ClinicalEvidence

Malaria: uncomplicated, caused by *Plasmodium falciparum*

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ABSTRACT

INTRODUCTION: Malaria is a major health problem in the tropics, with 300 to 500 million new clinical cases annually, most of them cases of uncomplicated malaria. An estimated 1.1 to 2.7 million deaths occur annually as a result of severe falciparum malaria. Uncomplicated malaria can progress to severe malaria, become chronic, or resolve, depending on host immunity and prompt access to appropriate treatment. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: Are artemisinin combination treatments more effective than non-artemisinin combination treatments in people living in endemic areas (excluding South-East Asia)? Which artemisinin combination treatment is most effective in people living in endemic areas? We searched: Medline, Embase, The Cochrane Library, and other important databases up to December 2007 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 25 systematic reviews, RCTs, or observational studies that met our inclusion criteria. CONCLUSIONS: In this systematic review, we present information relating to the effectiveness and safety of the following interventions: amodiaquine plus sulfadoxine–pyrimethamine; artemether–lumefantrine; artesunate plus mefloquine; artesunate plus amodiaquine; and artesunate plus sulfadoxine–pyrimethamine.

QUESTIONS

INTERVENTIONS

ARTEMISININS VERSUS NON-ARTEMISININS

Likely to be beneficial

Unlikely to be beneficial

WHICH ARTEMISININ COMBINATION IS MOST EFFECTIVE?

Likely to be beneficial

Unknown effectiveness

Unlikely to be beneficial

Covered elsewhere in Clinical Evidence

Malaria: prevention in travellers

Malaria: severe, life-threatening

Key points

- Uncomplicated malaria is where the person has symptomatic infection with malaria parasites, but no signs of vital organ disturbance.

  Uncomplicated malaria can progress to severe malaria, become chronic, or resolve, depending on host immunity and prompt access to appropriate treatment.

  Severe malaria is more likely to develop in people with no prior immunity, and accounts for over one million deaths worldwide each year.

  The choice between treatment regimens depends partly on background drug-resistance patterns in the relevant country or region.

- In most RCTs, artemether–lumefantrine was more effective than amodiaquine plus sulfadoxine–pyrimethamine. However, it was not more effective in all RCTs.

- Artesunate plus amodiaquine is more effective at curing a current infection than amodiaquine plus sulfadoxine–pyrimethamine, but, in terms of people being parasite free at day 28, there is little to choose between them, since the risk of new infections appears greater with artesunate plus amodiaquine.

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- Amodiaquine plus sulfadoxine–pyrimethamine achieved higher cure rates than artesunate plus sulfadoxine–pyrimethamine. Gametocyte clearance was better with artesunate plus sulfadoxine–pyrimethamine.
- Evidence suggests that a six-dose regimen of artemether–lumefantrine is more effective than a four-dose regimen.
- Both artemether–lumefantrine (6 doses) and artesunate plus amodiaquine were effective, but artemether–lumefantrine (6 doses) was superior in some trials.
- Artesunate plus mefloquine performs better than artemether–lumefantrine in terms of cure in some areas where this has been studied.
- The choice between artesunate plus amodiaquine and artesunate plus sulfadoxine–pyrimethamine depends on background drug-resistance patterns in the relevant country or region.
- We found insufficient evidence on the effects of artemer–lumefantrine (6 doses) versus artesunate plus sulfadoxine–pyrimethamine, artesunate plus mefloquine versus artesunate plus amodiaquine, or artesunate plus mefloquine versus artesunate plus sulfadoxine–pyrimethamine.

DEFINITION

Malaria is a parasite transmitted by *Anopheles* mosquitoes. There are four types of human malaria: *falciparum*, *vivax*, *ovale*, and *malariae*. The *falciparum* type is the most important cause of illness and death, and *Plasmodium falciparum*, the responsible organism, is known to develop resistance to antimalarial drugs. [1] This review covers treatments for *falciparum* malaria only, in a population of adults and children living in endemic malarial areas exposed (seasonally or all year round) to malaria. It does not cover treatment of malaria in non-immune travellers, pregnant women, and people infected with HIV. Repeated episodes of *falciparum* malaria result in temporary and incomplete immunity. Therefore, adults living in areas where malaria is common are often found to be "semi-immune" — presenting with asymptomatic or chronic forms of malaria, with clinical episodes attenuated by their immunity. **"Severe malaria"** is defined as a form of symptomatic malaria with signs of vital organ disturbance (WHO 2000). [1] Any person with symptomatic malaria who does not develop any such signs is defined as having **"uncomplicated malaria"**. This review assesses the effectiveness of antimalarial drugs only in people with uncomplicated malaria.

INCIDENCE/ PREVALENCE

Malaria is a major health problem in the tropics, with 300 to 500 million new clinical cases annually, most of them cases of uncomplicated malaria. An estimated 1.1 to 2.7 million deaths occur annually as a result of severe *falciparum* malaria. [1]

AETIOLOGY/ RISK FACTORS

The malaria parasite is transmitted by infected *Anopheles* mosquitoes. Risk factors for developing the disease include exposure to infected mosquitoes (living in an endemic area; housing that allows mosquitoes to enter and absence of mosquito nets; and living in an area where *Anopheles* mosquitoes can thrive). Risk factors in relation to severity of the illness relate to host immunity, determined mainly by exposure to the parasite, and therefore varying with level of transmission in the area, and the age of the host. Malaria is uncommon in the first 6 months of life (fetal haemoglobin is protective); it is, however, common in children over 6 months of age. In areas of intense transmission, infection is attenuated by host immunity in older age groups; however, morbidity and mortality can also be high in adults in areas of less-intense transmission.

PROGNOSIS

Uncomplicated malaria may progress to severe malaria, become chronic, or resolve with effective treatment or the development of improved immunity. The outcome is therefore dependent on host immunity and prompt access to effective treatment. In the absence of effective treatment, people with no or low immunity are at increased risk of developing severe malaria (see review on malaria: severe, life-threatening) resulting in high morbidity and mortality.

AIMS OF INTERVENTION

To alleviate symptoms; to prevent progression to severe disease; to cure the infection, with minimal adverse effects.

OUTCOMES

Treatment effectiveness (variously measured) including: clinical failure rate (defined as the proportion of people with symptoms of malaria plus parasitaemia at or before day 28); clinical failure rate at time frames other than day 28 (where no 28-day evidence is available); total failure rate (defined as clinical failure rate plus the proportion of people with asymptomatic parasitaemia at day 28); parasitological failure rate (defined as proportion of people with parasitaemia at day 28); parasitological failure rate at time frames other than day 28 (where no 28-day evidence is available); early treatment failure (evidence of clinical or parasitological symptoms during the first 3 days of follow-up); adequate clinical and parasitological response (ACPR) rate; parasitological conversion rate; parasitological success rate; fever clearance time; rate of progression to severe disease; and need for rescue treatment (quinine treatment given in the case of treatment failure). Day 14 failure does not sufficiently predict treatment failure in trials of drugs with a terminal elimination half life of more than a few days. [2] Some of the differences in rates of treatment failure at day 14 may result from differences in elimination kinetics between the drugs. For comparisons of most drugs,

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follow-up to day 28 is adequate, although shorter follow-up data are reported if 28-day outcomes are not available. With mefloquine, however, 42-day follow-up is preferable because of its longer half life. Where 42-day or longer follow-up data are not available, 28-day outcomes are reported. **Transmission potential** including gametocytaemia rate; gametocyte clearance time. **Adverse effects** requiring admission to hospital or discontinuation of treatment.

METHODS

The contributors searched the Cochrane Infectious Diseases Group's trials register, Cochrane Central Register of Controlled Trials (Central) published in The Cochrane Library, 2007, Issue 3, Medline 1966 to November 2007, Embase 1980 to November 2007, and Lilacs; using the term arte* in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Higgins 2006). The contributors conducted their search and identified the questions in collaboration with the WHO Malaria Technical Guidelines Development Group for evidence-based guidelines for uncomplicated malaria treatment that draw explicitly on this review. An independent *Clinical Evidence* search and appraisal was also completed in December 2007. We searched: Medline and Embase to December 2007, Cochrane Central Register of Controlled Trials Issue 4 2007, The Cochrane Database of Systematic reviews, Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment Database and the TRIP database. Results of the *Clinical Evidence* search and appraisal were compared with the contributor search, and any additional studies found were assessed by the contributors. Results were then assessed and sorted into groups for the various drug combinations examined. Study design criteria for evaluation in this review were: published systematic reviews and RCTs in any language, including open studies, and containing more than 20 individuals of whom more than 80% were followed up. We have excluded certain questions irrelevant to current policies because of drug resistance — namely those examining the following: monotherapy (globally) with chloroquine, sulfadoxine–pyrimethamine, amodiaquine; combination therapy with chloroquine (globally); and non-artemisinin combinations (and artemisinin in combination with amodiaquine or sulfadoxine–pyrimethamine) in South-East Asia. In addition, because quinine has traditionally been reserved for treatment failures or severe malaria because of its toxicity, it is not reviewed here. We have summarised results from RCTs in each option under the overall outcome headings of treatment effectiveness, transmission potential, and adverse effects (see outcomes section). To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to statistics such as relative risks (RRs) and odds ratios (ORs).

QUESTION Are artemisinin combination treatments more effective than non-artemisinin combination treatments in people living in endemic areas (excluding South-East Asia)?

OPTION ARTEMETHER–LUMEFANTRINE (6 DOSES) VERSUS AMODIAQUINE PLUS SULFADOXINE–PYRIMETHAMINE

Treatment effectiveness

Artemether–lumefantrine compared with amodiaquine plus sulfadoxine–pyrimethamine Artemether–lumefantrine (6 doses) may be more effective than amodiaquine plus sulfadoxine-pyrimethamine at increasing treatment success (measured by either total failure, PCR-unadjusted or PCR-adjusted treatment failure, or PCR-unadjusted or PCR-adjusted ACPR) at 28 days in children in Rwanda, Tanzania, and Uganda, but not at improving treatment success (PCR-unadjusted or PCR-adjusted ACPR) at 28 days in adults and children in Senegal. Artemether–lumefantrine (6 doses) may be less effective than amodiaquine plus sulfadoxine-pyrimethamine at improving PCR-unadjusted treatment failure rates at 28 and 42 days or PCR-unadjusted risk of recurrent symptomatic malaria at 28 days in people aged 6 months or older in Burkina Faso, but may be no less effective at improving PCR-adjusted treatment failure rates or PCR-adjusted risk of recurrent symptomatic malaria.

Transmission potential

Artemether–lumefantrine compared with amodiaquine plus sulfadoxine–pyrimethamine Artemether–lumefantrine (6 doses) seems to be more effective than amodiaquine plus sulfadoxine-pyrimethamine at decreasing gametocyte carriage between 2 and 21 days in children in Rwanda, Tanzania, and Uganda, and at decreasing gametocyte carriage during follow-up in people aged 6 months or older in Burkina Faso. We don't know whether it is more effective at decreasing gametocyte carriage in adults and children in Senegal.

