

Chloroquine or amodiaquine combined with sulfadoxine–pyrimethamine for uncomplicated malaria: a systematic review

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Summary

OBJECTIVE To compare the efficacies against uncomplicated falciparum malaria of chloroquine (CQ), amodiaquine (AQ), sulfadoxine–pyrimethamine (SP) and combinations of these inexpensive drugs.

METHODS We searched Medline, Embase, Cochrane CENTRAL Register of Controlled Trials, BIOSIS, Web of Science, African Index Medicus, DARE, Digital Dissertations and Current Controlled Trials for randomised or quasi-randomised controlled trials conducted between 1991 and June 2004 regardless of language and geography. We also contacted malaria experts, searched reference lists, and contacted individual authors for unreported study characteristics and additional data. Unpublished data were sought and included in the analyses.

RESULTS Thirteen randomised trials ($n = 4248$) were identified and the summary relative risks of treatment failure at 28 days were calculated. There was marginal benefit in adding CQ to SP, compared with SP monotherapy (RR = 0.74, 95% CI 0.54–1.02). Combining AQ with SP was associated with a significantly lower risk of treatment failure than SP monotherapy (RR = 0.35, 95% CI 0.15–0.82) and AQ monotherapy (RR = 0.59, 95% CI 0.42–0.83). AQ plus SP was associated with a significantly lower risk of treatment failure than CQ plus SP (RR = 0.42, 95% CI 0.25–0.72). Serious adverse events were rare and did not increase with combination therapy.

CONCLUSION Amodiaquine plus SP remains an efficacious, affordable and safe option for treating malaria in certain settings.

keywords amodiaquine, chloroquine, combination therapy, malaria, review, sulfadoxine–pyrimethamine

Introduction

In sub-Saharan Africa, the control of malaria relies largely on treatment with effective, safe and affordable drugs. The emergence and spread of antimalarial drug resistance has seriously compromised this strategy and been linked to increases in malaria-associated morbidity and mortality (Snow *et al.* 1999; Bloland 2001; WHO/UNICEF 2003). Chloroquine (CQ), the least expensive and most readily available antimalarial drug, has lost its efficacy in most parts of Africa (Bloland *et al.* 1998; EANMAT 2001). The most common replacement for CQ, sulfadoxine–pyrimethamine (SP), benefits from low cost and the ease of a single-dose treatment regimen. However, SP resistance has developed quickly in other parts of the world following its widespread use, and this same phenomenon appears to now be occurring in Africa

(WHO/UNICEF 2003). Amodiaquine (AQ), a 4-aminoquinoline similar in structure to CQ, was a standard antimalarial, but its use markedly decreased after it was found to cause myelosuppression and hepatic toxicity (Nefel *et al.* 1986; EANMAT 2001). However, these toxicities were rare and noted almost entirely in non-Africans using chronic AQ chemoprophylaxis. AQ appears to have minimal toxicity comparable with CQ and less than SP when used as a short course therapy for malaria (Olliaro *et al.* 1996). Studies from West and East Africa have shown that AQ has markedly greater activity than CQ against CQ-resistant parasites, and thus may be an effective and inexpensive alternative to CQ (Nevill *et al.* 1994; Brasseur *et al.* 1999; van Dillen *et al.* 1999; Gorissen *et al.* 2000; Sowunmi *et al.* 2001).

The strategy of combining drugs with different modes of action and mechanisms of resistance, a standard approach

in the treatment of tuberculosis and HIV, provides a potential means of an improving antimalarial therapeutic efficacy and delaying the emergence and spread of drug resistance (White *et al.* 1999). Combination antimalarial regimens containing artemisinin-based compounds have been of particular interest; however, there are concerns regarding the cost and availability of artemisinin-based combination therapy (ACT), especially in Africa, where limited resources and a very high malarial burden are particular concerns (Snow *et al.* 2003). Combinations of CQ or AQ with SP are attractive because of low cost, wide availability and familiarity to clinicians. A systematic review published in 2001 reported that CQ or AQ combined with SP shortened fever clearance time compared with SP alone and improved parasite clearance compared with CQ or AQ alone, but not SP alone, after 28 days of follow-up (McIntosh 2001). More recently, there has been an increased interest in combination therapy with CQ + SP or AQ + SP. In this systematic review, we update the comparative efficacies of CQ + SP and AQ + SP to each other or to monotherapy with the individual drugs from randomised or quasi-randomised trials conducted after 1990. We also summarise the adverse events reported in the studies to address the concerns of AQ safety. In reviewing the many studies in a systematic approach, we hope to provide clinicians and policy-makers a convenient yet evidence-based summary of the primary literature in which to base their decisions.

Methods

Search strategy

Two reviewers independently screened citations in the following electronic databases for relevant articles: Medline, Embase, Cochrane CENTRAL Register of Controlled Trials, BIOSIS, Web of Science, African Index Medicus, DARE, Digital Dissertations and Current Controlled Trials. The MESH headings included 'malaria', 'malaria, falciparum', 'sulfadoxine', 'pyrimethamine', 'CQ' and 'AQ'. Additional non-MESH terms were 'Fansidar', 'sulphadoxine–pyrimethamine', 'randomised clinical trials' and 'treatment'. The search was limited to randomised or quasi-randomised-controlled trials conducted between 1991 and June, 2004. No restrictions were placed on language or geography. We also contacted experts in the field of malaria and searched reference lists from primary and review articles. Individual authors were contacted for unreported study characteristics and additional data. Unpublished data were sought and included in the analyses. Conference abstracts were excluded because of insufficient data.

