15040556
Abacassamo F, Enosse S, Aponte JJ, Gomez-Olive FX, Quinto L, Mabunda S, Barreto A, Magnussen P, Ronn AM, Thompson R, Alonso PL
Efficacy of chloroquine, amodiaquine, sulphadoxine-pyrimethamine and combination therapy with artesunate in Mozambican children with non-complicated malaria.
Trop Med Int Health. 2004 Feb;9(2):200-8.
This paper reports a two-phase study in Manhica district, Mozambique: first we assessed the clinical efficacy and parasitological response of Plasmodium falciparum to chloroquine (CQ), sulphadoxine-pyrimethamine (SP) and amodiaquine (AQ), then we tested the safety and efficacy in the treatment of uncomplicated malaria, of three combinations: AQ + SP, artesunate (AR) + SP and AQ + AR. Based on the WHO (1996, WHO/MAL/96.1077) in vivo protocol, we conducted two open, randomized, clinical trials. Children aged 6-59 months with axillary body temperature > or = 37.5 degrees C and non-complicated malaria were randomly allocated to treatment groups and followed up for 21 days (first and second trial) and 28 days (first trial). The therapeutic efficacy of AQ (91.6%) was better than that of SP (82.7%) and CQ (47.1%). After 14 days, 69% of the strains were parasitologically resistant to CQ, 21.4% to SP and 26% to AQ. Co-administration of AQ + SP, AR + SP and AQ + AR was safe and had 100% clinical efficacy at 14-day follow-up. The combination therapies affected rapid fever clearance time and reduced the incidence of gametocytaemia during follow-up.

12709893
Abdin MZ, Israr M, Rehman RU, Jain SK
Artemisinin, a novel antimalarial drug: biochemical and molecular approaches for enhanced production.
Planta Med. 2003 Apr;69(4):289-99.
Artemisinin, a sesquiterpene lactone containing an endoperoxide bridge, has been isolated from the aerial parts of Artemisia annua L. plants. It is effective against both drug-resistant and cerebral malaria-causing strains of Plasmodium falciparum. The relatively low yield (0.01-0.8 %) of artemisinin in A. annua is a serious limitation to the commercialization of the drug. Therefore, the enhanced production of artemisinin either in cell/tissue culture or in the whole plant of A. annua is highly desirable. It can be achieved by a better understanding of the biochemical pathway leading to the synthesis of artemisinin and its regulation by both exogenous and endogenous factors. Furthermore, genetic engineering tools can be employed to overexpress gene(s) coding for enzyme(s) associated with the rate limiting step(s) of artemisinin biosynthesis or to inhibit the enzyme(s) of other pathway competing for its precursors. These aspects which may be employed to enhance the yield of artemisinin both in vitro and in vivo are discussed in this review.

15814029
Adam I, A-Elbasit IE, Elbashir MI
Efficacies of mefloquine alone and of artesunate followed by mefloquine, for the treatment of uncomplicated, Plasmodium falciparum malaria in eastern Sudan.
Ann Trop Med Parasitol. 2005 Mar;99(2):111-7.
In late 2003, the efficacies of mefloquine monotherapy and of an artesunate-mefloquine combination, for the oral treatment of uncomplicated, Plasmodium falciparum malaria, were investigated and compared in New Halfa, in eastern Sudan. Of the patients who completed the 28 days of follow-up, 40 were treated only with single-dose mefloquine (at a dose of 25 mg/kg), and 38 with artesunate (at 4 mg/kg. day) for 3 days followed by single-dose mefloquine (at 15 mg/kg), given on the third day.Compared with those given the combination, the patients given mefloquine alone were more likely to suffer nausea, vomiting and dizziness (25.0% v. 2.6%; P=0.005) and to be found gametocytaemic (12.5% v. 0%; P=0.02) after treatment, and more likely to be found febrile (i.e. with a temperature >37.5 degrees C) on day 2 (25.0% v. 2.6%; P=0.005), although no patients were found febrile on day 3. Six of the patients--three (7.5%) of those given mefloquine only and three (7.9%) of those given the combination (P>0.05)--appeared to be treatment failures. Parasite genotyping indicated, however, that, although five of these six patients had true recrudescences, one (who had been treated with the combination) had been re-infected during the follow-up. The true frequencies of cure were therefore 92.5% after mefloquine alone and 94.7% after the combination (P>0.05). Thus, although the treatments appeared equally effective in clearing parasitaemias, the combination was better at clearing gametocytaemias and was less likely to cause adverse side-effects. It remains unclear why mefloquine given alone was almost 10-fold more likely to trigger adverse effects than treatment with a combination that contained the same drug. This may be a reflection of the different mefloquine doses and, for the patients given the combination, of the use of artesunate before the mefloquine treatment.

16004704
Adam I, A-Elbasit IE, Idris SM, Malik EM, Elbashir MI
A comparison of the efficacy of artesunate plus sulfadoxine-pyrimethamine with that of sulfadoxine-pyrimethamine alone, in the treatment of uncomplicated, Plasmodium falciparum malaria in eastern Sudan.
Ann Trop Med Parasitol. 2005 Jul;99(5):449-55.

In an open, randomized, clinical trial, conducted in New Halfa, eastern Sudan, in September-October 2004, the efficacies and adverse effects of artesunate plus sulfadoxine-pyrimethamine (SP), in the treatment of uncomplicated, Plasmodium falciparum malaria, were compared with those of SP alone. Patients were randomized to receive either artesunate (4 mg/kg. day) on days 0-2 plus SP (25 mg sulfadoxine/kg) on day 0 or the SP alone, and then followed-up for 28 days. Sixty patients completed follow-up. Compared with the 30 given artesunate plus SP (ASP), the 30 given SP alone were much more likely to be febrile (30% v. 3.3%; P=0.006) and parasitaemic (50% v. 6.7%; P0.05). The frequencies of gametocytaemia during follow-up were, however, much lower in the ASP arm than in the SP-only (0.0% v. 23.3%; P=0.005).Thus, although the problems posed by adverse effects were similar in the two treatment arms, ASP appeared markedly better, in terms of fever- and parasite-clearance times and the prevalence of post-treatment gametocytaemia, than SP alone.

16436287
Adam I, Ali DM, Abdalla MA
Artesunate plus sulfadoxine-pyrimethamine in the treatment of uncomplicated Plasmodium falciparum malaria during pregnancy in eastern Sudan.
Trans R Soc Trop Med Hyg. 2006 Jan 24;.
Malaria during pregnancy is associated with serious adverse effects; these could be avoided with effective treatment. Artesunate plus sulfadoxine-pyrimethamine (AS+SP) is a promising antimalarial combination; however, few data are available on its safety during pregnancy. The present study was carried out in New Halfa Hospital, eastern Sudan, between September 2004 and March 2005. Thirty-two pregnant Sudanese women with uncomplicated Plasmodium falciparum malaria were treated with AS+SP at a mean of 29.7 weeks of gestation. The patients were followed-up until delivery and the babies were followed-up until the age of 1 month. The drug was well tolerated, the parasitaemia was cleared and the patients were symptom-free within 2 days. All the patients delivered full-term live babies. One of the babies died on the fourth day; none of the women died and there was no miscarriage, stillbirth, or congenital abnormalities in the newborn babies. Thus, this small descriptive study failed to detect unintended effects of AS+SP during pregnancy.

16212206
Adam I, Ibrahim MH, A/elbasit IA, Elbashir MI
Efficacy of sulfadoxin pyrimethamine for uncomplicated Plasmodium falciparum malaria in a small sample of Sudanese children.
East Mediterr Health J. 2004 May;10(3):309-14.
A prospective clinical trial was carried out to determine in vivo efficacy of sulfadoxine/pyrimethamine for the treatment of uncomplicated Plasmodium falciparum malaria in children in New Halfa. Forty patients were enrolled; 31 completed the 28-day follow-up. Six (19.4%) patients showed recurrence of parasitaemia during follow-up, while the rest (80.6%) cleared the parasites and responded fully to treatment. All the failures were late treatment failures. Parasite genotyping showed that 1 (16.7%) of the 6 cases of late parasitaemia was due to reinfection while the rest (83.4%) were due to true recrudescence. During the follow-up period 22.6% of patients showed gametocytaemia. The high level of treatment failure as well as gametocytaemia necessitates the introduction of artesunate in this combination therapy.

8699174
Adams PA, Berman PA, Egan TJ, Marsh PJ, Silver J
The iron environment in heme and heme-antimalarial complexes of pharmacological interest.
J Inorg Biochem. 1996 Jul;63(1):69-77.
Mossbauer spectroscopy has been utilized to probe the electronic environment of iron in a number of Ferriprotoporphyrin IX complexes of relevance to malaria. The markedly different iron environments found for the complexes of hemin with quinine, chloroquine, and the Chinese herbal antimalarial artesunate suggest that these compounds act by protecting the heme from polymerization to insoluble hemozoin, and by facilitating the transport of the protected heme to the food vacuole membrane where it is able to exercise its cytotoxic redox catalytic activity. Mossbauer parameters determined here for purified malaria pigment and synthetic beta-hematin confirm the chemical identical-ness of these species. The Mossbauer spectra of the complexes are discussed in light of the proposed structures of the complexes.

11978332
Adjuik M, Agnamey P, Babiker A, Borrmann S, Brasseur P, Cisse M, Cobelens F, Diallo S, Faucher JF, Garner P, Gikunda S, Kremsner PG, Krishna S, Lell B, Loolpapit M, Matsiegui PB, Missinou MA, Mwanza J, Ntoumi F, Olliaro P, Osimbo P, Rezbach P, Some E, Taylor WR
Amodiaquine-artesunate versus amodiaquine for uncomplicated Plasmodium falciparum malaria in African children: a randomised, multicentre trial.
Lancet. 2002 Apr 20;359(9315):1365-72.

BACKGROUND: Increasing drug resistance limits the choice of efficacious chemotherapy against Plasmodium falciparum malaria in Africa. Amodiaquine still retains efficacy against P falciparum in many African countries. We assessed the safety, treatment efficacy, and effect on gametocyte carriage of adding artesunate to amodiaquine in three randomised trials in Kenya, Senegal, and Gabon. METHODS: We enrolled 941 children (400 in Kenya, 321 in Senegal, and 220 in Gabon) who were 10 years or older and who had uncomplicated P falciparum malaria. Patients were randomly assigned amodiaquine (10 mg/kg per day for 3 days) plus artesunate (4 mg/kg per day for 3 days) or amodiaquine (as above) and placebo (for 3 days). The primary endpoints were parasitological cure rates at days 14 and 28. Analysis was by intention to treat and by an evaluability method. FINDINGS: Both regimens were well tolerated. Six patients in the amodiaquine-artesunate group and five in the amodiaquine group developed early, drug-induced vomiting, necessitating alternative treatment. By intention-to-treat analysis, the day-14 cure rates for amodiaquine-artesunate versus amodiaquine were: 175/192 (91%) versus 140/188 (74%) in Kenya (D=16.7% [95% CI 9.3-24.1], p

14723987
Adjuik M, Babiker A, Garner P, Olliaro P, Taylor W, White N
Artesunate combinations for treatment of malaria: meta-analysis.
Lancet. 2004 Jan 3;363(9402):9-17.
BACKGROUND: Addition of artemisinin derivatives to existing drug regimens for malaria could reduce treatment failure and transmission potential. We assessed the evidence for this hypothesis from randomised controlled trials. METHODS: We undertook a meta-analysis of individual patients' data from 16 randomised trials (n=5948) that studied the effects of the addition of artesunate to standard treatment of Plasmodium falciparum malaria. We estimated odds ratios (OR) of parasitological failure at days 14 and 28 (artesunate combination compared with standard treatment) and calculated combined summary ORs across trials using standard methods. FINDINGS: For all trials combined, parasitological failure was lower with 3 days of artesunate at day 14 (OR 0.20, 95% CI 0.17-0.25, n=4504) and at day 28 (excluding new infections, 0.23, 0.19-0.28, n=2908; including re-infections, 0.30, 0.26-0.35, n=4332). Parasite clearance was significantly faster (rate ratio 1.98, 95% CI 1.85-2.12, n=3517) with artesunate. In participants with no gametocytes at baseline, artesunate reduced gametocyte count on day 7 (OR 0.11, 95% CI 0.09-0.15, n=2734), with larger effects at days 14 and 28. Adding artesunate for 1 day (six trials) was associated with fewer failures by day 14 (0.61, 0.48-0.77, n=1980) and day 28 (adjusted to exclude new infections 0.68, 0.53-0.89, n=1205; unadjusted including reinfections 0.77, 0.63-0.95, n=1958). In these trials, gametocytes were reduced by day 7 (in participants with no gametocytes at baseline 0.11, 0.09-0.15, n=2734). The occurrence of serious adverse events did not differ significantly between artesunate and placebo. INTERPRETATION: The addition of 3 days of artesunate to standard antimalarial treatments substantially reduce treatment failure, recrudescence, and gametocyte carriage.

15495107
Afolabi BB, Okoromah CN
Intramuscular arteether for treating severe malaria.
Cochrane Database Syst Rev. 2004 Oct 18;(4):CD004391.
BACKGROUND: Quinine and artemisinin drugs are used in severe malaria, but quinine resistance is increasing. Arteether is a recently developed artemisinin derivative that is oil soluble, has a long elimination half life, and is more stable than other derivatives. OBJECTIVES: To compare intramuscular arteether with other antimalarial drugs to treat severe malaria. SEARCH STRATEGY: We searched the Cochrane Infectious Diseases Group Specialized Register (August 2004), CENTRAL (The Cochrane Library Issue 3, 2004), MEDLINE (1966 to August 2004), EMBASE (1980 to August 2004), U.S. National Library of Medicine (NLM) Gateway (1953 to 1965), Web Science Citation (1981 to August 2004), LILACS (August 2004), Google search engine (August 2004), conference proceedings, and reference lists. We also contacted researchers, organizations, and pharmaceutical companies to help identify trials. SELECTION CRITERIA: Randomized and quasi-randomized controlled trials of intramuscular arteether in adults and children with severe malaria. DATA COLLECTION AND ANALYSIS: We independently assessed the methodological quality of the trials and extracted data, and analysed data using Review Manager 4.2. MAIN RESULTS: Two small trials (n = 194) met the inclusion criteria. Both trials compared arteether with quinine in children with cerebral malaria and reported on similar outcomes. There was no statistically significant difference in the number of deaths (relative risk 0.75, 95% confidence interval 0.43 to 1.30; n = 194, 2 trials), neurological complications (relative risk 1.18, 95% confidence interval 0.31 to 4.46; n = 58, 1 trial), or other outcomes including time to regain consciousness, parasite clearance time, and fever clearance time. The meta-analyses lack statistical power to detect important differences. REVIEWERS' CONCLUSIONS: More trials with a larger number of participants are needed before a firm conclusion about the efficacy and safety of arteether can be reached.

