Malaria: uncomplicated, caused by *Plasmodium falciparum*

Search date November 2006
David Taylor-Robinson, Katharine Jones, and Paul Garner

QUESTIONS

INTERVENTIONS

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.

- Evidence suggests that artemether–lumefantrine is more effective than amodiaquine plus sulfadoxine–pyrimethamine.
- 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.
- Amodiaquine plus sulfadoxine–pyrimethamine achieved higher cure rates than artesunate plus sulfadoxine–pyrimethamine . Gametocyte clearance was better with artesunate plus sulfadoxine–pyrimethamine.

  Public health specialists believe that amodiaquine resistance will progress rapidly and limit the usefulness of the non-artemisinin combination if it is used regularly. On the other hand, amodiaquine and sulfadoxine–pyrimethamine are currently available in many countries, whereas artemisinin supplies are limited.

- 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 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.

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 (World Health Organization 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 300–500 million new clinical cases annually, most of them cases of uncomplicated malaria. An estimated 1.1–2.7 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

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) ; parasitological conversion rate; parasitological success rate; fever-clearance time; gametocytaemia rate; gametocyte clearance time ; rate of progression to severe disease; need for rescue treatment (quinine treatment given in the case of treatment failure); and adverse effects requiring admission to hospital or discontinuation of treatment. 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, 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.

METHODS

BMJ Clinical Evidence search and appraisal November 2006. The following databases were used to identify studies for this systematic review: Medline 1966 to November 2006, Embase 1980 to November 2006, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2006, Issue 4. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into

Practice (TRIP), and National Institute for Health and Clinical Excellence (NICE). Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using predetermined criteria to identify relevant studies. 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. There was no minimum length of follow-up required to include studies. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. We conducted the search and identified the questions in collaboration with the World Health Organization Malaria Technical Guidelines Development Group for evidence-based guidelines for uncomplicated malaria treatment that draw explicitly on this review. 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 performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 13).

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

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

Treatment failure

Artemether–lumefantrine compared with amodiaquine plus sulfadoxine–pyrimethamine Artemether–lumefantrine is more effective at reducing treatment failure rates at 28 days compared with amodiaquine plus sulfadoxine (high-quality evidence).

For GRADE evaluation of malaria: uncomplicated, caused by Plasmodium falciparum, see table, p 13 .

Benefits: We found one systematic review (search date 2005) [3] which identified one RCT. [4] The primary outcome measure of the review was total failure . The review reported 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 [29%] with artemether–lumefantrine *v* 369/463 [80%] with amodiaquine plus sulfadoxine–pyrimethamine; RR 0.36, 95% CI 0.32 to 0.42). [3] 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).

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. [4]

Comment: Concealment was adequate in the trial. [3] The trial was conducted in an area where malaria transmission is perennial, and where a high level of resistance to sulfadoxine–pyrimethamine and chloroquine has been recorded. [4]

Clinical guide:
Artemether–lumefantrine is more effective than amodiaquine plus sulfadoxine–pyrimethamine.

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

Treatment failure

Artesunate plus amodiaquine compared with amodiaquine plus sulfadoxine– pyrimethamine Artesunate plus amodiaquine may be more effective than amodiaquine plus sulfadoxine–pyrimethamine in reducing treatment failure rates (excluding new infections) at 28 days in children with uncomplicated malaria, but may be no more effective in the need for rescue therapy (low-quality evidence).

Fever resolution

Artesunate plus amodiaquine compared with amodiaquine plus sulfadoxine–pyrimethamine Artesunate plus amodiaquine is more effective at 3 days in reducing the time to fever resolution compared with amodiaquine plus sulfadoxine-pyrimethamine (moderate-quality evidence).

Recrudescence

Artesunate plus amodiaquine compared with amodiaquine plus sulfadoxine–pyrimethamine Artesunate plus amodiaquine may increase recrudescence rates at 28 days compared with amodiaquine plus sulfadoxine–pyrimethamine (low-quality evidence).

For GRADE evaluation of malaria: uncomplicated, caused by Plasmodium falciparum, **see table, p 13** **.**

Benefits:

We found three RCTs. [4] [5] [6] The first three-arm RCT compared artesunate plus amodiaquine versus amodiaquine plus sulfadoxine–pyrimethamine. [5] It found that artesunate plus amodiaquine significantly reduced the risk of clinical treatment failure compared with amodiaquine plus sulfadoxine–pyrimethamine at 28 days, although there was no significant difference in need for rescue therapy (278 children in Uganda aged 6 months to 10 years, randomised to the artesunate plus amodiaquine and amodiaquine plus sulfadoxine–pyrimethamine arms; polymerase chain reaction-adjusted clinical treatment failure [per protocol analysis]: 9% with amodiaquine plus sulfadoxine–pyrimethamine *v* 2% with artesunate plus amodiaquine; difference 7%, 95% CI 1% to 13%; P = 0.018; rescue treatment [per protocol analysis]: 13% with amodiaquine plus sulfadoxine–pyrimethamine *v* 12% with artesunate plus amodiaquine; difference +1%, 95% CI –7% to +9%; P = 0.854). [5] The RCT also found that artesunate plus amodiaquine significantly reduced time to fever resolution compared with amodiaquine plus sulfadoxine–pyrimethamine, although by day 3 fever had cleared in most children (afebrile at day 2: 101/129 [78%] with artesunate plus amodiaquine v 83/130 [64%] with amodiaquine plus sulfadoxine–pyrimethamine; P = 0.02; afebrile at day 3: absolute figures not presented, significance assessment not performed). The second four-arm RCT compared artesunate plus amodiaquine versus amodiaquine plus sulfadoxine–pyrimethamine. [4] It found that artesunate plus amodiaquine significantly reduced parasitological failure and clinical failure rate at 28 days, and was associated with fewer gametocytes at day 14 compared with amodiaquine plus sulfadoxine–pyrimethamine (1022 children aged 4–59 months in North East Tanzania, randomised to artesunate plus amodiaquine and amodiaquine plus sulfadoxine–pyrimethamine arms; polymerase chain reaction [PCR]-adjusted parasitological failure rate: 193/472 [40%] with artesunate plus amodiaquine *v* 282/463 [61%] with amodiaquine plus sulfadoxine–pyrimethamine; OR 0.43, 95% CI 0.34 to 0.59; P < 0.0001; clinical failure rate: 52/472 [11%] with artesunate plus amodiaquine *v* 87/463 [19%] with amodiaquine plus sulfadoxine–pyrimethamine; OR 0.56, 95% CI 0.37 to 0.77; P = 0.0008; gametocytes: 38/318 [12%] with artesunate plus amodiaquine *v* 73/284 [26%] with amodiaquine plus sulfadoxine–pyrimethamine; significance assessment not performed). [4] The third RCT, undertaken in four separate districts in Uganda (Jinja, Arua, Apac, Tororo), compared artesunate plus amodiaquine versus amodiaquine plus sulfadoxine–pyrimethamine. [6] The results were reported separately for the four sites. The RCT found that, at two sites with high transmission, artesunate plus amodiaquine was associated with a higher risk for recurrent infection (recrudescence [relapse caused by recurrence of the original infection] and new infection) and new infection at day 28, with no significant difference detected at the other two sites (1537 children in total aged 6 months or greater; PCR-unadjusted risk of recurrent infection [per protocol analysis]: Tororo site: 59% with amodiaquine plus sulfadoxine–pyrimethamine *v* 74% with artesunate plus amodiaquine, P < 0.05; Apac site: 36% *v* 52%, P less than 0.05; Jinja site, 28% *v* 19%, difference reported as not significant, P value not provided; Arua site: 53% *v* 51%, difference reported as not significant, P value not provided). [6] In contrast, the RCT found that artesunate plus amodiaquine was associated with a lower risk of recrudescence at three sites, although this only reached statistical significance at one site (Jinja site: risk difference 9%, 95% CI 3% to 15%, P = 0.009). The proportion of people with a temperature above 37.5° celcius on day 2 did not differ between the two groups at any of the sites. The proportion of people with gametocytes during follow-up was significantly lower in the artesunate plus amodiaquine group at one of the sites (Arua site: 49% with amodiaquine plus sulfadoxine–pyrimethamine *v* 36% with artesunate plus amodiaquine; P less than 0.05), but was not significantly different between groups at the other three sites. [6]

Harms:

The first RCT found no significant difference between treatments in adverse events of moderate or greater severity when people who needed rescue therapy were excluded from analyses (absolute figures not reported; difference reported as not significant; P value not reported). [5] Six serious adverse events were reported with amodiaquine plus sulfadoxine–pyrimethamine (3 convulsions; 1 vomiting; 1 pyomyositis; and 1 thrombocytopenia, neutropenia, and anaemia) and one with artesunate plus amodiaquine (measles). Most of these were attributable to severe malaria or other illnesses. The child with thrombocytopenia was noted to have had it at enrolment, but it worsened and became life threatening, and severe anaemia and neutropenia developed. A bone marrow biopsy revealed hypoplastic marrow of undetermined cause with all cell lines present. Additional severe laboratory-related adverse events included one case of anaemia with artesunate plus