Study selection

We systematically reviewed reports, published and unpublished, of randomised or quasi-randomised clinical trials comparing the efficacy of CQ or AQ in combination with SP. Studies were included if they fulfilled all of the following selection criteria: (1) study of uncomplicated malaria because of *Plasmodium falciparum* mono-infection, (2) data collection after 1990, (3) report of the risk of treatment failure at day 14 or 28, (4) inclusion of at least one comparison of the efficacy of CQ or AQ + SP (comparison group) to either drug alone (reference group) or AQ + SP (comparison group) to CQ + SP (reference group). Two independent reviewers judged study eligibility, and disagreements were resolved by consensus.

Data abstraction and quality assessment

The two reviewers independently abstracted data from the included studies using a previously piloted data abstraction form. Disagreements were discussed and resolved by consensus. Reviewers were not blinded to details of the publications. The following information was abstracted from each study: (1) number of patients randomised and completing the study, (2) location(s) in which the study was conducted, (3) the last year of data collection, (4) local malaria endemicity, (5) median or mean ages of study participants, (6) pre-treatment geometric mean parasite density (GMPD), (7) dosing and timing of drug administration, (8) proportions of patients with serious adverse events and non-serious adverse events, (9) proportion of patients who failed therapy after 14 and/or 28 days of follow-up, and (10) study quality according to the Jadad quality criteria for clinical trials measuring internal validity according to randomisation, blinding, and withdrawal (ranges from 0 to 5, with a score greater than 3 considered high quality) (Jadad *et al.* 1996).

Study endpoint

Outcomes of interest were the risk of parasitological treatment failure after 14 and 28 days of follow-up. For studies included in this review, treatment outcomes were classified according to the 1973 WHO (RI-RIII) classification system (WHO 1973) or the more recent 1996 WHO guidelines (WHO 1996), which were updated in 2003 (WHO 2003). Using a composite of criteria from these three outcome classification systems, treatment failure was defined as any of the following: (1) severe malaria or danger signs (persistent vomiting, prostration, convulsions, or impaired consciousness) in the presence of parasitemia, (2) parasitemia on day 2 higher than day 0, (3) parasitemia

on day 3 $\geq 25\%$ of count on day 0, (4) parasitemia on day 3 with axillary temperature ≥ 37.5 °C, (5) parasitemia on days 4–28 with an axillary temperature ≥ 37.5 °C or history of fever, or (6) parasitemia on days 7–28 irrespective of temperature. Although molecular genotyping has been used to distinguish recrudescence from new infections, treatment outcomes adjusted by genotyping were not included in this review because of limited data and a lack of standardisation for interpretation of genotyping results.

Statistical analysis

The unit of analysis was defined as each comparison consisting of a combination therapy (comparison group) *vs.* either drug alone (reference group) or AQ + SP (comparison group) *vs.* CQ + SP (reference group). Consequently, trials with more than two arms could contribute more than one comparison. In trials with multiple sites, data were pooled across treatment arms. Stratified analyses were performed for each of the following treatment groups: (1) CQ + SP *vs.* CQ, (2) CQ + SP *vs.* SP, (3) AQ + SP *vs.* AQ, (4) AQ + SP *vs.* SP, and (5) AQ + SP *vs.* CQ + SP. Extracted data were entered in SPSS 12.0 (SPSS Inc., IL, USA) and analysed using STATA 8.0 (Stata Corporation, TX, USA) and Comprehensive Meta-Analysis (Biostat, NJ, USA). We used a random effects model for combining binary data to estimate the summary relative risk of treatment failure for the comparison *vs.* the reference groups. We performed the chi-squared test for heterogeneity with a *P*-value of ≤ 0.10 considered evidence of significant heterogeneity across trials. Assessments for publication bias were made by visual inspection for asymmetry in a Begg's funnel plot and the Egger's test (Egger *et al.* 1997; Sterne *et al.* 2001). Egger's linear regression and Begg's rank correlation tests are statistical tests for examining the association between the effect estimates and their variances (or their SEs). Begg's funnel plot with asymmetry or Egger's test with *P*-value ≤ 0.1 suggests publication bias.

Results

Description of included studies

The study selection process is outlined in Figure 1. We identified 13 randomised or quasi-randomised-controlled trials eligible for inclusion in our systematic review involving 4248 patients with a total of 24 comparisons (Bakyaita *et al.* 2005; Bojang *et al.* 1998; Staedke *et al.* 2001, 2004; Basco *et al.* 2002; Dorsey *et al.* 2002; Schellenberg *et al.* 2002; Sowunmi 2002; Gasasira *et al.* 2003; Rwagacondo *et al.* 2003; Schwobel *et al.* 2003; Ndyo-