16436700

Afonso A, Hunt P, Cheesman S, Alves AC, Cunha CV, do Rosario V, Cravo P
Malaria parasites can develop stable resistance to artemisinin but lack mutations in candidate genes atp6 (encoding the sarcoplasmic and endoplasmic reticulum Ca2+ ATPase), tctp, mdr1, and cg10.
Antimicrob Agents Chemother. 2006 Feb;50(2):480-9.
Resistance of Plasmodium falciparum to drugs such as chloroquine and sulfadoxine-pyrimethamine is a major problem in malaria control. Artemisinin (ART) derivatives, particularly in combination with other drugs, are thus increasingly used to treat malaria, reducing the probability that parasites resistant to the components will emerge. Although stable resistance to artemisinin has yet to be reported from laboratory or field studies, its emergence would be disastrous because of the lack of alternative treatments. Here, we report for the first time, to our knowledge, genetically stable and transmissible ART and artesunate (ATN)-resistant malaria parasites. Each of two lines of the rodent malaria parasite Plosmodium chabaudi chabaudi, grown in the presence of increasing concentrations of ART or ATN, showed 15-fold and 6-fold increased resistance to ART and ATN, respectively. Resistance remained stable after cloning, freeze-thawing, after passage in the absence of drug, and transmission through mosquitoes. The nucleotide sequences of the possible genetic modulators of ART resistance (mdr1, cg10, tctp, and atp6) of sensitive and resistant parasites were compared. No mutations in these genes were identified. In addition we investigated whether changes in the copy number of these genes could account for resistance but found that resistant parasites retained the same number of copies as their sensitive progenitors. We believe that this is the first report of a malaria parasite with genetically stable and transmissible resistance to artemisinin or its derivatives.

10770199
Agbenyega T, Angus BJ, Bedu-Addo G, Baffoe-Bonnie B, Guyton T, Stacpoole PW, Krishna S
Glucose and lactate kinetics in children with severe malaria.
J Clin Endocrinol Metab. 2000 Apr;85(4):1569-76.
Children with severe malaria often present with lactic acidosis and hypoglycemia. Although both complications independently predict mortality, mechanisms underlying their development are poorly understood. To study these metabolic derangements we sequentially allocated 21 children with falciparum malaria and capillary lactate concentrations of 5 mmol/L or more to receive either quinine or artesunate as antimalarial therapy, and dichloroacetate or saline placebo for lactic acidosis. We then administered a primed infusion (90 min) of L-[3-13C1]sodium lactate and D-[6,6-D2]glucose to determine the kinetics of these substrates. The mean (SD) glucose disposal rate in all patients was 56 (16) micromol/kg x min, and the geometric mean (range) lactate disposal rate was 100 (66-177) micromol/kg x min. Glucose and lactate disposal rates were positively correlated ($r = 0.62$; $P = 0.005$). Artesunate was associated with faster parasite clearance, lower insulin/glucose ratios, and higher glucose disposal rates than quinine. Lactate disposal was positively correlated with plasma lactate concentrations ($r = 0.66$; $P = 0.002$) and time to recovery from coma ($r = 0.82$; $P < 0.001$; $n = 15$). Basal lactate disposal rates increased with dichloroacetate treatment. Elevated glucose turnover in severe malaria mainly results from enhanced anaerobic glycolysis. Quinine differs from artesunate in its effects on glucose kinetics. Increased lactate production is the most important determinant of lactic acidosis.

16135201
Agnamey P, Brasseur P, Cisse M, Gaye O, Dumoulin J, Rigal J, Taylor WR, Olliaro P
Economic evaluation of a policy change from single-agent treatment for suspected malaria to artesunate-amodiaquine for microscopically confirmed uncomplicated falciparum malaria in the Oussouye District of south-western Senegal.
Trop Med Int Health. 2005 Sep;10(9):926-33.
Senegal is changing policy for case management of uncomplicated falciparum malaria, which hitherto is diagnosed clinically and treated with chloroquine or intramuscular quinine. The WHO recommends artemisinin-based combinations for treating falciparum malaria, preferably based on a parasitological diagnosis. There are no economic projections if such a policy were introduced in Senegal. We have conducted a preliminary economic assessment of such a policy change. The study took place in the chloroquine-resistant district of Oussouye in south-western Senegal. We reviewed clinic registers of the district health posts (n=5) from 1996 to 2001, and piloted artesunate combined with amodiaquine (at 4 and 10 mg/kg/day x 3 days respectively) (AS--AQ) for treating slide-proven falciparum malaria during two rainy seasons (2000 and 2001) at one health centre. These data were used to calculate current direct patient costs (clinic visit, diagnosis, drugs) of malaria treatment and project future costs for the district. The robustness of the model was tested by allowing for different drug failure rates and costs of diagnosis. During 1996--2001, the mean number of primary treatments per year was 7654 for a mean, direct cost of 17,452 US dollars to the community. Clinical diagnosis resulted in over-treatment: 56% and 66% in the wet and dry seasons respectively. Current policy leads to substantial drug wastage and excess direct costs for the community. The direct costs of implementing AS-AQ for slide-proven malaria would be 8,150 US dollars (53% less expensive). Studies examining the public health effect and economics of deploying AS--AQ on a wider scale are underway in Senegal.

16251300
Akoachere M, Buchholz K, Fischer E, Burhenne J, Haefeli WE, Schirmer RH, Becker K
In vitro assessment of methylene blue on chloroquine-sensitive and -resistant Plasmodium falciparum strains reveals synergistic action with artemisinins.
Antimicrob Agents Chemother. 2005 Nov;49(11):4592-7.
Methylene blue (MB) represents a promising antimalarial drug candidate for combination therapies against drug-resistant parasite strains. To support and facilitate the application of MB in future field trials, we studied its antiparasitic effects in vitro. MB is active against all blood stages of both chloroquine (CQ)-sensitive and CQ-resistant P. falciparum strains with 50% inhibitory concentration (IC50) values in the lower nanomolar range. Ring stages showed the highest susceptibility. As demonstrated by high-performance liquid chromatography-tandem mass spectrometry on different cell culture compartments, MB is accumulated in malarial parasites. In drug combination assays, MB was found to be antagonistic with CQ and other quinoline antimalarials like piperaquine and amodiaquine; with mefloquine and quinine, MB showed additive effects. In contrast, we observed synergistic effects of MB with artemisinin, artesunate, and artemether for all tested parasite strains. Artemisinin/MB combination concentration ratios of 3:1 were found to be advantageous, demonstrating that the combination of artemisinin with a smaller amount of MB can be recommended for reaching maximal therapeutic effects. Our in vitro data indicate that combinations of MB with artemisinin and related endoperoxides might be a promising option for treating drug-resistant malaria and should be studied in future field trials. Resistance development under this drug combination is unlikely to occur.

11036031
Akompong T, Eksi S, Williamson K, Haldar K
Gametocytocidal activity and synergistic interactions of riboflavin with standard antimalarial drugs against growth of Plasmodium falciparum in vitro.
Antimicrob Agents Chemother. 2000 Nov;44(11):3107-11.
Our previous studies have shown that riboflavin has activity against Plasmodium falciparum asexual-stage parasites in vitro. In the present study we examine the gametocytocidal activity of riboflavin and the interaction of riboflavin with some commonly used antimalarial drugs against the asexual forms of P. falciparum in vitro. The addition of riboflavin to P. falciparum cultures killed gametocytes at all stages, even those at late stages (III to V), which are not affected by many of the commonly used antimalarials. Combinations of riboflavin with mefloquine, pyrimethamine, and quinine showed a marked potentiation of the activities of these drugs against asexual-stage parasites in vitro. The combination of riboflavin with artemisinin was additive, while that with chloroquine was mildly antagonistic. High doses of riboflavin are used clinically to treat several inborn errors of metabolism with no adverse side effects. Its efficacy in combination with standard antimalarial drugs in treating and preventing the transmission of P. falciparum malaria can therefore be evaluated in humans.

10413044
Akompong T, VanWye J, Ghori N, Haldar K
Artemisinin and its derivatives are transported by a vacuolar-network of Plasmodium falciparum and their anti-malarial activities are additive with toxic sphingolipid analogues that block the network.
Mol Biochem Parasitol. 1999 Jun 25;101(1-2):71-9.
There is great need to identify and characterize drug targets and chemotherapeutic strategies against malaria. Here we show that a vacuolar-network induced by the human malaria parasite Plasmodium falciparum, is a major import pathway for artemisinin, a leading, new anti-malarial that is known to be effective against drug resistant strains. We also show that artemisinin-treatment induces aberrant, budding of a vacuolar-network membrane protein and its antimalarial activity is additive with toxic sphingolipid analogues that block the network. The data suggest that artemisinin alters membrane protein export from the vacuolar-network and combinations with anti-network reagents have the potential to provide powerful new chemotherapy for drug resistant malaria.

14527676
Aldieri E, Atragene D, Bergandi L, Riganti C, Costamagna C, Bosia A, Ghigo D
Artemisinin inhibits inducible nitric oxide synthase and nuclear factor NF-kB activation.
FEBS Lett. 2003 Sep 25;552(2-3):141-4.
Artemisinin is a natural product used as an alternative drug in the treatment of severe and multidrug-resistant malaria. In the present work we show that artemisinin shares with other sesquiterpene lactones the ability to inhibit the activation of the nuclear factor NF-kB: by this mechanism, artemisinin, as well as parthenolide, inhibits nitric oxide synthesis in cytokine-stimulated human astrocytoma T67 cells. These results suggest that artemisinin, in addition to its antiparasitic properties, could also exert a therapeutic effect on neurological complications of malaria.

9927829
Alecrim M das G, Alecrim W, Macedo V
Plasmodium vivax resistance to chloroquine (R2) and mefloquine (R3) in Brazilian Amazon region.
Rev Soc Bras Med Trop. 1999 Jan-Feb;32(1):67-8.
We report for the first time a patient with malaria due to Plasmodium vivax who showed R2 resistance to chloroquine and R3 resistance to mefloquine in the Brazilian Amazon region based on WHO clinical criteria for diagnosis of malaria resistance. Failure was observed with unsupervised oral chloroquine, chloroquine under rigorous supervision and mefloquine in the same scheme. Finally, the patient was cured with oral artesunate.

12806458
Alecrim MG, Carvalho LM, Andrade SD, Arcanjo AR, Alexandre MA, Alecrim WD
[Treatment of children with malaria Plasmodium falciparum with derivatives artemisinin]
Rev Soc Bras Med Trop. 2003 Mar-Apr;36(2):223-6. Epub 2003 Jun 10.
From January 1996 to December 1998, artemisinin derivatives were prescribed to 108 children infected with Plasmodium falciparum. The therapeutic effect was evaluated. Only children with moderate or severe malaria were included. Group I (intravenous artesunate; n = 62): 50.8% with moderate malaria and 49.2% with severe malaria; 53.2% with mild parasitemia, 22.6% with moderate parasitemia and 24.2% with high parasitemia; Group II (intramuscular artemether [Paluter]; n = 46): 67.4% with moderate malaria and 32.6% with severe malaria; 52.2% with mild parasitemia, 36.2% with moderate parasitemia and 15.2% with high parasitemia; clinical amelioration and clearance of parasitemia showed no statistical difference between the groups. All patients cleared the parasitemia at the seventh day of follow-up (D7). In order to avoid recrudescence, mefloquine or clindamycin was used.

10881128
Alecrim MG, Carvalho LM, Fernandes MC, de Andrade SD, Loureiro AC, Arcanjo AR, Alecrim WD
[Malaria treatment with artesunate (retocaps) in children of the Brazilian Amazon]
Rev Soc Bras Med Trop. 2000 Mar-Apr;33(2):163-8.
We evaluated the clinical and therapeutic response to artesunate retocaps in 32 children admitted to the Fundacao de Medicina Tropical do Amazonas (Amazon Foundation of Tropical Medicine) with clinical characteristics of moderate and severe malaria. Of these, 29 were infected with P. falciparum and 3 with P. vivax. They improved clinically 24 hours after the beginning of therapy, with 33. 3% of patients without fever, and after 48 hours, 77.2% of the children had no fever. The monitoring of asexual forms of the parasites showed that on D2 (day 2 of treatment) 58.6% of children with P. falciparum infection had no more parasites in the blood stream, on D4 all children had negative slides both for P. falciparum and for P. vivax infection. In a long-term follow up, we found 66.6% recrudescence in P. falciparum patients. The results enabled the conclusion that artesunate retocaps are efficient in practice and their use rapidly reduces the parasitemia and improves the patients' clinical picture. However, in P. falciparum malaria the recrudescence rate was very high. We observed no side effects from this drug.

9172420
Alin MH
In vitro susceptibility of Tanzanian wild isolates of Plasmodium falciparum to artemisinin, chloroquine, sulfadoxine/pyrimethamine and mefloquine.
Parasitology. 1997 Jun;114 (Pt 6):503-6.
A 30-h in vitro susceptibility test of Plasmodium falciparum wild isolates to artemisinin, chloroquine, sulfadoxine/pyrimethamine and mefloquine was performed in Kibaha, Tanzania. A sigmoid Emax model was fitted to all data for each isolate and drug combination. Artemisinin and mefloquine exhibited 100% growth inhibition against all isolates tested (n = 69-74). The EC30 values for artemisinin and mefloquine were 44 and 146 nM respectively. Chloroquine and sulfadoxine/ pyrimethamine resistance was 30% and 13% respectively. Susceptibility parameters (EC50,90,95 and 92 values and s) varied between compounds and isolates indicating the different sensitivity of P. falciparum isolates. No correlation between susceptibility parameters of artemisinin and the other compounds was found. The high in vitro activities of artemisinin and mefloquine indicate their potential role for the treatment of multidrug-resistant malaria in Africa.