Benefits:

We found two systematic reviews (search date 2005) [3] [4] and five subsequent RCTs [5] [6] [7] [8] [9] comparing artemether–lumefantrine (6 doses) versus amodiaquine plus sulfadoxine–pyrimethamine. The systematic reviews both identified the same single RCT [10] comparing artemether–lumefantrine (6 doses) versus amodiaquine plus sulfadoxine–pyrimethamine in Tanzania and came to similar conclusions. We have reported one review in detail to illustrate the findings.

The primary outcome measure of the review was total failure. [3] The review found significantly fewer total failures on day 28 with artemether–lumefantrine (6 doses) compared with amodiaquine plus sulfadoxine–pyrimethamine (1 RCT, 948 children in Tanzania; total failure at day 28: 141/485

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[29%] with artemether–lumefantrine *v* 369/463 [80%] with amodiaquine plus sulfadoxine–pyrimethamine; RR 0.36, 95% CI 0.32 to 0.42). It reported that artemether–lumefantrine (6 doses) also significantly reduced gametocyte carriage at day 14 (617 children, gametocyte carriage on day 14: 20/333 [6%] with artemether–lumefantrine *v* 73/284 [26%] with amodiaquine plus sulfadoxine–pyrimethamine; RR 0.23, 95% CI 0.15 to 0.37).

The first subsequent RCT, a three-arm trial, had a longitudinal design where children were allocated to a treatment regimen for all episodes of malaria over a period of time. [9] It found that the polymerase chain reaction (PCR) unadjusted risk of parasitological treatment failure at day 28 was significantly lower with artemether–lumefantrine compared with amodiaquine plus sulfadoxine–pyrimethamine, and the difference was increased further with PCR adjustment (455 children aged 1–10 years in Uganda; PCR-unadjusted risk of treatment failure: 7% with artemether–lumefantrine*v* 26% with amodiaquine plus sulfadoxine–pyrimethamine; HR 4.38, 95% CI 1.99 to 9.63; P < 0.001; PCR-adjusted risk of treatment failure: 1% artemether–lumefantrine *v* 14% amodiaquine plus sulfadoxine–pyrimethamine; HR 14.7, 95% CI 3.59 to 59.9; P < 0.001). The proportion of participants still febrile at day 1 was significantly higher with artemether–lumefantrine compared with amodiaquine plus sulfadoxine–pyrimethamine (fever on day 1: 128/202 [63%] with artemether–lumefantrine *v* 101/253 [40%] with amodiaquine plus sulfadoxine–pyrimethamine; P < 0.05). The difference between groups was no longer significant at day 2 (P value not reported). It found that gametocyte carriage was lower in the group treated with artemether–lumefantrine at baseline and throughout the first 14 days after treatment. The difference between groups was significant from day 3 onwards (gametocyte carriage, days 4–14: 7/202 [4%] with artemether–lumefantrine *v* 33/253 [14%] with amodiaquine plus sulfadoxine–pyrimethamine; P < 0.05). The change in haemoglobin levels during the first 14 days of follow-up was similar in both groups (mean change in haemoglobin, day 0–14: 0.09 g/dL with artemether–lumefantrine *v* 0.16 g/dL with amodiaquine plus sulfadoxine–pyrimethamine; no statistical significance test between groups reported). [9]

The second subsequent RCT found that the adequate clinical and parasitological response (ACPR) at day 28 was significantly higher with artemether–lumefantrine whether adjusted by PCR or not (500 children aged 1–5 years in Rwanda; PCR-unadjusted ACPR at day 28: 210/241 [87%] with artemether–lumefantrine *v* 158/247 [64%] with amodiaquine plus sulfadoxine–pyrimethamine; P value not reported; PCR-adjusted ACPR at day 28: 233/241 [97%] with artemether–lumefantrine *v* 196/247 [79%] with amodiaquine plus sulfadoxine–pyrimethamine; P < 0.0001). [8] The RCT found no significant difference in fever clearance at days 1–3 between the two groups. It found that, during follow-up at days 2, 3, 7, 14, and 21, the proportion of people carrying gametocytes was significantly lower with artemether–lumefantrine compared with amodiaquine plus sulfadoxine–pyrimethamine (results presented graphically; P value not reported). [8]

The third subsequent five-arm RCT found no significant difference between groups in ACPR at day 28 whether adjusted by PCR or not (310 people aged 2–60 years in Senegal; PCR-unadjusted ACPR at day 28: 149/149 [100%] with artemether–lumefantrine *v* 159/161 [99%] with amodiaquine plus sulfadoxine–pyrimethamine; reported as not significant, P value not reported; PCR-adjusted ACPR at day 28: 149/149 [100%] with artemether–lumefantrine *v* 161/161 [100%] with amodiaquine plus sulfadoxine–pyrimethamine; reported as not significant, P value not reported). [7] Gametocyte carriage was more common in the group treated with artemether–lumefantrine at day 7, but more common in the group treated with amodiaquine plus sulfadoxine–pyrimethamine at day 14 (gametocyte carriage at day 7: 6% with artemether–lumefantrine *v* 12% with amodiaquine plus sulfadoxine–pyrimethamine; at day 14: 3% with artemether–lumefantrine *v* 0% with amodiaquine plus sulfadoxine; no test of significance reported). No gametocytes were observed in either group after day 14. [7]

The fourth subsequent three-arm RCT found that the risk of treatment failure was significantly higher in the group treated with artemether–lumefantrine at both day 28 and day 42 (345 people aged 6 months or older in Burkina Faso; PCR-unadjusted risk of treatment failure at day 28: 20.1% with artemether–lumefantrine *v* 6.2% with amodiaquine plus sulfadoxine–pyrimethamine; risk difference 13.8%, 95% CI 7.0% to 20.7%; P < 0.001; PCR-unadjusted risk of treatment failure at day 42: 30.9% with artemether–lumefantrine *v* 11.6% with amodiaquine plus sulfadoxine–pyrimethamine; risk difference 19.4%, 95% CI 11.0% to 27.7%; P < 0.001; absolute numbers not reported). [6] The difference was no longer significant between groups after adjustment by PCR (PCR-adjusted risk of treatment failure at day 28: 3.4% with artemether–lumefantrine *v* 3.9% with amodiaquine plus sulfadoxine–pyrimethamine; risk difference –0.1%, 95% CI –4.4% to +3.3%; P = 0.79; PCR-adjusted risk of treatment failure at day 42: 4.1% with artemether–lumefantrine *v* 3.9% with amodiaquine plus sulfadoxine–pyrimethamine; risk difference +0.2%, 95% CI –3.9% to +4.3%; P = 0.91; absolute numbers not reported). Significantly more people had persistence of fever on day 1 in the group treated with artemether–lumefantrine (fever on day 1: 91/188 [48%] with artemether–lumefantrine *v* 60/184 [33%] with amodiaquine plus sulfadoxine–pyrimethamine; P < 0.05), but the difference was no longer significant at day 2. The appearance of gametocytes during follow-up was rare (no

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statistical significance test between groups reported). Haemoglobin increased in both groups, but was significantly lower in the artemether–lumefantrine group at the last day of follow-up (mean haemoglobin at last day of follow-up: 11.3 g/dL with artemether–lumefantrine *v* 11.8 g/dL with amodiaquine plus sulfadoxine–pyrimethamine; P < 0.05). [6]

The fifth subsequent RCT found that the risk of recurrent symptomatic malaria and recurrent parasitaemia were significantly higher in the group treated with artemether–lumefantrine at day 28 compared with amodiaquine plus sulfadoxine–pyrimethamine (521 people aged 6 months or older in Burkina Faso; PCR-unadjusted risk of recurrent symptomatic malaria: 25/245 [10%] with artemether–lumefantrine *v* 4/233 [2%] with amodiaquine plus sulfadoxine–pyrimethamine; P = 0.0001; PCR-unadjusted risk of recurrent parasitaemia: 37/245 [15%] with artemether–lumefantrine *v* 11/233 [5%] with amodiaquine plus sulfadoxine–pyrimethamine; P = 0.0002). [5] Neither results were significant when adjusted by PCR (PCR-adjusted risk of recurrent symptomatic malaria: 1.2% with artemether–lumefantrine *v* 0.4% with amodiaquine plus sulfadoxine–pyrimethamine; P = 0.62; PCR-adjusted risk of recurrent parasitaemia: 1.6% with artemether–lumefantrine *v* 0.4% with amodiaquine plus sulfadoxine–pyrimethamine; P = 0.37). It found that significantly more people remained febrile at day 1 in the group treated with artemether–lumefantrine (66/261 [25%] with artemether–lumefantrine *v* 34/260 [13%] with amodiaquine plus sulfadoxine–pyrimethamine; P = 0.0004). However, by day 2, nearly all fevers had resolved, and there was no significant difference between groups (P = 0.32). Gametocytes were detected during follow-up in seven people, all of them in the amodiaquine plus sulfadoxine–pyrimethamine treatment group (gametocyte carriage during follow-up: 0/261 [0%] artemether–lumefantrine *v* 7/260 [3%] amodiaquine plus sulfadoxine–pyrimethamine; P = 0.007). There was no significant difference in the increase in haemoglobin observed in both groups during follow-up. [5]

Harms:

The RCT included in the review reported one death in the amodiaquine plus sulfadoxine–pyrimethamine group shortly after randomisation (considered to be caused by disease severity at the point of entry into the study), and one death at day 20 in the artemether–lumefantrine group. [10] The first subsequent RCT found no significant difference between groups in the frequency of serious adverse events (serious adverse events: 14/202 [7%] with artemether–lumefantrine *v* 16/253 [6%] with amodiaquine plus sulfadoxine–pyrimethamine; P value not reported). [9] Anorexia (P < 0.05) and weakness (P < 0.05) were significantly more common with amodiaquine plus sulfadoxine–pyrimethamine. There was no significant difference between groups in the frequency of cough, abdominal pain, vomiting, diarrhoea, or pruritus.

The second subsequent RCT found no significant difference in the incidence of adverse events between the two groups (121/251 [48%] with artemether–lumefantrine *v* 130/249 [52%] with amodiaquine plus sulfadoxine–pyrimethamine; P = 0.37). [8] The incidence of specific adverse effects was not reported.

The third subsequent five-arm RCT reported no severe adverse events. [7] Reported adverse effects were described as minor, such as mild gastroenteritis, dizziness, pruritus, asthenia, and vomiting, and it did not report on differences between groups. Twenty-five percent of patients were randomly selected for a full blood count and liver and renal function tests on days 0, 14, and 28. They reported only mild, self-correcting fluctuations, and no severe alterations in renal or hepatic function. [7]

The fourth subsequent three-arm RCT reported that both regimens were well tolerated with no severe adverse events. [6] Pruritus was significantly more common with amodiaquine plus sulfadoxine–pyrimethamine (P < 0.05). There was no significant difference between groups in the incidence of cough, abdominal pain, headache, vomiting, anorexia, diarrhoea, or weakness. [6]

The fifth subsequent RCT reported one severe adverse reaction in each group; both had a fall in haemoglobin below 50 g/L. [5] Pruritus was significantly more common in the group treated with amodiaquine plus sulfadoxine–pyrimethamine (P < 0.0001). There was no significant difference between groups in the incidence of cough, coryza, vomiting, abdominal pain, anorexia, headache, weakness, or diarrhoea.