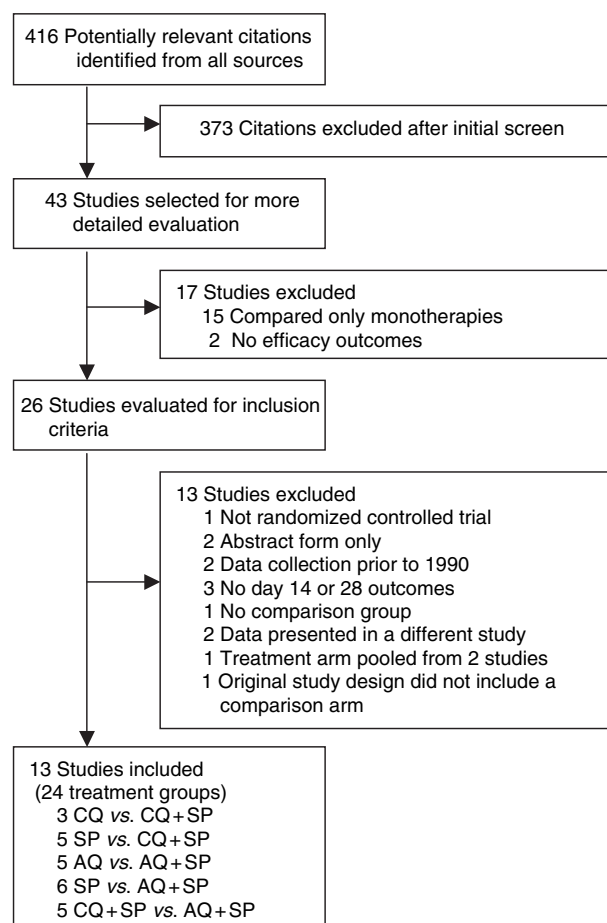


Figure 1 Flow diagram of study selection and reasons for exclusion.

mugenyeni *et al.* 2004; Talisuna *et al.* 2004). At the time of the review, 11 studies were published and two were in press (Bakyaita *et al.* 2005; Staedke *et al.* 2004). All trials were reported in English. The median number of patients with treatment outcomes from each individual treatment group was 128, ranging from 24 to 534 patients.

Study characteristics and quality assessment

The characteristics of the studies are summarised in Table 1. Twelve studies (92%) provided treatment outcomes after 14 days of follow-up, one study (8%) provided treatment outcomes only after 28 days of follow-up, and eight studies (62%) provided treatment outcomes after both 14 and 28 days of follow-up. Twelve studies (92%) were conducted in Africa (East Africa = 9, West Africa = 3) and one in Laos. Most patients enrolled in the studies

J. Hwang *et al.* **Amodiaquine combined with sulfadoxine–pyrimethamine for uncomplicated malaria****Table 1** Summary of studies included in the systematic review

Author, year	Year*	City, country	Endemicity†	Quality assessment score‡	Mean/median age (range)	Geometric mean parasite density	Drugs	Risk of failure day 14 (%)	Risk of failure day 28 (%)
Bojang <i>et al.</i> (1998)	1995	Upper River, Gambia	Unknown	4	4.3 (1–10)	62045	Sulfadoxine–pyrimethamine (SP)	–	15/150 (10%)
Schellenberg <i>et al.</i> (2002)	1999	Ifakara, Tanzania	High	3	2.3 (1.9–2.7)	47517	chloroquine (CQ) + SP Amodiaquine (AQ)	–	7/141 (5%) 61/97 (63%)
Staedke <i>et al.</i> (2001)	2000	Kampala, Uganda	Medium	3	4 (0.5–50)	32331	AQ + SP AQ	31/97 (32%) 28/89 (31%)	33/82 (40%) 29/81 (36%)
Basco <i>et al.</i> (2002)	2001	Akom II, Cameroon	High	3	3 (0.3–9.9)	15287	AQ + SP AQ	21/131 (16%) 34/131 (26%) 14/138 (10%)	–
Dorsey <i>et al.</i> (2002)	2001	Kampala, Uganda	Medium	3	3 (0.5–5)§	28000	AQ + SP SP	3/61 (5%) 0/62 (0%)	8/59 (14%) 9/59 (15%)
Ndyomugenyi <i>et al.</i> (2004)	2001	Kabale, Uganda	Low	3	18.5 (1–54)	1436	AQ + SP CQ	0/62 (0%) 68/215 (32%) 3/164 (2%) 4/40 (10%)	0/59 (0%) 95/215 (44%)¶ 20/164 (12%)¶
Rwagaondo <i>et al.</i> (2003)	2001	Kicukiro/Mashesha/Rukara, Rwanda	High	2	2.3 (0.5–<5)§	12250	CQ + SP AQ	5/27 (19%) 2/29 (7%)	–
Schwobel <i>et al.</i> (2003)	2001	Attrapeu, Laos	High	4	8 (1–70)	10591	AQ + SP CQ	2/103 (2%) 1/132 (1%) 13/29 (45%)	24/103 (23%) 22/131 (17%)
Sowunmi (2002)	2001	Ibadan, Nigeria	High	3	6 (0.5–10)	57643	SP CQ + SP CQ	5/28 (18%) 4/24 (17%) 26/74 (35%)	–
Gasasira <i>et al.</i> (2003)	2002	Kampala, Uganda	Medium	4	6 (0.5–50)	32577	AQ CQ + SP AQ + SP SP	1/82 (1%) 0/72 (0%) 0/75 (0%) 41/140 (29%)	38/74 (51%) 1/82 (1%) 0/72 (0%) 0/75 (0%)
Talisuna <i>et al.</i> (2004)	2002	Tororo, Uganda	High	1	1.6 (0.5–<5)§	13113	CQ + SP AQ + SP SP	26/152 (17%) 1/136 (1%) 13/80 (16%)	–
Bakyaite <i>et al.</i> (2005)	2003	Kyenjojo/Mubende/Kanungu, Uganda	High	4	2.7 (1–11)	18429	CQ + SP AQ + SP AQ + SP	11/101 (11%) 0/84 (0%) 238/523 (46%)	48/79 (61%) 48/100 (48%) 13/80 (16%)
Staedke <i>et al.</i> (2004)	2003	Kampala, Uganda	Medium	4	4.3 (2.1–7)	26995	CQ + SP CQ + SP AQ + SP	68/534 (13%) 9/125 (7%) 3/129 (2%)	402/523 (77%) 253/534 (47%) 72/125 (58%) 23/129 (18%)

* Last year of data collection.