8799526
Alin MH, Ashton M, Kihamia CM, Mtey GJ, Bjorkman A
Clinical efficacy and pharmacokinetics of artemisinin monotherapy and in combination with mefloquine in patients with falciparum malaria.
Br J Clin Pharmacol. 1996 Jun;41(6):587-92.
1. The aim of this study was to assess the pharmacokinetics, clinical efficacy and safety of artemisinin alone and in combination with mefloquine. 2. Thirty-eight adults with symptomatic Plasmodium falciparum malaria

were randomly assigned to receive either artemisinin (500 mg single dose followed by another 500 mg on day 1 and then 250 mg twice daily for 4 days) or artemisinin (500 mg single dose followed by 750 mg on day 1 and then 250 mg three times daily for one more day) in co-administration with mefloquine (250 mg three times daily for the first day). All drug administration was by the oral route. Patients were hospitalized at the Kibaha Designated District Hospital, Kibaha, Tanzania, for 6 days and a follow up for 3 weeks was performed. 3. Treatment with the artemisinin/mefloquine combination resulted in a shorter parasite clearance time (PCT) of 24 (22, 27; 95% confidence interval) h vs 31 (27, 36) h and fever subsidence time (FST) of 14 (12, 16) h vs 20 (18, 23) h compared with artemisinin monotherapy. The 95% CI for the difference of the PCT and FST were 1.7, 12 and 3, 10, respectively. Parasites were detected in 7 out of 17 patients (41%) receiving artemisinin monotherapy at the 3rd and 4th week follow up visits. No parasites were detected after the combination therapy. 4. The maximum plasma concentrations (Cmax) were similar after artemisinin monotherapy (615.4 +/- 387.0 ng ml-1) and in combination with mefloquine (851.8 +/- 523.6 ng ml-1). Elimination half-lives (t1/2) were also identical at 2.2 +/- 0.6 h and 2.5 +/- 0.7 h, respectively. However, the AUC values were higher ($P < 0.05$) after combination therapy (3252 +/- 1873 ng ml-1 h) than after monotherapy (2234 +/- 1502 ng ml-1 h). The oral clearance values were lower ($P < 0.05$) after combination therapy (195.4 +/- 86.9 l h-1) than after monotherapy (314.3 +/- 189.4 l h-1). PCT and FST normalized to initial parasitaemia correlated with AUC(0, t) ($rs = 0.56$, $P = 0.02$, $rs = 0.58$, $P = 0.01$, respectively) and with Cmax ($rs = 0.62$, $P = 0.01$, $rs = 0.68$, $P = 0.005$, respectively) in the artemisinin monotherapy only. 5. One patient on the combination therapy developed a psychiatric condition and two patients on the monotherapy developed skin itch.

8561267
Alin MH, Kihamia CM, Bjorkman A, Bwijo BA, Premji Z, Mtey GJ, Ashton M
Efficacy of oral and intravenous artesunate in male Tanzanian adults with Plasmodium falciparum malaria and in vitro susceptibility to artemisinin, chloroquine, and mefloquine.
Am J Trop Med Hyg. 1995 Dec;53(6):639-45.
The clinical efficacy of oral and intravenous (iv) artesunate was compared in an open randomized trial in 50 male adult patients with uncomplicated Plasmodium falciparum malaria in Kibaha, Tanzania. Oral artesunate treatment was started with 2 x 50 mg initially followed by 50 mg 12 hr later and then 50 mg twice a day for four days (total dose = 550 mg or 9.6 mg/kg). Intravenous artesunate administration began with 2 x 0.8 mg/kg initially followed by 0.8 mg/kg 12 hr later and then 0.8 mg/kg twice a day for four days (total dose = 8.8 mg/kg). The mean +/- SD parasite clearance times (PCTs) were nearly identical at 23.4 +/- 5.9 hr and 24.2 +/- 7.2 hr after oral and iv administration, respectively. Mean +/- SD fever subsidence times (FSTs) were also similar at 18.7 +/- 8.3 hr and 21.0 +/- 4.8 hr, respectively. All patients remained negative for P. falciparum for at least 14 days. Recrudescence/reinfection occurred between days 21 and 28 in five of 25 patients (20%) after oral treatment and in four of 25 patients (16%) after iv treatment. The mean erythrocyte count and hemoglobin concentration were slightly reduced after iv treatment but remained in the normal range. Otherwise, there was no change in blood biochemistry, hematology, and electrocardiograms monitored prior to and during the last dose. It is concluded that treatment with oral and iv artesunate was equally efficacious and well tolerated. A 24-hr in vitro susceptibility test of P. falciparum to artemisinin, chloroquine, and mefloquine was performed in samples from all patients. The three compounds exhibited 100% inhibition with the exception of three isolates, which showed chloroquine resistance. Parameter estimates of a sigmoid Emax model (drug concentration at which 50% of the growth inhibition occurs [EC50]), the sigmoidicity factor s and EC95 fitted to the growth inhibition data differed between compounds and isolates, indicating different sensitivity of P. falciparum isolates. There was no correlation between artemisinin and mefloquine EC50 values, while artemisinin and chloroquine EC50 values showed weak correlation ($r2 = 0.223$, $P = 0.006$). There was no correlation between parameters describing clinical outcome (the PCT, the time needed for reduction of the parasite density to 50% and 95% of the initial parasitemia, and the FST) and those describing in vitro susceptibility.

10437302
Ambroise-Thomas P
[Current data on major novel antiamalaria drugs: Artemisinin (qinghaosu) derivatives]
Bull Acad Natl Med. 1999;183(4):797-80; discussion 810-3.
Artemisinin or Qinghaosu (QHS) and its derivatives (mainly artemether and artesunate) are novel and the most rapidly acting antimalarial drugs, effective in adults and children against all the Plasmodium of humans, including multi-drug resistant Plasmodium falciparum. Resistance to these drugs has not been identified so far. QHS derivatives are very well tolerated and there is no evidence of serious clinical toxicity in man. The neurotoxicity seen in animals after high doses of certain compounds has not been reported in humans. In the treatment of severe malaria, QHS administered by either the intramuscular (artemether and artesunate) or intravenous (artesunate) route, are at least as effective as quinine, and are simpler to use. Intramuscular artemether appears to be an excellent alternative to intravenous quinine, which is specially important since quinine resistance is common in Asia and a decrease of sensitivity to quinine has been reported in Africa.

For the treatment of uncomplicated malaria, the use of QHS must be highly selective. Treatment by QHS is only totally justifiable in areas where multi-drug resistant strains are prevalent and always concurrently with an other effective, longer-acting, antimalarial drug (mefloquine, preferably). This combination approach is associated with an accelerated antimalarial response. It avoids or limits the risk of recrudescences, and protects both drugs from the development of resistance. Artemether and artesunate have also been administered by the rectal route with highly promising results for treatment of severe malaria. This route eliminates several disadvantages or risks associated with injections. The best indication for rectal administration will be probably a rescue treatment of severe malaria in rural and poorly equipped dispensaries before transfer to hospital for treatment using conventional modalities. All QHS derivatives should not be used for chemophophylaxis.

11258051
Ambroise-Thomas P
[Treatment of malaria: prevention of resistance by combinations of antimalarial agents]
Med Trop (Mars). 2000;60(3):219-22.

10212889
Ambroise-Thomas P
The rational use of qinghaosu and its derivatives in the treatment of malaria in 1998.
Med Trop (Mars). 1998;58(3 Suppl):6-8.

14698358
Amos S, Chindo BA, Abbah J, Vongtau HO, Edmond I, Binda L, Akah PA, Wambebe C, Gamaniel KS
Postsynaptic dopamine (D(2))-mediated behavioural effects of high acute doses of artemisinin in rodents.
Brain Res Bull. 2003 Dec 30;62(3):255-60.
Artemisinin or qinghaosu is the active principle of quinghao (Artemisia annua L.) developed from Chinese traditional medicine, which is now widely used around the world against falciparum malaria. Behavioural effects of high acute doses of artemisinin were studied on spontaneous motor activity (SMA), exploratory behavior, apomorphine-induced stereotype behavior and pentobarbital sleeping time in mice and rats in order to provide additional evidence on its safety profile on the central nervous system (CNS). Effects of the drug on bromocriptine-induced hyperactivity in short term reserpinised mice were also evaluated. Intraperitoneal (i.p.) injection of artemisinin at doses of 50 and 100mg/kg, significantly (P

15917511
Anderson TJ, Nair S, Qin H, Singlam S, Brockman A, Paiphun L, Nosten F
Are transporter genes other than the chloroquine resistance locus (pfcrt) and multidrug resistance gene (pfmdr) associated with antimalarial drug resistance?
Antimicrob Agents Chemother. 2005 Jun;49(6):2180-8.
Mu et al. (Mu, J., M. T. Ferdig, X. Feng, D. A. Joy, J. Duan, T. Furuya, G. Subramanian, L. Aravind, R. A. Cooper, J. C. Wootton, M. Xiong, and X. Z. Su, Mol. Microbiol. 49:977-989, 2003) recently reported exciting associations between nine new candidate transporter genes and in vitro resistance to chloroquine (CQ) and quinine (QN), with six of these loci showing association with CQ or QN in a southeast Asian population sample. We replicated and extended this work by examining polymorphisms in these genes and in vitro resistance to eight drugs in parasites collected from the Thailand-Burma border. To minimize problems of multiple testing, we used a two-phase study design, while to minimize problems caused by population structure, we analyzed parasite isolates collected from a single clinic. We first examined associations between genotype and drug response in 108 unique single-clone parasite isolates. We found strong associations between single nucleotide polymorphisms in pfmdr and mefloquine (MFQ), artesunate (AS), and lumefantrine (LUM) response. We also observed associations between an ABC transporter (G7) and response to QN and AS and between another ABC transporter (G49) and response to dihydro-artemisinin (DHA). We reexamined significant associations in an independent sample of 199 unique single-clone infections from the same location. The significant associations with pfmdr-1042 detected in the first survey remained. However, with the exception of the G7-artesunate association, all other associations observed with the nine new candidate transporters disappeared. We also examined linkage disequilibrium (LD) between markers and phenotypic correlations between drug responses. We found minimal LD between genes. Furthermore, we found no correlation between chloroquine and quinine responses, although we did find expected strong correlations between MFQ, QN, AS, DHA, and LUM. To conclude, we found no evidence for an association between 8/9 candidate genes and response to eight different antimalarial drugs. However, the consistent association observed between a 3-bp indel in G7 and AS response merits further investigation.

16432535
Anfosso L, Efferth T, Albini A, Pfeffer U
Microarray expression profiles of angiogenesis-related genes predict tumor cell response to artemisinins.
Pharmacogenomics J. 2006 Jan 24;.
Artemisinin (ARS) and its derivatives are used for the second-line therapy of malaria infections with Plasmodium falciparum and P. vivax. ARSs also reveal profound antitumor activity in vitro and in vivo. In the present investigation, we correlated the mRNA expression data of 89 angiogenesis-related genes obtained by microarray hybridization from the database of the US National Cancer Institute with the 50% growth inhibition concentration values for eight ARSs (ARS, arteether (ARE), artesunate (ART), artemisetene, arteanuine B, dihydroartemisinylester stereoisomers 1 and 2). The constitutive expression of 30 genes correlated significantly with the cellular response to ARSs. By means of hierarchical cluster analysis and cluster image mapping expression, profiles were identified that determined significantly the cellular response to ART, ARE, artemether and dihydroartemisinylester stereoisomer 1. We have exemplarily validated the microarray data of six out of these 30 genes by real-time RT-PCR in seven cell lines. The fact that sensitivity and resistance of tumor cells could be predicted by the mRNA expression of angiogenesis-related genes indicate that ARSs reveal their antitumor effects at least in part by inhibition of tumor angiogenesis. As many chemopreventive drugs exert antiangiogenic features, ARSs might also be chemopreventive in addition to their cytotoxic effects.The Pharmacogenomics Journal advance online publication, 24 January 2006; doi:10.1038/sj.tpj.6500371.

11850261
Angus BJ, Thaiaporn I, Chanthapadith K, Suputtamongkol Y, White NJ
Oral artesunate dose-response relationship in acute falciparum malaria.
Antimicrob Agents Chemother. 2002 Mar;46(3):778-82.
The combination of an oral artemisinin derivative (usually artesunate) and mefloquine has become standard treatment for multidrug-resistant falciparum malaria in several parts of Southeast Asia. The doses of artesunate used in monotherapy and combination treatment have largely been derived empirically. In order to characterize the in vivo dose-response relationship for artesunate and thus rationalize dosing, 47 adult patients with acute uncomplicated falciparum malaria and parasitemia > or = 1% were randomized to receive a single oral dose of artesunate varying between 0 and 250 mg together with a curative dose of oral mefloquine. Acceleration of parasite clearance was used as the pharmacodynamic variable. An inhibitory sigmoidal maximum effect (Emax) pharmacodynamic model typical of a dose-response curve was fitted to the relationship between dose and shortening of parasite clearance time (PCT). The Emax was estimated as 28.6 oral h, and the 50% effective concentration was 1.6 mg/kg of body weight. These results imply that there is no reduction in PCTs with the use of single doses of artesunate higher than 2 mg/kg, and this therefore reflects the average lower limit of the maximally effective dose.

11414467
Anothay O, Pongvongsa T, Maharat N, Sirivichayakul C, Chantavanich P, Silachamroon U, Looareesuwan S
Clinical presentation of childhood malaria in Savannakhet province, Lao PDR.
Southeast Asian J Trop Med Public Health. 2000;31 Suppl 1:85-90.
A descriptive study on the clinical presentation of childhood malaria was conducted in Savannakhet Province, Lao People's Democratic Republic. It is aimed to describe the clinical features and to determine the association between the severity of malaria and the initiation or delay of treatment. A total number of 92 children 1-14 years of age with confirmed malaria diseases were enrolled in this study. Fifty-six cases (60.9%) had illness for less than 3 days before hospitalized and 36 cases (39.1%) for more than 3 days. Twenty-nine cases (31.5%) had self antimalarial medication before admission (9 cases of chloroquine, 16 cases of quinine and 4 cases of artesunate). Ten cases (10.9%) had abnormal consciousness of which 7 cases (7.6%) had confusion but responded to verbal command and 3 cases (3.3%) were in coma not respond to painful stimuli but had reflex. Two cases 2.2%) had convsulsions, 11 cases (12.0%) had dehydration, 47 cases (51.1%) had vomiting, 18 cases (19.6%) had hepatomegaly and 19 cases (20.7%) had splenomegaly. There was a statistically significant association between consciousness levels and the duration of illness before admission < or = 3 days and > 3 days ($p = 0.01$) while there is no significant difference between parasitemia density and the duration of illness before admission ($p > 0.05$).

16398620
Anstey NM, Price RN, White NJ
Improving the availability of artesunate for treatment of severe malaria. Artesunate reduces mortality and should now be the treatment of choice in severe malaria in adults: good news for countries in our region, but registration in Australia must wait.
Med J Aust. 2006 Jan 2;184(1):1-2.

15499533
Ashley EA, Krudsood S, Phaiphun L, Srivilairit S, McGready R, Leowattana W, Hutagalung R, Wilairatana P, Brockman A, Looareesuwan S, Nosten F, White NJ
Randomized, controlled dose-optimization studies of dihydroartemisinin-piperaquine for the treatment of uncomplicated multidrug-resistant falciparum malaria in Thailand.
J Infect Dis. 2004 Nov 15;190(10):1773-82. Epub 2004 Oct 18.
BACKGROUND: Dihydroartemisinin-piperaquine (DP) is a new and relatively inexpensive artemisinin-containing fixed-combination antimalarial treatment. An adult treatment course contained 6.4 mg/kg dihydroartemisinin (DHA), which is >40% lower than the level in most artemisinin-containing combinations. This raised the possibility that the efficacy of the current coformulation may not be optimal in the treatment of multidrug-resistant falciparum malaria. METHODS: In 2 large randomized, controlled studies in Thailand, the recommended dose of DP was compared with a regimen with additional artemisinin derivative (12 mg/kg; DP+) and with mefloquine plus artesunate (MAS3). RESULTS: A total of 731 patients were included: 201 in a hospital-based study and 530 in a community study. Day-28 cure rates in the hospital-based study were 100% (95% confidence interval [CI], 93.9%-100%) in the MAS3 and DP+ groups and 98.3% (95% CI, 91%-99.7%) in the DP group, with a single recrudescence on day 21. In the community study, polymerase chain reaction genotyping-adjusted cure rates on day 63 were 96.1% (95% CI, 92.6%-99.7%) in the DP group, 98.3% (95% CI, 96.1%-100%) in the DP+ group, and 94.9% (95% CI, 91.2%-98.6%) in the MAS3 group (P=.2). Adverse events were few, with an excess of mild abdominal pain in the DP group. CONCLUSIONS: The current dosage of DP (6.4 mg/kg DHA and 51.2 mg/kg piperaquine phosphate) given over the course of 48 h is highly effective, safe, and well tolerated for the treatment of multidrug-resistant falciparum malaria, and its efficacy is not improved by the addition of more DHA.

