and those prematurely discontinued, withdrawn, or lost to follow up, no true intent-to-treat analysis could be performed here. Obtaining raw data has partially rectified the problem, although a selection bias still remains in favour of sensitivity. In contrast, the criteria adopted in the analysis of efficacy (that is, missing data counted as failures) will introduce a bias toward resistance. In fact, non-attendees were shown to do well in an ad-hoc study in Kenya (C.Nevill, unpublished). The availability of data to reanalyze has led us to identify two populations, the “evaluable” patients, and those actually assessed at each target visit. The denominator did not vary substantially, though, and nor did the level of significance of the comparisons in the sets of patients.

The data are mainly from Africa (Eastern, Central, and Western countries) and, although a wide range of malaria epidemiological patterns and levels of drug resistance are represented, care should be taken in transposing these results elsewhere. In this review, amodiaquine (AQ) was found to be significantly more effective than chloroquine (CQ) in clearing parasites. With respect to sulphadoxine-pyrimethamine (SP), no difference in parasitological outcomes was observed within 7 days of study. However, SP showed superiority during longer-term follow up. This finding is not unexpected owing to the long half life of SP. Whether the difference observed is due to recrudescence parasites, or to re-in-

fections, cannot be verified. As reported previously, an improvement in symptomatic amelioration was apparent with AQ. This could be ascribed to the anti-inflammatory/antipyretic effect of the aminoquinolines.

Based on the results of this review, AQ (when administered at a dose of up to 35 mg/kg, over 3 days) appears to be no more toxic than CQ or SP when used for treating adults and children with uncomplicated falciparum malaria. Under these conditions of use, and within the limitations of the sample size, no severe, life-threatening or fatal adverse reaction occurred.

Location and year of study are potential confounders particularly for the comparison with SP. The efficacy of this drug is known to decline with use, due to the selection of parasites with increasing numbers of mutations in their genome associated with resistance.

After oral intake, AQ is rapidly and extensively metabolised to a pharmacologically active metabolite, desethylamodiaquine. Both AQ and desethylamodiaquine are chemically unstable in aqueous solutions, and undergo transformation yielding a protein-arylate quinone imine (Maggs 1988). The mechanism of toxicity of AQ seems not to be related to direct toxicity of the parent compound or metabolites in bone marrow cell precursors (Winstanley 1990), but rather to the immunogenic properties of the quinone imine (Clarke 1990). It is still unclear why, while most people exposed would have antidrug antibody, only very few people suffer from organ specific toxicity.

So far, serious and life-threatening adverse drug reactions have been described only during prophylaxis. Based on reported rates, the risk of serious adverse drug reactions associated with the prophylactic use of AQ can be estimated to be approximately 1:2,100 treatments for agranulocytosis; 1:15,500 for hepatotoxicity; and 1:30,000 for aplastic anaemia, with a total case fatality rate of 1:15,650 (Phillips-Howard, personal communication). The risk of fatal adverse drug reactions to AQ is in the same order of magnitude to that to SP.

Thus, AQ treatment appears to be safer than AQ prophylaxis.

## AUTHORS' CONCLUSIONS

### Implications for practice

This review has collected convincing evidence of amodiaquine (AQ) superiority over chloroquine (CQ), even in areas with considerable CQ resistance. Clearly, therefore, there is a role for AQ in areas with CQ resistance although the lifespan of that role may be curtailed by partial AQ cross resistance with CQ.

The comparison with sulphadoxine-pyrimethamine (SP) is potentially more important in view of the value of low cost antimalarial drugs and the concerns around the lifespan of long half-life sulfadugs after introduction for wide use in sub-Saharan Africa.

While the faster symptomatic recovery with AQ would not necessitate concurrent antipyretics, the longer protection induced by SP may prove a hazard long-term as it could encourage the selection of resistant parasites.

This review makes the most comprehensive attempt to date to identify all published and unpublished trials relevant to the inclusion criteria. Another review (A. Rietveld and P. Trigg, unpublished data), using a different methodology, also assessed the World Health Organisations (WHO) recommendation to no longer use AQ for treatment in malaria control programmes. This review was more prudent than practical, particularly in light of the limited availability of alternative affordable antimalarial drugs. When CQ, AQ, and SP are no longer effective, the next antimalarial drugs in line cost at least 7 to 60 times as much (A.Rietveld, personal communication). This places a full treatment course financially out of reach of many patients.

In terms of adverse events, this review of Randomised Controlled Trials (RCTs) has not identified a problem. It is apparent that serious and life threatening adverse drug reactions have been described only during prophylaxis in case reports.

### Implications for research

The review supports the continued use of AQ in the treatment of uncomplicated malaria, with the proviso that there is partial cross resistance between CQ and AQ, and that monitoring of

effectiveness, as well as surveillance for evidence of toxicity, must continue.

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

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

#### Brazil 1983-84

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	

#### Burkina Faso 1998

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

#### Cameroon 1998

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

#### Cameroon-Bangangte92

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-

**Cameroon-Bangangte92** *(Continued)*

Notes	-
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**Cameroon-Centre 1994**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Cameroon-East 1993**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Cameroon-Hevécam88-9**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Cameroon-Hévécam2001**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-

**Cameroon-Hévécam2001** (Continued)

Notes	-
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**Cameroon-Kumba1992**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Cameroon-South 1988**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Cameroon-South 1994a**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Cameroon-South 1994b**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-

**Cameroon-South 1994b** (Continued)

Notes	-
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**Cameroon-Yaounde 92**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Cameroon-Yaounde97-9**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**China 1986**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Colombia-Antioquia98**

Methods	see Appendices
Participants	-
Interventions	-

**Colombia-Antioquia98** (Continued)

Outcomes	-
Notes	-

**Congo 1992**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Congo-Brazzaville 86**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Congo-Brazzaville90**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Congo-P Noire 1986**

Methods	see Appendices
Participants	-

**Congo-P Noire 1986** *(Continued)*

Interventions	-
Outcomes	-
Notes	-

**Cote d'Ivoire 1993**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Equatorial Guinea 91**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Gabon 1997-8**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Gabon-Libreville 98**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Gambia 1994**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Kenya 1989**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Kenya-Eldoret 1994**

Methods	see Appendices
Participants	·
Interventions	·
Outcomes	·
Notes	·

**Kenya-Entosopia 91**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Kenya-Entosopia 94**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Kenya-Kibwezi 1997**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Kenya-Kilifi 1993**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Kenya-Malindi 1984**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Kenya-Malla 1994**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Kenya-Migori 1990**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Kenya-Mombasa 90**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Kenya-Nangina 1993**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Kenya-Ortum 1991**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Kenya-Sololo 1993**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Kenya-Taveta 1994**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Kenya-Turiani 1991**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Kenya-Turiani 1992**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Kenya-West 1987**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Madagascar 1983-4**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Madagascar 1985-6**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Malawi 1985**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Mozambique 1986**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Nigeria-Ibadan 1984**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Nigeria-Ibadan 1990**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Nigeria-Ibadan 2000**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Philippines 1984-5**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Senegal-Dakar 1996-8**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Senegal-Mlomp 1996-8**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Sénégal-Diohine 1996**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Tanzania-Centre 1988**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

**Tanzania-Kigoma 1997**

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

### Uganda-Kampala 1999

Methods	see Appendices
Participants	-
Interventions	-
Outcomes	-
Notes	-

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

Africa 1999	-
AfricaMadagascar83-6	Does not meet inclusion criteria.
Benin-Cotonou 1989	Does not meet inclusion criteria.
Cameroon 1987-90	-
Cameroon 1990a	Does not meet inclusion criteria.
Cameroon 1990b	-
Cameroon 1993-4	Does not meet inclusion criteria.
Cameroon 1996	-
Cameroon 1999	-
Cameroon 2000	-
Cameroon-Bafoussam00	-
Cameroon-Edea 1987	Does not meet inclusion criteria.
Cameroon-Eséka 1999	-
Cameroon-Mengang1999	-
Cameroon-Nlongkak 99	-
Cameroon-S Est 1993	Does not meet inclusion criteria.
Cameroon-S West 1989	Does not meet inclusion criteria.

(Continued)

Cameroon-South 1993	Does not meet inclusion criteria.
Cameroon-Urban 1990	-
Cameroon-Yaounde 96	-
Cameroon-Yaounde1988	Does not meet inclusion criteria.
Cameroon-Yaounde87-8	-
Congo 1985-9	-
Congo 1986-90	-
Cote d'Ivoire 1990	Does nor meet inclusion criteria.
Cote d'Ivoire 1995	-
Gabon 1995	-
India 1952	-
India 1989-90	Does not meet inclusion criteria.
India 1989-92	-
Kenya 1993	-
Kenya 1998	-
Liberia 2000-01	-
Madagascar 1983a	Does not meet inclusion criteria.
Madagascar 1983b	-
Madagascar 1983c	-
Pakistan 1997	-
PapuaNewGuinea 1989	Does not meet inclusion criteria.
PapuaNewGuinea 1991	Does not meet inclusion criteria.
RCA 1984-6	Does not meet inclusion criteria.
Rwanda 1986	Does not meet inclusion criteria.
Sénégal 1997	-

(Continued)

Tanzania 1988	Does not meet inclusion criteria.
Uganda 1988	-
Uganda-Kampala 94-7	-
Zanzibar 1989	Does not meet inclusion criteria.

## DATA AND ANALYSES

### Comparison 1. Amodiaquine vs chloroquine in symptomatic participants

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitological conversion	35		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Day 7	27	2464	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.42 [3.65, 5.35]
1.2 Day 14	18	1610	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.44 [5.09, 8.15]
1.3 Day 21 to 28	3	502	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.62 [2.49, 5.29]
2 Adverse events	8	824	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.85 [0.50, 1.42]

### Comparison 2. Amodiaquine vs chloroquine in asymptomatic participants

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitological conversion on day 7	9	1129	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.64 [2.65, 5.00]

### Comparison 3. Amodiaquine vs sulphadoxine-pyrimethamine in symptomatic participants

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitological conversion	19		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 day 7	14	1642	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.73 [0.53, 1.01]
1.2 day 14	14	1607	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.86 [0.64, 1.14]
1.3 day 21-28	7	667	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.41 [0.28, 0.61]
2 Adverse events	3	232	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.68 [0.84, 3.38]

### Comparison 4. AQ VS. CQ in symptomatic participants: Africa (sensitivity analysis)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitological conversion	32		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 day 7	25	2371	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.94 [4.06, 6.02]
1.2 day 14	16	1539	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.86 [5.38, 8.75]
1.3 day 21-28	3	502	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.62 [2.49, 5.29]

**Comparison 5. AQ vs SP in symptomatic participants: Africa (sensitivity analysis)**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitological conversion	16		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 day 7	12	1505	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.57, 1.13]
1.2 day 14	13	1576	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.84 [0.63, 1.12]
1.3 day 21-28	6	596	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.44 [0.29, 0.66]