† High, holoendemic or hyperendemic; medium, mesoendemic; low, hypoendemic.

‡ Jadad quality score (Score >3 is high, 3 = medium, and =2 is low).

§ Range of age not stated in results. The reported range is obtained from the inclusion criteria.

¶ Because of the lack of parasitologic failure rate, clinical failure rate was substituted.

were children. Nine studies (69%) enrolled only children under the age of 12 years and the median age of study participants was <9 years for all studies, with the exception of one study carried out in a low endemicity area of Uganda (Ndyomugenyi *et al.* 2004). All studies utilised standard dosing regimens for CQ and AQ (once a day for 3 days; total dose 25–30 mg/kg) and SP was given on the day of the diagnosis (single dose of 25 mg/kg of sulfadoxine and 1.25 mg/kg of pyrimethamine).

The quality of the studies varied widely, with 38% of high quality (Jadad score ≥ 4), 46% of medium quality (Jadad score = 3), and 15% of low quality (Jadad score ≤ 2). Most trials (12 of 13) had shortcomings in blinding, with study drugs not identical in taste or color. Only one study failed to describe the reasons for withdrawal or dropout (Bojang *et al.* 1998). Three studies (23%) failed to report an appropriate method of generating the sequence of randomisation, and one study was quasi-randomised with alternate drug allocation (Talisuna *et al.* 2004). In terms of loss to follow-up, most studies reported percentages less than or near 10%, and only two reported >25% (Bojang *et al.* 1998; Schellenberg *et al.* 2002).

Efficacy of CQ + SP *vs.* CQ or SP alone

Three studies compared the treatment efficacy of CQ + SP *vs.* CQ after 14 days of follow-up and one study compared treatment efficacy after 28 days (Table 2 and Figure 2). After 14 days, there was a trend towards a benefit with CQ + SP, but this difference did not reach statistical significance (summary RR = 0.23, 95% CI 0.04–1.50, $P = 0.13$) (Table 2). There was a significant heterogeneity across these three studies ($P = 0.02$), which can be explained by one study that, unlike the other two, did not show a benefit with CQ + SP, likely because of a much lower risk of treatment failure with CQ monotherapy

(10%) compared with the other two studies (35–45%).

The one study that extended follow-up to 28 days showed a significantly lower risk of treatment failure with CQ + SP (0%) compared with CQ alone (51%) (P -value <0.001) (Sowunmi 2002).

Four studies compared the treatment efficacy of CQ + SP *vs.* SP after 14 days of follow-up and two studies compared treatment efficacy after 28 days (Table 2 and Figure 2). After 14 days, there was a significantly lower risk of treatment failure with CQ + SP compared with SP monotherapy (summary RR = 0.61, 95% CI 0.43–0.87, $P = 0.006$) and no evidence of heterogeneity across the studies (Table 2). After 28 days of follow-up, there was a trend towards a lower risk of treatment failure with CQ + SP compared with SP alone, but this difference did not reach the statistical significance (summary RR = 0.74, 95% CI 0.54–1.02, $P = 0.07$) and there was no evidence of heterogeneity across the studies (Table 2).

Efficacy of AQ + SP *vs.* AQ or SP alone

Five studies compared the treatment efficacy of AQ + SP *vs.* AQ after 14 days of follow-up and four studies compared treatment efficacy after 28 days (Table 2 and Figure 2). After 14 days, there was a significantly lower risk of treatment failure with AQ + SP compared with AQ alone (summary RR = 0.67, 95% CI 0.46–0.97, $P = 0.03$) and no evidence of heterogeneity across the studies (Table 2). Results were similar when follow-up was extended to 28 days, with a significantly lower risk of treatment failure with AQ + SP than with AQ monotherapy (summary RR = 0.59, 95% CI 0.42–0.83, $P = 0.002$) and no evidence of heterogeneity across the studies (Table 2).

Six studies compared the treatment efficacy of AQ + SP *vs.* SP after 14 days of follow-up and four studies

Table 2 Summary effect measures for the treatment comparisons after 14 and 28-day follow-up

Comparison Treatment arm	Reference Treatment Arm	14 day follow-up					28 day follow-up				
		<i>n</i> *	RR†	95% CI‡	<i>P</i> -value	Test of heterogeneity§	<i>n</i> *	RR†	95% CI‡	<i>P</i> -value	Test of heterogeneity§
CQ + SP	CQ	3	0.23	0.04–1.50	0.13	0.02	1	0.01	0.01–0.21	<0.01	1.00
CQ + SP	SP	4	0.61	0.43–0.87	<0.01	0.81	2	0.74	0.54–1.02	0.07	0.29
AQ + SP	AQ	5	0.67	0.46–0.97	0.03	0.79	4	0.59	0.42–0.83	<0.01	0.33
AQ + SP	SP	6	0.17	0.05–0.60	<0.01	<0.01	4	0.35	0.15–0.82	0.01	<0.01
AQ + SP	CQ + SP	5	0.22	0.11–0.45	<0.01	0.16	4	0.42	0.25–0.72	<0.01	<0.01

* Number of trials included in the computation of the summary relative risk. Studies without outcomes in either arm were excluded.