16028147
Ashley EA, McGready R, Hutagalung R, Phaiphun L, Slight T, Proux S, Thwai KL, Barends M, Looareesuwan S, White NJ, Nosten F
A randomized, controlled study of a simple, once-daily regimen of dihydroartemisinin-piperaquine for the treatment of uncomplicated, multidrug-resistant falciparum malaria.
Clin Infect Dis. 2005 Aug 15;41(4):425-32. Epub 2005 Jul 15.
BACKGROUND: Dihydroartemisinin-piperaquine (DP) is a fixed-combination antimalarial drug increasingly deployed in Southeast Asia. The current regimen involves 4 doses given over 3 days. Simplification of the dose regimen should facilitate treatment adherence and thereby increase effectiveness. METHODS: In a randomized, controlled, 3-arm trial conducted along the northwestern border of Thailand, the standard 4-dose course of DP (DP4) was compared to an equivalent dose given as a once-daily regimen (DP3) and to the standard treatment of mefloquine-artesunate (MAS3). RESULTS: A total of 499 patients were included in the study. Times to fever and parasite clearance were similar in all groups. The PCR genotyping-adjusted cure rates at day 63 after treatment initiation were 95.7% (95% confidence interval [95% CI], 92.2%-98.9%) for MAS3, 100% for DP4, and 99.4% (95% CI, 98.1%-100%) for DP3. The DP4 and DP3 cure rates were significantly higher than that for MAS3 (P=.008 and P=.03, respectively). All regimens were well tolerated. There were 3 deaths (1 in the MAS3 group and 2 in the DP3 group), all of which were considered to be unrelated to treatment. Rates of other adverse events were comparable between the groups, except for diarrhea, which was more common in the DP4 group (P=.05 vs. the MAS3 group). CONCLUSIONS: A once-daily, 3-dose regimen of DP is a highly efficacious treatment for multidrug-resistant falciparum malaria. This simple, safe, and relatively inexpensive fixed combination could become the treatment of choice for falciparum malaria.

16258328
Ashley EA, White NJ
Artemisinin-based combinations.
Curr Opin Infect Dis. 2005 Dec;18(6):531-6.
PURPOSE OF REVIEW: Artemisinin-based combination treatments have been the mainstay of treatment for falciparum malaria in Southeast Asia for more than 10 years and are now increasingly recommended as first-line treatment throughout the rest of the world. RECENT FINDINGS: A large multicentre randomised trial conducted in East Asia has shown a 35% reduction in mortality from severe malaria following treatment with parenteral artesunate compared with quinine. There is increasing evidence that artemisinin-based combination treatments are safe and rapidly effective. Artemether-lumefantrine (six doses) has been shown to be very effective in large trials reported from Uganda and Tanzania. A once daily three-dose treatment of dihydroartemisinin piperaquine, a newer fixed combination, was a highly efficacious and well tolerated treatment for multi-drug resistant falciparum malaria in Southeast Asia. SUMMARY: Early diagnosis and treatment of uncomplicated malaria with effective drugs remains a priority as part of a comprehensive

malaria control strategy. Artemisinin-based combination treatments have consistently been shown to be highly effective and safe. The challenge is to make them accessible in tropical countries.

9585803
Ashton M, Nguyen DS, Nguyen VH, Gordi T, Trinh NH, Dinh XH, Nguyen TN, Le DC
Artemisinin kinetics and dynamics during oral and rectal treatment of uncomplicated malaria.
Clin Pharmacol Ther. 1998 Apr;63(4):482-93.
OBJECTIVE: To compare parasite clearance times after oral and rectal administration of artemisinin in adults with uncomplicated malaria and to relate pharmacodynamics with artemisinin kinetics and to disclose any pharmacokinetic changes during treatment. METHODS: Thirty male Vietnamese patients with falciparum malaria were randomized to treatment with 500 mg artemisinin daily by either the oral or rectal route of administration. Parasite densities in capillary blood were determined by microscopy every 4 to 6 hours. Artemisinin plasma concentrations on the first and last day of treatment were determined by HPLC and unbound fractions in plasma were determined by ultrafiltration. RESULTS: Mean parasite clearance times and 95% confidence intervals (95% CI) were 25 (95% CI, 16 to 33) and 29 (95% CI, 23 to 35) hours during oral and rectal treatment, respectively. The bioavailability after rectal relative to oral artemisinin was 30%. Artemisinin areas under the plasma concentration-time curve (AUC) on the fifth (last) day of oral or rectal treatment were 30% (95% CI, 4% to 56%) and 40% (95% CI, -6% to 91%), respectively, of those after the first dose. The fraction unbound in plasma was 15% (95% CI, 12% to 19%), increasing marginally during treatment. No relationship was found between main clinical end points and drug exposure, although indices for the rapidity of response onset were lower after oral treatment and correlated to unbound AUC values (rS = -0.7; $p < 0.001$). CONCLUSIONS: The similarity in parasite clearance times despite lower drug levels during rectal treatment suggests that initial oral doses may be unnecessarily high. The singular time dependency of artemisinin pharmacokinetics, attributed to autoinduction of drug elimination, has possible implications for combination chemotherapy. Decreasing artemisinin concentrations during treatment may partly explain recrudescences and increase the risk for resistance development.

14738799
Attaran A, Barnes KI, Curtis C, d'Alessandro U, Fanello CI, Galinski MR, Kokwaro G, Looareesuwan S, Makanga M, Mutabingwa TK, Talisuna A, Trape JF, Watkins WM
WHO, the Global Fund, and medical malpractice in malaria treatment.
Lancet. 2004 Jan 17;363(9404):237-40.

8773952
Augustijns P, D'Hulst A, Van Daele J, Kinget R
Transport of artemisinin and sodium artesunate in Caco-2 intestinal epithelial cells.
J Pharm Sci. 1996 Jun;85(6):577-9.
Artemisinin and its derivatives are becoming interesting alternatives to the commonly used antimalarial drugs because they are efficient in treating severe and multidrug resistant forms of Plasmodium falciparum malaria. A major drawback is the occurrence of recrudescence some time after treatment. Moderate oral bioavailability has been suggested as a possible cause. As one of the factors that might limit absorption after oral administration, we studied the intestinal permeability using an in vitro system of the intestinal mucosa, Caco-2. Concentrations of artemisinin were determined by UV after alkaline degradation, while for sodium artesunate, a capillary electrophoresis method was developed. Artemisinin easily crossed the epithelial cells by passive diffusion (Papp = 30.4 +/- 1.7 x 10(-6) cm s-1, pH 7.4). Permeability of the hemisuccinate analogue, sodium artesunate, was 8-fold lower (Papp = 4.0 +/- 0.4 x 10(-6) cm s-1 at pH 7.4) and strongly dependent on pH, which might result in site dependent resorption in an in vivo situation. Enzyme catalyzed ester hydrolysis of sodium artesunate in Caco-2 monolayers to the biologically active metabolite, dihydroartemisinin, was moderate. The results indicate that the transepithelial permeability is probably not a limiting factor in the overall absorption process after oral administration of artemisinin or sodium artesunate. Solubility, dissolution rate, stability, and first-pass metabolism are suggested as alternative limiting factors.

10437953
Aursudkij B, Wilairatana P, Vannaphan S, Walsh DS, Gordeux VR, Looareesuwan S
Pulmonary edema in cerebral malaria patients in Thailand.
Southeast Asian J Trop Med Public Health. 1998 Sep;29(3):541-5.
Pulmonary edema is a serious complication of falciparum malaria that usually occurs in association with cerebral malaria, acute renal failure, high parasitemias, or delayed antimalarial treatment. From 1993 to 1996, 120 adult patients admitted to the intensive care unit of the Bangkok Hospital for Tropical Diseases were enrolled in a prospective study to assess the combination of artesunate and mefloquine for the treatment of cerebral malaria. Twenty-five patients (21%) presented with pulmonary edema and a majority

developed complications in other organs as well, especially acute renal failure. In most patients (19 of 25), pulmonary edema was noted on the first day of admission and was associated with higher parasitemias and levels of acidemia, than in patients without pulmonary edema. Ten of the 25 patients diagnosed with pulmonary edema developed signs consistent with adult respiratory distress syndrome (ARDS). The mean central venous pressure when pulmonary edema was diagnosed was markedly lower in ARDS than in non-ARDS patients, supporting the argument that fluid imbalance is not essential for malaria-induced lung injury. Seven of 10 patients with ARDS died, 5 within 24 hours of admission, but there were no deaths in the 15 pulmonary edema patients without ARDS. Early diagnosis and prompt treatment remain important principles to reduce the morbidity and mortality associated with complicated falciparum malaria. This report emphasizes that ARDS, when concurrently occurs, is a poor prognostic clinical indicator in cerebral malaria.

10437674
Avery BA, Venkatesh KK, Avery MA
Rapid determination of artemisinin and related analogues using high-performance liquid chromatography and an evaporative light scattering detector.
J Chromatogr B Biomed Sci Appl. 1999 Jun 25;730(1):71-80.
Artemisinin and its analogues are a class of compounds of current interest in the treatment of drug-resistant malaria. These antimalarials are preferentially taken up into malaria infected erythrocytes as compared to uninfected erythrocytes, a fact that may represent an important parameter in drug potency. Numerous methods for the analysis of specific artemisinin analogues have been developed, but most are not widely adaptable to a large range of analogues. In this paper we describe a high-performance liquid chromatographic method developed and validated for artemisinin and several analogues of artemisinin using a readily available evaporative light scattering detector. This quantitation method was found to be straight forward, rapid, inexpensive and reproducible. Standard calibration curves constructed for six artemisinin compounds were linear with the detection limit determined between 6 and 60 ng. The intra- and inter-day accuracy were found to be 2.75% and 4.15%, respectively with less than 3% variation in precision. The validated assay was applied to a mixture of artemisinin derivatives, where they were easily separated and quantitated.

11784134
Avery MA, Alvim-Gaston M, Rodrigues CR, Barreiro EJ, Cohen FE, Sabnis YA, Woolfrey JR
Structure-activity relationships of the antimalarial agent artemisinin. 6. The development of predictive in vitro potency models using CoMFA and HQSAR methodologies.
J Med Chem. 2002 Jan 17;45(2):292-303.
Artemisinin (1) is a unique sesquiterpene peroxide occurring as a constituent of Artemisia annua L. Because of the effectiveness of Artemisinin in the treatment of drug-resistant Plasmodium falciparum and its rapid clearance of cerebral malaria, development of clinically useful semisynthetic drugs for severe and complicated malaria (artemether, artesunate) was prompt. However, recent reports of fatal neurotoxicity in animals with dihydroartemisinin derivatives such as artemether have spawned a renewed effort to develop nontoxic analogues of artemisinin. In our effort to develop more potent, less neurotoxic agents for the oral treatment of drug-resistant malaria, we utilized comparative molecular field analysis (CoMFA) and hologram QSAR (HQSAR), beginning with a series of 211 artemisinin analogues with known in vitro antimalarial activity. CoMFA models were based on two conformational hypotheses: (a) that the X-ray structure of artemisinin represents the bioactive shape of the molecule or (b) that the hemin-docked conformation is the bioactive form of the drug. In addition, we examined the effect of inclusion or exclusion of racemates in the partial least squares (pls) analysis. Databases derived from the original 211 were split into chiral (n = 157), achiral (n = 34), and mixed databases (n = 191) after leaving out a test set of 20 compounds. HQSAR and CoMFA models were compared in terms of their potential to generate robust QSAR models. The r(2) and q(2) (cross-validated r(2)) were used to assess the statistical quality of our models. Another statistical parameter, the ratio of the standard error to the activity range (s/AR), was also generated. CoMFA and HQSAR models were developed having statistically excellent properties, which also possessed good predictive ability for test set compounds. The best model was obtained when racemates were excluded from QSAR analysis. Thus, CoMFA of the n = 157 database gave excellent predictions with outstanding statistical properties. HQSAR did an outstanding job in statistical analysis and also handled predictions well.

12213073
Avery MA, Alvim-Gaston M, Vroman JA, Wu B, Ager A, Peters W, Robinson BL, Charman W
Structure-activity relationships of the antimalarial agent artemisinin. 7. Direct modification of (+)-artemisinin and in vivo antimalarial screening of new, potential preclinical antimalarial candidates.
J Med Chem. 2002 Sep 12;45(19):4321-35.
On the basis of earlier reported quantitative structure-activity relationship studies, a series of 9beta-16-(arylalkyl)-10-deoxoartemisinins were proposed for synthesis. Several of the new compounds 7 and 10-14 were synthesized employing the key synthetic intermediate 23. In a second approach, the natural product

(+)-artemisinic acid was utilized as an acceptor for conjugate addition, and the resultant homologated acids were subjected to singlet oxygenation and acid treatment to provide artemisinin analogues. Under a new approach, we developed a one step reaction for the interconversion of artemisinin 1 into artemisitene 22 that did not employ selenium-based reagents and found that 2-arylethyliodides would undergo facile radical-induced conjugate addition to the exomethylene lactone of 22 in good yield. The lactone carbonyls were removed sequentially by diisobutylaluminum hydride reduction followed directly by a second reduction (BF(3)-etherate/Et(3)SiH) to afford the desired corresponding pyrans. Six additional halogen-substituted aromatic side chains were installed via 22 furnishing the bioassay candidates 15-20. The analogues were examined for in vitro antimalarial activity in the W-2 and D-6 clones of Plasmodium falciparum and were additionally tested in vivo in Plasmodium berghei- and/or Plasmodium yoelii-infected mice. Several of the compounds emerged as highly potent orally active candidates without obvious toxicity. Of these, two were chosen for pharmacokinetic evaluation, 14 and 17.