Comment:

In the RCT identified by the reviews, [10] allocation concealment was adequate. [3] Malaria transmission is perennial, with high levels of resistance to chloroquine and sulfadoxine–pyrimethamine.

In the first subsequent RCT, allocation concealment was adequate. [9] Transmission in the trial area was mesoendemic, with peaks in two rainy seasons. Resistance to amodiaquine and sulfadoxine–pyrimethamine as individual agents is widespread.

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In the second RCT, allocation concealment was adequate. [8] The RCT was conducted in rural sites in Rwanda, where malaria transmission is variable. It reported that resistance to amodiaquine plus sulfadoxine–pyrimethamine is increasing. [8]

In the third subsequent RCT, concealment was not described. [7] The trial was conducted at five sites where the transmission of malaria was moderate, with a peak in the rainy season. [7] High levels of chloroquine resistance have been demonstrated in Senegal.

In the fourth subsequent three-arm RCT, allocation concealment was adequate. [6] Malaria was described as holoendemic, with transmission principally in the rainy season.

In the fifth subsequent RCT allocation concealment was adequate. [5] Malaria was described as holoendemic, with transmission principally in the rainy season.

Clinical guide:
In most trials, artemether–lumefantrine is more effective than amodiaquine plus sulfadoxine–pyrimethamine.

OPTION ARTESUNATE (3 DAYS) PLUS AMODIAQUINE VERSUS AMODIAQUINE PLUS SULFADOXINE–PYRIMETHAMINE

Treatment effectiveness
Artesunate plus amodiaquine compared with amodiaquine plus sulfadoxine–pyrimethamine Artesunate plus amodiaquine is more effective than amodiaquine plus sulfadoxine–pyrimethamine in improving PCR-adjusted treatment success (measured by treatment failure or ACPR) at 28 days in children in Tanzania, Uganda, and Rwanda, but not in improving PCR-adjusted ACPR in children in Madagascar, or adults and children in Senegal. However, we don't know whether artesunate plus amodiaquine is more effective than amodiaquine plus sulfadoxine–pyrimethamine in improving PCR-unadjusted treatment success (measured by treatment failure or ACPR) at 28 days in children or adults.

Transmission potential
Artesunate plus amodiaquine compared with amodiaquine plus sulfadoxine–pyrimethamine Artesunate plus amodiaquine may be more effective than amodiaquine plus sulfadoxine-pyrimethamine at decreasing gametocyte carriage in children in Mozambique, Tanzania, and Uganda, but not in children in Madagascar or Rwanda.

Benefits:

We found one systematic review (search date 2005) [4] and four subsequent RCTs [7] [9] [11] [12] comparing artesunate plus amodiaquine versus amodiaquine plus sulfadoxine–pyrimethamine. The systematic review [4] included four RCTs. [10] [13] [14] [15] The review found no significant difference in polymerase chain reaction (PCR) unadjusted treatment failure between groups at 28 days (4 RCTs, 2962 children in Mozambique, Tanzania, and Uganda; PCR-unadjusted treatment failure: 534/1482 [36%] with artesunate plus amodiaquine *v* 603/1480 [41%] with amodiaquine plus sulfadoxine–pyrimethamine; RR 1.12, 95% CI 0.81 to 1.54; P = 0.5). However, there was significant heterogeneity between RCTs included in the analysis (I^2 = 89.2%; P < 0.0001). The review found a significantly increased risk of PCR-adjusted treatment failure with amodiaquine plus sulfadoxine–pyrimethamine at 28 days (3 RCTs, 1829 children in Tanzania and Uganda; PCR-adjusted treatment failure: 86/907 [10%] with artesunate plus amodiaquine *v* 158/922 [17%] with amodiaquine plus sulfadoxine–pyrimethamine; RR 1.70, 95% CI 1.16 to 2.49; P = 0.007). The review also found a significantly higher gametocyte carriage with amodiaquine plus sulfadoxine–pyrimethamine compared with artesunate plus amodiaquine (4 RCTs, 2826 children in Mozambique, Tanzania, and Uganda; gametocyte carriage: 287/1420 [20%] with artesunate plus amodiaquine *v* 386/1406 [27%] with amodiaquine plus sulfadoxine–pyrimethamine; RR 1.33, 95% CI 1.13 to 1.57; P < 0.0006).

The first subsequent RCT, a three-arm trial, had a longitudinal design where children were allocated to a treatment regimen for all episodes of malaria over a period of time. [9] It found that the PCR-unadjusted risk of parasitological treatment failure at day 28 was significantly lower with artesunate plus amodiaquine compared with amodiaquine plus sulfadoxine–pyrimethamine, and this difference was increased further with PCR adjustment (485 children aged 1–10 years in Uganda; PCR-unadjusted risk of treatment failure: 17% artesunate plus amodiaquine *v* 26% with amodiaquine plus sulfadoxine–pyrimethamine; HR 1.58, 95% CI 1.01 to 2.47; P = 0.04: PCR-adjusted risk of treatment failure: 5% with artesunate plus amodiaquine *v* 14% with amodiaquine plus sulfadoxine–pyrimethamine; HR 3.21, 95% CI 1.36 to 7.59; P = 0.008). [9] Gametocyte carriage on days 4 to 14 was significantly lower with artesunate plus amodiaquine (gametocyte carriage days 4–14: 14/232 [6%] with artesunate plus amodiaquine *v* 33/253 [14%] with amodiaquine plus sulfadoxine–pyrimethamine; P < 0.05), but there was no significant difference between groups on days before this. [9]

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The second subsequent RCT, a five-arm trial, found no significant difference in adequate clinical and parasitological response (ACPR) at day 28, whether PCR adjusted or not (521 people aged 1–75 years in Senegal; PCR-unadjusted ACPR: 351/360 [98%] with artesunate plus amodiaquine *v* 159/161 [99%] with amodiaquine plus sulfadoxine–pyrimethamine; reported as not significant, P value not reported; PCR-adjusted ACPR: 360/360 [100%] with artesunate plus amodiaquine *v* 161/161 [100%] with amodiaquine plus sulfadoxine–pyrimethamine; reported as not significant, P value not reported). [7] Gametocyte carriage was lower in the group treated with artesunate plus amodiaquine during the first week of follow-up, but differences between groups were not tested statistically (gametocyte carriage on day 7: 0% with artesunate plus amodiaquine *v* 12% with amodiaquine plus sulfadoxine–pyrimethamine; no test of significance reported). No gametocytes were observed in either group on or after day 14. [7]

The third subsequent RCT, a five-arm trial, found no significant difference between groups in adequate clinical and parasitological response at day 28, whether PCR adjusted or not (166 children aged 6 months–15 years in Madagascar; PCR-unadjusted ACPR: 64/76 [84%] with artesunate plus amodiaquine *v* 75/79 [95%] with amodiaquine plus sulfadoxine–pyrimethamine; reported as not significant, P value not reported; PCR-adjusted ACPR: 70/76 [92%] with artesunate plus amodiaquine *v* 76/79 [96%] with amodiaquine plus sulfadoxine–pyrimethamine; reported as not significant, P value not reported). [11] There was no significant difference between groups in gametocyte carriage at days 0, 7, 14, 21, or 28.

The fourth subsequent RCT, a three-arm trial, found improved adequate clinical and parasitological response at day 28, whether PCR adjusted or not, with artesunate plus amodiaquine (510 children aged 12–59 months in Rwanda; PCR-unadjusted ACPR: 206/252 [82%] with artesunate plus amodiaquine *v* 189/258 [74%] with amodiaquine plus sulfadoxine–pyrimethamine; significance test not reported; PCR-adjusted ACPR: 231/252 [92%] with artesunate plus amodiaquine *v* 216/258 [85%] with amodiaquine plus sulfadoxine–pyrimethamine; P = 0.01). [12] No differences were found in gametocyte prevalence between groups (further details not reported).

Harms: The systematic review found no significant difference in the incidence of serious adverse events between groups (3 RCTs, 2837 children in Tanzania and Uganda; serious adverse events: 6/1421 [0.4%] with artesunate plus amodiaquine *v* 18/1416 [1%] with amodiaquine plus sulfadoxine–pyrimethamine; P = 0.23). [4] The first subsequent RCT found no significant difference in the frequency of severe adverse events (serious adverse events: 15/232 [6%] with artesunate plus amodiaquine *v* 16/253 [6%] with amodiaquine plus sulfadoxine–pyrimethamine; reported as not significant, P value not reported). [9] There was no significant difference between groups in the frequency of cough, abdominal pain, vomiting, diarrhoea, or pruritus. Anorexia ($P < 0.05$) and weakness ($P < 0.05$) were significantly more common with amodiaquine plus sulfadoxine–pyrimethamine. [9] The second subsequent RCT found no serious adverse events in either trial arm. [7] One person treated with amodiaquine plus sulfadoxine–pyrimethamine presented with a slight increase in creatinine levels, without any serious clinical signs. [7] The third RCT, found no serious adverse effects attributable to trial medication. [11] The fourth RCT found no differences in the frequency of a range of 21 adverse events between groups (participants with 1 or more adverse event; 47/252 [19%] with artesunate plus amodiaquine *v* 54/258 [21%] with amodiaquine plus sulfadoxine–pyrimethamine; reported as not significant, P value not reported). [12]

Comment: Concealment was adequate in the four trials identified by the systematic review. [4] The Mozambique trial was conducted in a region with seasonal transmission; the Tanzania trial in a holoendemic area; the first Uganda trial in a mesoendemic area; and the other Uganda trial was in 4 areas with low, high, high, and very high transmission. The review did not comment on resistance patterns. [4] In the first subsequent RCT, allocation concealment was adequate. [9] Transmission in the trial area was mesoendemic, with peaks in two rainy seasons. Resistance to amodiaquine and sulfadoxine–pyrimethamine as individual agents is widespread. In the second subsequent RCT, concealment is not described. [7] The trial was conducted at five sites where the transmission of malaria is moderate, with a peak in the rainy season. High levels of chloroquine resistance have been demonstrated in Senegal. In the third RCT, allocation concealment was unclear and transmission is described as low and predominantly seasonal. [11] In the fourth subsequent RCT, allocation concealment was unclear, and details are not provided about transmission in the three trial sites. [12]

Clinical guide: Artesunate plus amodiaquine is more effective than amodiaquine plus sulfadoxine–pyrimethamine in clearing the current infection. In terms of people being parasite free at day

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28, artesunate plus amodiaquine was also more effective in some trials, though there is little to choose between them. These findings are relevant in endemic malarious areas of Africa.