† Summary relative risk of treatment failure calculated by random effects model.

‡ 95% CI.

§ Test for heterogeneity: $P < 0.10$ suggests significant heterogeneity in the risk ratios.

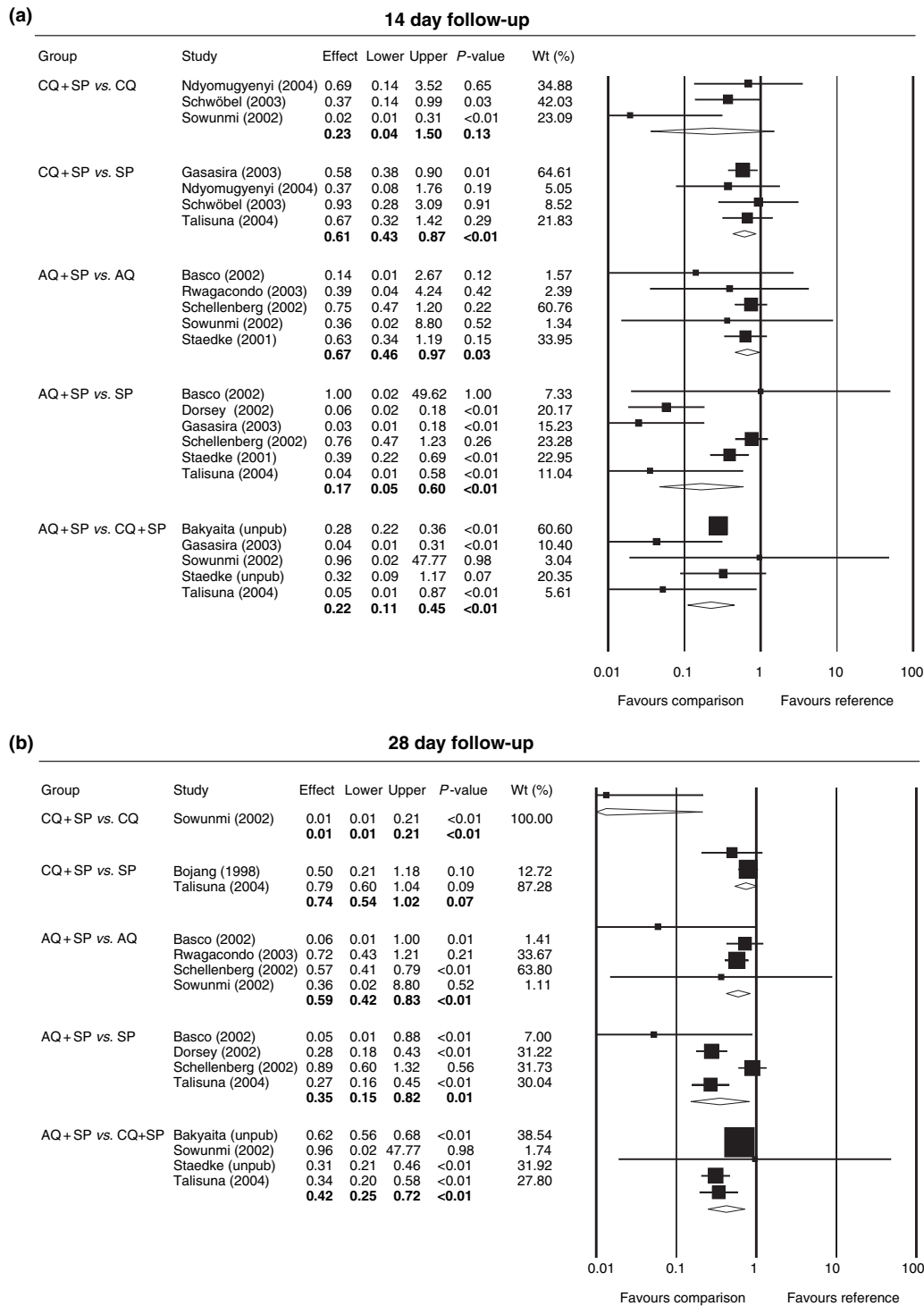


Figure 2 Forest plots of meta-analysis output for the relative risk of treatment failure after 14 and 28 days of follow-up for the five different treatment comparisons. Dark squares and lines represent the relative risks and 95% CI for each individual study. The open diamonds represent the summary random effects relative risks with 95% CI. Relative risks less than one indicate an improved efficacy with the comparison treatment arm.

compared treatment efficacy after 28 days (Table 2 and Figure 2). After 14 days, there was a significantly lower risk of treatment failure with AQ + SP compared with SP monotherapy (summary RR = 0.17, 95% CI 0.05–0.60, $P = 0.006$). Results after 28 days were similar, with a significantly lower risk of treatment failure with AQ + SP compared with SP (summary RR = 0.35, 95% CI 0.15–0.82, $P = 0.01$). For the comparisons of AQ + SP *vs.* SP, there was a significant heterogeneity across the studies, with both 14 and 28 day follow-up. This can be explained by one study from Cameroon, which had no failures in either the AQ + SP or SP treatment groups after 14 days (Basco *et al.* 2002) and one study from a high transmission site in Tanzania, which did not show a benefit of combining AQ with SP in the setting of the high risks of treatment failure for both AQ and SP monotherapies (Schellenberg *et al.* 2002).