amodiaquine, one case of transient asymptomatic neutropenia with amodiaquine plus sulfadoxine–pyrimethamine, and one case of increased alanine transaminase associated with clinical hepatitis that resolved by day 28 with amodiaquine plus sulfadoxine–pyrimethamine. In the second RCT, one child in the amodiaquine plus sulfadoxine–pyrimethamine group died on the day of randomisation; no children died in the artesunate plus amodiaquine group. [4] Severity of disease was thought to be the probable cause of death. One other possible serious adverse event was recorded: a child needed hospitalisation for a rash on day 20. The authors did not state in which treatment arm this child was, but stated that the rash was thought to be unrelated to the study drug. The third RCT found eight people with serious adverse events in the amodiaquine plus sulfadoxine–pyrimethamine group (2 episodes of anaemia, 2 of convulsions, 1 of oedema, 2 of mental status change, 2 of respiratory illness, and 1 of weakness) compared with four in the artesunate plus amodiaquine group (1 episode of anaemia, 1 of convulsions, 1 of dehydration and 1 of respiratory illness). [6] Only ten of the serious adverse events were thought to be possibly related to study medications in the trial, but these were not disaggregated between treatment groups. Two people died in the amodiaquine plus sulfadoxine–pyrimethamine group (1 of suspected malnutrition and 1 of heart failure secondary to a presumed congenital heart defect).

Comment:

Concealment was adequate in the three trials. [4] [5] [6] The first RCT was conducted in an urban centre where malaria is mesoendemic, arising perennially with peaks during the two rainy seasons. [5] Fourteen-day clinical treatment failure rates of 7% with amodiaquine and 2% with amodiaquine plus sulfadoxine–pyrimethamine had been reported from the site shortly before the study began. The authors of the second study did not comment on the malaria endemicity or resistance patterns in the study site. [4] The third RCT was conducted in four sites; one peri-urban with medium-high endemnicity (Jinja), and three rural with very high endemnicity (Arua, Apac and Tororo). [6]

Clinical guide:

In terms of cure of the current infection, artesunate plus amodiaquine is more effective than amodiaquine plus sulfadoxine–pyrimethamine. 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. These findings are relevant in endemic malarious areas of Africa.

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

Treatment failure

Artesunate plus sulfadoxine–pyrimethamine compared with amodiaquine plus sulfadoxine–pyrimethamine Artesunate plus sulfadoxine-pyrimethamine may be less effective at reducing treatment failure rates at 28 days compared with amodiaquine plus sulfadoxine–pyrimethamine (very low-quality evidence).

For GRADE evaluation of interventions for malaria: uncomplicated, caused by Plasmodium falciparum, **see table, p 13** **.**

Benefits:

We found one systematic review [7] and two subsequent RCTs. [8] [9] The systematic review (search date 2005, 4 RCTs, 775 people) compared artesunate plus sulfadoxine–pyrimethamine versus amodiaquine plus sulfadoxine–pyrimethamine. [7] 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 people in Uganda, Ghana, and Rwanda; polymerase chain reaction [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). It found that amodiaquine plus sulfadoxine–pyrimethamine also resulted in significantly fewer treatment failures when new infections were excluded (3 RCTs, 649 people 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). 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). [7] The first subsequent eight-arm RCT compared artesunate plus sulfadoxine–pyrimethamine versus amodiaquine plus sulfadoxine–pyrimethamine in two arms of the trial. [8] It found similar results in the proportion of total failures at day 28 between the two trial arms, but did not test significance between groups (147 adults and children in Colombia; total failure at day 28: 2/57 [3.4%] with artesunate plus sulfadoxine–pyrimethamine *v* 2/90 [2.2%] with amodiaquine plus sulfadoxine–pyrimethamine; no statistical significance test reported).The second subsequent four-arm RCT compared artesunate plus sulfadoxine–pyrimethamine versus amodiaquine plus sulfadoxine–pyrimethamine in Kenya. [9] It found that the proportion of adequate clinical parasitological response was higher with amodiaquine plus

sulfadoxine–pyrimethamine compared with artesunate plus sulfadoxine–pyrimethamine (adequate clinical parasitological response at day 28: 131/160 [82%] with artesunate plus sulfadoxine–pyrimethamine *v* 100/115 [87%] with amodiaquine plus sulfadoxine–pyrimethamine; no statistical significance test between groups reported). It found that gametocyte prevalence over 28 days was significantly higher with amodiaquine plus sulfadoxine–pyrimethamine, whether measured using microscopy (P less than 0.001) or by genetic typing (P = 0.007). [9]

Harms: The systematic review reported that one participant 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). [7] 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; the paper describing these effects is in preparation. [8] The second subsequent RCT did not report on adverse effects. [9]

Comment: Concealment was adequate in one, and unclear in three of the four RCTs included in the systematic review. [7] 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. [8] 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. [9] 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. Public health specialists believe that amodiaquine resistance will progress rapidly and limit the usefulness of the non-artemisinin combination if it is used regularly. On the other hand, amodiaquine and sulfadoxine–pyrimethamine are currently available in many countries, whereas artemisinin supplies are limited.

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

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

Cure rates

Six-dose regimen compared with four-dose regimen A six-dose regimen of artemether–lumefantrine is more effective at increasing cure rates at 28 days compared with a four-dose regimen (moderate-quality evidence).