13678403
Avery MA, Muraleedharan KM, Desai PV, Bandyopadhyaya AK, Furtado MM, Tekwani BL
Structure-activity relationships of the antimalarial agent artemisinin. 8. design, synthesis, and CoMFA studies toward the development of artemisinin-based drugs against leishmaniasis and malaria.
J Med Chem. 2003 Sep 25;46(20):4244-58.
Artemisinin (1) and its analogues have been well studied for their antimalarial activity. Here we present the antimalarial activity of some novel C-9-modified artemisinin analogues synthesized using artemisitene as the key intermediate. Further, antileishmanial activity of more than 70 artemisinin derivatives against Leishmania donovani promastigotes is described for the first time. A comprehensive structure-activity relationship study using CoMFA is discussed. These analogues exhibited leishmanicidal activity in micromolar concentrations, and the overall activity profile appears to be similar to that against malaria. Substitution at the C-9beta position was shown to improve the activity in both cases. The 10-deoxo derivatives showed better activity compared to the corresponding lactones. In general, compounds with C-9alpha substitution exhibited lower antimalarial as well as antileishmanial activities compared to the corresponding C-9beta analogues. The importance of the peroxide group for the observed activity of these analogues against leishmania was evident from the fact that 1-deoxyartemisinin analogues did not exhibit antileishmanial activity. The study suggests the possibility of developing artemisinin analogues as potential drug candidates against both malaria and leishmaniasis.

15040558
Avila JC, Villaroel R, Marquino W, Zegarra J, Mollinedo R, Ruebush TK
Efficacy of mefloquine and mefloquine-artesunate for the treatment of uncomplicated Plasmodium falciparum malaria in the Amazon region of Bolivia.
Trop Med Int Health. 2004 Feb;9(2):217-21.
We assessed the efficacy of mefloquine monotherapy and mefloquine-artesunate (MQ-AS) combination therapy for the treatment of Plasmodium falciparum malaria at four sites in the Bolivian Amazon region. Patients with uncomplicated P. falciparum infections between 5 and 60 years of age were randomly assigned to be treated with either MQ (15 mg/kg in a single oral dose) or MQ (15 mg/kg) plus AS (4 mg/kg daily for 3 days). A total of 143 patients were enrolled and followed for 28 days. None of the 73 patients who received MQ alone or the 70 patients who received MQ-AS combination therapy had recurrences of parasitaemia during the 28-day follow-up period. Asexual parasite densities fell significantly more rapidly and the proportion of patients with gametocytes was significantly lower on days 7-28 in patients treated with MQ-AS than in those treated with MQ alone. All patients tolerated the medications well. After this study, the Bolivian Ministry of Public Health changed its treatment policy for uncomplicated P. falciparum malaria in the Amazon region to combination therapy with MQ-AS to slow or prevent the development of resistance.

12641404
Awad MI, Alkadru AM, Behrens RH, Baraka OZ, Eltayeb IB
Descriptive study on the efficacy and safety of artesunate suppository in combination with other antimalarials in the treatment of severe malaria in Sudan.
Am J Trop Med Hyg. 2003 Feb;68(2):153-8.
Documentation on the efficacy of artesunate in Africa is limited, and no experience of artesunate use in Sudan is documented. Severe malaria in rural areas of Sudan, where facilities for the safe and effective use of parenteral quinine are lacking, is a frequent problem. Early treatment with artesunate suppositories would provide a simple method for use by unskilled staff and would be an alternative approach to treat malaria in settings with poor resources. We describe a hospital-based study of rectal artesunate in 100 adult patients with severe falciparum malaria with a dose derived from pharmacokinetic data (200 mg every 8 hours) over 3 days, which halted progression of severe disease and had a low fatality rate. The dosage schedule led to a rapid clinical response and reduced parasite clearance and fever subsidence times of (31.5 +/- 10.1 hours) and (31.4 +/- 11.1 hours). The sequential treatment of rectal artesunate with either doxycycline or

pyrimethamine/sulfadoxine or mefloquine resulted in similar clinical cure rates of around 100%, and the combination of artesunate with either doxycycline or pyrimethamine/sulfadoxine was equally effective as mefloquine in preventing recrudescence. There were no significant adverse effects or signs of toxicity related to the treatment observed during the 28-day follow-up. The combination regimens could be used in areas where there is limited access to parenteral therapy for malaria.

12773055
Bachi MD, Korshin EE, Hoos R, Szpilman AM, Ploypradith P, Xie S, Shapiro TA, Posner GH
A short synthesis and biological evaluation of potent and nontoxic antimalarial bridged bicyclic beta-sulfonyl-endoperoxides.
J Med Chem. 2003 Jun 5;46(12):2516-33.
The syntheses and in vitro antimalarial screening of 50 bridged, bicyclic endoperoxides of types 9-13 are reported. In contrast to antimalarial trioxanes of the artemisinin family, but like yingzhaosu A and arteflene, the peroxide function of compounds 9-13 is contained in a 2,3-dioxabicyclo[3.3.1]nonane system 6. Peroxides 9 and 10 (R(1) = OH) are readily available through a multicomponent, sequential, free-radical reaction involving thiol-monoterpenes co-oxygenation (a TOCO reaction). beta-Sulfenyl peroxides 9 and 10 (R(1) = OH) are converted into beta-sulfinyl and beta-sulfonyl peroxides of types 11-13 by controlled S-oxidation and manipulation of the tert-hydroxyl group through acylation, alkylation, or dehydration followed by selective hydrogenation. Ten enantiopure beta-sulfonyl peroxides of types 12 and 13 exhibit in vitro antimalarial activity comparable to that of artemisinin (IC(50) = 6-24 nM against Plasmodium falciparum NF54). In vivo testing of a few selected peroxides against Plasmodium berghei N indicates that the antimalarial efficacies of beta-sulfonyl peroxides 39a, 46a, 46b, and 50a are comparable to those of some of the best antimalarial drugs and are higher than artemisinin against chloroquine-resistant Plasmodium yoelii ssp. NS. In view of the nontoxicity of beta-sulfonyl peroxides 39a, 46a, and 46b in mice, at high dosing, these compounds are regarded as promising antimalarial drug candidates.

11127248
Bakshi R, Hermeling-Fritz I, Gathmann I, Alteri E
An integrated assessment of the clinical safety of artemether-lumefantrine: a new oral fixed-dose combination antimalarial drug.
Trans R Soc Trop Med Hyg. 2000 Jul-Aug;94(4):419-24.
Artemether-lumefantrine (A-L), a new fixed-dose oral antimalarial drug, combines the fast onset of action of artemether (an artemisinin derivative) in terms of parasite clearance with the high cure rate of lumefantrine in the treatment of acute uncomplicated Plasmodium falciparum malaria. The extensive clinical trial database of A-L has allowed a comprehensive evaluation of its tolerability and safety in a total of 1869 patients (including 243 children aged 5-12 years and 368 children aged < 5 years). The most commonly reported and possibly related adverse effects following A-L therapy involved the gastro-intestinal (abdominal pain, anorexia, nausea, vomiting, diarrhoea) and central nervous (headache, dizziness) systems. Pruritus and rash were reported by < 2% of patients. More than 90% of the reported adverse events, many of which overlapped considerably with the clinical symptomatology or evolution of acute malaria, were rated mild to moderate in intensity. Compared to A-L, significantly higher incidences of vomiting and pruritus were observed with chloroquine, dizziness, nausea and vomiting with mefloquine, somnolence with pyrimethamine + sulfadoxine, and vomiting and dizziness with quinine. There were no serious or persistent neurological side-effects related to A-L administration. A-L did not lead to any clinically relevant alterations of the laboratory parameters. Serial electrocardiographic data were available for 713 patients. The frequency of QT interval prolongations was similar to or lower than that observed with chloroquine, mefloquine, or artesunate + mefloquine; these changes were considerably less frequent than with quinine or halofantrine. All patients with QT prolongation remained asymptomatic and no adverse clinical cardiac events were reported. Artemether-lumefantrine can thus be expected to show, both in children and in adults, a favourable safety profile for the treatment of acute, uncomplicated, P. falciparum malaria; it could as well be a reserve treatment option for travellers to endemic countries.

11578659
Balint GA
Artemisinin and its derivatives: an important new class of antimalarial agents.
Pharmacol Ther. 2001 May-Jun;90(2-3):261-5.
Artemisinin and its derivatives are a potent new class of antimalarials, originated from Artemisia annua, L. The clinical efficacy of these drugs is characterized by an almost immediate onset and rapid reduction of parasitaemia. Their efficacy is high in such areas as well where multidrug-resistance is rampant, but in these areas, their combination with other (effective) antimalarials (e.g., mefloquine) is highly recommended. In this short review, the chemical structures, pharmacological properties, and clinical uses of artemisinin drugs are discussed.

1596283
Bangchang KN, Karbwang J, Back DJ
Mefloquine metabolism by human liver microsomes. Effect of other antimalarial drugs.
Biochem Pharmacol. 1992 May 8;43(9):1957-61.
A number of drugs have been studied for their effect on the metabolism of the antimalarial drug mefloquine by human liver microsomes (N = 6) in vitro. The only metabolite generated was identified as carboxymefloquine by co-chromatography with the authentic standard. Ketoconazole caused marked inhibition of carboxymefloquine formation with IC50 and Ki values of 7.5 and 11.2 microM, respectively. The inhibition of ketoconazole, a known inhibitor of cytochrome P450 isozymes, and the dependency of metabolite formation on the presence of NADPH indicated that cytochrome P450 isozyme(s) catalysed metabolite production. Of compounds actually or likely to be coadministered with mefloquine to malaria patients only primaquine and quinine produced marked inhibition (IC50, 17.5 and 122 microM; Ki, 8.6 and 28.5 microM, respectively). However, despite these in vitro data with primaquine, clinical studies have failed to show any significant effect of single dose primaquine on the pharmacokinetics of mefloquine. With quinine, because peak plasma concentrations are very close to the Ki value, there is likely to be inhibition of mefloquine metabolism in patients receiving both drugs. Sulfadoxine, artemether, artesunate and tetracycline did not significantly inhibit carboxymefloquine formation.

1510705
Bangchang KN, Karbwang J, Back DJ
Primaquine metabolism by human liver microsomes: effect of other antimalarial drugs.
Biochem Pharmacol. 1992 Aug 4;44(3):587-90.
A number of drugs have been studied for their effect on the metabolism of the antimalarial drug primaquine by human liver microsomes (N = 4) in vitro. The only metabolite generated was identified as carboxyprimaquine by co-chromatography with the authentic standard. Ketoconazole, a known inhibitor of cytochrome P450 isozymes, caused marked inhibition of carboxyprimaquine formation with IC50 and K(i) values of 15 and 6.7 microM, respectively. This finding and the dependency of metabolite formation on NADPH indicates that cytochrome P450 isozyme(s) catalysed metabolite production. Of compounds actually or likely to be coadministered with primaquine to malaria patients, only mefloquine produced any inhibition (K(i) = 52.5 microM). Quinine, artemether, artesunate, halofantrine and chloroquine did not significantly inhibit metabolite formation. It seems unlikely that the concurrent administration of mefloquine, or other antimalarials, with primaquine will lead to appreciably altered disposition.

15078261
Barennes H, Nagot N, Valea I, Koussoube-Balima T, Ouedraogo A, Sanou T, Ye S
A randomized trial of amodiaquine and artesunate alone and in combination for the treatment of uncomplicated falciparum malaria in children from Burkina Faso.
Trop Med Int Health. 2004 Apr;9(4):438-44.
Combining artesunate (AR) with existing antimalarial drugs may improve cure rates, delay emergence of resistance and reduce parasite clearance time. In order to investigate the latter, we conducted a randomized clinical trial testing the AR plus amodiaquine (AQ) combination for the treatment of uncomplicated Plasmodium falciparum malaria in Burkina Faso. Children aged 1-15 years were randomly assigned to either AQ (10 mg/kg) or AR (4 mg/kg first day then half dose) or AQ + AR (AQAR) as a single daily dose under supervision for three consecutive days for all groups. Follow-up lasted 28 days. Primary endpoints were parasite and fever clearance time. Eighty-seven children were evaluated: 27 received AQ, 27 AR and 33 AQAR. Using an intention to treat analysis, fever clearance time was similar in the three groups. However, it was significantly faster in the AR (1.21 days; P = 0.02) and AQAR groups (1.19 days; P < 0.01) than in the AQ group (1.46 days) when excluding other concomitant causes of fever. Parasite clearance time was faster in AR (1.13 days; P = 0.008) and AQAR groups (1.13 days; P < 0.01) than in the AQ group (1.6 days). All children cleared their parasites by day 14, including the child with Late Parasitological Failure (LPF) at day 7 after rescue treatment. Only one child (4%) from the AR group and one (4%) from the AQ group presented with asymptomatic parasitaemia at day 7 and day 21, respectively (LPF). Gametocyte carriage was not detectable in any group during follow-up nor was any adverse reaction observed. While resistance to first-line treatment (chloroquine) is already established in the country, AQ and AR used alone or in combination therapy proved highly efficacious in our study. Burkina Faso stands in a very good situation for an internationally recommended switch to AR-containing combination as first-line treatment for uncomplicated malaria. Including AQ in this regimen seems the best option.

16187798
Barnes KI, Durrheim DN, Little F, Jackson A, Mehta U, Allen E, Dlamini SS, Tsoka J, Bredenkamp B, Mthembu DJ, White NJ, Sharp BL
Effect of Artemether-Lumefantrine Policy and Improved Vector Control on Malaria Burden in KwaZulu-Natal, South Africa.

PLoS Med. 2005 Nov;2(11):e330. Epub 2005 Oct 4.
BACKGROUND: Between 1995 and 2000, KwaZulu-Natal province, South Africa, experienced a marked increase in Plasmodium falciparum malaria, fuelled by pyrethroid and sulfadoxine-pyrimethamine resistance. In response, vector control was strengthened and artemether-lumefantrine (AL) was deployed in the first Ministry of Health artemisinin-based combination treatment policy in Africa. In South Africa, effective vector and parasite control had historically ensured low-intensity malaria transmission. Malaria is diagnosed definitively and treatment is provided free of charge in reasonably accessible public-sector health-care facilities. METHODS AND FINDINGS: We reviewed four years of malaria morbidity and mortality data at four sentinel health-care facilities within KwaZulu-Natal's malaria-endemic area. In the year following improved vector control and implementation of AL treatment, malaria-related admissions and deaths both declined by 89%, and outpatient visits decreased by 85% at the sentinel facilities. By 2003, malaria-related outpatient cases and admissions had fallen by 99%, and malaria-related deaths had decreased by 97%. There was a concomitant marked and sustained decline in notified malaria throughout the province. No serious adverse events were associated causally with AL treatment in an active sentinel pharmacovigilance survey. In a prospective study with 42 d follow up, AL cured 97/98 (99%) and prevented gametocyte developing in all patients. Consistent with the findings of focus group discussions, a household survey found self-reported adherence to the six-dose AL regimen was 96%. CONCLUSION: Together with concurrent strengthening of vector control measures, the antimalarial treatment policy change to AL in KwaZulu-Natal contributed to a marked and sustained decrease in malaria cases, admissions, and deaths, by greatly improving clinical and parasitological cure rates and reducing gametocyte carriage.