Efficacy of AQ + SP *vs.* CQ + SP

Five studies compared the treatment efficacy of AQ + SP *vs.* CQ + SP after 14 days of follow-up and four studies compared treatment efficacy after 28 days (Table 2 and Figure 2). After 14 days, there was a significantly lower risk of treatment failure with AQ + SP compared with CQ + SP (summary RR = 0.22, 95% CI 0.11–0.45, $P < 0.001$). Results after 28 days were similar, with a significantly lower risk of treatment failure with AQ + SP compared with CQ + SP (summary RR = 0.42, 95% CI 0.25–0.72, $P < 0.001$). Significant heterogeneity across these studies can be explained by a single study from Nigeria, which had no treatment failures after 14 or 28 days in both the CQ + SP and AQ + SP treatment arms (Sowunmi 2002). All of the studies that showed a significant benefit of AQ + SP compared with CQ + SP were carried out in Uganda.

Adverse events

Ten of 13 studies reported the results of safety monitoring. Eight of those 10 studies reported no serious adverse events (Bojang *et al.* 1998; Staedke *et al.* 2001; Basco *et al.* 2002; Dorsey *et al.* 2002; Schellenberg *et al.* 2002; Sowunmi 2002; Gasasira *et al.* 2003; Rwagacondo *et al.* 2003). Two studies comparing CQ + SP to AQ + SP reported serious adverse events, which were not statistically different in frequency and mostly attributable to severe malaria, including convulsions, severe anaemia and vomiting (Staedke *et al.* 2004; Bakyaite *et al.* 2005). In terms of non-serious adverse events, there were no consistent patterns. Of note, most of the statistically significant non-serious adverse outcomes occurred with SP therapy. AQ + SP was

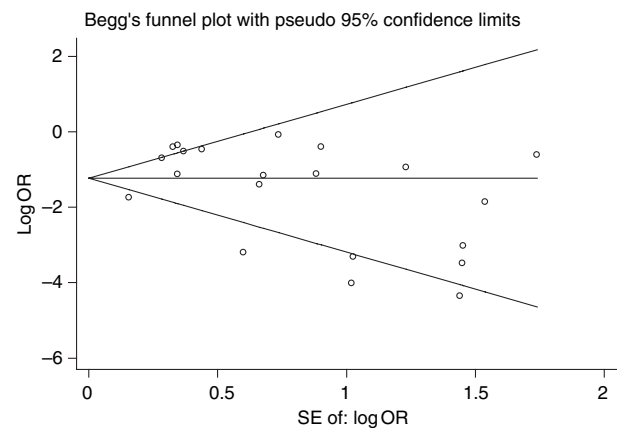


Figure 3 Test for publication bias by Begg's funnel plot of the log of the odds ratio (OR) against the SE of the log of the OR. The line in the center represents the summary OR. Each open circle represents the OR for treatment failure after 14 days of follow-up. Log_or on the y-axis is log of the OR whereas the x-axis is the SE of the log of the OR.

associated with a higher incidence of fatigue, headache and vomiting than with AQ alone in one study (Basco *et al.* 2002); whereas vomiting and breathing problems were more common with SP compared with AQ in another study (Schellenberg *et al.* 2002).

Publication bias

The lack of funnel asymmetry in the Begg's funnel plot and the results of the Egger's test (P -value = 0.58) suggest no clear evidence of publication bias (Figure 3). However, these assessments for publication bias should be interpreted with the caution in the setting of limited numbers of studies and the inclusion of studies with small sample sizes (Egger *et al.* 1997; Sterne *et al.* 2001).

Discussion

The major intervention available for the control of malaria remains prompt effective treatment, but the spread of drug resistance has seriously compromised this strategy. Combination therapy ideally improves efficacy and delays the development of resistance. A good deal of attention is now being paid to ACT regimens, as these appear to be highly efficacious (Adjuik *et al.* 2004), but their use is constrained by high cost ranging from US\$ 2 to 9 (Laxminarayan 2004; Baird 2005) and limited availability (Cyranoski 2004). Therefore, at present, the vast majority of episodes of malaria in Africa are treated with CQ, AQ, SP, or combinations of these drugs, which range in cost from US\$ 0.10 to 0.34 (Baird 2005). In this context, it is appropriate

to summarise recent data on the efficacies of these agents. Our systematic review identified advantages of combination therapies over monotherapies, as expected, although analyses were complicated by the inclusion of many studies with only 14 day outcomes, which markedly underestimate failure rates (Stepniewska *et al.* 2004). Resistance levels were unacceptably high at most sites with any of the tested monotherapies and with CQ + SP. This is not a new observation, but it is critically important, because most of Africa still relies on one of these therapies for the treatment of malaria. In contrast, AQ + SP significantly decreased the risk of treatment failure compared with monotherapies and to CQ + SP, and generally provided excellent therapeutic efficacy. Serious adverse events occurred in only two of 10 studies and were primarily attributed to malaria and not study drugs. Specifically, there was no evidence for an increased risk of serious or non-serious adverse events with AQ + SP. These results suggest that, as we await optimal regimens, AQ + SP currently offers the best regimen that is actually available and affordable for the treatment of uncomplicated malaria in certain areas of Africa.