OPTION ARTESUNATE (3 DAYS) PLUS SULFADOXINE–PYRIMETHAMINE VERSUS AMODIAQUINE PLUS SULFADOXINE–PYRIMETHAMINE

Treatment effectiveness

Artesunate plus sulfadoxine–pyrimethamine compared with amodiaquine plus sulfadoxine–pyrimethamine Artesunate plus sulfadoxine–pyrimethamine may be less effective than amodiaquine plus sulfadoxine–pyrimethamine at reducing both PCR-unadjusted and PCR-adjusted treatment failure at 28 days in children aged 6 months to 5 years in Uganda, Ghana, and Rwanda. We don't know about Colombia or Kenya, as RCTs did not test differences between groups.

Transmission potential

Artesunate plus sulfadoxine–pyrimethamine compared with amodiaquine plus sulfadoxine–pyrimethamine Artesunate plus sulfadoxine–pyrimethamine may be more effective than amodiaquine plus sulfadoxine–pyrimethamine at reducing gametocyte carriage at 7 days in Uganda, and at reducing gametocyte prevalence over 28 days in Kenya.

Benefits:

We found two systematic reviews (search date 2005), [4] [16] which pooled data, and two subsequent RCTs [17] [18] comparing artesunate plus sulfadoxine–pyrimethamine versus amodiaquine plus sulfadoxine–pyrimethamine. The second review [4] included the same RCTs as the first review [16] and came to similar conclusions, although for this comparison it analysed data on the basis of number of treatments given, rather than people randomised. We have therefore reported the first review, which analysed by people randomised in order to illustrate the findings. The first review found four RCTs [14] [19] [20] [21] comparing artesunate plus sulfadoxine–pyrimethamine versus amodiaquine plus sulfadoxine–pyrimethamine. [16] The review found that significantly fewer participants failed treatment with amodiaquine plus sulfadoxine–pyrimethamine compared with artesunate plus sulfadoxine–pyrimethamine at day 28 (3 RCTs, 652 children aged 6 months–5 years in Uganda, Ghana, and Rwanda; PCR-unadjusted treatment failure: 43/327 [13%] with amodiaquine plus sulfadoxine–pyrimethamine *v* 74/325 [23%] with artesunate plus sulfadoxine–pyrimethamine; RR 0.59, 95% CI 0.42 to 0.83; P = 0.002). It found that amodiaquine plus sulfadoxine–pyrimethamine also resulted in significantly fewer treatment failures when new infections were excluded (3 RCTs, 649 children aged 6 months–5 years in Uganda, Ghana, and Rwanda; PCR-adjusted treatment failure: 28/324 [9%] with amodiaquine plus sulfadoxine–pyrimethamine *v* 47/325 [14%] with artesunate plus sulfadoxine–pyrimethamine; RR 0.62, 95% CI 0.40 to 0.96; P = 0.03). It found that gametocyte carriage was significantly higher at day 7 with amodiaquine plus sulfadoxine–pyrimethamine compared with artesunate plus sulfadoxine–pyrimethamine (1 RCT, 220 people in Uganda; gametocyte carriage at day 7: 40/118 [34%] with amodiaquine plus sulfadoxine–pyrimethamine *v* 15/102 [15%] with artesunate plus sulfadoxine–pyrimethamine; RR 2.31, 95% CI 1.36 to 3.92). [16]

The first subsequent RCT, an eight-arm trial, found similar results in the proportion of total failures at day 28 between the two relevant trial arms, but did not test significance between groups (147 adults and children in Colombia; total failure at day 28: 2/90 [2%] amodiaquine plus sulfadoxine–pyrimethamine *v* 2/57 [3%] artesunate plus sulfadoxine–pyrimethamine; no statistical significance test reported). [17]

The second subsequent four-arm RCT found that the proportion of adequate clinical and parasitological response (ACPR) was lower with artesunate plus sulfadoxine–pyrimethamine compared with amodiaquine plus sulfadoxine–pyrimethamine, but did not test significance between groups (Kenya; ACPR at day 28: 100/115 [87%] with amodiaquine plus sulfadoxine–pyrimethamine *v* 131/160 [82%] with artesunate plus sulfadoxine–pyrimethamine; no statistical significance test between groups reported). [18] It found that gametocyte prevalence over 28 days was significantly higher with amodiaquine plus sulfadoxine–pyrimethamine, whether measured using microscopy (P < 0.001) or by genetic typing (P = 0.007).

Harms:

The first systematic review [16] reported that one person progressed to severe malaria in the amodiaquine plus sulfadoxine–pyrimethamine group (1 RCT, 113 people in Uganda: 1/59 with amodiaquine plus sulfadoxine–pyrimethamine *v* 0/54 with artesunate plus sulfadoxine–pyrimethamine; RR 2.75, 95% CI 0.11 to 66.1). The review reported that the RCTs generally did not describe the methods used to report adverse events, and did not provide numbers. One included RCT reported “no severe adverse reactions attributable to treatment”; one reported “no major drug-related adverse effects”; one reported “no severe adverse reactions to trial drugs"; and that “mild adverse reactions did not differ between the three treatment groups”. The first subsequent RCT specifically sought adverse effects; [17] the paper describing these effects is in preparation. The second subsequent RCT did not report on adverse effects. [18]

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Comment: Concealment was adequate in one, and unclear in three, of the four RCTs included in the systematic review. [16] All the included RCTs were in Africa. The RCT in Ghana was in a hyperendemic area. There was seasonal transmission in the trials in Mozambique. There was stable transmission with seasonal peaks in Rwanda. The trial in Uganda was in a mesoendemic area. There was sulfadoxine–pyrimethamine resistance described in the trials in Rwanda and Uganda.

In the first subsequent RCT, allocation concealment was adequate. [17] It was conducted in an area where "the whole population is exposed to the risk of malaria", and there is chloroquine resistance. In the second subsequent RCT, allocation concealment was unclear. [18] The RCT was conducted in Kenya in an area of high and perennial malaria transmission, and there is no comment on local resistance patterns. Chloroquine and sulfadoxine–pyrimethamine resistance is common in many areas of sub-Saharan Africa.

Clinical guide: Amodiaquine plus sulfadoxine–pyrimethamine achieved higher cure rates than artesunate plus sulfadoxine–pyrimethamine. Gametocyte clearance was better with artesunate plus sulfadoxine–pyrimethamine

QUESTION Which artemisinin combination treatment is most effective in people living in endemic areas?

OPTION ARTEMETHER–LUMEFANTRINE (6 DOSES) VERSUS ARTEMETHER–LUMEFANTRINE (4 DOSES)

Treatment effectiveness
Six-dose regimen compared with four-dose regimen A six-dose regimen of artemether–lumefantrine seems to be more effective than a four-dose regimen at increasing both PCR-unadjusted and PCR-adjusted parasitological cure rates at 28 days in adults and children in Thailand. A six-dose regimen of artemether–lumefantrine seems to be more effective than a four-dose regimen at increasing PCR-unadjusted ACPR rate at 28 days in adults and children in Senegal, but not in increasing PCR-adjusted ACPR rates.

Transmission potential
Six-dose regimen compared with four-dose regimen We don't know whether a six-dose regimen of artemether–lumefantrine regimen is more effective than a four-dose regimen at improving gametocyte carriage or gametocyte clearance time in people in Thailand or Senegal.

Benefits: We found one systematic review [22] and one subsequent five-arm RCT [7] comparing artemether–lumefantrine (6 doses) versus artemether–lumefantrine (4 doses). The systematic review (search date 2005) [22] identified one RCT [23] comparing three artemether–lumefantrine regimens: a four-dose regimen over 3 days, a six-dose regimen over 3 days, and a six-dose regimen over 5 days. The RCT found a significantly higher rate of parasitological cure at 28 days with the six-dose regimen given over 3 days compared with the four-dose regimen given over 3 days (238 adults and children randomised to the 3-day regimens, in Thailand; PCR-unadjusted parasitological cure rate for ITT population at day 28: 96/118 [81%] with 6-dose regimen *v* 85/120 [71%] with 4-dose regimen; P < 0.001; PCR-adjusted parasitological cure rate for evaluable population: 93/96 [97%] with 6-dose regimen *v* 85/102 [83%] with 4-dose regimen; P < 0.001). [23] There was no statistically significant difference in the median fever clearance times between the four-dose regimen and the two six-dose regimens (P value not reported). There was no statistically significant difference in the gametocyte clearance time in comparisons between the four-dose and six-dose regimens (P = 0.5). [23]

The subsequent RCT found that the adequate clinical and parasitological response (ACPR) at 28 days was significantly higher in the group treated with the six-dose regimen compared with the four-dose regimen (289 people aged 2–63 years in Senegal; PCR-unadjusted ACPR at day 28: 149/149 [100%] artemether–lumefantrine [6 doses] *v* 116/140 [83%] artemether–lumefantrine [4 doses]; P < 0.001). [7] When adjusted by PCR, the difference between groups was no longer significant (PCR-adjusted ACPR at day 28: 149/149 [100%] with artemether–lumefantrine [6 doses] *v* 136/140 [96%] with artemether–lumefantrine [4 doses]; P = 0.06). The RCT found that gametocyte carriage was more common in the group treated with artemether–lumefantrine [6 doses] during the first 2 weeks after treatment, but did not test the significance of differences between groups (gametocyte carriage at day 7: 6% with artemether–lumefantrine [6 doses] *v* 0% with artemether–lumefantrine [4 doses]; day 14: 3% with artemether–lumefantrine [6 doses] *v* 0% with artemether–lumefantrine [4 doses]; no test of significance reported). No gametocytes were observed in either group after day 14. [7]

Harms: The RCT identified by the review reported all adverse events to be mild or moderate in severity, and possibly attributable to malaria. [23] It found no adverse cardiovascular effects. It found four serious adverse events, but the authors did not consider these to be related to treatment. The RCT

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found no changes in QRS duration and PR interval during treatment in 66 people who had regular ECG monitoring. Similarly, it found no differences in mean and median QTc (heart rate-corrected QT interval) values between treatments. [23] The subsequent RCT reported no serious adverse events. [7] Adverse effects were described as minor, such as mild gastroenteritis, dizziness, pruritus, asthenia, and vomiting, and reported no differences between the groups (no statistical analysis between groups reported). A quarter of participants were randomly selected for blood counts and liver and renal function tests at day 1, 14, and 28. They reported no severe alterations in renal or hepatic function. [7]

Comment: In the RCT identified by the review, concealment was adequate. [23] The RCT was conducted in an area of multi-drug resistance. Transmission was not stated. In the subsequent RCT, concealment was not described. [7] The trial was conducted at five sites where the transmission of malaria is moderate, with a peak in the rainy season. High levels of chloroquine resistance have been demonstrated in Senegal.