For GRADE evaluation of interventions for malaria: uncomplicated, caused by Plasmodium falciparum, **see table, p 13** **.**

Benefits: We found one systematic review (search date 2005, 1 RCT, 359 people, Thailand). [10] The RCT identified by the review compared 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. [11] 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, Thailand; polymerase chain reaction [PCR]-unadjusted parasitological cure rate for intention to treat population at day 28: 96/118 [81%] with 6-dose regimen *v* 85/120 [71%] with 4-dose regimen; P less than 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 less than 0.001). [11] 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 provided). [10] There was no statistically significant difference in the gametocyte clearance time in comparisons between the four-dose and six-dose regimens (P = 0.5; trial authors’ calculation). [10]

Harms: The RCT identified by the review reported all adverse events to be mild or moderate in severity and possibly attributable to malaria. [11] 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

found no changes in QRS duration and PR interval during treatment in 66 people who had regular electrocardiographic monitoring. Similarly, it found no differences in mean and median QTc (heart rate-corrected QT interval) values between treatments.

Comment: Concealment was adequate. The trial was conducted in an area of multi-drug resistance. Transmission was not stated.

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

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

Cure rates
Artemether–lumefantrine compared with artesunate plus amodiaquine We don't know whether artemether–lumefantrine may be more effective at increasing cure rates at 28 days compared with artesunate plus amodiaquine (very low-quality evidence).

Recrudescence
Artemether–lumefantrine compared with artesunate plus amodiaquine Artemether–lumefantrine may be more effective at reducing recrudescence rates at 28 days compared with artesunate plus amodiaquine (low-quality evidence).

For GRADE evaluation of interventions for malaria: uncomplicated, caused by Plasmodium falciparum, see table, p 13 .

Benefits: We found one systematic review [3] and four subsequent RCTs [12] [13] [14] [15] that compared artemether–lumefantrine (6-dose regimen) versus artesunate plus amodiaquine. The review (search date 2005) identified one four-arm RCT. [4] It 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 randomised to artesunate plus amodiaquine and artemether–lumefantrine arms, in Tanzania; polymerase chain reaction [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). The first subsequent RCT, a four-arm trial, found no difference between the treatment groups in cure at day 28 (105 children aged 6-59 months randomised to artesunate plus amodiaquine and artemether–lumefantrine arms in Ghana; adequate clinical and parasitological response PCR-unadjusted day 28: 38/54 [70%] with artesunate plus amodiaquine *v* 39/51 [76%] with artemether–lumefantrine, significance assessment between groups not performed). [12] It found that treatment with artesunate plus amodiaquine was associated with shorter fever clearance times (fever clearance: 1.0 day with artesunate plus amodiaquine *v* 1.2 days with artemether–lumefantrine; P = 0.006). Gametocytaemia peaked on day 1 (7/53 [13.2%] with artesunate plus amodiaquine *v* 6/51 [11.8%] with artemether–lumefantrine) and declined to 2% on days 7 and 14 (1/51 [2%] with artesunate plus amodiaquine *v* 1/47 [2%] with artemether–lumefantrine). [12] 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, Zanzibar; PCR-unadjusted day 28 cure rate: 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 less than 0.001; PCR-adjusted day 28 cure rate 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 0.9 to 7.40, P = 0.76; PCR-adjusted day 28 cure rate 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). [13] It found that absence of fever on day 1 was observed in a significantly higher proportion of people treated with artesunate plus amodiaquine compared with artemether–lumefantrine (absence of fever on day 1: 162/205 [79%] with artesunate plus amodiaquine *v* 134/199 [67%] with artemether–lumefantrine; 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). [13] The third subsequent RCT (137 children aged 6–59 months in Angola) found no difference in recurrent parasitaemia at day 28 or cure rate at day 28 (PCR-unadjusted recurrent parasitaemia: 2/61 [3.2%] with artemether-lumefantrine *v* 4/64 [6.2%] with artesunate plus amodiaquine; P = 0.72; polymerase chain reaction-adjusted cure rate: 100% with artemether–lumefantrine *v* 100% with artesunate plus amodiaquine, 95% CI,

94–100% in both groups). [14] Only one (1.5%) child in the artesunate plus amodiaquine group had gametocytes on day 28 compared with five (7.3%) children in the artemether-lumefantrine group and three (4.3%) children in the artesunate plus amodiaquine group at baseline. [14] The fourth RCT (419 children aged 1–10 yrs in Uganda) found that the risk of recurrent symptomatic malaria by day 28 was significantly lower for participants treated with artemether–lumefantrine than for those treated with artesunate plus amodiaquine (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). [15] It found a significant benefit in favour of artemether–lumefantrine compared with artesunate plus amodiaquine for the risk of recurrent parasitemia (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: 0/201 [0%] with artesunate plus amodiaquine *v* 2/202 [1%] with artemether–lumefantrine; risk difference –1.0%; 95%CI –2.4% to 0.4%; PCR-adjusted recurrent parasitaemia: 2/202 [0%] 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 provided). 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). [15]