**Comparison 6. AQ vs SP in symptomatic participants: Africa after 1990 (sensitivity analysis)**

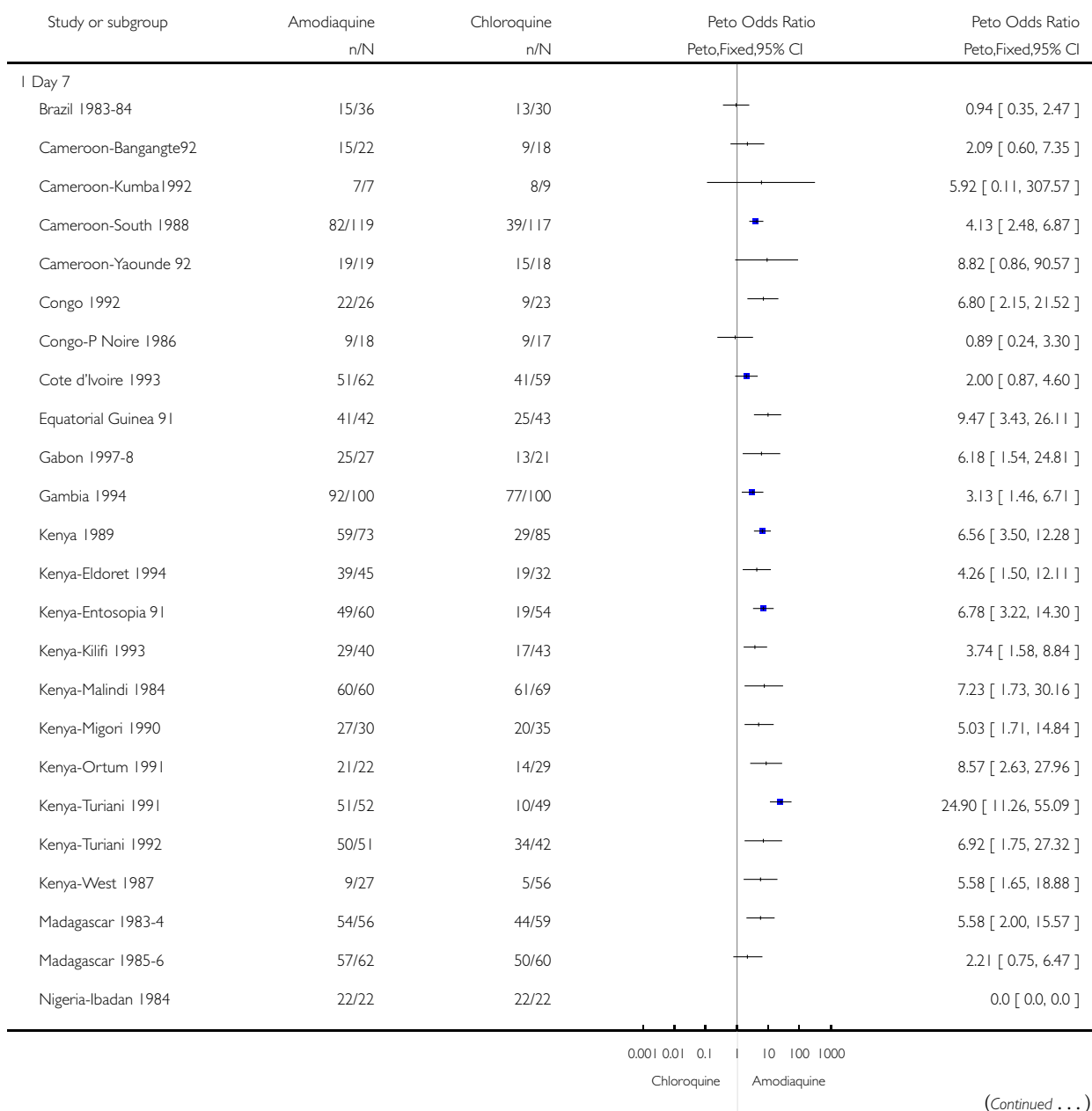
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitological conversion	13		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 day 7	8	1189	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.81 [0.57, 1.15]
1.2 day 14	10	1344	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.92 [0.68, 1.23]
1.3 day 21-28	4	475	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.58 [0.37, 0.91]

## Analysis 1.1. Comparison 1 Amodiaquine vs chloroquine in symptomatic participants, Outcome 1 Parasitological conversion.

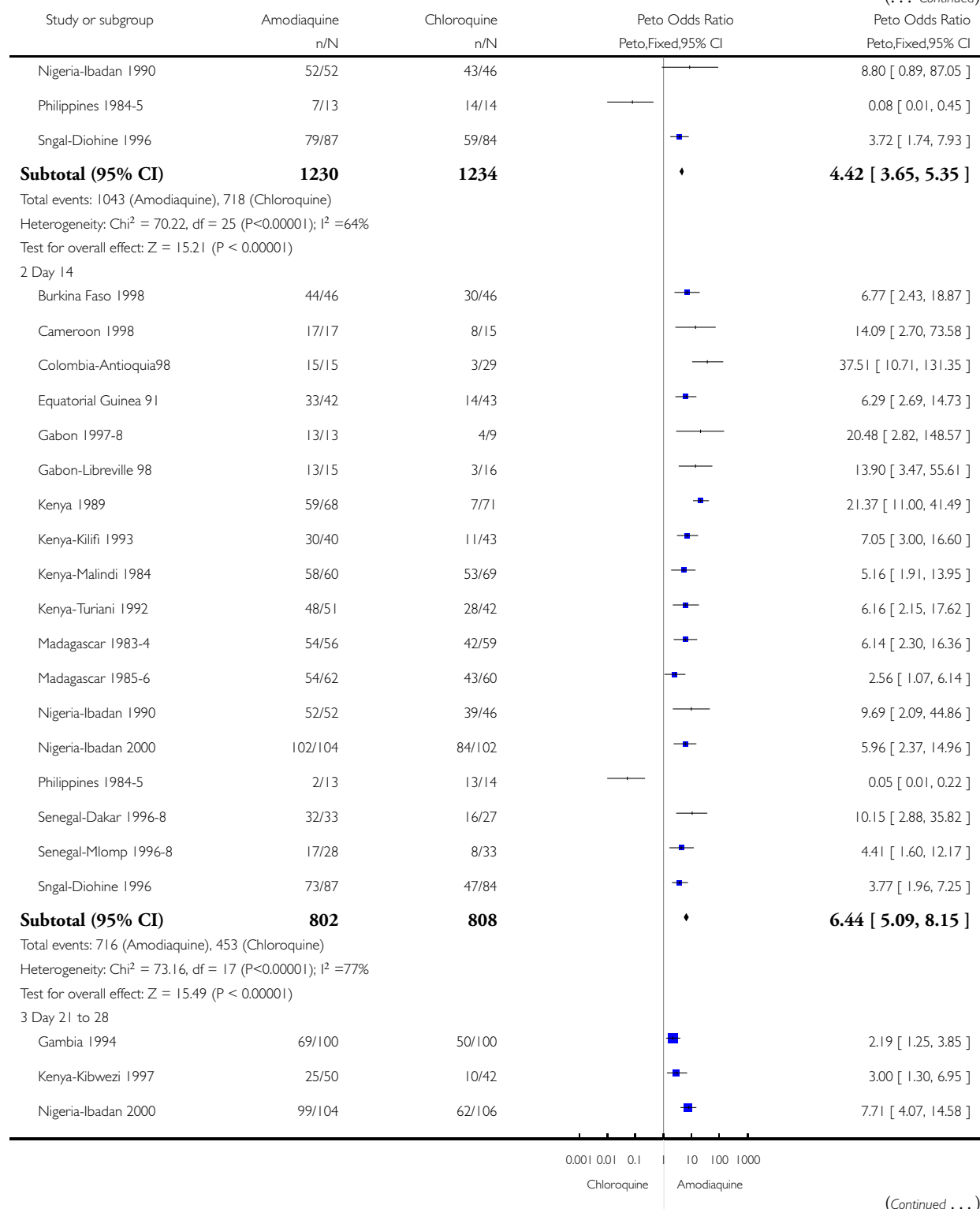
Review: Amodiaquine for treating malaria

Comparison: 1 Amodiaquine vs chloroquine in symptomatic participants

Outcome: 1 Parasitological conversion

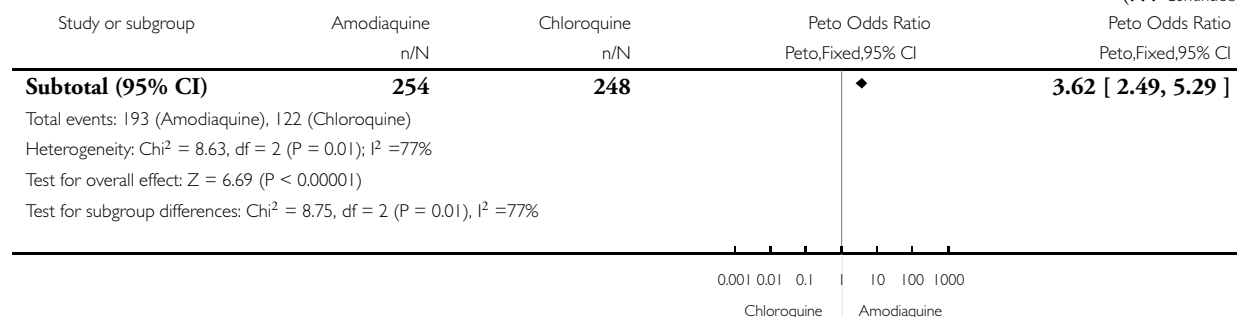


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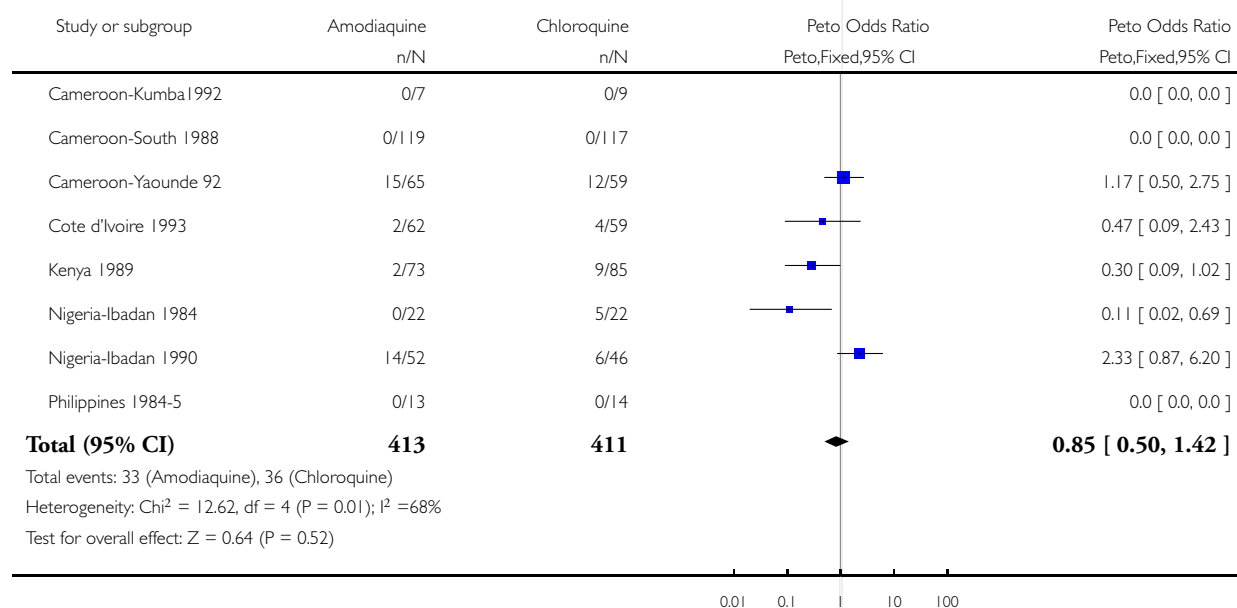