15145633
Barnes KI, Mwenechanya J, Tembo M, McIlleron H, Folb PI, Ribeiro I, Little F, Gomes M, Molyneux ME
Efficacy of rectal artesunate compared with parenteral quinine in initial treatment of moderately severe malaria in African children and adults: a randomised study.
Lancet. 2004 May 15;363(9421):1598-605.
BACKGROUND: Many patients with malaria of increasing severity cannot take medicines orally, and delay in injectable treatment can be fatal. We aimed to assess the reliability of absorption, antimalarial efficacy, and tolerability of a single rectal dose of artesunate in the initial management of moderately severe falciparum malaria. METHODS: 109 children and 35 adults were randomly assigned to rectal artesunate (single dose of about 10 mg/kg) or parenteral quinine treatment (10 mg/kg at 0, 4, and 12 h). The primary endpoint was the proportion of patients with peripheral asexual parasitaemia of less than 60% of that at baseline after 12 h. Secondary endpoints were clinical response and concentrations of drug in plasma. Analysis was by intention-to-treat. FINDINGS: All artesunate-treated patients had pharmacodynamic or pharmacokinetic evidence of adequate drug absorption. 80 (92%) of 87 artesunate-treated children had a 12 h parasite density lower than 60% of baseline, compared with three of 22 (14%) receiving quinine (relative risk 0.09 [95% CI 0.04-0.19]; p

15878154
Barnes KI, White NJ
Population biology and antimalarial resistance: The transmission of antimalarial drug resistance in Plasmodium falciparum.
Acta Trop. 2005 Jun;94(3):230-40.
Malaria morbidity and mortality continue to increase across sub-Saharan Africa. This is largely as a result of the continued use of chloroquine and sulfadoxine-pyrimethamine, despite widespread resistance. Although eliminating the asexual stages of Plasmodium falciparum is the focus of treatment of individual symptomatic patients, at a population level, reducing the carriage of gametocytes - the sexual stage responsible for infection of the mosquito vector - is necessary to limit the transmission of malaria parasites and the spread of antimalarial resistance. The probability of a mosquito being infected depends on the prevalence, duration and density of viable gametocyte carriage in the human host, although additional humoral and leukocyte factors also affect transmissibility. There is a log-sigmoid relationship between gametocyte density in the patients' blood and infectivity to the mosquito. The infectivity and thus transmission potential associated with a particular antimalarial treatment can be characterised as a function of blood gametocyte density and time, summing these over the acute and all subsequent recrudescences of that infection. Gametocyte carriage and infectivity to mosquitoes is consistently higher in patients infected with drug resistant compared with drug sensitive malaria parasites. It is the ratio of transmission potential in drug resistant versus sensitive infections that drives the spread of resistance. Early access to highly effective antimalarial treatment reduces the risk of disease progression and limits gametocyte carriage. The remarkable spread of sulfadoxine-pyrimethamine (SP) resistance across vast regions results from the very high post-treatment prevalence and density of gametocyte carriage following SP treatment. In areas of low intensity malaria transmission, the gametocyte-reducing effect of widespread use of artemisinin-based combination therapy has resulted in a sustained decrease in malaria transmission and a decrease in the spread of resistance. Malaria treatment policy should be based primarily on therapeutic efficacy against asexual stages, but should also consider

transmission reduction potential. Artemisinin-based combination therapies are the only antimalarials currently available which rapidly reduce both asexual and gametocyte stages of the P. falciparum lifecycle.

8536555
Barradell LB, Fitton A
Artesunate. A review of its pharmacology and therapeutic efficacy in the treatment of malaria.
Drugs. 1995 Oct;50(4):714-41.
Artesunate is an antimalarial agent, available in oral, rectal and parenteral formulations, that provides a rapid clinical effect in patients with Plasmodium falciparum malaria. The rapidity of effect, availability of an intravenous and intramuscular formulation and convenient dosage regimen make artesunate an ideal candidate for the treatment of severe malaria, including cerebral disease. While some results have been promising, there is no clear evidence to date that artesunate reduces mortality in patients with cerebral malaria to any greater extent than standard quinine therapy. When given as monotherapy, treatment should be continued for at least 5 to 7 days to prevent recrudescence. Combination therapy with mefloquine allows artesunate to be administered over 3 days or less, with a satisfactory clinical outcome maintained. Although optimal dosages remain to be determined, this combination continues to provide the rapid onset of clinical effect observed with artesunate monotherapy, but decreases the rate of recrudescence to 2% (i.e. radical cure rate of 98%) when used as treatment in patients with uncomplicated malaria from areas with a high risk of multidrug-resistance falciparum malaria. Although assessment of tolerability is complicated by the difficulty of distinguishing between disease- and treatment-related events, artesunate and artesunate-mefloquine combinations appear to be well tolerated in adults and children. Indeed, it is possible that prior administration of artesunate may reduce the incidence of mefloquine-induced vomiting. Clinical findings to date have not revealed any pattern of resistance to artesunate after use of the drug. However, given the history of the development of resistance to other antimalarial drugs, the use of artesunate should be restricted to areas of multidrug resistance, the drug should be used in combination with a longer acting agent such as mefloquine, and it should be used in regimens that provide radical cure rates of 90 to 100%. If used according to these treatment principles, artesunate will provide a well tolerated and valuable addition to the current extremely limited treatment options for multidrug-resistant falciparum malaria, a widespread parasitic disease associated with considerable mortality.

12224572
Basco LK, Ringwald P
Molecular epidemiology of malaria in Cameroon. X. Evaluation of PFMDR1 mutations as genetic markers for resistance to amino alcohols and artemisinin derivatives.
Am J Trop Med Hyg. 2002 Jun;66(6):667-71.
Mutations at five positions in the Plasmodium falciparum multidrug-resistance gene 1 (pfmdr1), initially thought to confer resistance to chloroquine, have been associated with in vitro resistance to amino alcohols and artemisinin derivatives in more recent studies. To assess the possible association between drug resistance phenotype and pfmdrl polymorphisms and establish the baseline pfmdr1 sequence data in Yaounde, Cameroon, the in vitro drug sensitivity pattern was determined for 64 clinical isolates by isotopic microtest. The pfmdr1 alleles were determined by a polymerase chain reaction and automatic sequencing. A large majority of isolates carried Tyr-86 (88%) and Phe-184 (91%) alleles. With the exception of one isolate with mixed codon 1246, all isolates had wild-type alleles Ser-1034, Asn-1042, and Asp-1246. There was no statistical association between codons 86 and 184 and in vitro response to chloroquine, amino alcohols, and artemisinin derivatives ($P > 0.05$). Our data do not seem to support the hypothesis that mutations in codons 86 and 184 influence the in vitro response to these drugs. Further monitoring of both in vitro response and pfmdrl polymorphisms is required to evaluate the potential role played by other pfmdr1 alleles in the determination of drug resistance in Africa.

11421367
Basco LK, Ringwald P
Molecular epidemiology of malaria in Yaounde, Cameroon. VII. Analysis of recrudescence and reinfection in patients with uncomplicated falciparum malaria.
Am J Trop Med Hyg. 2000 Nov-Dec;63(5-6):215-21.
In an endemic area where malaria transmission is intense and continuous, reappearance of asexual parasites may be ascribed to either recrudescence or reinfection. To distinguish between recrudescence and reinfection after oral treatment with chloroquine, amodiaquine, pyronaridine, sulfadoxine-pyrimethamine, halofantrine, or artesunate, three polymorphic markers (circumsporozoite protein, merozoite surface antigens 1 and 2) from pre-treatment and post-treatment samples were amplified by the polymerase chain reaction, and the in vitro response to chloroquine was determined for comparison. Of 52 paired samples, 22 (42%) were reinfections. Recrudescence occurred more frequently on or before Day 14 (22 of 30 cases, 73%). Except for one case, all reinfections were observed beyond Day 14. The phenotype determination was not sufficiently precise to distinguish between recrudescence and reinfection. Our results suggest that beyond

Day 14 (and until Day 42), recrudescence and reinfection cannot be distinguished at our study site unless molecular techniques are used and that some results derived from the polymerase chain reaction need to be compared with the microscopic examination of thick blood smear to exclude gametocyte carriers without asexual parasites after treatment.

12163917
Basco LK, Same-Ekobo A, Ngane VF, Ndounga M, Metoh T, Ringwald P, Soula G
Therapeutic efficacy of sulfadoxine-pyrimethamine, amodiaquine and the sulfadoxine-pyrimethamine-amodiaquine combination against uncomplicated Plasmodium falciparum malaria in young children in Cameroon.
Bull World Health Organ. 2002;80(7):538-45.
OBJECTIVE: To evaluate the therapeutic efficacy of sulfadoxine-pyrimethamine, amodiaquine, and the sulfadoxine-pyrimethamine-amodiaquine combination for the treatment of uncomplicated Plasmodium falciparum malaria in young children in Cameroon. METHODS: In a randomized study we evaluated the effectiveness and tolerance of (i) sulfadoxine-pyrimethamine (SP) (25 mg/kg body weight of sulfadoxine and 1.25 mg/kg of pyrimethamine in a single oral dose), (ii) amodiaquine (AQ) (30 mg/kg body weight in three divided daily doses), and (iii) the sulfadoxine-pyrimethamine-amodiaquine combination (SP+AQ) (same doses as in the other two treatment groups, given simultaneously on day 0) in young children in southern Cameroon. The parasitological and clinical responses were studied until day 28 in accordance with the modified 1996 WHO protocol for the evaluation of the therapeutic efficacy of antimalarial drugs. FINDINGS: Of 191 enrolled patients, 6 and 8 were excluded or lost to follow-up before day 14 and between day 14 and day 28, respectively. For the AQ-treated patients, parasitological and clinical evaluation on day 14 showed late treatment failure in 2 of 61 (3.3%) and adequate clinical response with parasitological failure in one (1.6%). There was an adequate clinical response in all patients treated with SP or SP+AQ. Therapeutic failure rates on day 28 were 13.6%, 10.2% and 0% in the SP, AQ, and SP+AQ groups, respectively. Anaemia improved in all three regimens. AQ produced faster fever clearance but was associated with more transient minor side-effects than SP. SP+AQ reduced the risk of recrudescence between day 14 and day 28 but increased the incidence of minor side-effects. CONCLUSION: SP+AQ can be recommended as a temporary means of slowing the spread of multidrug resistance in Plasmodium falciparum in Africa while the introduction of other combinations, including artemisinin derivatives, is awaited.

8704940
Batty KT, Davis TM, Thu LT, Binh TQ, Anh TK, Ilett KF
Selective high-performance liquid chromatographic determination of artesunate and alpha- and beta-dihydroartemisinin in patients with falciparum malaria.
J Chromatogr B Biomed Appl. 1996 Mar 3;677(2):345-50.
A novel solid-phase extraction and a robust high-performance liquid chromatographic (HPLC) separation procedure for artesunate and alpha- and beta-dihydroartemisinin, using post-column alkali decomposition and UV detection is described. Extraction was performed with Bond-Elut Phenyl solid-phase extraction cartridges and analysis by HPLC was carried out using a Waters Symmetry C8 5-microns 150 x 3.9 mm I.D. column. The mobile phase was 50% acetonitrile in 0.1 M acetate buffer (pH 4.8) delivered at a flow-rate of 0.7 ml/min. The column eluate was mixed with 1.2 M potassium hydroxide in 90% methanol delivered at 0.3 ml/min, in a 1-ml reaction coil at 69 degrees C, to form UV-absorbing chromophores which were detected at 290 nm. The recovery of all analytes was greater than 80%. There was no significant difference in the peak-area ratio of alpha- and beta-dihydroartemisinin in plasma. Preliminary pharmacokinetic data from six adult Vietnamese patients who received 120 mg of artesunate by intravenous injection for the treatment of acute falciparum malaria are presented. Despite limited data, the mean half-life of artesunate was approximately 3.5 min while that for dihydroartemisinin was 34 min. These data confirm the relatively rapid clearance of both artesunate and its principle active metabolite, dihydroartemisinin.

8722489
Batty KT, Ilett KF, Davis T, Davis ME
Chemical stability of artesunate injection and proposal for its administration by intravenous infusion.
J Pharm Pharmacol. 1996 Jan;48(1):22-6.
Artesunate, the only artemisinin analogue that can be given intravenously, produces rapid parasite and fever clearance in falciparum malaria. A significant therapeutic problem is a high, late recrudescence rate, probably due to short half-lives of both artesunate and its active metabolite dihydroartemisinin relative to conventional dosing intervals. One method of extending the duration of action of artesunate could be to administer the drug by infusion rather than bolus injection, provided that it is chemically stable at ambient temperature. Artesunate was found to be stable in 0.9% w/v sodium chloride at 9 degrees C, 23 degrees C and 36.5 degrees C for 130, 10.6 and 1.6 h, respectively. Interpolating from an Arrhenius plot, artesunate should be stable for approximately 4 h at 30 degrees C, a temperature representative of ambient conditions in tropical countries. Exposure to light did not affect the degradation rate. Single compartment

pharmacokinetic modelling was used to evaluate potential differences in artesunate and dihydroartemisinin plasma concentrations following administration of artesunate by intravenous bolus or infusion. A bolus injection of artesunate at a dose of 4 mg kg-1 gives a peak concentration of 5.3 mg L-1, falling to 0.005 mg L-1 at 5 h. The same dose infused over 4 h results in a peak concentration of 0.92 mg L-1, falling to 0.005 mg L-1 at 8 h. Simultaneous modelling of dihydroartemisinin showed that while its peak plasma concentration was reduced by 27% and the peak delayed by 2.5 h following artesunate administration by infusion, substantially higher concentrations were maintained compared with those predicted after bolus artesunate. These data indicate that artesunate can be administered as a high-dose intravenous infusion, thus avoiding high plasma concentrations. This strategy also has the potential to prolong the duration of antimalarial effect and reduce toxicity, and consequently improve clinical outcome in seriously ill patients.

15025754
Batty KT, Ilett KF, Davis TM
Protein binding and alpha : beta anomer ratio of dihydroartemisinin in vivo.
Br J Clin Pharmacol. 2004 Apr;57(4):529-33.
AIMS: To determine the ratio of alpha : beta anomers and the protein binding of dihydroartemisinin (DHA) in vivo. METHODS: 10-[(3)H]-DHA was synthesized by reduction of artemisinin with sodium boro-[(3)H]-hydride and purified with preparative thin layer chromatography. A solution of (3)H-DHA (2000 ng in 20 micro l) was added to 2 ml whole blood from 15 healthy volunteers and 22 Vietnamese patients with falciparum or vivax malaria. The blood was centrifuged and the plasma stored at -25 degrees C until analysed by HPLC with radiochromatographic detection. Protein-free ultrafiltrate of the plasma was assayed to determine the free fraction of DHA and the in vivo ratio of alpha-DHA : beta-DHA. RESULTS: The DHA fraction unbound (mean +/- SD) was 0.068 +/- 0.032 in Vietnamese patients with falciparum malaria (n = 17), 0.065 +/- 0.009 in Vietnamese patients with vivax malaria (n = 5), 0.117 +/- 0.015 in Vietnamese volunteers (n = 7) and 0.092 +/- 0.020 in Caucasian volunteers (n = 8). The ratios of alpha-DHA : beta-DHA for the four groups were 6.3 +/- 0.9, 6.9 +/- 0.8, 6.9 +/- 0.6 and 5.4 +/- 0.8, respectively. CONCLUSIONS: DHA is approximately 93% protein-bound in patients with malaria infection and there is a preferential existence in vivo of the alpha-DHA anomer. Knowledge of this stereochemistry may be valuable in elucidation of the mechanisms of DHA action and/or toxicity, and in the synthesis of new trioxane antimalarials.