Clinical guide: Evidence suggests that a six-dose regimen of artemether–lumefantrine is more effective that a four-dose regimen.

OPTION ARTEMETHER–LUMEFANTRINE (6 DOSES) VERSUS ARTESUNATE (3 DAYS) PLUS AMODIAQUINE (EXCLUDING SOUTH-EAST ASIA)

Treatment effectiveness

Artemether–lumefantrine compared with artesunate plus amodiaquine Artemether–lumefantrine may be more effective than artesunate plus amodiaquine at increasing PCR-unadjusted treatment success. However, results were inconsistent among RCTs depending on the outcome measure reported, the analysis undertaken, and by geographical location. We don't know whether artemether–lumefantrine is more effective than artesunate plus amodiaquine at increasing PCR-adjusted treatment success.

Transmission potential

Artemether–lumefantrine compared with artesunate plus amodiaquine We don't know whether artemether–lumefantrine is more effective than artesunate plus amodiaquine at reducing gametocyte carriage.

Benefits: We found one systematic review [22] and seven subsequent RCTs [7] [9] [24] [25] [26] [27] [28] comparing artemether–lumefantrine (6 doses) versus artesunate plus amodiaquine. The review (search date 2005) [22] identified one four-arm RCT, [10] which found that treatment with artemether–lumefantrine resulted in a significant reduction in parasitological failures, but no difference in clinical failures compared with amodiaquine plus artesunate after 28 days (1034 children in Tanzania; PCR-unadjusted parasitological failure: 103/485 [21%] with artemether–lumefantrine *v* 193/472 [40%] with artesunate plus amodiaquine; OR 0.4, 95% CI 0.3 to 0.5; PCR-unadjusted clinical failure: 38/485 [8%] with artemether–lumefantrine *v* 52/472 [11%] with artesunate plus amodiaquine; OR 0.7, 95% CI 0.4 to 1.1). It found that artemether–lumefantrine significantly reduced gametocyte carriage on day 14 compared with artesunate plus amodiaquine (gametocyte carriage on day 14: 20/333 [6%] with artemether–lumefantrine *v* 38/318 [12%] with artesunate plus amodiaquine; RR 0.50, 95% CI 0.30 to 0.84). [10]

The first subsequent RCT, [24] a four-arm trial, found similar rates between the treatment groups in adequate clinical and parasitological response (ACPR) at day 28 (105 children aged 6–59 months in Ghana; PCR-unadjusted ACPR at day 28: 39/51 [76%] with artemether–lumefantrine *v* 38/54 [70%] with artesunate plus amodiaquine; significance assessment between groups not performed). It found that treatment with artemether–lumefantrine was associated with significantly longer fever clearance times (fever clearance: 1.2 days artemether–lumefantrine *v* 1.0 days artesunate plus amodiaquine; P = 0.006). Gametocytaemia peaked on day 1 (6/51 [12%] with artemether–lumefantrine *v* 7/53 [13%] with artesunate plus amodiaquine) and declined to 2% on days 7 and 14 (1/47 [2%] with artemether–lumefantrine *v* 1/51 [2%] with artesunate plus amodiaquine). [24]

The second subsequent RCT found that treatment with artemether–lumefantrine was associated with higher cure rates at day 28 compared with artesunate plus amodiaquine (408 children in Zanzibar; PCR-unadjusted cure rate at day 28: 183/197 [93%] with artemether–lumefantrine *v* 149/206 [72%] with artesunate plus amodiaquine; OR 5.00, 95% CI 2.68 to 9.33; P < 0.001; PCR-adjusted cure rate at day 28 with uncertain results defined as reinfections: 192/197 [97%] with artemether–lumefantrine *v* 193/206 [94%] with artesunate plus amodiaquine; OR 2.59, 95% CI 0.90 to 7.40; P = 0.76; PCR-adjusted cure rate at day 28 with uncertain results defined as recrudescences: 192/197 [97%] with artemether–lumefantrine *v* 188/206 [91%] with artesunate plus amodiaquine; OR 3.68, 95% CI 1.34 to 10.10; P = 0.012). [25] It found that absence of fever on day 1 was observed in a significantly smaller proportion of people treated with artemether–lumefantrine compared with artesunate plus amodiaquine (absence of fever on day 1: 134/199 [67%]

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artemether–lumefantrine *v* 162/205 [79%] artesunate plus amodiaquine; OR 0.55, 95% CI 0.35 to 0.86; P = 0.008). It found that gametocyte carriage was similar in both groups (day 7, detectable gametocyte counts: 4 children with artesunate plus amodiaquine *v* 1 child with artemether–lumefantrine; further details not reported). [25]

The third subsequent RCT found no significant difference in recurrent parasitaemia at day 28 or cure rate at day 28 (137 children aged 6–59 months in Angola; PCR-unadjusted recurrent parasitaemia: 2/61 [3%] with artemether–lumefantrine *v* 4/64 [6%] with artesunate plus amodiaquine; P = 0.72; PCR-adjusted cure rate: 100% with artemether–lumefantrine *v* 100% with artesunate plus amodiaquine, 95% CI 94% to 100% in both groups). [26] Five (7.3%) children in the artemether–lumefantrine group had gametocytes on day 28 compared with only one (1.5%) child in the artesunate plus amodiaquine group.

The fourth subsequent RCT found that the risk of recurrent symptomatic malaria at day 28 was significantly lower for people treated with artemether–lumefantrine than for those treated with artesunate plus amodiaquine (419 children aged 1–10 years in Uganda; unadjusted early treatment failure and late clinical failure: 27% with artemether–lumefantrine *v* 42% with artesunate plus amodiaquine; risk difference 15%, 95% CI 5.9% to 24.2%; P = 0.001). [27] It found a significant benefit in favour of artemether–lumefantrine compared with artesunate plus amodiaquine for the risk of recurrent parasitaemia (unadjusted early treatment failure, late clinical failure, and late parasitological failure: 51% with artemether–lumefantrine *v* 66% with artesunate plus amodiaquine; risk difference 16%, 95% CI 6.2% to 25.2%; P = 0.001). This difference between groups was mostly caused by more late clinical failures in the artesunate plus amodiaquine group (late clinical failure: 26% with artemether–lumefantrine *v* 42% with artesunate plus amodiaquine; risk difference 16%, 95% CI 6.4% to 24.7%; P = 0.001); the risk of early treatment failure and late parasitological failure was similar between the treatment groups (P = 1.0 and P = 0.89, respectively). Genotyping revealed that nearly all episodes of recurrent malaria were because of new infections (PCR-adjusted recurrent symptomatic malaria: 2/202 [1%] with artemether–lumefantrine *v* 0/201 [0%] with artesunate plus amodiaquine; risk difference –1%; 95% CI –2.4% to +0.4%; PCR-adjusted recurrent parasitaemia: 2/202 [1%] with artemether–lumefantrine *v* 0/201 [0%] with artesunate plus amodiaquine; risk difference –1%, 95% CI –2.4% to +0.4%). The proportion of participants with any gametocytes during follow-up was significantly lower in the artemether–lumefantrine group (20% with artemether–lumefantrine *v* 31% with artesunate plus amodiaquine; reported as significant, P value not reported). Similar results were found for participants with newly emerging gametocytes during follow-up (5% with artemether–lumefantrine *v* 15% with artesunate plus amodiaquine; no statistical test reported). [27]

The fifth subsequent three-arm RCT had a longitudinal design where children were allocated to a treatment regimen for all episodes of malaria over a period of time. [9] It found that the PCR-unadjusted risk of treatment failure at 28 days was significantly lower with artemether–lumefantrine compared with artesunate plus amodiaquine (434 episodes of malaria in children aged 1–10 years in Uganda; PCR-unadjusted risk of treatment failure at day 28: 17% with artesunate plus amodiaquine *v* 7% with artemether–lumefantrine; HR 2.77, 95% CI 1.22 to 6.30; P = 0.02). The result was still of borderline significance after adjustment by PCR (PCR-adjusted risk of treatment failure at day 28: 5% with artesunate plus amodiaquine *v* 1% with artemether–lumefantrine; HR 4.56, 95% CI 0.99 to 21.0; P = 0.05). The prevalence of fever was rapidly reduced in both groups (fever on day 3: 6/202 [3%] with artemether–lumefantrine *v* 11/232 [5%] with artesunate plus amodiaquine; reported as not significant, P value not reported). The prevalence of gametocyte carriage was lower in the group treated with artemether–lumefantrine at baseline, and remained lower during the first 14 days after initiation of treatment (no statistical significance test between groups reported). The change in haemoglobin levels during the first 14 days of follow-up was similar in both groups (mean change in haemoglobin day 0–14: 0.09 g/dL with artemether–lumefantrine *v* –0.03 g/dL with artesunate plus amodiaquine; no statistical significance test between groups reported). [9]

The sixth subsequent five-arm RCT found no significant difference between groups in the adequate clinical and parasitological response rate at day 28, whether PCR adjusted or not (509 people aged 2–75 years in Senegal; PCR-unadjusted ACPR at day 28: 149/149 [100%] with artemether–lumefantrine *v* 351/360 [98%] artesunate plus amodiaquine; PCR-adjusted ACPR at day 28: 149/149 [100%] with artemether–lumefantrine *v* 360/360 [100%] with artesunate plus amodiaquine; reported as not significant, P values not provided). [7] Gametocyte carriage was more common in the group treated with artemether–lumefantrine during the first 2 weeks after treatment (gametocyte carriage day 7: 6% with artemether–lumefantrine *v* 0% with artesunate plus amodiaquine; day 14: 3% with artemether–lumefantrine *v* 0% with artesunate plus amodiaquine; no test of significance performed). No gametocytes were observed in either group after day 14. [7]

The seventh subsequent RCT, a three-arm trial also including an artesunate plus sulfadoxine–pyrimethamine arm (91 children), found that the proportion of PCR-unadjusted recurrent para-

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sitaemias at 28 days was lower with artemether–lumefantrine (106 children) compared with artesunate plus amodiaquine (101 children) (children aged 7–59 months in the Republic of Congo; PCR-unadjusted proportion of recurrent parasitaemia at day 28: 13/100 [13%] with artemether–lumefantrine *v* 31/97 [32%] with artesunate plus amodiaquine *v* 21/85 [24.7%] with artesunate plus sulfadoxine–pyrimethamine; between-group analysis, P = 0.006; direct statistical analysis of artemether–lumefantrine *v* artesunate plus amodiaquine not reported). [28] There was no significant difference between artemether–lumefantrine and artesunate plus amodiaquine once the figures were adjusted by PCR, although there were increased losses to follow-up (results based on 154/207 [74%] children initially randomised in the 2 arms; PCR-adjusted treatment failure at 28 days: 0/87 [0%] with artemether–lumefantrine *v* 1/67 [2%] with artesunate plus amodiaquine; P = 0.4). The proportion of people still febrile at day 3 was similar between groups (8/105 [8%] with artemether–lumefantrine *v* 3/101 [3%] with artesunate plus amodiaquine; no statistical significance test between groups reported). The proportion of cases with gametocytaemia decreased in both groups during follow-up, but gametocytaemia had been significantly lower in the group treated with artemether–lumefantrine at baseline. There was an increase in the mean haemoglobin during follow-up in both groups, but the mean haemoglobin had been significantly lower in the group treated with artemether–lumefantrine at baseline. [28]