### Analysis 1.2. Comparison 1 Amodiaquine vs chloroquine in symptomatic participants, Outcome 2 Adverse events.

Review: Amodiaquine for treating malaria

Comparison: 1 Amodiaquine vs chloroquine in symptomatic participants

Outcome: 2 Adverse events

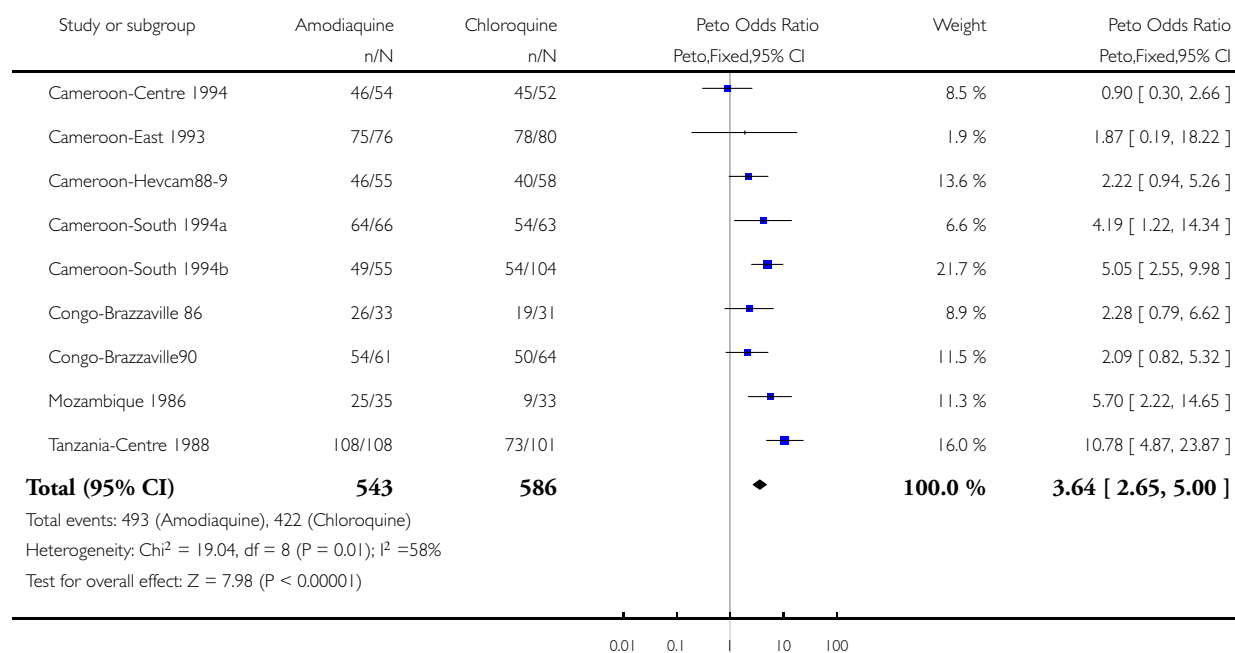


## Analysis 2.1. Comparison 2 Amodiaquine vs chloroquine in asymptomatic participants, Outcome 1 Parasitological conversion on day 7.

Review: Amodiaquine for treating malaria

Comparison: 2 Amodiaquine vs chloroquine in asymptomatic participants

Outcome: 1 Parasitological conversion on day 7

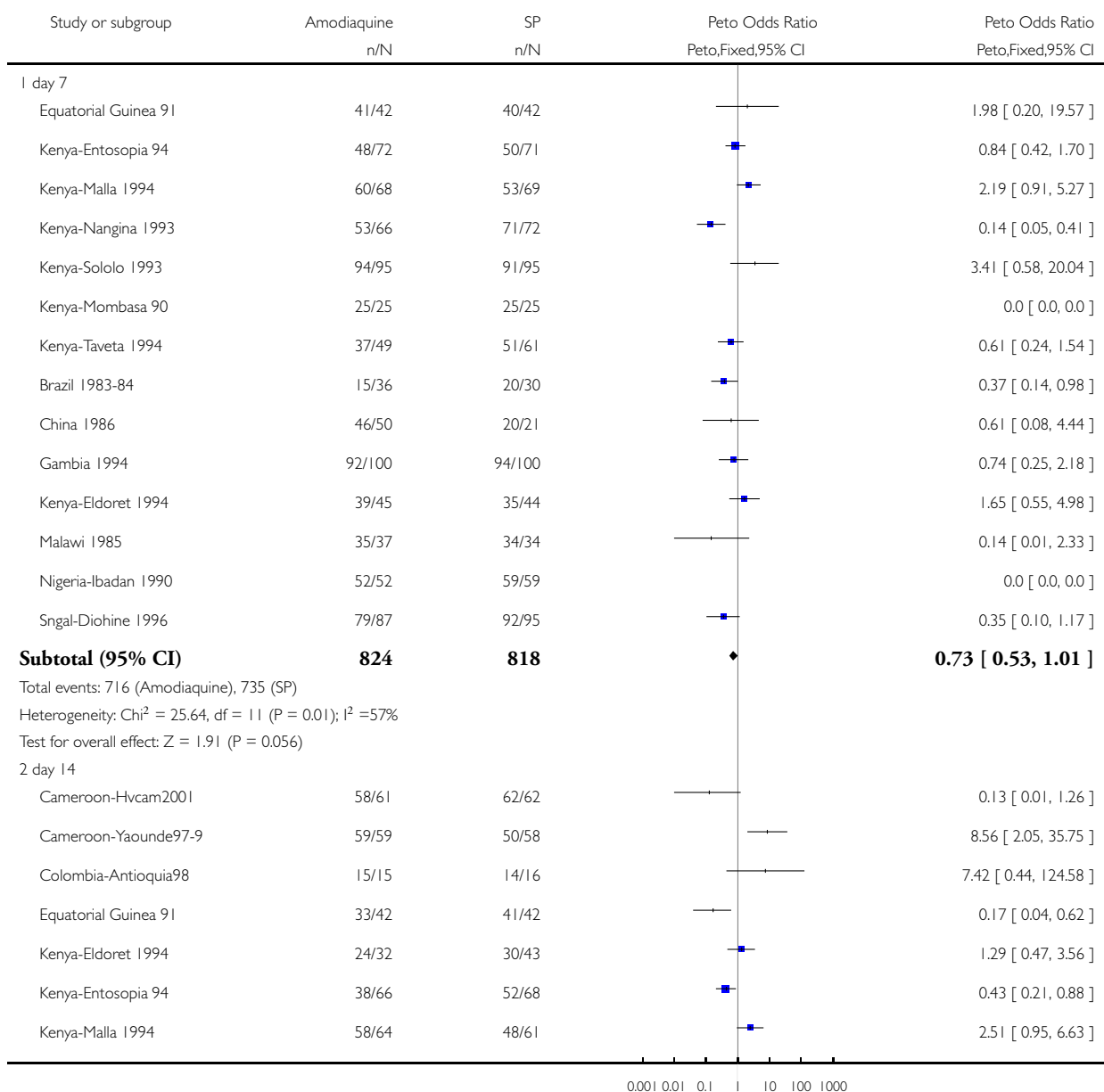


### Analysis 3.1. Comparison 3 Amodiaquine vs sulphadoxine-pyrimethamine in symptomatic participants, Outcome 1 Parasitological conversion.

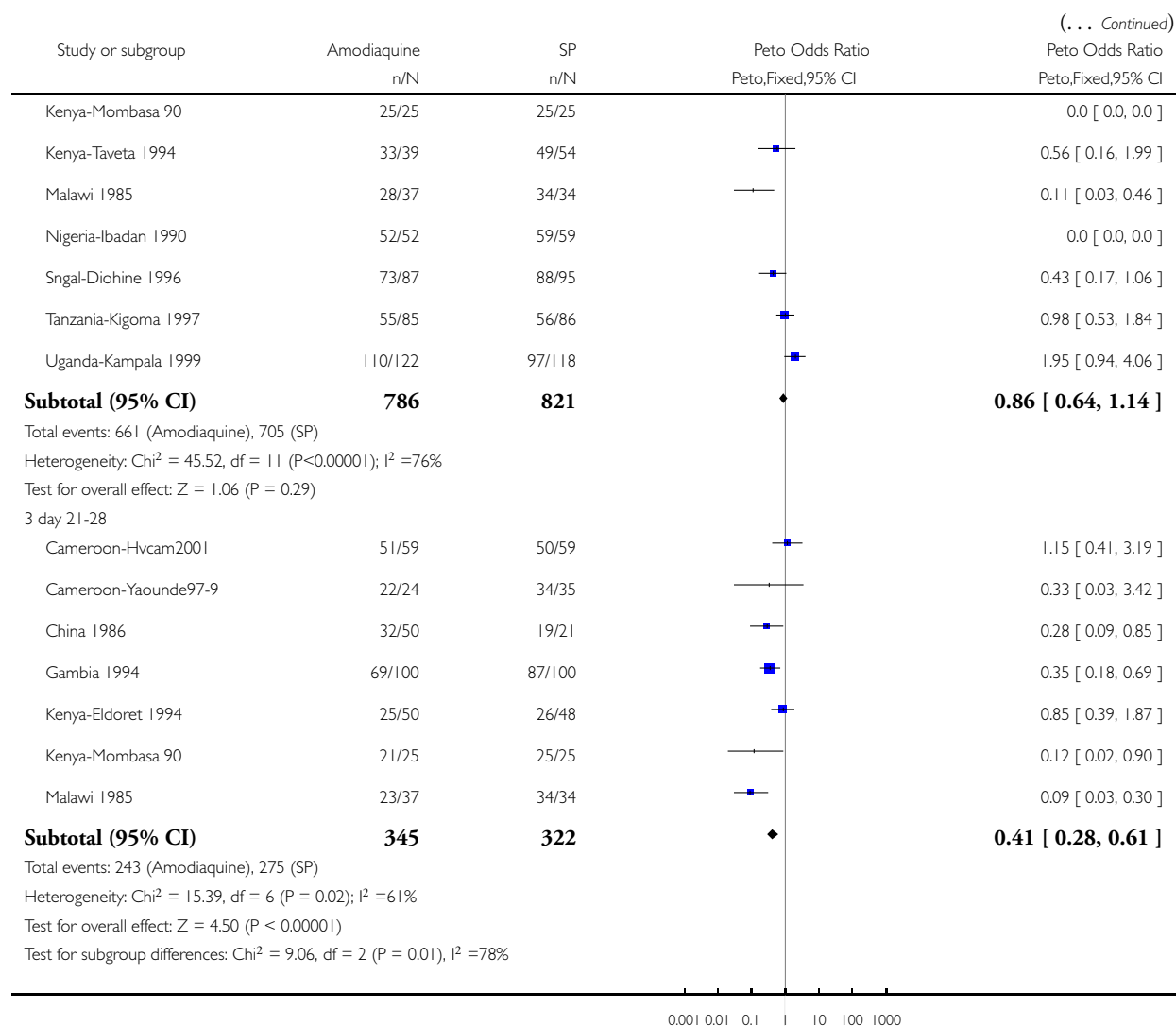
Review: Amodiaquine for treating malaria

Comparison: 3 Amodiaquine vs sulphadoxine-pyrimethamine in symptomatic participants

Outcome: 1 Parasitological conversion



(Continued . . .)