9840605
Batty KT, Le AT, Ilett KF, Nguyen PT, Powell SM, Nguyen CH, Truong XM, Vuong VC, Huynh VT, Tran QB, Nguyen VM, Davis TM
A pharmacokinetic and pharmacodynamic study of artesunate for vivax malaria.
Am J Trop Med Hyg. 1998 Nov;59(5):823-7.
To investigate the pharmacokinetic and pharmacodynamic properties of artesunate (ARTS) and its active metabolite dihydroartemisinin (DHA) in Plasmodium vivax infections, 12 male Vietnamese adults with slide-positive vivax malaria received either intravenous ARTS (120 mg; group 1) or oral ARTS (100 mg; group 2) with the alternative preparation given 8 hr later in a randomized, open, cross-over study. Following intravenous injection, ARTS had a peak plasma drug concentration (Cmax) of 35.6 microM (13.7 mg/L), an elimination half-life (t1/2) of 2.2 min, a clearance (CL) of 3.0 L/hr/kg, and a volume of distribution (V) of 0.16 L/kg. Dihydroartemisinin had a Cmax of 7.7 microM (2.2 mg/L), a tmax of 8 min, a t1/2 of 37 min, an apparent CL of 1.1 L/hr/kg, and an apparent V of 0.9 L/kg. Following oral ARTS, the mean relative bioavailability of DHA was 85%, the Cmax was 3.0 microM (0.85 mg/L), the tmax was 75 min, and t1/2 was 40 min. The mean time to 50% reduction in the parasite count (PCT50) and median fever clearance time were 3 hr and 16 hr, respectively. Following intravenous ARTS (group 1), the PCT50 for total parasites, rings, trophozoites, and gametocytes was 3.3 hr, 3.2 hr, 4.0 hr, and 3.6 hr, respectively. This study confirms that ARTS is effective against P. vivax, with rapid clearance of sexual and asexual forms of the parasite. Artesunate is a suitable initial treatment for vivax malaria, or when the plasmodial species cannot be reliably identified.

9491824
Batty KT, Thu LT, Davis TM, Ilett KF, Mai TX, Hung NC, Tien NP, Powell SM, Thien HV, Binh TQ, Kim NV
A pharmacokinetic and pharmacodynamic study of intravenous vs oral artesunate in uncomplicated falciparum malaria.
Br J Clin Pharmacol. 1998 Feb;45(2):123-9.
AIMS: To obtain comprehensive pharmacokinetic and pharmacodynamic data for artesunate (ARTS) and its active metabolite dihydroartemisinin (DHA) following i.v. and oral administration of ARTS to patients with acute, uncomplicated falciparum malaria. METHODS: Twenty-six Vietnamese patients with falciparum malaria were randomized to receive either i.v. ARTS (120 mg; group 1) or oral ARTS (100 mg; group 2), with the alternative preparation given 8 h later in an open crossover design. Mefloquine (750 mg) was administered at 24 h. Plasma concentrations of ARTS and DHA were determined by h.p.l.c. assay.

Pharmacokinetic parameters were calculated by non-compartmental methods. The time to 50% parasite clearance (PCT50) was calculated by linear interpolation of parasite density determinations. Linear least squares and multiple linear regression analyses were used to evaluate pharmacokinetic-pharmacodynamic relationships. RESULTS: Following i.v. bolus, ARTS had a peak concentration of 29.5 microM (11 mg l[-1]), elimination t1/2 = 2.7 min, CL = 2.33 l h(-1) kg(-1) and V = 0.14 l kg(-1). The Cmax for DHA was 9.3 microM (2.64 mg l[-1]), t1/2 = 40 min, CL =0.75 l h(-1) kg(-1) and V = 0.76 l kg(-1). Following oral ARTS, relative bioavailability of DHA was 82%, Cmax was 2.6 microM (0.74 mg l[-1]), t1/2 = 39 min, and MAT = 67 min. Overall, the PCT50 and fever clearance time (FCT) were 6.5 h and 24 h, respectively. There was no correlation between PCT50 or FCT and AUC, Cmax or MRT for DHA. CONCLUSIONS: Despite rapid clearance of ARTS and DHA in patients with uncomplicated falciparum malaria, prompt parasite and fever clearance were achieved. High relative bioavailability of DHA following oral ARTS administration, and clinical outcomes comparable with those after i.v. ARTS, support the use of the oral formulation in the primary care setting.

12783311
Begum K, Kim HS, Kumar V, Stojiljkovic I, Wataya Y
In vitro antimalarial activity of metalloporphyrins against Plasmodium falciparum.
Parasitol Res. 2003 Jun;90(3):221-4. Epub 2003 Mar 12.
The in vitro antimalarial activity against Plasmodium falciparum and heme polymerization were evaluated for ten metalloporphyrins: gallium protoporphyrin IX (GaPPIX), sodium salt of gallium protoporphyrin IX, silver protoporphyrin IX, palladium protoporphyrin IX, cobalt protoporphyrin IX, manganese protoporphyrin IX, tin protoporphyrin IX (SnPPIX), chromium protoporphyrin IX, gallium deuteroporphyrin IX (GaDPIX) and gallium hematoporphyrin IX. Metalloporphyrins inhibited parasite growth with 50% inhibitory concentrations (IC(50)) ranging from 15.5 microM to 190 microM. In trophozoite lysate-mediated heme polymerization assays, SnPPIX, GaPPIX and GaDPIX exerted potent inhibitory activity similar to that of artemisinin and chloroquine.

15597707
Bei ZC, Wang JY
[Construction of the subtracted cDNA libraries related to artemisinin-resistance of Plasmodium berghei]
Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi. 2004 Jun;22(3):139-43.
OBJECTIVE: To construct the subtracted cDNA libraries related to artemisinin-resistance of Plasmodium berghei using suppression subtractive hybridization PCR (SSH PCR). METHODS: Total RNA was extracted from the artemisinin-sensitive (NS) and artemisinin-resistant (AR) strains of Plasmodium berghei K173. The cDNA synthesis followed the protocol of super SMART cDNA synthesis kit. Taking the NS as driver, AR as tester and reverse, two subtractions were performed by SSH PCR. Enriched different expressed cDNA was cloned into pMD18-T vector to construct subtractive libraries. RESULTS: The subtracted cDNA libraries of NS-AR and AR-NS contained 395 and 506 positive clones respectively. The PCR results of 108 clones picked randomly from each library showed 100 and 104 positive inserts contained in the plasmids respectively, and distributing in 250-2000 bp. CONCLUSION: The successful construction of the subtracted cDNA libraries related to artemisinin-resistance of P. berghei enable us to identify the different expressed genes involved in the resistance mechanism.

16243458
Bell A
Antimalarial drug synergism and antagonism: mechanistic and clinical significance.
FEMS Microbiol Lett. 2005 Dec 15;253(2):171-84. Epub 2005 Oct 7.
Interactions between antimicrobial agents provide clues as to their mechanisms of action and influence the combinations chosen for therapy of infectious diseases. In the treatment of malaria, combinations of drugs, in many cases acting synergistically, are increasingly important in view of the frequency of resistance to single agents. The study of antimalarial drug interactions is therefore of great significance to both treatment and research. It is therefore worrying that the analysis of drug-interaction data is often inadequate, leading in some cases to dubious conclusions about synergism or antagonism. Furthermore, making mechanistic deductions from drug-interaction data is not straightforward and of the many reported instances of antimalarial synergism or antagonism, few have been fully explained biochemically. This review discusses recent findings on antimalarial drug interactions and some pitfalls in their analysis and interpretation. The conclusions are likely to have relevance to other antimicrobial agents.

16103941
Bell A
Recent developments in the chemotherapy of malaria.
IDrugs. 2000 Mar;3(3):310-7.
Malaria remains a major infectious disease and is worsening in some areas, partly because of the spread of resistance to established antimalarial drugs. New drugs are urgently needed to combat the protozoan

parasite, Plasmodium. This review covers new developments, including artemisinin derivatives, synthetic peroxides, folate pathway inhibitors, primaquine analogs and proteinase inhibitors. However, few of these agents are in clinical trials and many are derived from chemical classes already used extensively against malaria. The emerging understanding of parasite biology and new technological developments in drug discovery offer hope of improvement, but this will require increased interest from the pharmaceutical industry.

9063354
Benakis A, Paris M, Loutan L, Plessas CT, Plessas ST
Pharmacokinetics of artemisinin and artesunate after oral administration in healthy volunteers.
Am J Trop Med Hyg. 1997 Jan;56(1):17-23.
This study was designed to determine the pharmacokinetic parameters of a new pharmaceutical form of artemisinin (a natural substance extracted from the Artemisia annua L. plant) and of one of its derivatives, artesunate, a semisuccinate of 12-hydroxy-artemisinin. These two compounds are widely used in the treatment of malaria. The new oral forms of these two compounds, in 250-mg tablets, were used in two parallel pharmacokinetic studies. For artemisinin, the mean pharmacokinetic parameters were maximum drug concentration (Cmax) = 0.36 microgram/ml; peak time (tmax) = 100 min; appearance half-life (t1/2 max) = 0.62 hr; distribution half-life (t1/2 alpha) = 2.61 hr; decline half-life (t1/2 beta) = 4.34 hr; and total area under the concentration-time curve (AUC) = 1.19 micrograms.hr/ml. For artesunate, its main metabolite, dihydroartemisinin, was measurable in the plasma. The mean pharmacokinetic parameters for dihydroartemisinin were appearance rate constant (Ka) = 2.11 hr-1; elimination rate constant (Ke) = 1.18 hr-1; biotransformation half-life = 0.33 hr; elimination half-life = 0.65 hr; and AUC = 0.74 microgram.hr/ml. Both pharmaceutical forms were well-tolerated and no undesirable side effects were observed in any of the subjects.

7778154
Benoit F, Valentin A, Pelissier Y, Marion C, Dakuyo Z, Mallie M, Bastide JM
Antimalarial activity in vitro of Cochlospermum tinctorium tubercle extracts.
Trans R Soc Trop Med Hyg. 1995 Mar-Apr;89(2):217-8.
Resistance of Plasmodium falciparum to current antimalarial compounds has drastically increased during the last few years and is now a major public health problem. We have studied plants traditionally used in Africa against malaria. Extracts of the tubercles of Cochlospermum tinctorium A. Rich, commonly used in Burkina Faso, were tested in vitro on 2 strains of P. falciparum, one (FcB1-Colombia) chloroquine resistant and the other (F32-Tanzania) chloroquine sensitive. Extracts were obtained by infusion and decoction. The 50% inhibitory concentrations (IC50) were determined by measuring [3H]hypoxanthine incorporation and also by microscopical examination which permitted the determination of parasite stages. We obtained similar results with fresh extracts, frozen extracts, and lyophilized extracts of C. tinctorum. IC50 values were of the order of 1-2 micrograms/mL, about one-tenth of those reported for extracts of neem leaves (Azadirachta indica) and about half the values reported for Artemisia annua extracts.

10991867
Benoit-Vical F, Robert A, Meunier B
In vitro and in vivo potentiation of artemisinin and synthetic endoperoxide antimalarial drugs by metalloporphyrins.
Antimicrob Agents Chemother. 2000 Oct;44(10):2836-41.
The in vitro potentiation of artemisinin by synthetic manganese porphyrin complexes has been recently reported (F. Benoit-Vical, A. Robert, and B. Meunier, Antimicrob. Agents Chemother. 43:2555-2558, 1999). Since the activity of artemisinin and synthetic antimalarial endoperoxides is related to their interaction with heme (S. R. Meshnick, A. Thomas, A. Ranz, C. M. Xu, and H. Z. Pan, Mol. Biochem. Parasitol. 49:181-190, 1991), an improvement of their efficiency may be expected in the presence of a synthetic metalloporphyrin having the same activating role as endogenous heme. With the aim to boost the activity of antimalarial endoperoxide drugs, we were thus led to evaluate the in vitro and in vivo potentiation of natural and synthetic drugs of this family by a nontoxic and cheap metalloporphyrin. The potentiation of artemisinin, beta-artemether, and arteflene (Ro 42-1611) by synthetic heme models is reported. In vitro studies on the chloroquine-resistant Plasmodium falciparum FcB1-Columbia strain indicate a synergistic effect of the manganese complex of meso-tetrakis(4-sulfonatophenylporphyrin) (Mn-TPPS) on the activity of artemisinin or beta-artemether, whereas this heme model has no influence on the activity of arteflene. A significant synergistic effect on rodent malaria was also observed in vivo between artemisinin and Mn-TPPS using Plasmodium vinckei petteri strain.

9705007
Benoit-Vical F, Valentin A, Cournac V, Pelissier Y, Mallie M, Bastide JM
In vitro antiplasmodial activity of stem and root extracts of Nauclea latifolia S.M. (Rubiaceae).

J Ethnopharmacol. 1998 Jul;61(3):173-8.
Aqueous extracts from Nauclea latifolia S.M. (Rubiaceae), a plant commonly used in Ivory Coast by traditional healers for the treatment of malaria, were tested on two strains of Plasmodium faliparum: FcB1-Colombia (chloroquine-resistant) and a Nigerian strain (chloroquine-sensitive). The extracts were obtained from stems and roots of the plant in two forms, infusion and decoction, both methods used by most traditional healers. The in vitro activity of N. latifolia extracts on P. falciparum was assessed both visually and by a radioactive method. The visual analysis allowed determination of the time of extract action on the erythrocytic cycle, as well as the parasitic stage of most inhibitory effect. Similar results were obtained applying fresh, frozen or lyophilized extracts. The IC50 values determined were within the range already reported for other antimalarial plants such as Azadirachta indica A. Juss (Meliaceae) or Artemisia annua L. (Asteraceae). Aqueous extracts of N. latifolia inhibited P. falciparum (FcB1 strain) mainly at the end of the erythrocytic cycle (32nd to 48th hour).