Harms:

The review [22] reported no harms for the included RCT. [10] The first subsequent RCT did not report on adverse events. [24]

The second subsequent RCT reported that both regimens were generally well tolerated. [25] No deaths occurred, but nine participants (2 with artemether–lumefantrine *v* 7 with artesunate plus amodiaquine group) developed clinically suspected severe malaria during the follow-up period, and received rescue treatment (reported as no significant difference between groups; P = 0.124). A moderate or severe adverse event was reported in 21/200 (10%) children treated with artemether–lumefantrine compared with 25/207 (12%) children treated with artesunate plus amodiaquine (unadjusted OR 0.85, 95% CI 0.46 to 1.58). All nine severe adverse events were associated with clinically suspected severe malaria, and thus could not be attributed to the intervention drugs by the authors of the trial. [25]

The third subsequent RCT did not report on harms. [26] The fourth subsequent RCT assessed participants for any new or worsening adverse event at each follow-up visit, and found that both treatments were well-tolerated. [27] Overall, 261 (65%) participants experienced any adverse event of moderate or greater severity, and there was no significant difference between the two treatment groups (adverse event of at least moderate severity: 125/202 [62%] with artemether–lumefantrine *v* 136/201 [68%] with artesunate plus amodiaquine; P = 0.25). No abnormalities in hearing or fine finger dexterity were detected. Serious adverse events occurred in two participants. One child treated with amodiaquine plus artesunate developed pneumonia on day 27, requiring admission to hospital, but the event was judged unrelated to study medications. A second participant, treated with artemether–lumefantrine, experienced a convulsion on day 0, which was judged unlikely to be related to the study medication. [27]

The fifth RCT found no significant difference in the frequency of severe adverse events between groups (14/202 [7%] with artemether–lumefantrine *v* 15/232 [6%] with artesunate plus amodiaquine; P value not reported). [9] There was also no significant difference between groups in the frequency of individual mild adverse events such as anorexia, cough, weakness, abdominal pain, vomiting, diarrhoea, and pruritus (P values not reported).

The sixth RCT reported no serious adverse effects in the trial arms. [7] Adverse effects are described as minor, such as mild gastroenteritis, dizziness, pruritus, asthenia, and vomiting. They did not report any differences between the groups. A quarter of participants were randomly selected for blood counts, and liver and renal function tests at day 1, 14, and 28. They reported only mild, self-correcting fluctuations and no severe alterations in renal or hepatic function. [7]

The seventh RCT reported no clinically severe adverse events. [28] The common adverse effects were vomiting, diarrhoea, abdominal pain, and anorexia (no figures reported).

Comment:

The RCT identified by the systematic review used adequate allocation concealment. [10] Malaria transmission was perennial and the study site was in an area of chloroquine and sulfadoxine–pyrimethamine resistance.

In the first subsequent RCT, allocation concealment was unclear. [24] Malaria transmission was markedly seasonal, and the therapeutic efficacy of amodiaquine in the study site was not reported.

In the second subsequent RCT, allocation concealment was unclear, and holoendemic transmission and resistance patterns were not stated. [25] Inclusion criteria were slightly different for very small

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children (<9 months or <9 kg body weight) because both regimens were not similarly licensed. However, the numbers of children in each group were similar.

In the third additional RCT, allocation concealment was unclear; transmission was mesoendemic, stable, and seasonal. [26] Drug-resistance patterns were not stated.

In the fourth additional RCT, allocation concealment was unclear, malaria was holoendemic, and local drug-resistance patterns were not stated. [27]

In the fifth RCT, allocation concealment was adequate. [9] Transmission in the trial area was mesoendemic, with peaks in two rainy seasons. Resistance to amodiaquine and sulfadoxine–pyrimethamine as individual agents is widespread.

In the sixth RCT, concealment was not described. [7] The RCT was carried out in five sites where the transmission of malaria was moderate, with a peak in the rainy season. High levels of chloroquine resistance have been demonstrated in Senegal.

In the seventh RCT, the method of allocation concealment was unclear. [28] PCR-adjusted results were only available for 78% of the randomised participants. There were also significant differences between the two groups at baseline (mean age: $P < 0.001$; mean weight: $P < 0.001$; MUAC: $P < 0.001$; mean haemoglobin: $P = 0.003$). Malaria was holoendemic in the trial location; resistance to both chloroquine and sulfadoxine–pyrimethamine was reported as high.

Clinical guide: Both treatments were effective in clearing the current infection, but in terms of people being parasite free at day 28, artemether–lumefantrine was more effective than artesunate plus amodiaquine in some trials.

OPTION ARTEMETHER–LUMEFANTRINE (6 DOSES) VERSUS ARTESUNATE PLUS SULFADOXINE–PYRIMETHAMINE (EXCLUDING SOUTH-EAST ASIA)

Treatment effectiveness

Artemether–lumefantrine (6 doses) versus artesunate plus sulfadoxine–pyrimethamine (excluding South-East Asia)

Artemether–lumefantrine (6 doses) may be more effective than artesunate plus sulfadoxine–pyrimethamine in improving PCR-adjusted and PCR-unadjusted treatment success at 28 days in children in the Republic of Congo, but we don't know whether it is more effective in adults and children in Eastern Sudan.

Transmission potential

Artemether–lumefantrine (6 doses) versus artesunate plus sulfadoxine–pyrimethamine (excluding South-East Asia)

We don't know whether artemether–lumefantrine (6 doses) is more effective than artesunate plus sulfadoxine–pyrimethamine in improving gametocyte carriage in children in the Republic of Congo.

Benefits:

We found two RCTs comparing artemether–lumefantrine (6 doses) versus artesunate plus sulfadoxine–pyrimethamine. [28] [29] The first RCT took place in Eastern Sudan. [29] It found higher PCR-unadjusted adequate clinical and parasitological response (ACPR) at 28 days with artemether–lumefantrine compared with artesunate plus sulfadoxine–pyrimethamine, but did not test the significance of differences between groups (160 adults and children; PCR-unadjusted ACPR at 28 days: 72/80 [90%] with artemether–lumefantrine *v* 65/77 [84%] with artesunate plus sulfadoxine–pyrimethamine; no statistical significance test between groups reported). The PCR-adjusted ACPR was similar between groups (PCR-adjusted ACPR at 28 days: 73/80 [91%] with artemether–lumefantrine *v* 72/77 [94%] artesunate plus sulfadoxine–pyrimethamine; no statistical significance test between groups reported). No secondary outcomes were reported.

The second RCT, a three-arm trial, also including an artesunate plus amodiaquine arm (101 children), compared artemether–lumefantrine (6-dose regimen; 106 children) versus artesunate plus sulfadoxine–pyrimethamine (91 children) in the Republic of Congo. [28] It found that the proportion of recurrent parasitaemias at 28 days was lower with artemether–lumefantrine compared with artesunate plus sulfadoxine–pyrimethamine (children aged 6–59 months; PCR-unadjusted proportion of recurrent parasitaemias at day 28: 13/100 [13%] with artemether–lumefantrine *v* 21/85 [25%] with artesunate plus sulfadoxine–pyrimethamine *v* 31/97 [32%] with artesunate plus amodiaquine; between-group analysis, $P = 0.006$; direct statistical analysis of artemether–lumefantrine *v* artesunate plus sulfadoxine–pyrimethamine not reported). The difference remained significant directly between artemether–lumefantrine and artesunate plus sulfadoxine–pyrimethamine after adjustment by PCR, although there were increased losses to follow-up (results based on 158/197 [81%] children initially randomised to the 2 arms; PCR-adjusted treatment failure at 28 days: 0/87 [0%] with artemether–lumefantrine *v* 7/71 [10%] with artesunate plus sulfadoxine–pyrimethamine; $P = 0.003$). The proportion of children still febrile at day 3 was similar between groups (8/105 [8%] with artemether–lumefantrine *v* 4/90 [4%] with artesunate plus sulfadoxine–pyrimethamine; no statistical

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significance test between groups reported). The proportion of cases with gametocytaemia decreased in both groups during follow-up, but gametocytaemia had been significantly lower in the group treated with artemether–lumefantrine at baseline. Hence, we have not reported these results further. [28]

Harms: The first RCT did not report adverse events. [29] The second RCT reported no clinically severe adverse events. [28] The common adverse effects were vomiting, diarrhoea, abdominal pain, and anorexia (no figures reported).

Comment: In the first RCT, allocation concealment was unclear. [29] The trial was conducted in an area of low endemicity, where the sensitivity of *P falciparum* to chloroquine is decreasing. In the second RCT, the method of allocation concealment was unclear. [28] PCR-adjusted results were only available for 80% of the randomised participants. There were also significant differences between the two groups at baseline, with children in the artemether–lumefantrine group being, on average, older and heavier (mean age: $P < 0.001$; mean weight: $P < 0.001$; MUAC: $P < 0.001$; mean haemoglobin: $P = 0.003$). Malaria is holoendemic in the trial location, resistance to both chloroquine and sulfadoxine–pyrimethamine are reported as high.

Clinical guide: In both trials, artemether–lumefantrine was more effective than artesunate plus sulfadoxine–pyrimethamine, but there were significant methodological flaws.

OPTION ARTEMETHER–LUMEFANTRINE (6 DOSES) VERSUS ARTESUNATE (3 DAYS) PLUS MEFLOQUINE

Treatment effectiveness

Artemether–lumefantrine compared with artesunate plus mefloquine Artemether–lumefantrine may be less effective than artesunate plus mefloquine at reducing PCR-unadjusted treatment failure at 42 days in people in Lao People's Democratic Republic, and at reducing PCR-unadjusted parasitological treatment failure at 42 days in people in Bangladesh, but not in reducing PCR-adjusted ACPR at 42 days in people in Bangladesh. We don't know whether artemether–lumefantrine is more effective than artesunate plus mefloquine at improving PCR-adjusted cure rates at 42 days in people on the Thai–Myanmar border, at improving PCR-unadjusted total failure rate at 28 days in people in Thailand, or at improving PCR-adjusted or PCR-unadjusted ACPR at 28 days in people in Senegal.

Transmission potential

Artemether–lumefantrine compared with artesunate plus mefloquine We don't know whether artemether–lumefantrine is more effective than artesunate plus mefloquine at reducing gametocyte carriage.