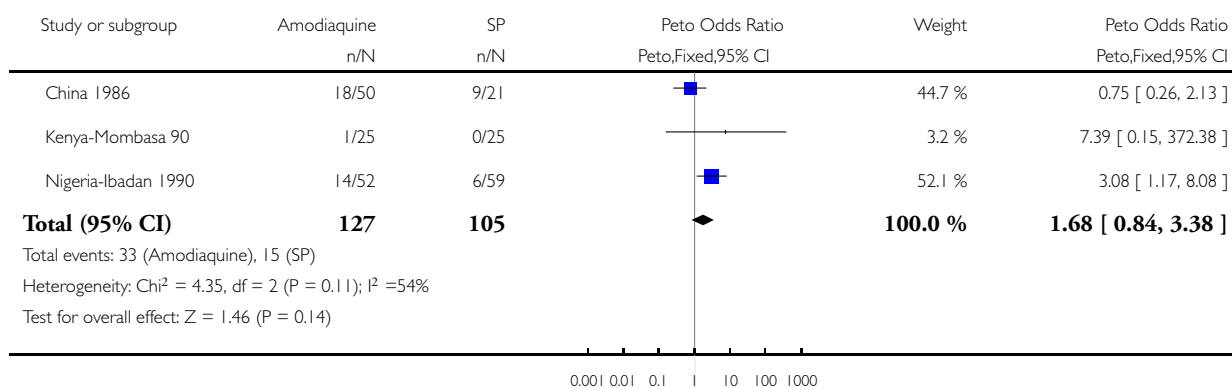


### Analysis 3.2. Comparison 3 Amodiaquine vs sulphadoxine-pyrimethamine in symptomatic participants, Outcome 2 Adverse events.

Review: Amodiaquine for treating malaria

Comparison: 3 Amodiaquine vs sulphadoxine-pyrimethamine in symptomatic participants

Outcome: 2 Adverse events

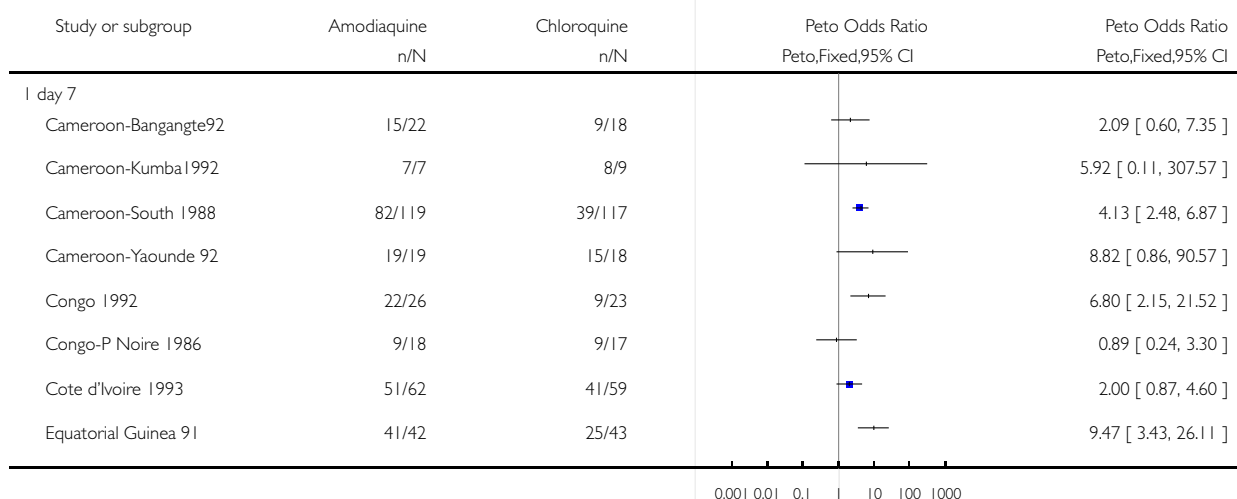


### Analysis 4.1. Comparison 4 AQ VS. CQ in symptomatic participants: Africa (sensitivity analysis), Outcome 1 Parasitological conversion.

Review: Amodiaquine for treating malaria

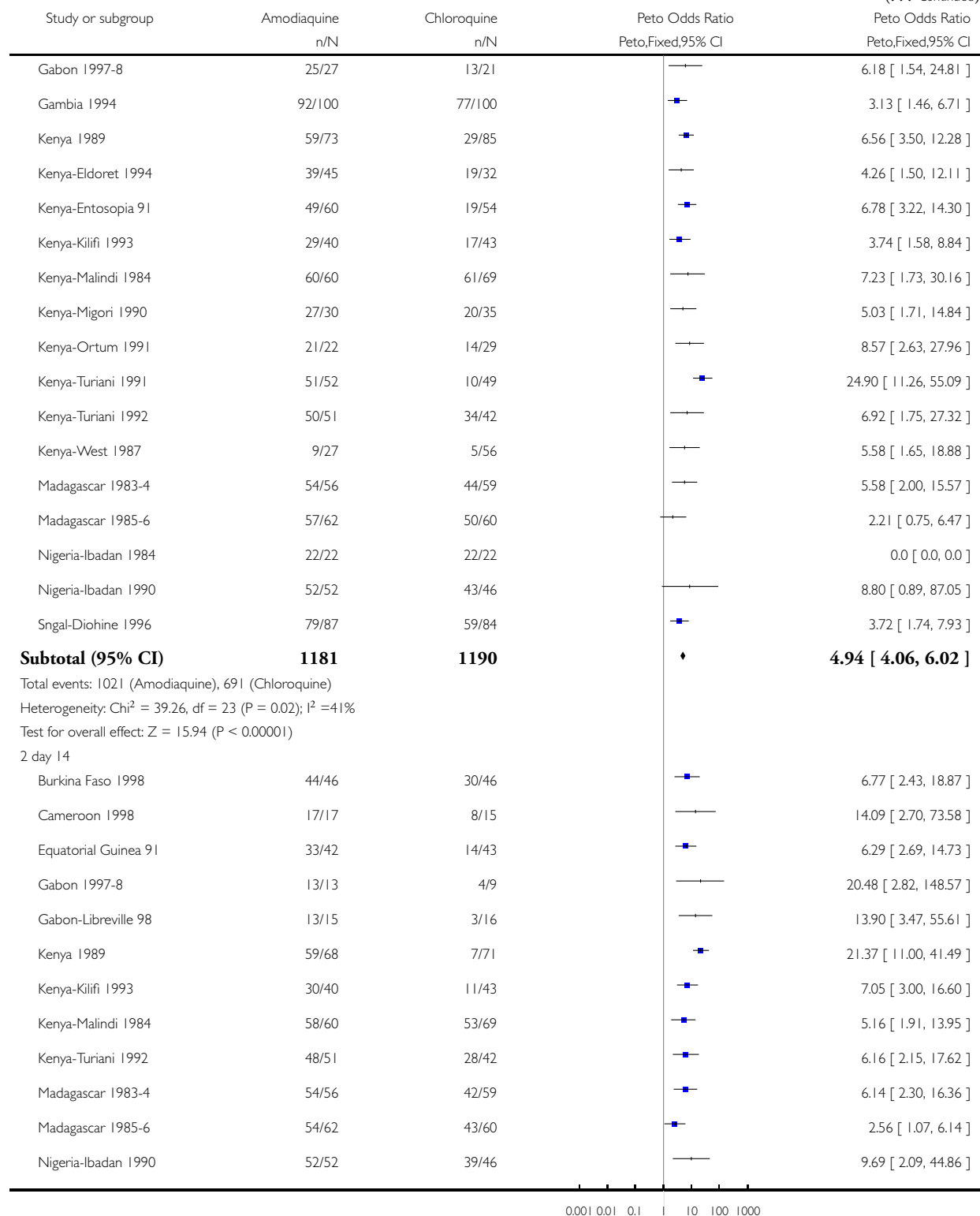
Comparison: 4 AQ VS. CQ in symptomatic participants: Africa (sensitivity analysis)