A prior systematic review of the same drugs considered studies from 1980 to 2000 in which all monotherapies remained quite efficacious, and identified relatively minor differences in efficacies between monotherapies and aminoquinoline–SP combinations (McIntosh 2001). Adding SP to CQ or AQ had no advantage in parasite clearance at day 7, but a significant advantage at day 28. The current review benefits from many recent drug trials and includes only relatively recent studies, which were generally larger and conducted in groups with more homogeneous ages, endemicity, and drug dosing than those reviewed previously. Thus, it seems appropriate to consider the findings of this new review most relevant for Africa at the present time.

Antimalarial drug use in Africa, at present, is haphazard, with many different national policies, and increasing inconsistency between policy and practice. Among regimens adopted over the last decade to replace CQ for the treatment of uncomplicated malaria are SP monotherapy, CQ + SP, AQ + SP, and, most recently, ACT. Indeed, many countries have very recently adopted ACT regimens as first-line therapy, in the light of its high efficacy and gametocidal effects, but few countries have yet implemented this change. Even with some outside support, the cost of ACT remains a major challenge. Another concern is safety, as there are few available data on the safety of ACT regimens in children and pregnant women (Bloland *et al.* 2003). An important operational concern is that ACT availability is currently far below needs in Africa (Cyranoski 2004). This problem will be magnified if ACT is to replace older regimens for all standard antimalarial indications, including the presumptive management of fever

without a definitive diagnosis of malaria, as advocated in home-based management of fever strategies (Nsungwa-Sabiiti *et al.* 2004). Indeed, the likelihood of adequate availability of ACT in the near future to treat the estimated 2.84 billion episodes of fever in sub-Saharan Africa (Snow *et al.* 2003) is low. In summary, while the need for an improved antimalarial therapy in Africa is urgent, the implementation of ACT is likely to remain inadequate in the foreseeable future, and other effective regimens are needed, especially over the next few years.

Considering the limitations of ACT, especially for the near future, are there other available regimens to help control malaria? A recent individualised patient data meta-analysis evaluating the efficacy of artesunate (AS) combination therapy showed that AS + SP was better than SP alone (summary OR = 0.32, 95% CI 0.26–0.41, *P*-value <0.0001) and AS + AQ was better than AQ alone (summary OR = 0.46, 95% CI 0.34–0.62, *P*-value <0.0001) after 28 days of follow-up (Adjuik *et al.* 2004). Using the same effect estimates (summary OR's), the benefits of AQ + SP in this systematic review was similar compared with SP alone (summary OR = 0.22, 95% CI 0.08–0.64, *P*-value <0.01) and AQ alone (summary OR = 0.41, 95% CI 0.21–0.80, *P*-value <0.01). How does AQ + SP directly compare with ACT? Data are limited, but a few East African studies have directly compared AQ + SP with ACT regimens. Considering the subsequent risk of malaria after treatment, AQ + SP was superior to AS + SP in Kampala, Uganda (Dorsey *et al.* 2002) and Rwanda (Rwagacondo *et al.* 2003), and it was equivalent or superior to AS + AQ at multiple other sites in East Africa (Abacassamo *et al.* 2004; Staedke *et al.* 2004). Thus, although many opinion leaders have suggested that ACT regimens offer performance that is superior to any other available regimen in Africa, available data comparing AQ + SP with ACT regimens do not support this claim. A concern with AQ + SP is that the continued spread of resistance to the component drugs will compromise the future efficacy of this combination. Indeed, the study included in this review with the highest risk of AQ + SP treatment failure was from Ifakara, Tanzania, an area with high rates of resistance to both individual drugs (Schellenberg *et al.* 2002). Another limitation is that there is insufficient safety data to support the current use of AQ + SP during pregnancy (Newman *et al.* 2003; Thomas *et al.* 2004).

It now seems clear that, for most of Africa, monotherapy with CQ, SP, or AQ, or combination therapy with CQ + SP is no longer an acceptable option for the treatment of uncomplicated malaria. However, our data suggest that AQ + SP remains appropriate, even for areas with moderate levels of resistance to AQ or SP, such as

Uganda. How then might AQ + SP be used for the treatment of malaria in the near future? First, it seems reasonable to continue its use in countries that have recently adopted it as first-line therapy (Rwanda, Mozambique and Senegal) unless randomised trials prove other available (e.g. ACT) regimens to be superior. Second, AQ + SP seems particularly attractive for areas with relatively low levels of resistance to AQ and SP, for example parts of West Africa. Use of this combination may well limit the selection of resistance to the individual drugs and provide a rather durable effective regimen. Third, it may be appropriate to use AQ + SP for presumptive home-based management of fever in some countries that use ACT for the treatment of confirmed cases of malaria. This approach would limit the inappropriate (and expensive) administration of ACT for those without malaria, while nonetheless providing a reasonably effective antimalarial regimen. Fourthly, particularly for the near future, when ACT is not available for most episodes of malaria, AQ + SP offers a marked improvement in efficacy over aminoquinoline or SP monotherapy. Indeed, our data suggest that, if AQ + SP could be implemented as first-line antimalarial therapy for all Africans without access to ACT, millions of recrudescing and subsequent episodes of malaria would be prevented.