Harms:

The review did not report any harms for the included RCT. [3] The first subsequent RCT did not report on adverse events. [12] The second subqequent RCT reported that both regimens were generally well tolerated. [13] No deaths occurred, but 9 participants (7 with artesunate plus amodiaquine group *v* 2 with artemether–lumefantrine) 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 severe or moderate adverse event was reported by 25/207 (12%) children with artesunate plus amodiaquine compared with 21/200 (10%) children treated with artemether–lumefantrine (unadjusted OR, 0.85; 95% CI, 0.46–1.58). 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. The third subsequent RCT did not report on harms. [14] The fourth RCT assessed participants for any new or worsening adverse event at each follow-up visit, and found that both treatments were well-tolerated. [15] Overall, 261 (65%) of 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 hospitalisation, 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. [15]

Comment:

The RCT [4] identified by the systematic review [3] used adequate allocation concealment. Malaria transmission was perennial and the study site was in an area of chloroquine and sulfadoxine–pyrimethamine resistance. [4] In the first subsequent RCT allocation concealment was unclear. [12] 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. [13] Inclusion criteria were slightly different for very small children (less than 9 months or less than 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. [14] Drug resistance patterns were not stated. In the fourth additional RCT, allocation concealment was unclear, malaria was holoendemic, and local drug re-

sistance patterns were not stated. [15] **Clinical guide**: Both treatments were effective, but artemether–lumefantrine (6 doses) was superior in some of the trials.

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

We found no clinically important results about artemether–lumefantrine (6 doses) compared with artesunate plus sulfadoxine–pyrimethamine in the treatment of people with uncomplicated malaria caused by plasmodium falciparum.

For GRADE evaluation of Malaria: uncomplicated, caused by Plasmodium falciparum, **see table, p 13** **.**

Benefits: We found no systematic reviews or RCTs that compared artemether–lumefantrine (6 doses) versus artesunate plus sulfadoxine–pyrimethamine.

Harms: We found no RCTs.

Comment: **Clinical guide:**
Indirect comparisons suggest that artemether–lumefantrine may be more efficacious than artesunate plus sulfadoxine–pyrimethamine.

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

Treatment failure
Artemether–lumefantrine compared with artesunate plus mefloquine Artemether–lumefantrine seems to be no more effective at reducing treatment failure rates at 28 days compared with artesunate plus mefloquine (moderate-quality evidence).

Cure rates
Artemether–lumefantrine compared with artesunate plus mefloquine Artemether–lumefantrine may be no more effective at increasing cure rates at 42 days compared with artesunate plus mefloquine (very low-quality evidence).

For GRADE evaluation of interventions for malaria: uncomplicated, caused by Plasmodium falciparum, **see table, p 13** **.**

Benefits: We found one systematic review [3] and two subsequent RCTs [16] [17] that compared artemether–lumefantrine versus artesunate plus mefloquine. The systematic review found that artemether–lumefantrine significantly increased treatment failures compared with artesunate plus mefloquine at 42 days (search date 2005, 2 RCTs, 315 people, in Lao People's Democratic Republic; polymerase chain reaction [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] Two other RCTs identified by the review 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, in Thai–Myanmar border; PCR-adjusted cure rate: 98.8% with artemether–lumefantrine *v* 96.3% with artesunate plus mefloquine; P = 0.08). [16] Parasite clearance times were short, and most people were clear of parasitaemia by day 2. The second subsequent three-arm RCT 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 randomised to the artemether–lumefantrine and artesunate plus mefloquine groups, in Bangladesh; PCR-adjusted ACPR rate: 99/102 [97%] with artemether–lumefantrine *v* 105/105 [100%] with artesunate plus mefloquine; P = 0.12). [17] However, if new infections were included, then artesunate plus mefloquine 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). [17]

Harms: One RCT included in the systematic review reported adverse events in 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 were more common with artesunate plus mefloquine (14/47 [30%] with artemether–lumefantrine *v* 22/53 [41.5%] with artesunate plus mefloquine; significance assessment not performed). One RCT reported adverse cardiac events separately, and found no clinically significant changes in the electrocardiographic intervals. Another RCT reported cardiac monitoring, and found no difference in the QTc interval (difference between the longest and shortest measurable interval on the 12-lead electrocardiogram, corrected for heart rate) between treatment groups. The first subsequent RCT reported no serious adverse events in either treatment group. [16] It found no significant difference between groups in numbers who vomited one or more doses of medication (AR for vomiting: 5/242 [2.1%] with artemether–lumefantrine *v* 2/242 [0.8%] 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. greater than 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). The second additional RCT reported no severe adverse clinical events. [17] The study reported that the frequency of mild adverse events (headache, nausea, vomiting, dizziness) was significantly higher with artesunate plus mefloquine than with artemether–lumefantrine (mild adverse events: results presented graphically; P less than 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.