Outcome: 1 Parasitological conversion

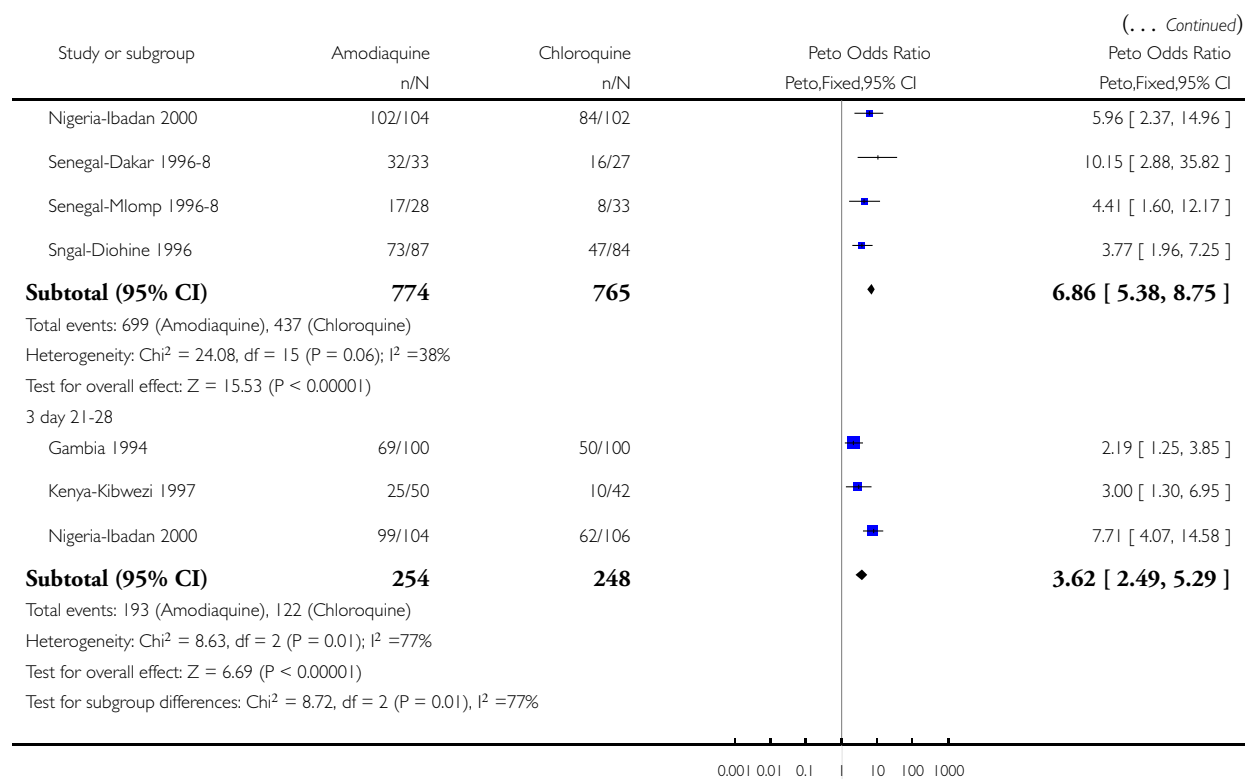


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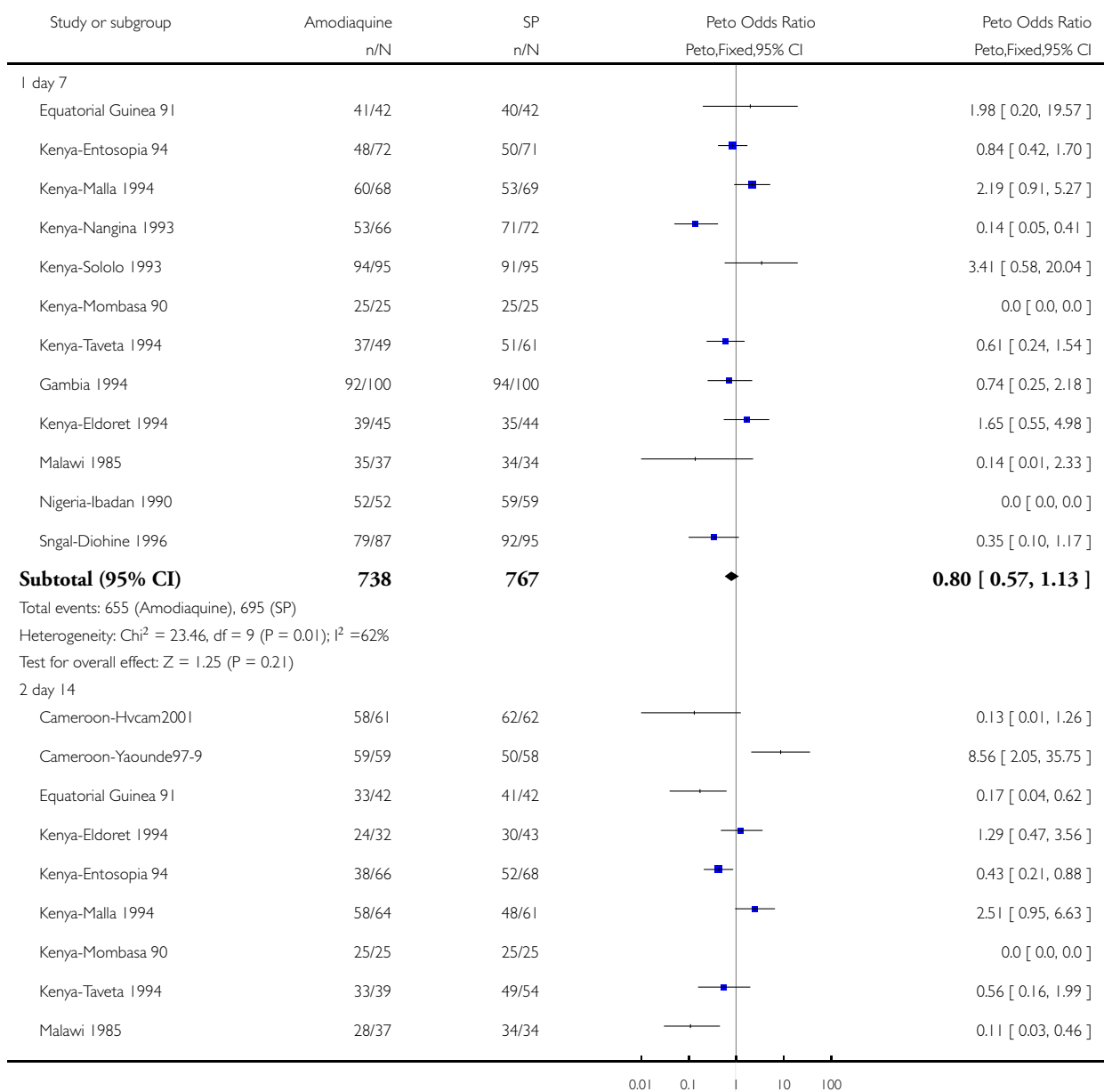


### Analysis 5.1. Comparison 5 AQ vs SP in symptomatic participants: Africa (sensitivity analysis), Outcome I Parasitological conversion.

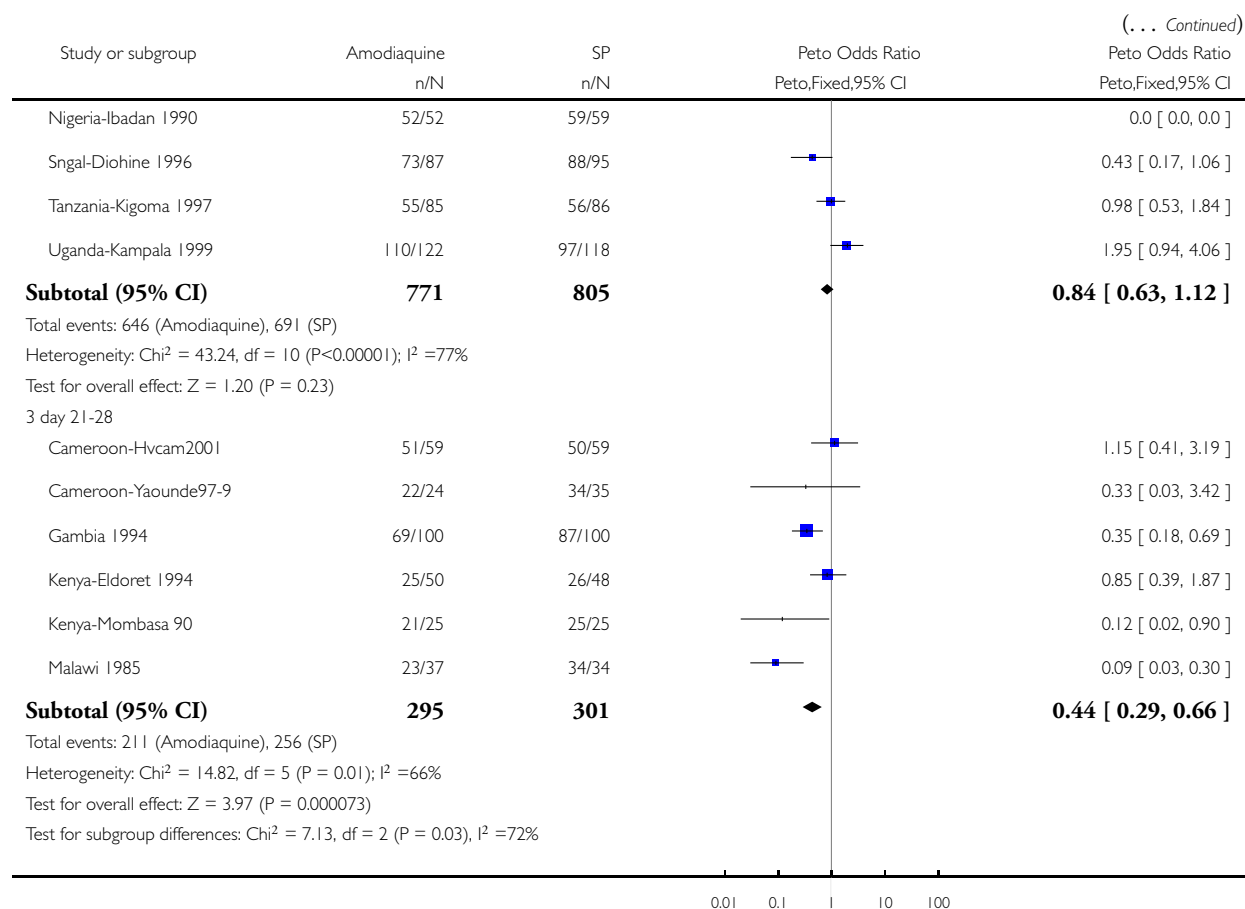
Review: Amodiaquine for treating malaria

Comparison: 5 AQ vs SP in symptomatic participants: Africa (sensitivity analysis)