Benefits: We found one systematic review [3] and three subsequent RCTs. [7] [30] [31] The systematic review (search date 2005) [3] identified four RCTs comparing artemether–lumefantrine versus artesunate plus mefloquine. The review found that artemether–lumefantrine significantly increased total failure compared with artesunate plus mefloquine at 42 days (2 RCTs, 315 people in Lao People's Democratic Republic; PCR-unadjusted treatment failure: 27/154 [18%] with artemether–lumefantrine *v* 10/161 [6%] with artesunate plus mefloquine; RR 2.93, 95% CI 1.48 to 5.80). [3] It found no significant difference between artemether–lumefantrine and artesunate plus mefloquine in total failure rate after 28 days (2 RCTs, 389 people in Thailand; PCR-unadjusted total failure rate: 11/289 [4%] with artemether–lumefantrine *v* 0/100 [0%] with artesunate plus mefloquine; RR 4.20, 95% CI 0.55 to 31.93; PCR-adjusted total failure rate: 9/289 [3%] with artemether–lumefantrine *v* 0/100 [0%] with artesunate plus mefloquine; RR 3.50, 95% CI 0.45 to 27.03). [3] The first subsequent RCT found no significant difference between artemether–lumefantrine and artesunate plus mefloquine in cure rates by day 42 (490 children and adults on the Thai–Myanmar border; PCR-adjusted cure rate: 99% with artemether–lumefantrine *v* 96% with artesunate plus mefloquine; $P = 0.08$). [30] Parasite clearance times were short, and most people were clear of parasitaemia by day 2.

The second subsequent three-arm RCT found that artesunate plus mefloquine significantly reduced parasitological treatment failure rate at day 42 compared with artemether–lumefantrine (PCR-unadjusted parasitological treatment failure: 20/121 [17%] with artemether–lumefantrine *v* 9/121 [7%] with artesunate plus mefloquine; $P = 0.039$). It found no significant difference between artemether–lumefantrine and artesunate plus mefloquine in PCR-adjusted adequate clinical and parasitological response (ACPR) at 42 days (242 children and adults in Bangladesh; PCR-adjusted ACPR: 99/102 [97%] artemether–lumefantrine *v* 105/105 [100%] artesunate plus mefloquine; $P = 0.12$). [31]

The third subsequent five-arm RCT found no significant difference between groups in the adequate clinical and parasitological cure rates at 28 days, whether PCR adjusted or not (294 people aged 2–65 years in Senegal; PCR-unadjusted ACPR at day 28: 149/149 [100%] with artemether–lumefantrine *v* 142/145 [98%] with artesunate plus mefloquine; reported as not significant, P value not reported; PCR-adjusted ACPR at day 28: 149/149 [100%] with artemether–lumefantrine *v* 145/145

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[100%] with artesunate plus mefloquine; reported as not significant, P value not reported). [7] Gametocyte carriage was more common in the group treated with artemether–lumefantrine during the first 2 weeks after treatment, but differences between groups were not tested statistically (gametocyte carriage day 7: 6% with artemether–lumefantrine *v* 0% with artesunate plus mefloquine; day 14: 3% with artemether–lumefantrine *v* 0% with artesunate plus mefloquine; no test of significance performed). No gametocytes were observed in either group after day 14. [7]

Harms:

In the systematic review, one included RCT reported adverse events separated into treatment groups. [3] It found one case (1/47 [2%]) of severe diarrhoea with artemether–lumefantrine, but none with artesunate plus mefloquine (0/50 [0%]; significance assessment not performed). The RCT reported gastrointestinal events and central nervous system disorders in both groups (gastrointestinal events: 6/47 [13%] with artemether–lumefantrine *v* 6/50 [12%] with artesunate plus mefloquine; significance assessment not performed; central nervous system disorders: 14/47 [30%] with artemether–lumefantrine *v* 22/53 [42%] with artesunate plus mefloquine; significance assessment not performed). Another included RCT reported adverse cardiac events separately, and found no clinically significant changes in the ECG intervals. [3] Another included RCT reported cardiac monitoring, and found no difference in the QTc interval (difference between the longest and shortest measurable interval on the 12-lead ECG, corrected for heart rate) between treatment groups. [3]

The first subsequent RCT reported no serious adverse events in either treatment group. [30] It found no significant difference between groups in numbers who vomited one or more doses of medication (AR for vomiting: 5/242 [2%] with artemether–lumefantrine *v* 2/242 [1%] with artesunate plus mefloquine; RR 2.5, 95% CI 0.5 to 12.7). Common mild adverse effects included gastrointestinal problems (abdominal pain, anorexia, nausea, diarrhoea, and late vomiting [e.g., >1 hour] after administration of treatment) and central nervous system effects (headache, dizziness). Overall, fewer people experienced adverse events with artemether–lumefantrine than with artesunate plus mefloquine, although this difference was not statistically significant (results presented graphically, difference reported as not significant, figures not reported). [30]

The second subsequent RCT reported no severe clinical adverse events. [31] The study reported that the frequency of mild adverse events (headache, nausea, vomiting, and dizziness) was significantly higher with artesunate plus mefloquine than with artemether–lumefantrine (mild adverse events: results presented graphically; $P < 0.05$). Other adverse events included sleeplessness, anorexia, skin itching/rash, epigastric pain, and excessive sweating with artesunate plus mefloquine, and blurred vision and anorexia with artemether–lumefantrine. [31]

The third subsequent RCT reported no serious adverse effects in the trial arms. [7] Adverse effects were described as minor, such as mild gastroenteritis, dizziness, pruritus, asthenia, and vomiting. It did not report on differences between the groups. A quarter of participants were randomly selected for blood counts and liver and renal function tests at day 1, 14, and 28. It reported only mild, self-correcting fluctuations, and no severe alterations in renal or hepatic function.

Comment:

Concealment was adequate in three of the RCTs included in the systematic review and unclear in one. [3] The RCTs conducted in Lao People's Democratic Republic were in areas of chloroquine and sulfadoxine–pyrimethamine resistance. Transmission was not specified in one trial, and was perennial in the other. The two trials conducted in Thailand included in the systematic review were in areas of low transmission. Resistance was not specified in one trial, and multi-drug resistance was reported in another. In the first subsequent RCT, allocation concealment was unclear. [30] The trial was conducted in an area of multi-drug resistance with low and unstable transmission reported. In the second subsequent RCT, allocation concealment was unclear. [31] The trial was conducted in an area of seasonal transmission with reported sulfadoxine–pyrimethamine resistance. In the third RCT, concealment was not described. [7] The RCT was carried out in five sites where the transmission of malaria was moderate, with a peak in the rainy season. High levels of chloroquine resistance have been demonstrated in Senegal.

Clinical guide: Both treatments were effective in clearing the current infection, but in terms of people being parasite free at day 42, artemether–lumefantrine was less effective than artesunate plus mefloquine.

OPTION ARTESUNATE PLUS AMODIAQUINE VERSUS ARTESUNATE PLUS SULFADOXINE–PYRIMETHAMINE (EXCLUDING SOUTH-EAST ASIA)

Treatment effectiveness

Artesunate plus amodiaquine compared with artesunate plus sulfadoxine–pyrimethamine We don't know whether artesunate plus amodiaquine is more effective than artesunate plus sulfadoxine–pyrimethamine at improving treatment effectiveness at 28 days in children aged 6 to 59 months.

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Transmission potential

Artesunate plus amodiaquine compared with artesunate plus sulfadoxine–pyrimethamine We don't know whether artesunate plus amodiaquine is more effective than artesunate plus sulfadoxine–pyrimethamine at reducing gametocyte carriage in children aged 6 to 59 months.

Benefits:

We found five RCTs [28] [32] [33] [34] [35] comparing artesunate plus amodiaquine versus artesunate plus sulfadoxine–pyrimethamine. The first RCT found no significant difference in adequate clinical and parasitological response (ACPR) after 28 days between artesunate plus amodiaquine and artesunate plus sulfadoxine–pyrimethamine (161 children aged 6–59 months in Sudan; PCR-adjusted ACPR: 51/55 [93%] artesunate plus amodiaquine *v* 52/57 [91%] artesunate plus sulfadoxine–pyrimethamine; difference reported as not significant, P value not reported). [32] The study reported that most children were afebrile by day 2, and gametocyte carriage remained low throughout the study (afebrile at day 2: 79/80 [99%] with artesunate plus amodiaquine *v* 78/81 [96%] with artesunate plus sulfadoxine–pyrimethamine; significance assessment not performed; day 14 gametocyte carriage: 3/80 [4%] with artesunate plus amodiaquine *v* 4/79 [5%] with artesunate plus sulfadoxine–pyrimethamine; day 28 gametocyte carriage: 2/68 [3%] with artesunate plus amodiaquine *v* 2/70 [3%] with artesunate plus sulfadoxine–pyrimethamine; significance assessments not performed). [32]

The second quasi-randomised RCT found a significantly higher rate of adequate clinical and parasitological response at day 28 with artesunate plus sulfadoxine–pyrimethamine compared with artesunate plus amodiaquine (269 children aged 6–59 months in Sudan; PCR-unadjusted ACPR rate: 105/117 [90%] with artesunate plus amodiaquine *v* 114/116 [98%] with artesunate plus sulfadoxine–pyrimethamine; P = 0.014). [33] In this RCT, treatment groups were allocated by alternate allocation.

The third RCT found that treatment with artesunate plus amodiaquine was associated with a lower rate of treatment failure by day 28 compared with artesunate plus sulfadoxine–pyrimethamine, regardless of whether new infections were included or not (180 children aged 6–59 months in the Democratic Republic of Congo; PCR-unadjusted failure rate: 14/83 [17%] with artesunate plus amodiaquine *v* 28/81 [35%] with artesunate plus sulfadoxine–pyrimethamine; P = 0.009; PCR-adjusted failure rate: 5/74 [7%] with artesunate plus amodiaquine *v* 13/66 [20%] with artesunate plus sulfadoxine–pyrimethamine; P = 0.02). [34] It found that fever clearance was complete within 2 to 3 days for both therapies, and found no significant difference between the two groups (no further data or P value reported). It reported that the two treatment groups showed no significant difference in gametocyte clearance rates (no P value reported). [34]

The fourth RCT found no significant difference between groups in the risk of recurrent parasitaemia at day 28 (220 children aged 6–59 months in Guinea; PCR-unadjusted risk of recurrent parasitaemia at day 28: 6/107 [6%] with artesunate plus amodiaquine *v* 9/106 [9%] with artesunate plus sulfadoxine–pyrimethamine; P = 0.41). [35] There remained no significant difference between groups when adjusted by PCR (PCR-adjusted risk of treatment failure at day 28: 1/102 [1%] with artesunate plus amodiaquine *v* 1/99 [1%] with artesunate plus sulfadoxine–pyrimethamine; P value not reported). Gametocyte carriage was significantly reduced in both groups at day 28 compared with baseline (no statistical significance test between groups reported). [35]

The fifth three-arm RCT compared artesunate plus amodiaquine versus artesunate plus sulfadoxine–pyrimethamine in the Republic of Congo. [28] It found that the risk of recurrent parasitaemia at day 28 was similar in both groups (192 children aged 6–59 months; PCR-unadjusted day 28 risk of recurrent parasitaemia: 31/97 [32%] with artesunate plus amodiaquine *v* 21/85 [25%] with artesunate plus sulfadoxine–pyrimethamine; no direct statistical significance test between groups reported). The difference between groups was not significant after adjustment by PCR, but there were increased losses to follow-up (results based on 138/192 [72%] of those initially randomised; PCR-adjusted treatment failure at 28 days: 1/67 [2%] with artesunate plus amodiaquine *v* 7/71 [10%] with artesunate plus sulfadoxine–pyrimethamine; P = 0.06). The proportion of children still febrile at day 3 was similar between groups (3/101 [3%] with artesunate plus amodiaquine *v* 4/90 [4%] artesunate plus sulfadoxine–pyrimethamine; no statistical significance test between groups reported). The proportion of cases with gametocytaemia decreased in both groups during follow-up (no statistical significance test between groups reported). [28]

Harms:

The first RCT reported "no significant adverse events" in either group. [32] The second RCT found no adverse events in either group during follow-up. [33]

In the third RCT, parents or guardians were asked for any potential adverse effects of the drugs, and the child's tolerability to the treatment at follow-up. [34] No adverse effects were reported, and both drug regimens were well tolerated. [34] The fourth RCT did not report on adverse events. [35]

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The fifth RCT reported no clinically severe adverse events. [28] The common adverse effects were vomiting, diarrhoea, abdominal pain, and anorexia (no figures given).