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 subsequent RCTs, allocation concealment was unclear. [16] [17] The first additional RCT was conducted in an area of multidrug resistance with low and unstable transmission reported. [16] The second additional RCT reported sulfadoxine–pyrimethamine resistance in an area of seasonal transmission. [17]

Clinical guide:

Artesunate plus mefloquine performs better than artemether–lumefantrine in terms of cure in areas where this has been studied.

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

Response rates

Artesunate plus amodiaquine compared with artesunate plus sulfadoxine–pyrimethamine We don't know whether artesunate plus amodiaquine is any more effective at increasing response rates at 28 days compared with artesunate plus sulfadoxine–pyrimethamine (very low-quality evidence).

Treatment failure

Artesunate plus amodiaquine compared with artesunate plus sulfadoxine–pyrimethamine Artesunate plus amodiaquine is more effective at reducing treatment failure rates at 28 days compared with artesunate plus sulfadoxine–pyrimethamine (moderate-quality evidence).

For GRADE evaluation of Malaria: uncomplicated, caused by Plasmodium falciparum, **see table, p 13 .**

Benefits:

We found three RCTs that compared artesunate plus amodiaquine versus artesunate plus sulfadoxine–pyrimethamine. [18] [19] [20] The first RCT found no significant difference in adequate clinical and parasitological response rate (ACPR) after 28 days between artesunate plus amodiaquine and artesunate plus sulfadoxine–pyrimethamine (161 children aged 6–59 months, in Sudan; polymerase chain reaction [PCR]-adjusted ACPR: 51/55 [93%] with artesunate plus amodiaquine *v* 52/57 [91%] with artesunate plus sulfadoxine–pyrimethamine; difference reported as not significant, figures not reported). [18] It found similar treatment failure rates in both groups at day 28 (PCR-unadjusted clinical or parasitological treatment failure: 29/80 [36%] with artesunate plus amodiaquine *v* 27/79 [34%] with artesunate plus sulfadoxine–pyrimethamine; PCR-adjusted treatment failure: 4/55 [7%] with artesunate plus amodiaquine *v* 5/57 [9%] with artesunate plus sulfadoxine–pyrimethamine; significance assessments not performed). [18] 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). 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). [19] 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; failure rate PCR unadjusted: 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). [20] It found that fever clearance was complete within 2–3 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 did not show a significant difference in gametocyte clearance rates (no P value reported). [20]

Harms: The first RCT reported that there were "no significant adverse events" in either group. [18] The second RCT found no adverse events in either group during follow-up. [19] In the third RCT, parents or guardians were asked for any potential side effects of the drugs, and the child's tolerability to the treatment at follow-up. [20] It stated that no adverse effects were reported, and that both drug regimens were well tolerated.

Comment: In the first RCT, allocation concealment was adequate. [18] 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%). [19] This study was conducted in an area of medium to high malaria endemicity. In the third RCT, allocation concealment was adequate. [20] 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.

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

GLOSSARY

Adequate clinical and parasitological response (ACPR) According to the World Health Organization definition, absence of parasitaemia at day 28 irrespective of axillary temperature and without previously meeting any of the World Health Organization criteria for early or late treatment failure, or late parasitological failure. [21]
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.
Polymerase chain reaction (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.
Total failure People presenting with clinical failure or with parasitaemia on day 28.
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 World Health Organization modified definitions of treatment failure in 2003 to include late parasitological failures. [21]
High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect
Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Artemether–lumefantrine (6 doses) versus artemether–lumefantrine (4 doses) One systematic review added; [10] benefits and harms data enhanced, categorisation unchanged (Likely to be beneficial).
Artemether–lumefantrine (6 doses) versus artesunate (3 days) plus amodiaquine (excluding South East Asia) Four RCTs added; [12] [13] [14] [15] benefits and harms data enhanced, categorisation unchanged (Likely to be beneficial).

Artesunate plus amodiaquine versus artesunate plus sulfadoxine–pyrimethamine (excluding South East Asia) One RCT added; [20] benefits and harms data enhanced, categorisation unchanged (Unknown effectiveness).
Artesunate (3 days) plus amodiaquine versus amodiaquine plus sulfadoxine–pyrimethamine One RCT added; [6] benefits and harms data enhanced, categorisation changed from Likely to be beneficial to Trade-off between benefits and harms.
Artesunate (3 days) plus sulfadoxine–pyrimethamine versus amodiaquine plus sulfadoxine–pyrimethamine One systematic review [7] and two RCTs added; [8] [9] benefits and harms data enhanced, categorisation changed from Unknown effectiveness to Unlikely to be beneficial.