Outcome: I Parasitological conversion



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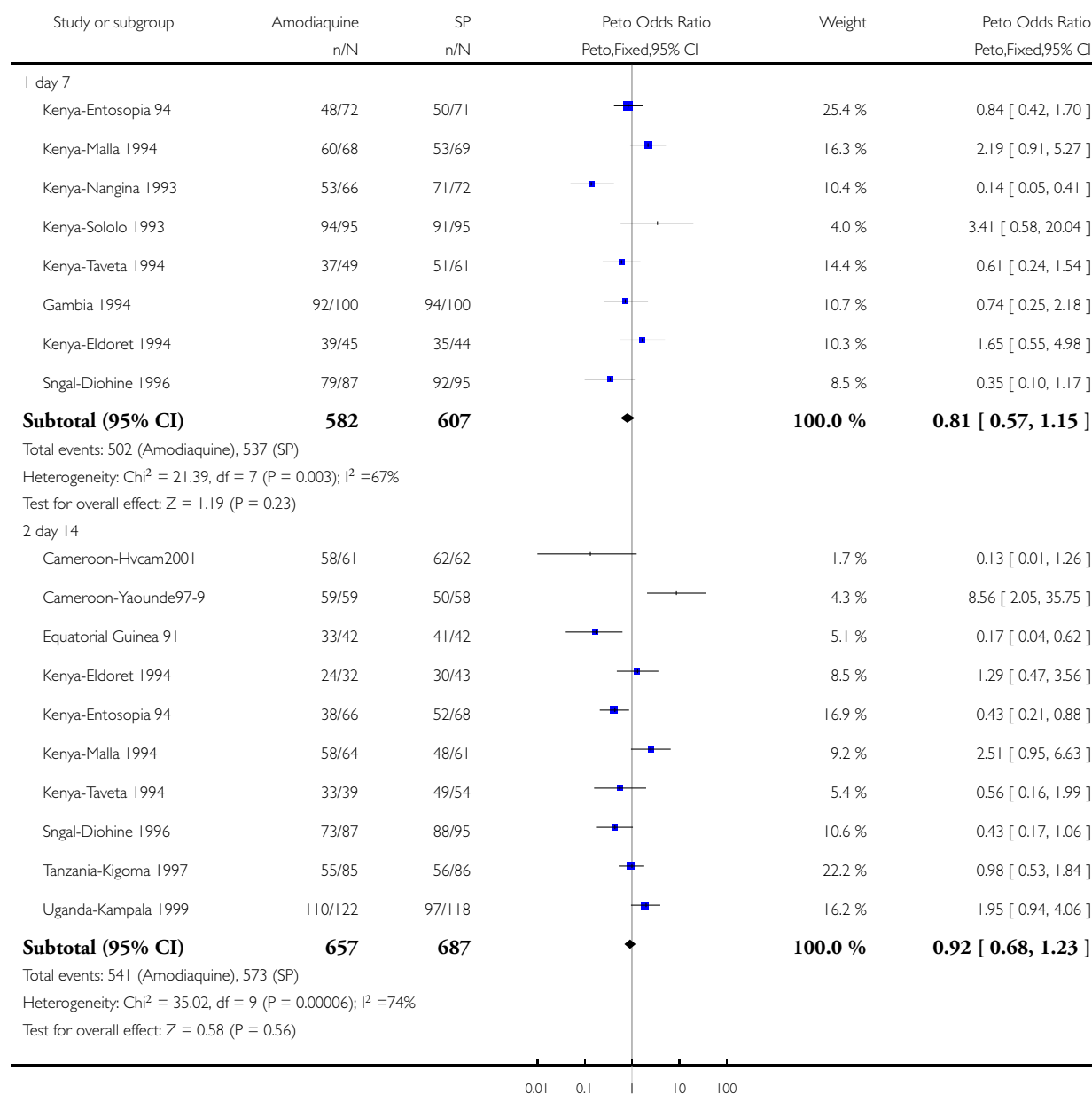


### Analysis 6.1. Comparison 6 AQ vs SP in symptomatic participants: Africa after 1990 (sensitivity analysis), Outcome 1 Parasitological conversion.

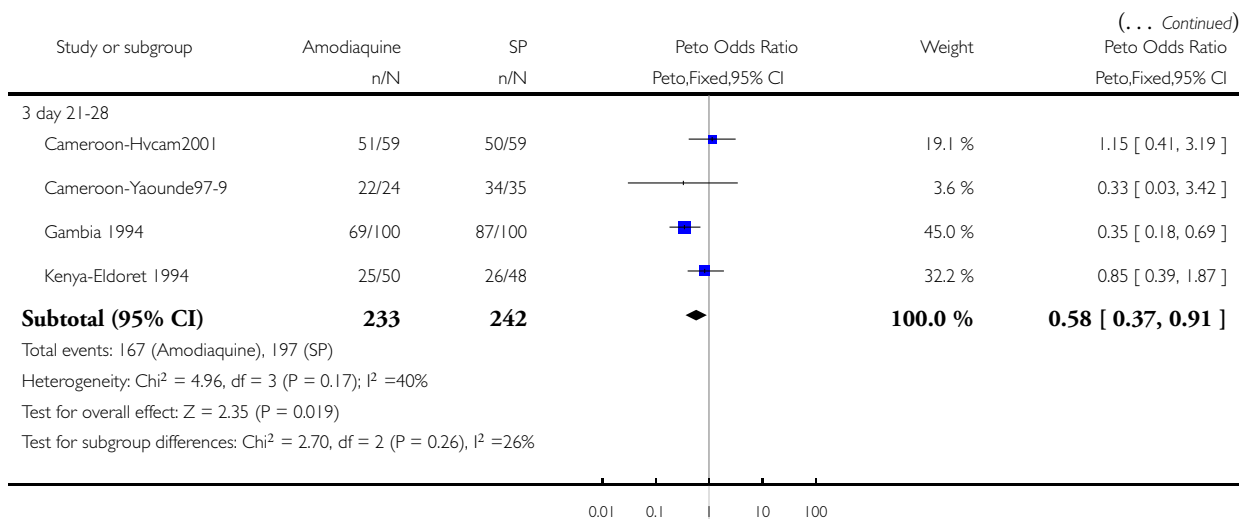
Review: Amodiaquine for treating malaria

Comparison: 6 AQ vs SP in symptomatic participants: Africa after 1990 (sensitivity analysis)

Outcome: 1 Parasitological conversion



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## APPENDICES

### Appendix I. References to studies conducted at several sites with different identifiers in the review

Burkina-Faso98 Cameroon98 Gabon-Libreville98 Senegal-Dakar 96-98 Senegal-Mlomp 96-98	Brasseur, et al. Amodiaquine remains effective for treating uncomplicated malaria in West and Central Africa. Transactions of the Royal Society of Tropical Medicine and Hygiene 1999;93:645-50.
CamerounBangangte92 Congo 92 CamerounYaounde92 CamerounKumba92	Brasseur P, et al. Interet de l'amodiaquine pour le traitement du paludisme a Plasmodium falciparum en Afrique de l'ouest et du centre [Interest of amodiaquine for the treatment of Plasmodium falciparum malaria in West and Central Africa]
Kenya-Entosopia 91 Kenya-Migori 1990 Kenya-Ortum 1991 Kenya-Turiani 1991 Kenya-Turiani 1992	Nevill C, et al. Amodiaquine not sulphadoxine-pyrimethamine should replace chloroquine for the primary treatment of non-severe P. falciparum malaria in Kenya
Kenya-Kibwezi97 Tanzania-Kigoma97	Gorissen E, et al. In vivo efficacy study of amodiaquine and sulphadoxine-pyrimethamine in Kibwezi, Kenya and Kigoma, Tanzania. Tropical Medicine and International Health 2000;5(6):459-63

## Appendix 2. Characteristics of included studies

Study	Country (location)	Year	AQ (mg/kg)	CQ (mg/kg)	SP (mg/kg)	Other comparators (mg/kg)	Follow up (days)
Brazil 1983-84	Brazil	1983-84	25	25	25		7
Burkina-Faso98	Burkina-Faso	1998	30	25			14
Cameroon98	Cameroon	1998	30	25			14
Cameroon-Centre 94	Cameroon (centre)	1994	25	25			7
Cameroon-Est 1993	Cameroon (east)	1993	25	25			7
Cameroon-Hevecam2001	Cameroon (Hevecam)	2001	30		single dose	AQ+SP	28
Cameroon-Hevecam88-9	Cameroon (Hevecam)	1988-9	25 (over 3 days)	25 (over 3 days)	inpatient (7 days)		14
Cameroon-Kumba 92	Cameroon (Kumba)	1992	35	25			7
Cameroon-South 88	Cameroon (South)	1988	35	??			7
Cameroon-South94a	Cameroon (South)	1994	25	25			7
Cameroon-South94b	Cameroon (South)	1994	25	25			7
Cameroon-Yaounde97-9	Cameroon (Yaounde)	1997-99	30 mg		single dose (over 3 days)		14 (28)
Cameroon-Bangangte92	Cameroon (Bangangte)	1992	25	25			7
Cameroon-Yaounde 92	Cameroon (Yaounde)	1992	25	25			7

(Continued)

China 1986	China	1986	1800 mg		1500	AQ+SP	28
Colombia-Antioquia98	Colombia (Antioquia)	1998	25	25	single dose		14
Congo 92	Congo	1992	25	25			7
Congo P-Noire 86	Congo (P-Noire)	1986	25	25			7
CongoBraz-zaville86	Congo (Braz-zaville)	1986	25	25			7
CongoBraz-zaville90	Congo (Braz-zaville)	1990	25, 30	25, 35			?
Equatorial-Guinea91	Equatorial Guinea	1991	25 (over 3 days)	25 (over 3 days)	single dose		14
Gabon-Libreville98	Gabon (Libreville)	1998	30	25			14
Gabon97-98	Gabon	1997-8	25 (over 3 days)	25 (over 3 days)			14
Gambia 94	Gambia	1994	25	25	single dose		28
Ivory Coast 93	Ivory Coast	1993	30 (over 3 days)	30 (over 3 days)			7
Kenya 1989	Kenya	1989	25	25			14
Kenya-Eldoret94	Kenya (Eldoret)	1994	27 (over 3 days)	25 (over 3 days)	single dose	Halofantrine: 24 mg/kg over 3 doses	28
Kenya-Entosopia 91	Kenya (Entosopia)	1991	25	25			7
Kenya-Entosopia 94	Kenya (Entosopia)	1994	30		single dose		14
Kenya-Kibwezi97	Kenya (Kibwezi)	1997	30 (over 3 days)		single dose		14
Kenya-Kilifi 1993	Kenya (Kilifi)	1993	25	25			14

(Continued)

Kenya-Malindi 1984	Kenya (Malindi)	1984	25	25			
Kenya-Malla 1994	Kenya (Malla)	1994	30		single dose		14
Kenya-Migori 1990	Kenya (Migori)	1990	25	25			7
Kenya-Mombasa 90	Kenya (Mombasa)	1990	25		single dose	SL/P:	24
Kenya-Nangina 1993	Kenya (Nangina)	1993	30		single dose		7
Kenya-Ortum 1991	Kenya (Ortum)	1991	25	25			7
Kenya-Sololo 1993	Kenya (Sololo)	1993	30				7
Kenya-Taveta 1994	Kenya (Taveta)	1994	30		single dose		14
Kenya-Turiani 1991	Kenya (Turiani)	1991	25	25			7
Kenya-Turiani 1992	Kenya (Turiani)	1992	25	25			14
Kenya-West 1987	Kenya (West)	1987	25	CQ: 25 im+po CQ: 25 + Fe		SP + quinine:	7
Madagascar 83/84	Madagascar	1983-4	15.6	25			28
Madagascar 85/86	Madagascar	1985-6	15.6	25			28
Malawi 1985	Malawi	1985	10 25	25	single dose		21

(Continued)

Mozambique 1986	Mozambique	1986	25-30	25-30	single dose	AQ +SP	28/35
Nigeria- Ibadan 84	Nigeria (Ibadan)	1984	15	25			28
Nigeria- Ibadan 90	Nigeria (Ibadan)	1990	25	25	single dose	Quinine: Mefloquine: 15 Mefloquine: 25	28
Nigeria- Ibadan2000	Nigeria (Ibadan)	2000	30 (over 3 days)	30			28
Philippines 84/85	Philippines	1984-5	25	25			14
Senegal- Dakar 96-98	Senegal (Dakar)	1996-8	30	25			14
Senegal- Mlomp 96-98	Senegal (Mlomp)	1996-8	30	25			14
Senegal- Diohine96	Senegal (Diohine)	1996	25 (over 3 days)	25	single dose		
Tanzania- Centre 88	Tanzania (centre)	1988	25	25	single dose	SL/P:	7
Tanzania- Kigoma97	Tanzania (Kigoma)	1997	30 (over 3 days)		single dose		14
Uganda- Kampala99	Uganda (Kampala)	1999	25 (over 3 days)		single dose	AQ+SP	14