Comment: In the first RCT, allocation concealment was adequate. [32] The study site exhibited marked seasonal transmission of malaria. No data for antimalarial efficacy were available. Allocation concealment was inadequate in the second quasi-randomised RCT, and losses to follow-up were high (15%). [33] This study was conducted in an area of medium to high malaria endemicity. In the third RCT, allocation concealment was adequate. [34] Malaria in the Democratic Republic of Congo is highly endemic and seasonal, with intense perennial transmission. Details of the drug regimens used were not stated in this study. In the fourth RCT, allocation concealment was unclear. [35] The trial was conducted in an area with seasonal perennial malaria. High rates of chloroquine, amodiaquine, and sulfadoxine–pyrimethamine resistance have been reported in neighbouring countries, but data from the study site are scarce. In the fifth RCT, the method of allocation concealment was unclear. [28] PCR-adjusted results were only available for 80% of the randomised participants. Malaria was holoendemic in the trial location; resistance to both chloroquine and sulfadoxine–pyrimethamine were reported as high.

Clinical guide: The choice between artesunate plus amodiaquine and artesunate plus sulfadoxine–pyrimethamine depends on the background resistance patterns in the relevant country or region.

OPTION ARTESUNATE PLUS MEFLOQUINE VERSUS ARTESUNATE PLUS AMODIAQUINE New

Treatment effectiveness

Artesunate plus mefloquine compared with artesunate plus amodiaquine We don't know whether artesunate plus mefloquine is more effective than artesunate plus amodiaquine at improving PCR-adjusted or PCR-unadjusted ACPR rates in adults and children in Senegal.

Transmission potential

Artesunate plus mefloquine compared with artesunate plus amodiaquine We don't know whether artesunate plus mefloquine is more effective than artesunate plus amodiaquine at improving gametocyte carriage in adults and children in Senegal.

Benefits: We found one five-arm RCT comparing artesunate plus mefloquine versus artesunate plus amodiaquine. [7] It found no significant difference between groups in unadjusted adequate clinical and parasitological response (ACPR) at 28 days (505 people aged 1–75 years in Senegal; PCR-unadjusted ACPR: 141/145 [97.9%] with artesunate plus mefloquine *v* 351/360 [97.5%] with artesunate plus amodiaquine; reported as not significant, P value not reported). When adjusted by PCR, there were no true recrudescences observed in either group (PCR-adjusted ACPR: 100% with artesunate plus mefloquine *v* 100% with artesunate plus amodiaquine; reported as not significant, P value not reported). Gametocyte carriage was higher in the group treated with artesunate plus mefloquine at day 3 but differences between groups were not tested statistically (gametocyte carriage at day 3: 2% with artesunate plus mefloquine *v* 0% with artesunate plus amodiaquine; statistical significance test not reported). No gametocytes were observed in either group at any point from day 7 to 28. [7]

Harms: There were no serious adverse events reported by the RCT. [7] The common adverse effects were minor gastrointestinal upset, dizziness, pruritus, weakness, and vomiting (statistical analysis between groups for adverse effects not reported). A quarter of participants were randomly selected for blood counts and liver and renal function tests at day 1, 14, and 28. The RCT reported no severe alterations in renal or hepatic function. [7]

Comment: In the RCT, concealment is not described. [7] The RCT was carried out in five sites where the transmission of malaria is moderate, with a peak in the rainy season. High levels of chloroquine resistance have been demonstrated in Senegal. This five-arm RCT was described as randomised. However, one arm (artesunate plus mefloquine) was twice as large as the other four arms, and the method of randomisation was not described. [7]

OPTION ARTESUNATE PLUS MEFLOQUINE VERSUS ARTESUNATE PLUS SULFADOXINE–PYRIMETHAMINE New

We found no direct information from RCTs about artesunate plus mefloquine versus artesunate plus sulfadoxine–pyrimethamine in the treatment of people with uncomplicated malaria caused by *Plasmodium falciparum*.

Benefits: We found no systematic review or RCTs comparing artesunate plus mefloquine versus artesunate plus sulfadoxine–pyrimethamine.

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Harms: We found no RCTs.

Comment: **Clinical guide:** The choice between artesunate plus mefloquine or artesunate plus sulfadoxine–pyrimethamine depends on background drug-resistance patterns in the relevant country or region.

GLOSSARY

Clinical failure Symptoms of malaria with parasitaemia on or before day 28.
Gametocytaemia Microscopic evidence of gametocytes in the blood.
Gametocyte clearance time Time to clearance of gametocytes from the blood after treatment.
Parasitological conversion Clearance of parasitaemia within a specified time after treatment.
Parasitological failure Parasitaemia detected within a specified time after treatment.
Parasitological success Absence of parasitaemia within a specified time after treatment.
Total failure People presenting with clinical failure or with parasitaemia on day 28.
Adequate clinical and parasitological response (ACPR) According to the WHO definition, absence of parasitaemia at day 28 irrespective of axillary temperature and without previously meeting any of the WHO criteria for early or late treatment failure, or late parasitological failure. [36]
PCR-adjusted treatment failure rate Parasitaemia on or by day 28 may be due to recrudescence of the original infection or caused by a new infection. PCR-adjusted values exclude parasitaemia caused by a new infection.
Treatment failure This term is used loosely in the literature, but it generally means total failure or failure (clinical or parasitological) within the period of follow-up. The WHO modified definitions of treatment failure in 2003 to include late parasitological failures. [36]

SUBSTANTIVE CHANGES

Artesunate plus mefloquine versus artesunate plus amodiaquine New option added. One RCT found which reported similar effects between groups in Senegal. [7] "Artesunate plus mefloquine versus artesunate plus amodiaquine" categorised as Unknown effectiveness.
Artesunate plus mefloquine versus artesunate plus sulfadoxine–pyrimethamine New option added. No RCTs found. "Artesunate plus mefloquine versus artesunate plus sulfadoxine–pyrimethamine" categorised as Unknown effectiveness.
Artemether–lumefantrine (6 doses) versus amodiaquine plus sulfadoxine–pyrimethamine One systematic review added, [4] which identified one RCT previously reported in this review. No new data added from the review. Five subsequent RCTs added comparing artemether–lumefantrine versus amodiaquine plus sulfadoxine in Uganda, Rwanda, Senegal, and Burkina Faso. [5] [6] [7] [8] [9] Categorisation of "Artemether–lumefantrine (6 doses) (probably more effective than amodiaquine plus sulfadoxine–pyrimethamine)" unchanged (Likely to be beneficial).
Artemether–lumefantrine (6 doses) versus artemether–lumefantrine (4 doses) One RCT in Senegal added. [7] Categorisation of "Artemether–lumefantrine (6 doses) (6-dose regimen more effective than a 4-dose regimen)" unchanged (Likely to be beneficial).
Artemether–lumefantrine (6 doses) versus artesunate (3 days) plus amodiaquine (excluding South-East Asia) Three RCTs added comparing artemether–lumefantrine (6 doses) versus artesunate (3 days) plus amodiaquine in Uganda, Senegal, and Republic of Congo. [7] [9] [28] Categorisation of "Artemether–lumefantrine (6 doses) (possibly more effective than artesunate plus amodiaquine)" unchanged (Likely to be beneficial).
Artemether–lumefantrine (6 doses) versus artesunate (3 days) plus mefloquine One RCT added comparing artemether–lumefantrine (6 doses) versus artesunate (3 days) plus mefloquine in Senegal. [7] Categorisation of "Artemether–lumefantrine (6 doses) (possibly less effective than artesunate [3 days] plus mefloquine)" unchanged (Unlikely to be beneficial).
Artemether–lumefantrine (6 doses) versus artesunate plus sulfadoxine–pyrimethamine (excluding South-East Asia) Two RCTs added comparing artemether–lumefantrine (6 doses) versus artesunate plus sulfadoxine–pyrimethamine in Eastern Sudan and in the Republic of Congo. [28] [29] Categorisation of "Artemether–lumefantrine (6 doses) versus artesunate plus sulfadoxine–pyrimethamine" unchanged (Unknown effectiveness).
Artesunate (3 days) plus sulfadoxine–pyrimethamine versus amodiaquine plus sulfadoxine–pyrimethamine One systematic review added, [4] which included the same four RCTs as one systematic review previously reported in this review, and came to similar conclusions. No new data added from the additional review. Categorisation of "Artesunate (3 days) plus sulfadoxine–pyrimethamine (possibly less effective than amodiaquine plus sulfadoxine–pyrimethamine)" unchanged (Unlikely to be beneficial).
Artesunate plus amodiaquine versus artesunate plus sulfadoxine–pyrimethamine (excluding South-East Asia) Two RCTs added comparing artesunate plus amodiaquine versus artesunate plus sulfadoxine–pyrimethamine in Guinea and the Republic of Congo. [28] [35] Categorisation of "Artesunate plus amodiaquine versus artesunate plus sulfadoxine–pyrimethamine (relative benefits unclear)" unchanged (Unknown effectiveness).
Artesunate (3 days) plus amodiaquine versus amodiaquine plus sulfadoxine–pyrimethamine One new systematic review added, which included four RCTs and pooled data, [4] and four subsequent RCTs added comparing artesunate plus amodiaquine versus amodiaquine plus sulfadoxine–pyrimethamine in Madagascar, Uganda, Senegal, and Rwanda. [7] [9] [11] [12] Categorisation of "Artesunate (3 days) plus amodiaquine (possibly more effective than amodiaquine plus sulfadoxine–pyrimethamine)" changed to Likely to be beneficial.

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