Over the last few years, a growing chorus has demanded the replacement of inadequate antimalarial regimens with newer, highly effective treatments. We agree strongly with this argument, as we find the continued treatment of millions of episodes of malaria with poorly effective drugs a great tragedy. However, available data suggest that it is a mistake to consider ACT the only logical replacement for older drugs. Considering our rapidly growing database of trials, and supported by this systematic review, we can see that, in addition to ACT, AQ + SP offers a highly effective antimalarial regimen for certain areas of Africa. Indeed, to avoid this regimen while ACT is unavailable will unnecessarily allow extensive morbidity and mortality because of the continued use of ineffective regimens to treat malaria.

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Combinaison de chloroquine ou d'amodiaquine avec sulfadoxine-pyriméthamine dans le traitement de la malaria non compliquée: Une révision systématique

OBJECTIF Comparer l'efficacité de la chloroquine, de l'amodiaquine de la sulfadoxine-pyriméthamine et des combinaisons de ces médicaments pas chers pour le traitement de la malaria falciparum non compliquée.

MÉTHODE Nous avons effectué une recherche sur Medline, Embase, Cochrane CENTRAL Register of Controlled Trials, BIOSIS, Web of Science, African Index Medicus, DARE, Digital Dissertations et Current Controlled Trials pour des essais cliniques randomisés ou quasi-randomisés conduits entre 1991 et juin 2004, quel que soit la langue et l'origine géographique.

Nous avons aussi contacté des experts de la malaria, recherché dans les listes de références et contacté les auteurs pour des études caractéristiques non publiées et pour des données supplémentaires. Les données non publiées ont été recherchées et incluses dans l'analyse.

RÉSULTATS 13 essais randomisés ($n = 4248$) ont été identifiés et le risque relatif de l'échec thérapeutique au 28^{ème} jour a été calculé. Il y avait un bénéfice marginal en ajoutant la chloroquine au sulfadoxine-pyriméthamine, comparée à la monothérapie sulfadoxine-pyriméthamine (RR = 0,74; IC95%: 0,54–1,02). La combinaison de l'amodiaquine avec la sulfadoxine-pyriméthamine était significativement associée à un plus faible risque d'échec thérapeutique comparée à la monothérapie sulfadoxine-pyriméthamine (RR = 0,35; IC95% 0,15–0,82) et à la monothérapie amodiaquine (RR = 0,59; IC95%: 0,42–0,83). La combinaison amodiaquine plus sulfadoxine-pyriméthamine était significativement associée avec un plus faible risque d'échec thérapeutique comparée à la combinaison chloroquine plus sulfadoxine-pyriméthamine (RR = 0,42; IC95%: 0,25–0,72). Les réactions adverses graves étaient rares et n'ont pas augmentées dans les traitements combinés.

CONCLUSION La combinaison amodiaquine plus sulfadoxine-pyriméthamine reste l'option efficace, abordable et sûre pour le traitement de la malaria dans certains endroits.

mots clés malaria, chloroquine, amodiaquine, sulfadoxine-pyriméthamine, thérapie combinée, révision

Cloroquina o amodiaquina combinadas con sulfadoxina-pirimetamina para tratar la malaria no complicada: una revisión sistemática

OBJETIVO Comparar la eficacia de la cloroquina, amodiaquina y sulfadoxina-pirimetamina y sus combinaciones, en el tratamiento de la malaria por falciparum no complicada.

MÉTODO Realizamos una búsqueda en Medline, Embase, Cochrane CENTRAL Register of Controlled Trials, BIOSIS, Web of Science, African Index Medicus, DARE, Digital Dissertations and Current Controlled Trials de ensayos aleatorizados o casi aleatorizados conducidos entre 1991 y Junio de 2004, sin tener en cuenta el idioma y el lugar. También contactamos expertos malariólogos, buscamos listas de referencias y contactamos autores para obtener las características no reportadas y datos adicionales de estudios individuales. Se buscaron datos no publicados y se incluyeron en el análisis.

RESULTADOS Se identificaron trece ensayos aleatorizados ($n = 4248$) y se calculó el riesgo relativo combinado de falla al tratamiento a los 28 días.

Había un beneficio marginal en añadir cloroquina a la sulfadoxina-pirimetamina, comparado con la monoterapia de sulfadoxina-pirimetamina (RR = 0,74, 95% IC 0,54–1,02). El combinar amodiaquina con sulfadoxina-pirimetamina se asoció con un riesgo significativamente menor de fallo terapéutico comparado con la monoterapia de sulfadoxina-pirimetamina (RR = 0,35, 95% CI 0,15–0,82) y la monoterapia de amodiaquina (RR = 0,59, 95% IC 0,42–0,83). La amodiaquina más sulfadoxina-pirimetamina se asoció significativamente a un menor riesgo de fallo terapéutico comparado cloroquina más sulfadoxina (RR = 0,42, 95% CI 0,25–0,72). Los eventos adversos graves fueron raros y no aumentaron con la terapia de combinación.

CONCLUSIÓN La amodiaquina con sulfadoxina-pirimetamina continúa siendo una opción eficaz, asequible y segura para el tratamiento de la malaria en algunas áreas.

palabras clave malaria, cloroquina, amodiaquina, sulfadoxina-pirimetamin, terapia de combinación, revisión