AQ, amodiaquine; CQ, chloroquine; SP, sulfadoxine-pyrimethamine

### Appendix 3. Participant characteristics

Study	Number of participants	P. falciparum malaria		Inclusion criteria	Age range	Male	Female
		Mild symptomatic	Asymptomatic				
Brazil 1983-84		Y		>1000 to 10,000 parasites/ul (thick smear)	All ages	Y	Y
Burkina-Faso98		Y		>1000 parasites/ul; >37.5 °C fever	All ages	Y	Y
Cameroon98		Y		>1000 parasites/ul; >37.5 °C fever	All ages	Y	Y
Cameroun-Centre 94	200 screened 115 eligible		Y	school children; no other details available	2 to 12 years	Y	Y
Cameroun-Est 1993	300 screened 156 eligible		Y	school children; ; no other details available	5 to 16 years	Y	Y
Cameroun-Hevecam2001	191 enrolled 185 evaluable (day 14) 177 evaluable (day 28)	Y		>2000 parasites/ul; <38 °C fever; >15% Ht	>10 years	Y	Y
Cameroun-Hevecam88-9	3082 screened 1783 "malaria" 170 eligible (reasons for exclusion reported) 166 evaluable (those who completed 14 days follow up, but incon-	Y		Inpatients  >1000 parasites/ul (thick film); fresh (negative test for chloroquine)	10 years	Y	Y

(Continued)

	sistent with data presented)						
Cameroun-Kumba 92	25 eligible	Y		>1000 trophozoites/ul [thick film/500 white blood cells; 8000 white blood cells/ul]; fresh (no antimalarial drugs 14 days prior)	? School children	Y	Y
Cameroun-South 88	3785 screened (1650 with suspected malaria) 505 P. falciparum positive 236 eligible 165 evaluable	Y		>1000 parasites [thick film/2000 white blood cells; 8000 white blood cells/ul]; fresh (no history of prior treatment with "effective dose" of 4-amodiaquine 38% of the participants included reported prior treatment)	9 to 12 years	Y	Y
Cameroun-South94a	409 screened		Y	school children; no other details available	4 to 17 years	Y	Y
Cameroun-South94b	970 screened		Y	school children; no other details available	1 to 14 years	Y	Y
Cameroun-Yaounde97-9	140 enrolled 117 evaluable (day 14)	Y		Age >5 years; >5000 parasites/ul [thick smear]; >37.5 °C fever; neg-	>5 years	Y	Y

(Continued)

				ative urine test			
Cameroun Bangangte92	148 eligible 123 evaluable	Y		>1000 parasites/ul [thick film/500 white blood cells; 8000 white blood cells/ul]; fresh (no antimalarial drugs 14 days prior)	1 to 55 years	Y	Y
Cameroun- Yaounde 92	148 eligible 123 evaluable	Y		>1000 parasites/ul [thick film/500 white blood cells; 8000 white blood cells/ul]; fresh (no antimalarial drugs 14 days prior)	1 to 55 years	Y	Y
China 1986	169 eligible 162 evaluable	Y		>500 parasites/ul; fresh (negative test for chloroquine, sulfadoxine-pyrimethamine; no treatment with 28 days prior)	> 12 years	Y	Y
Colombia- Antioquia98		Y		>900; <80,000 parasites/ul; fresh (negative test for chloroquine, sulfadoxine-pyrimethamine)	> 1 year	Y	Y
Congo 92	148 eligible 123 evaluable	Y		>1000 parasites/ul [thick film/500 white blood cells; 8000	1 to 55 years	Y	Y

(Continued)

				white blood cells/ul); fresh (no antimalarial drugs 14 days prior)			
Congo Noire 86	P- 602 P. falciparum positive 44 eligible 24 evaluable	Y		>1000 parasites/ul; fresh (no prior antimalarial drugs, negative urine test)	6 months to 15 years	Y	Y
CongoBrazzaville86	241 screened 150 P. falciparum positive 75 eligible 64 evaluable		Y	school children >1000 parasites/ul [thick film/200 white blood cells, 6000 white blood cells)	6 to 7 years	Y	Y
CongoBrazzaville90			Y	school children >1000 parasites/ul [thick film/1000 white blood cells, 6000 white blood cells]	6 to 8 years	Y	Y
Equatorial-Guinea91	3082 screened 1763 "malaria" 170 eligible (reason for exclusion reported) 166 evaluable (who completed 14 day follow up, but inconsistent with data presented)	Y		Inpatients >1000 parasites ul (thick film); fresh case (negative test for chloroquine)	<10 years	Y	Y

(Continued)

Gabon-Libreville98		Y		>1000 parasites/ul; >37.5C fever	All ages	Y	Y
Gabon97-98	74 enrolled 48 evaluable day 7 22 evaluable day 14	Y		>1000 parasites/ul	1 to 15 years	Y	Y
Gambia 94	30 excluded	Y		>5000 parasites/ul; no prior treatment	6 to 10 years	Y	Y
Ivory Coast 93	295 screened 136 P. falciparum positive 121 eligible 100 evaluable	Y		>1000 parasites/ul [thick smear]; fresh cases (no anti-malarial drugs 5 days prior)	1 to 15 years	Y	Y
Kenya 1989	158 eligible 139 evaluable	Y		[thick film/200 white blood cells]; fresh (negative test for chloroquine)			
Kenya-Eldoret94		Y		Entry parasitaemia and fever no specified  Haemoglobin >5g/dl  Inpatients for =/> 2 days	Mean age 61.7 to 67.5 months	Y	Y
Kenya-Entosopia 91		Y		[thick film/200 white blood cells]; fresh (negative test for chloroquine)			

(Continued)

Kenya-Entosopia 94		Y		[thick film/200 white blood cells]; fresh (negative test for chloroquine)			
Kenya-Kibwezi97	103 randomized 75 eligible 67 evaluable (75 participants presented for intention-to-treat)	Y		>1000 to <250,000 parasites/ul; haemoglobin 4.9 g/dl	<10 years	Y	Y
Kenya-Kilifi 1993		Y		[thick film/200 white blood cells]; fresh (negative test for chloroquine)			
Kenya-Malindi 1984	423 screened 188 P. falciparum positive 139 evaluable	Y		School children  [thick film/300 white blood cells]; fresh (no treatment prior 14 days; negative test for chloroquine)	6 to 17 years	Y	Y
Kenya-Malla 1994		Y		[thick film/200 white blood cells]; fresh (negative test for chloroquine)			

(Continued)

Kenya-Migori 1990		Y		[thick film/200 white blood cells]; fresh (negative test for chloro- quine)			
Kenya- Mombasa 90	728 screened 76 eligible 73 evaluable	Y		>10 parasites/ 300 white blood cells [thick smear = 200 trophozoites/ ul?]; fresh (no antimalarial drug 2 months prior, negative urine test)	7 to 16 years	Y	Y
Kenya- Nangina 1993		Y		[thick film/200 white blood cells]; fresh (negative test for chloro- quine)			
Kenya-Ortum 1991		Y		[thick film/200 white blood cells]; fresh (negative test for chloro- quine)			
Kenya-Sololo 1993		Y		[thick film/200 white blood cells]; fresh (negative test for chloro- quine)			
Kenya-Taveta 1994		Y		[thick film/200 white blood cells];			

(Continued)

				fresh (negative test for chloroquine)			
Kenya-Turiani 1991		Y		[thick film/200 white blood cells]; fresh (negative test for chloroquine)			
Kenya-Turiani 1992		Y		[thick film/200 white blood cells]; fresh (negative test for chloroquine)			
Kenya-West 1987	142 eligible 98 evaluable	Y		>500 to <100,000 trophozoits/ul [300 white blood cells, adjusted to 6,000 white blood cells]; fresh (no anti-malarial drugs during prior 2 weeks) [ELISA test for chloroquine done, but not reason for exclusion]	6 months to 4 years	Y	Y
Madagascar 83/84	1521 screened 134 eligible	Y		>0.01% parasitaemia [thin smear, 10K red blood cells]; fresh (negative test for chloroquine)	1 to 16 years	Y	Y

(Continued)

Madagascar 85/86	2298 screened 782 P. fal- ciparum posi- tive 122 eligible 115 evaluable	Y		>500 tropho- zoites/ul [thin smear, 10K red blood cells]; fresh (negative test for chloro- quine)	1 to 34 years	Y	Y
Malawi 1985		Y		<2000 trophozoites/ ul [thick smear/100 fields]; fresh (negative urine test for chloroquine)	< 5 years	Y	Y
Mozambique 1986	200 eligible 131 evaluable	Y		School children  >800 tropho- zoites/ul [1/500 white blood cells]; fresh (no treatment during prior 2 weeks); micro- scopist blinded	School children	Y	Y
Nigeria- Ibadan 84	87 eligible 44 evaluable	Y		microscopi- cally con- firmed malaria (no detail pro- vided)	1 to 10 years	Y	Y
Nigeria- Ibadan 90	3203 screened 2009 P. fal- ciparum posi- tive 427 eligi- ble 325 evalu- able	Y		>3000 trophozoites/ ul [thick smear/ 1000 white blood cells, 6000 white blood cells]; fresh (negative test for chloro- quine, sulfadoxine- pyrimethamine)			

(Continued)

Nigeria-Ibadan2000	503 screened 276 <i>P. falciparum</i> positive 230 eligible/enrolled 228 evaluable	Y		>2000 parasites/ul [thick film/500 white blood cells assume 6000/ul]; fresh (negative test for chloroquine, sulfadoxine-pyrimethamine, or history of treatment)	< 10 years	Y	Y
Philippines 84/85		Y		>1000 trophozoites/ul; fresh (no treatment 3 weeks prior; negative urine test for chloroquine and sulfadoxine-pyrimethamine)			
Senegal-Dakar 96-98		Y		>1000 parasites/ul; >37.5 C fever	All ages	Y	Y
Senegal-Mlomp 96-98		Y		>1000 parasites/ul; >37.5 C fever	All ages	Y	Y
Senegal-Diohine96	319 enrolled 266 evaluable	Y		<5000 parasites/ul; PCV <17%	6 months to 16 years	Y	Y
Tanzania-Centre 88	3258 screened 1995 <i>P. falciparum</i> positive 560 eligible 401 evaluable		Y	School children  >400 trophozoites/ul [/? white blood cells]; fresh (negative urine chloroquine test)	7 to 18 years	Y	Y

(Continued)

Tanzania-Kigoma97	171 randomized/eligible 134 evaluable (intention-to-treat presented for 171 participants)	Y		>1000 to <250,000 parasites/ul; haemoglobin >4.9 g/dl	< 10 years	Y	Y
Uganda-Kampala99	1914 screened 668 randomized 445 enrolled 400 evaluable	Y		age >6 years; >5 kg; >38C fever; PCV >17%	> 6 years	Y	Y