REFERENCES

1. World Health Organization. WHO expert committee on malaria (twentieth report). *World Health Organ Tech Rep Ser* 2000;892:1–74 (available online at http://mosquito.who.int/docs/ecr20_toc.htm; last accessed 16 February 2005).
2. Stepniewska K, Taylor WR, Mayxay M, et al. *In vivo* assessment of drug efficacy against *Plasmodium falciparum* malaria: duration of follow-up. *Antimicrob Agents Chemother* 2004;48:4271–4280. [PubMed]
3. Omari AAA, Gamble C, Garner P. Artemether-lumefantrine (six-dose regimen) for treating uncomplicated falciparum malaria (Cochrane review). In: The Cochrane Library, Issue 4, 2006. Chichester, UK: John Wiley & Sons. Search date 2005; primary sources Medline, Embase, Lilacs, Cochrane Central Register of Controlled Trials, and Cochrane Infectious Diseases Group Specialised Register.
4. Mutabingwa TK, Anthony D, Heller A, et al. Amodiaquine alone, amodiaquine+sulfadoxine-pyrimethamine, amodiaquine+artesunate, and artemether-lumefantrine for outpatient treatment of malaria in Tanzanian children: a four-arm randomised effectiveness trial. *Lancet* 2005;365:1474–1480.
5. Staedke SG, Mpimbaza A, Kamya MR, et al. Combination treatments for uncomplicated falciparum malaria in Kampala, Uganda: randomised clinical trial. *Lancet* 2004;364:1950–1957.
6. Yeka A, Banek K, Bakyaita N, et al. Artemisinin versus nonartemisinin combination therapy for uncomplicated malaria: randomized clinical trials from four sites in Uganda. *PLoS Med* 2005;2:e190.
7. Bukirwa H, Critchley J. Sulfadoxine-pyrimethamine plus artesunate versus sulfadoxine-pyrimethamine plus amodiaquine for treating uncomplicated malaria (Cochrane review). In: The Cochrane Library, Issue 4, 2006. Chichester, UK: John Wiley & Sons. Search date 2005; primary sources Medline, Embase, Lilacs, Cochrane Central Register of Controlled Trials, and Cochrane Infectious Diseases Group Specialised Register.
8. Blair S, Carmona-Fonseca J, Pineros JG, et al. Therapeutic efficacy test in malaria falciparum in Antioquia, Colombia. *Malar J* 2006;5:14.
9. Bousema JT, Schneider P, Gouagna LC, et al. Moderate effect of artemisinin-based combination therapy on transmission of Plasmodium falciparum. *J Infect Dis* 2006;193:1151–1159.
10. Omari AA, Gamble C, Garner P. Artemether-lumefantrine (four-dose regimen) for treating uncomplicated falciparum malaria (Cochrane review). In: The Cochrane Library, Issue 4, 2006. Chichester, UK: John Wiley & Sons. Search date 2005; primary sources Medline, Embase, Lilacs, Cochrane Central Register of Controlled Trials, and Cochrane Infectious Diseases Group Specialised Register.
11. Vugt MV, Wilairatana P, Gemperli B, et al. Efficacy of six doses of artemether lumefantrine (benflumetol) in multidrug-resistant *Plasmodium falciparum* malaria. *Am J Trop Med Hyg* 1999;60:936–942.
12. Koram KA, Abuaku B, Duah N, et al. Comparative efficacy of antimalarial drugs including ACTs in the treatment of uncomplicated malaria among children under 5 years in Ghana. *Acta Tropica* 2005;95:194–203.
13. Martensson A, Stromberg J, Sisowath C, et al. Efficacy of artesunate plus amodiaquine versus that of artemether-lumefantrine for the treatment of uncomplicated childhood Plasmodium falciparum malaria in Zanzibar, Tanzania. *Clin Infect Dis* 2005;41:1079–1086.
14. Guthmann JP, Cohuet S, Rigutto C, et al. High efficacy of two artemisinin-based combinations (artesunate + amodiaquine and artemether + lumefantrine) in Caala, Central Angola. *Am J Trop Med Hyg* 2006;75:143–145.
15. Bukirwa H, Yeka A, Kamya MR, et al. Artemisinin combination therapies for treatment of uncomplicated malaria in Uganda. *PLoS Clin Trials* 2006;1:e7.
16. Hutagalung R, Paiphun L, Ashley EA, et al. A randomized trial of artemether-lumefantrine versus mefloquine-artesunate for the treatment of uncomplicated multi-drug resistant *Plasmodium falciparum* on the western border of Thailand *Malar J* 2005;4:46.
17. van den Broek IV, Maung UA, Peters A, et al. Efficacy of chloroquine + sulfadoxine pyrimethamine, mefloquine + artesunate and artemether + lumefantrine combination therapies to treat *Plasmodium falciparum* malaria in the Chittagong Hill Tracts, Bangladesh. *Trans R Soc Trop Med Hyg* 2005;99:727–735.
18. Hamour S, Melaku Y, Keus K, et al. Malaria in the Nuba Mountains of Sudan: baseline genotypic resistance and efficacy of the artesunate plus sulfadoxine-pyrimethamine and artesunate plus amodiaquine combinations. *Trans R Soc Trop Med Hyg* 2005;99:548–554.
19. van den Broek I, Amsalu R, Balasegaram M, et al. Efficacy of two artemisinin combination therapies for uncomplicated falciparum malaria in children under 5 years, Malakal, Upper Nile, Sudan. *Malar J* 2005;4:14.
20. Swarthout TD, van denBroek,IV, Kayembe G, et al. Artesunate + amodiaquine and artesunate + sulphadoxine-pyrimethamine for treatment of uncomplicated malaria in Democratic Republic of Congo: a clinical trial with determination of sulphadoxine and pyrimethamine-resistant haplotypes. *Tropic Med Int Health* 2006;11:1503–1511.
21. World Health Organization. Assessment and monitoring of antimalarial drug efficacy for the treatment of uncomplicated malaria. 2003. http://mosquito.who.int/resistance.html (last accessed 16 February 2005).
22. Omari AA, Gamble C, Garner P. Artemether-lumefantrine (six-dose regimen) for treating uncomplicated falciparum malaria. [Review] [46 refs]. *Cochrane Database of Systematic Reviews* 2005;?:CD005564-