#### Appendix 4. Outcomes

Study	Parasitological conversion (day)	Safety		Other
		Adverse events	Laboratory-based outcomes	
Brazil 1983-84	7			In vivo sensitivity: S/RI, RII, RIII.  Parasite clearance time.
Burkina-Faso98	1, 2, 3, 7, 14, (28)	Yes	Haematology  Liver enzymes	In vivo sensitivity at day 14, (28): S/RI, RII, RIII.  ACR  ETF  LTF  In vitro sensitivity.  IC50
Cameroon98	1, 2, 3, 7, 14, (28)	Yes	Haematology  Liver enzymes	Report d14, (28)  In vivo sensitivity: S/RI, RII, RIII

(Continued)

				ACR ETF LTF In vitro sensitivity IC50
Cameroun-Centre 94	3, 7			
Cameroun-Est 1993	3, 7			
Cameroun-Hevecam2001	2, 3, 7, 14, 28	Yes		Clinical outcome: day 2, 3, 7, 14, 28 % parasite negative ACR parasite negative/positive: day 14, 28 Parasite clearance time Fever clearance time Hb
Cameroun-Hevecam88-9	1 to 7, 14			In vivo sensitivity: S, RI, RII, RIII Parasite clearance time
Cameroun-Kumba 92	1 to 3, 5, 7	Yes		
Cameroun-South 88	7		Liver function tests	
Cameroun-South94a	3, 7			
Cameroun-South94b	3, 7			
Cameroun-Yaounde97-9	1 to 3, 7, 14	Yes		ACR parasite positive/negative; day 14 (28) Fever clearance time Parasite clearance time Gametocyte carriage: day 3, 7, 14.

(Continued)

Cameroun Bangangte92	1 to 3, 5, 7			Parasite clearance time Fever clearance time
CamerounYaounde 92	1 to 3, 5, 7, 14			Parasite clearance time Fever clearance time
China 1986	28	Yes		Parasite clearance time Fever clearance time In vivo sensitivity: S, RI, RII, RIII
Colombia-Antioquia98	1 to 3, 5, 7, 14			In vivo sensitivity: S, RI, RII, RIII ACR ETF LTF
Congo 92	1, 3, 5, 7			Parasite clearance time Fever clearance time
Congo P-Noire 86	7			
CongoBrazzaville86	7			In vivo sensitivity: S, RI, RII, RIII Parasite clearance time
CongoBrazzaville90	7			
EquatorialGuinea91	0, 1 to 7, 10, 14			Parasite present on d7, 14 In vivo sensitivity: S, RI, RII, RIII Parasite clearance time
Gabon-Libreville98	1, 2, 3, 7, 14, (28)	Yes	Haematology Liver enzymes	Report day 14, (28) In vivo sensitivity: S/RI, RII, RIII

(Continued)

				ACR ETF LTF In vitro sensitivity IC50
Gabon97-98	0 to 3, 7, 14		Haematology (including diff. count) Biochemistry	ACR ECF LCT In vivo sensitivity: S/RI, RII, RIII
Gambia 94	7, 28			
Ivory Coast 93	1, 2, 7	Yes	Yes	Parasite clearance time
Kenya 1989	7, 14	Yes	Yes	In vivo sensitivity: S, RI, RII, RIII Parasite clearance time Fever clearance time
Kenya-Eldoret94	2, 3, 7, 14, 28			In vivo sensitivity on days 7 and 28 on evaluable participants and intention-to-treat: S, RI, RII, RIII Haemoglobin
Kenya-Entosopia 91	1 to 4, 7			
Kenya-Entosopia 94	1 to 4, 7, 14			Parasite clearance time Fever clearance time
Kenya-Kibwezi97	1, 2, 7, 14			In vivo sensitivity on day 14 on evaluable participants and intention-to-treat: S, RI, RII, RIII
Kenya-Kilifi 1993	1 to 4, 7, 14			

(Continued)

Kenya-Malindi 1984	7, 14			In vivo sensitivity: S, RI, RII, RIII
Kenya-Malla 1994	1 to 4, 7, 14			Parasite clearance time Fever clearance time
Kenya-Migori 1990	1 to 3, 7			
Kenya-Mombasa 90	28			Parasite clearance time
Kenya-Nangina 1993	1 to 3, 7			
Kenya-Ortum 1991	1 to 4, 7			
Kenya-Sololo 1993	1 to 4, 7			
Kenya-Taveta 1994	1 to 4, 7, 14			Parasite clearance time Fever clearance time
Kenya-Turiani 1991	1 to 4, 7			
Kenya-Turiani 1992	1 to 4, 7, 14			
Kenya-West 1987	7		Reticulocytes Haemoglobin Red blood cells Ht monitored day 0 and day 7	In vivo sensitivity: S, RI+ II, RIII
Madagascar 83/84	7, 14, 28			
Madagascar 85/86	7, 14, 28			
Malawi 1985	7, 14, 21			
Mozambique 1986	7, 14, 28			In vivo sensitivity: S, RI, RII, RIII
Nigeria-Ibadan 84	28	Yes		In vivo sensitivity: RI Parasite clearance time Fever clearance time

(Continued)

Nigeria-Ibadan 90	1 to 4, 7, 14			Parasite clearance time Fever clearance time
Nigeria-Ibadan2000	1 to 4, (7), 14, 28	Yes	Haemoglobin White blood cells at days 0 and 7	In vivo sensitivity at days 14, 21, and 28: S/RI, RII, RIII
Philippines 84/85	7, 14	Yes		In vivo sensitivity: S, RI, RII, RIII
Senegal-Dakar 96-98	1, 2, 3, 7, 14, (28)	Yes	Haematology Liver enzymes	In vivo sensitivity at days 14, (28): S/RI, RII, RIII ACR ETF LTF In vitro sensitivity IC50 Drug levels
Senegal-Mlomp 96-98	1, 2, 3, 7, 14, (28)	Yes	Haematology Liver enzymes	In vivo sensitivity at days 14, (28): S/RI, RII, RIII ACR ETF LTF In vitro sensitivity IC50 Drug levels
Senegal-Diohine96	4, 7, 14			In vivo sensitivity: S/RI, RII, RIII Gametocytaemia

(Continued)

Tanzania-Centre 88	7									In vivo sensitivity: S, RI, RII, RIII Parasite clearance time
Tanzania-Kigoma97	1, 2, 7, 14									In vivo sensitivity at day 14 (evaluable participants and intention-to-treat): S, RI, RII, RIII
Uganda-Kampala99	1 to 3, 7, 14		Yes			Haematology Blood chemistry				In vivo sensitivity: S, RI, RII, RIII ACR ETF LTF Parasite clearance time Fever clearance time Gametocytes

## Appendix 5. Evaluable participants for parasitological outcomes at day 7, 14, and 28

	Number of participants						Total AQ participants in comparison		
	Asymptomatic		Symptomatic				CQ	add. SP	Total
	AQ	CQ	AQ	CQ	AQ	SP			
Day 7	108	101	1230	1234	824	818	1230	549	1779
add. day 14	0	0	258	268	342	340	258	342	600
add. day 28	0	0	50	42	0	0	50	0	50
Total reported	108	101	1538	1544	1166	1158	1538	891	2429

AQ, amodiaquine; CQ, chloroquine; SP, sulfadoxine-pyrimethamine

## Appendix 6. Summary of results

Comparison	Day	Number of studies	Non-African	Africa	Year 1991+	#AQ	Succ AQ	%Succ AQ	# comp	Succ Comp	% Succ Comp	Odds ratio (95% confidence interval)
Chloroquine	7	27	2	25	15	1230	1043	85	1234	718	58	4.42 (3.65 to 5.35)
Chloroquine	14	18	1	17	12	802	716	89	808	453	56	6.44 (5.09 to 8.15)
Chloroquine	28	3	0	3	3	254	193	76	248	122	49	3.62 (2.49 to 5.29)
Chloroquine - asymptomatic	7	9	0	9	4	543	493	91	586	422	72	3.64 (2.65 to 5.00)
Sulfadoxine-pyrimeth	7	14	2	12	9	824	716	87	818	735	90	0.73 (0.53 to 1.01)
Sulfadoxine-pyrimeth	14	14	0	14	11	786	661	84	821	705	86	0.86 (0.64 to 1.14)
Sulfadoxine-pyrimeth	28	7	1	6	4	345	243	70	322	273	85	0.41 (0.28 to 0.61)

## WHAT'S NEW

Last assessed as up-to-date: 3 February 2003.

5 August 2009	Amended	Tables 1 to 6 for this review formerly available on the Infectious Diseases' web site - <a href="http://cidg.cochrane.org/en/related/reviews.html">http://cidg.cochrane.org/en/related/reviews.html</a> have been added to the Appendix of the review as Appendices 1 to 6.
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## HISTORY

Protocol first published: Issue 1, 1995

Review first published: Issue 2, 1996

12 February 2009	Amended	Contact details updated
23 September 2008	Amended	Converted to new review format with minor editing.
25 August 2005	Amended	Since 2001 the World Health Organization has recommended that single-agent treatment of uncomplicated falciparum malaria should be replaced with antimalarial drug combinations. This recommendation is supported by evidence generated by an individual patient data (IPD) meta-analysis of randomized studies. As a consequence, amodiaquine should no longer be used alone. Whether amodiaquine is effective and the degree of parasite resistance, in a given setting, is important now only to predict whether a combination including amodiaquine should be tested in that location.
27 August 2003	Amended	EMBASE search date corrected.
28 February 2003	Amended	Title modified, and most review sections edited.
4 February 2003	New search has been performed	New studies found and included or excluded.
3 September 1996	Amended	Several review sections edited.

## CONTRIBUTIONS OF AUTHORS

Piero Olliaro extracted the data in the first and second edition of the review; the second person extracting data independently was Ms Mussano and Philippe Brasseur (1st edition), and Pierre Ringwald (2nd edition). Dr Olliaro entered the data and this was checked by Ms Mussano.

## DECLARATIONS OF INTEREST

We certify that we have no affiliations with or involvement in any organization or entity with a direct financial interest in the subject matter of the review (eg, employment, consultancy, stock ownership, honoraria, expert testimony).

## SOURCES OF SUPPORT

### Internal sources

- UNDP/World Bank/WHO Tropical Diseases Programme, World Health Organization, Switzerland.
- Liverpool School of Tropical Medicine, UK.

### External sources

- Department for International Development, UK.

## NOTES

February 2003: review updated and text amended; tables describing studies revised.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Amodiaquine [\*therapeutic use]; Antimalarials [\*therapeutic use]; Chloroquine [therapeutic use]; Drug Combinations; Malaria, Falciparum [\*drug therapy]; Pyrimethamine [therapeutic use]; Randomized Controlled Trials as Topic; Sulfadoxine [therapeutic use]

### MeSH check words

Humans