David Taylor-Robinson
Liverpool School of Tropical Medicine
Liverpool
UK

Katharine Jones
Liverpool School of Tropical Medicine
Liverpool
UK

Paul Garner
Liverpool School of Tropical Medicine
Liverpool
UK

Competing interests: DTR, KJ, and PG declare that they have no competing interests.

TABLE **GRADE evaluation of interventions for malaria: uncomplicated, caused by *Plasmodium falciparum***

Important outcomes	**Cure rates, treatment failure, recrudescence, adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
Are artemisinin combination treatments more effective than non-artemisinin combination treatments in people living in endemic areas (excluding South East Asia)?									
1 (948) [22]	Treatment failure	Artemether–lumefantrine *v* amodiaquine plus sulfadoxine–pyrimethamine	4	0	0	0	+1	High	Effect size point added for relative risk between 0.2 to 0.5
2 (1213) [4] [16]	Treatment failure	Artesunate plus amodiaquine *v* amodiaquine plus sulfadoxine–pyrimethamine	4	–2	0	0	0	Low	Quality point deducted for incomplete reporting of results and flaws in study design
1 (259) [5]	Fever resolution	Artesunate plus amodiaquine *v* amodiaquine plus sulfadoxine–pyrimethamine	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (1537) [6]	Recrudescence	Artesunate plus amodiaquine *v* amodiaquine plus sulfadoxine–pyrimethamine	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
7 (1448) [7] [8]	Treatment failure	Artesunate plus sulfadoxine–pyrimethamine *v* amodiaquine plus sulfadoxine–pyrimethamine	4	–2	–1	0	0	Very low	Quality point deducted for methodological flaws and incomplete reporting of results. Consistency point deducted for conflicting results
Which artemisinin combination treatment is most effective in people living in endemic areas?									
1 (238) [11]	Cure rates	Six-dose regimen *v* four-dose regimen (artemether–lumefantrine)	4	0	0	–1	0	Moderate	Directness point deducted for uncertainty about transmission rates
4 (1679) [12] [13] [14]	Cure rates	Artemether–lumefantrine *v* artesunate plus amodiaquine	4	–1	–1	–3	0	Very low	Quality point deducted for methodological flaws. Consistency point deducted for conflicting results. Directness points deducted for differences in inclusion criteria, uncertainty about transmission rates, and resistance patterns
1 (419) [16]	Recrudescence	Artemether–lumefantrine *v* artesunate plus amodiaquine	4	–1	0	–1	0	Low	Quality point deducted for methodological flaws. Directness point deducted for uncertainty about resistance patterns
4 (704) [22]	Treatment failure	Artemether–lumefantrine *v* artesunate plus mefloquine	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results
1 (490) [16]	Cure rates	Artemether–lumefantrine *v* artesunate plus mefloquine	4						Quality point deducted for methodological flaws. Consistency point deducted for conflicting results. Directness points deducted for uncertainty about transmission and resistance rates
2 (345) [18] [17]	Response	Artesunate plus amodiaquine *v* artesunate plus sulfadoxine–pyrimethamine	4	–2	–1	0	0	Very low	Quality points deducted for methodological flaws and poor follow-up. Consistency point deducted for conflicting results
2 (223) [20]	Treatment failure	Artesunate plus amodiaquine *v* artesunate plus sulfadoxine–pyrimethamine	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results

Important outcomes	Cure rates, treatment failure, recrudescence, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion.
Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.