9534999
Berens RL, Krug EC, Nash PB, Curiel TJ
Selection and characterization of Toxoplasma gondii mutants resistant to artemisinin.
J Infect Dis. 1998 Apr;177(4):1128-31.
Toxoplasma gondii infection, like malaria, is sensitive to inhibition by artemisinin (ART). Mechanisms of action for ART in malaria treatment have been proposed, but little is known about its effects in T. gondii infection. To better understand its inhibitory effects on T. gondii, mutants resistant to ART were selected by progressive culture in permissive levels of the drug. Five clonal isolates were established and characterized. The isolates were approximately 65-fold less sensitive to ART than is the parental RH and showed cross-resistance to the ART derivatives dihydroartemisinin and artemether. In addition to ART resistance, 1 clone (C9) formed morphologically unusual parasitophorous vacuoles and another (A2) was avirulent for mice and protected mice from challenge with the wild type. These clonal T. gondii mutant isolates will be useful for the study of not only the mechanism of action of ART but also parasite vacuole biology and virulence factors.

16273263
Berger TG, Dieckmann D, Efferth T, Schultz ES, Funk JO, Baur A, Schuler G
Artesunate in the treatment of metastatic uveal melanoma--first experiences.
Oncol Rep. 2005 Dec;14(6):1599-603.
Artesunate (ART) is a derivative of artemisinin, the active principle of the Chinese herb Artemisia annua L. Artesunate is approved for the treatment of multidrug-resistant malaria and has an excellent safety profile. It has been shown that Artesunate, apart from its anti-malarial activity, has cytotoxic effects on a number of human cancer cell lines, including leukemia, colon cancer and melanoma. We report on the first long-term treatment of two cancer patients with ART in combination with standard chemotherapy. These patients with metastatic uveal melanoma were treated on a compassionate-use basis, after standard chemotherapy alone was ineffective in stopping tumor growth. The therapy-regimen was well tolerated with no additional side effects other than those caused by standard chemotherapy alone. One patient experienced a temporary response after the addition of ART to Fotemustine while the disease was progressing under therapy with Fotemustine alone. The second patient first experienced a stabilization of the disease after the addition of ART to Dacarbazine, followed by objective regressions of splenic and lung metastases. This patient is still alive 47 months after first diagnosis of stage IV uveal melanoma, a situation with a median survival of 2-5 months. Despite the small number of treated patients, ART might be a promising adjuvant drug for the treatment of melanoma and possibly other tumors in combination with standard chemotherapy. Its good tolerability and lack of serious side effects will facilitate prospective randomized trials in the near future.

8758072
Bethell DB, Phuong PT, Phuong CX, Nosten F, Waller D, Davis TM, Day NP, Crawley J, Brewster D, Pukrittayakamee S, White NJ
Electrocardiographic monitoring in severe falciparum malaria.
Trans R Soc Trop Med Hyg. 1996 May-Jun;90(3):266-9.
Electrocardiographic monitoring over 24 h was performed with 53 patients with severe Plasmodium falciparum malaria (11 adults and 42 children) to assess the frequency of unrecognized cardiac arrhythmias. Nine patients (17%) died, 5 during the monitoring period and 4 afterwards. Pauses lasting 2-3 s were observed in 3 children, a single couplet in one, and a further child experienced frequent supraventricular ectopic beats which had not been detected clinically. In none of the patients who died could death be attributed to cardiac arrhythmia. Furthermore, no abnormality was detected which could have resulted from the often large doses of quinine, chloroquine or the artemisinin derivatives used for treatment. These results suggest that the heart is remarkably resilient even in the face of heavy parasite sequestration and other vital organ dysfunction, and that deaths from cardiac arrhythmias in severe malaria are rare. The need for routine cardiac monitoring of patients with severe and complicated P. falciparum malaria is questionable.

9196768
Bethell DB, Teja-Isavadharm P, Cao XT, Pham TT, Ta TT, Tran TN, Nguyen TT, Pham TP, Kyle D, Day NP, White NJ
Pharmacokinetics of oral artesunate in children with moderately severe Plasmodium falciparum malaria.
Trans R Soc Trop Med Hyg. 1997 Mar-Apr;91(2):195-8.
The pharmacokinetic properties of oral artesunate (3 mg/kg) were determined in 10 Vietnamese children, aged from 6 to 15 years, with acute falciparum malaria of moderate severity. Plasma concentrations were measured using a bioassay and expressed in terms of antimalarial activity equivalent to dihydroartemisinin, the principal biologically active metabolite. Oral artesunate was absorbed rapidly with a mean time to peak plasma bioactivity of 1.7 h (95% confidence interval [95% CI] 0.8-2.6). There was wide variation in peak plasma concentrations with a mean value equivalent to 664 ng of dihydroartemisinin/mL (95% CI 387-9410, range 179-1395) and a four-fold variation in the area under the plasma concentration-time curves. Elimination from plasma was rapid with a mean (95% CI) half-life of 1.0 h (95% CI 0.8-1.4). Plasma antimalarial levels were below the limit of detection in all cases by 12 h, despite the relatively high dose of artesunate used. Oral artesunate is rapidly absorbed and rapidly eliminated in children with moderately severe malaria but there is considerable variation between individuals.

14522258
Bhasin VK, Nair L
ACT now--with caution--for malaria treatments.
Lancet Infect Dis. 2003 Oct;3(10):609.

15567117
Bhattarai A, Maini-Thapar M, Ali AS, Bjorkman A
Amodiaquine during pregnancy.
Lancet Infect Dis. 2004 Dec;4(12):721-2; discussion 722.

9632675
Bhisutthibhan J, Pan XQ, Hossler PA, Walker DJ, Yowell CA, Carlton J, Dame JB, Meshnick SR
The Plasmodium falciparum translationally controlled tumor protein homolog and its reaction with the antimalarial drug artemisinin.
J Biol Chem. 1998 Jun 26;273(26):16192-8.
Artemisinin and its derivatives are important new antimalarial drugs. When Plasmodium falciparum-infected erythrocytes are incubated with [10-3H]dihydroartemisinin, several malaria-specific proteins become labeled. One of these proteins is the P. falciparum translationally controlled tumor protein (TCTP) homolog. In vitro, dihydroartemisinin reacts covalently with recombinant TCTP in the presence of hemin. The association between drug and protein increases with increasing drug concentration, plateauing at approximately 1 drug/TCTP molecule. By Scatchard analysis, there appear to be 2 hemin binding sites on TCTP with dissociation constants of approximately 18 microM. When the single cysteine moiety is blocked by pretreatment with iodoacetamide, hemin binding is not affected, whereas drug binding is reduced by two-thirds. Thus, TCTP reacts with artemisinin in situ and in vitro in the presence of hemin and appears to bind to hemin. The function of the malarial TCTP and the role of this reaction in the mechanism of action of artemisinin await elucidation.

10535309
Bhisutthibhan J, Philbert MA, Fujioka H, Aikawa M, Meshnick SR
The Plasmodium falciparum translationally controlled tumor protein: subcellular localization and calcium binding.
Eur J Cell Biol. 1999 Sep;78(9):665-70.
Artemisinin derivatives are endoperoxide antimalarials widely used to treat falciparum malaria in areas where drug resistance is common. In Plasmodium falciparum-infected erythrocytes, radiolabeled artemisinin derivatives have been shown to react with malarial proteins, one of which is the Translationally Controlled Tumor Protein (TCTP). The P. falciparum TCTP was found by immunofluorescence to be located in both the cytoplasm and food vacuoles. Immunoelectron microscopy shows that it is present in the parasite cytoplasm as well as in its food vacuolar and limiting membranes. Like other TCTPs, the P. falciparum protein binds to calcium. Further studies on the physiological role of TCTP may aid in understanding the mechanism of action of endoperoxide antimalarials.

8916803
Bich NN, De Vries PJ, Van Thien H, Phong TH, Hung LN, Eggelte TA, Anh TK, Kager PA

Efficacy and tolerance of artemisinin in short combination regimens for the treatment of uncomplicated falciparum malaria.
Am J Trop Med Hyg. 1996 Oct;55(4):438-43.
Two oral regimens comprising a single dose of 20 mg/kg of artemisinin followed by three days of quinine, 10 mg/kg three times a day (AQ), or doxycycline, 4 mg/kg once a day (AD), were compared with a standard seven-day course of oral quinine, 10 mg/kg three times a day (Q), in the treatment of uncomplicated falciparum malaria. Of 161 treated patients, 157 could be included in the analysis. The mean +/- SD parasite clearance time was 43 +/- 14 hr for AQ and 41 +/- 19 hr for AD, and significantly longer for quinine: 66 +/- 24 hr (P = 0.0001). Treatment failure occurred in one Q and in 3 AD patients. The recrudescence rate was 16% for Q, 28% for AQ, and significantly worse for AD: 67% (P = 0.0001). Adverse effects were mainly limited to cinchonism. The conclusion is that a seven-day course of quinine is still effective in the initial treatment of uncomplicated falciparum malaria in Vietnam, but one should pay attention to possible recrudescence. The addition of a single 20 mg/kg per os dose of artemisinin allows for shortening the duration of treatment, with faster parasite clearance, comparable efficacy, and better tolerance, but with no reduction of recrudescence. The combination of artemisinin with three days of doxycycline is also not effective in preventing recrudescence.

11044263
Bijl HM, Kager J, Koetsier DW, van der Werf TS
Chloroquine- and sulfadoxine-pyrimethamine-resistant Falciparum malaria in vivo - a pilot study in rural Zambia.
Trop Med Int Health. 2000 Oct;5(10):692-5.
BACKGROUND: Chloroquine (CQ) and Sulfadoxine-Pyrimethamine (SP) are the predominantly used antimalarials in Zambia and other parts of East Africa, but increasing resistance of P. falciparum is a major concern. METHODS: Seventy consecutive patients with uncomplicated falciparum malaria were enrolled. In 43 patients, no prior CQ use could be demonstrated by history and urianalysis (qualitative test, Dill & Glazko) and these patients were given CQ; the other 27 had taken CQ before and received SP. RESULTS: Combined R-II and R-III CQ-resistance was 58% (60% in under-fives), which is the range previously reported from Zambia. By contrast, SP-resistance (R-II and R-III) was much higher (26%) than previously reported (3% - 17%). The history of prior CQ intake correlated well with the results of the Dill-Glazko test; there was no evidence for prior SP intake to explain these results. CONCLUSION: If our findings of SP resistance are confirmed, other drugs such as quinine, atovaquone/proguanil and artemisinin are required to treat malaria in Zambia.

11833740
Bilia AR, Lazari D, Messori L, Taglioli V, Temperini C, Vincieri FF
Simple and rapid physico-chemical methods to examine action of antimalarial drugs with hemin: its application to Artemisia annua constituents.
Life Sci. 2002 Jan 4;70(7):769-78.
Malaria is a major health problem in many countries and according to an estimate of the WHO, more than 500 million infections occur per year. Artemisinin, a sesquiterpene from Artemisia annua L., has received considerable attention as a promising and potent antimalarial drug for its stage speciticity, its rather low toxicity, effectiveness against drug-resistant Plasmodium species and activity against cerebral malaria. From recent studies it seems that hemin is primarily involved in the antimalarial activity of the constituents of Artemisia annua L. Thus, the interaction of a compound with hemin may represent a crucial screening test to define its efficacy. In this study the interaction between artemisinin and hemin was investigated by UltraViolet/Visible (UV/Vis) spectrophotometry and High Performance Liquid Chromatography/Diode Array Detector/Mass Spectrometry (HPLC/DAD/MS). In addition, some flavonols isolated from Artemisia annua L. were also tested to investigate their possible role in the interaction between artemisinin and hemin. These two simple physico-chemical methods can be useful as rapid and widespread screening methods for the search of other alkylating antimalarial constituents from natural sources or for the evaluation of the activity of semisynthetic analogues of artemisinin.

11422013
Binh TQ, Ilett KF, Batty KT, Davis TM, Hung NC, Powell SM, Thu LT, Thien HV, Phuong HL, Phuong VD
Oral bioavailability of dihydroartemisinin in Vietnamese volunteers and in patients with falciparum malaria.
Br J Clin Pharmacol. 2001 Jun;51(6):541-6.
AIMS: To obtain comprehensive bioavailability data for artesunate (ARTS) and its active metabolite dihydroartemisinin (DHA) following their separate oral administration to Vietnamese volunteers and to patients with acute, uncomplicated falciparum malaria. METHODS: Volunteers were randomized to receive either i.v. ARTS (120 mg) followed by oral ARTS (150 mg) 8 h later (Group 1, n = 10), or i.v. ARTS (120 mg) followed by oral DHA (120 mg) 8 h later. Patients, also received oral ARTS (150 mg; Group 3, n = 8) or DHA

(120 mg; Group 2, n = 7), in a randomized cross-over study design. Multiple blood samples were collected after each administration and plasma ARTS and/or DHA concentrations were determined by h.p.l.c. Pharmacokinetic descriptors were obtained from noncompartmental analysis and bioavailability was calculated from AUC data. In the patients, the time to 50% parasite clearance (PCT50) and fever clearance time (FCT) also were measured. RESULTS: In Group 1 (volunteers), the mean (95% CI) absolute bioavailability of oral ARTS was 80% (62,98%), while in Group 2 (volunteers), the bioavailability of oral DHA was 45% (34,56%). In the patients (Group 3), the bioavailability of oral DHA relative to oral ARTS was 88% (49,127%). The median PCT50 and FCT were 2.3 and 28 h, respectively. CONCLUSIONS: The study shows that the absolute bioavailability of DHA was significantly lower than that for ARTS in healthy volunteers. The bioavailability of ARTS in volunteers was consistent with previous studies in patients with uncomplicated falciparum malaria. The dose-normalized Cmax and AUC(0,infinity) for DHA were significantly greater in patients with falciparum malaria than in healthy volunteers. The high relative bioavailability of DHA in the patients may have been due to lower first-pass clearance. We conclude that, for the treatment of malaria, DHA is likely to be a suitable oral substitute for ARTS. Based on our mean AUC measurements, it appears that equal doses of DHA and ARTS (mg basis) should give equivalent systemic exposure to bioactive DHA in uncomplicated falciparum malaria.

10442116
Birku Y, Makonnen E, Bjorkman A
Comparison of rectal artemisinin with intravenous quinine in the treatment of severe malaria in Ethiopia.
East Afr Med J. 1999 Mar;76(3):154-9.
OBJECTIVE: To compare the clinical efficacy and safety of artemisinin suppository with quinine injection. DESIGN: Comparative open randomised study. SETTING: A government regional referral hospital in Ethiopia. SUBJECTS: Sixty five adult patients of both sexes: 32 for artemisinin and 33 for quinine with complicated severe falciparum malaria. MAIN OUTCOME MEASURES: Therapeutic responses and adverse reactions. RESULTS: The clinical and laboratory data in both groups of patients on admission were comparable. The parasite clearance time (PCT), fever subsidence time (FST) and coma resolution time (CRT) were shorter in the artemisinin treated group. There was no significant different in the parasitological cure rates in both arms of treatment. No correlation was observed between the initial parasite density and PCT or FST in both groups of treatment. Mortality rates were similar both in the artemisinin and quinine groups. The common adverse effects observed in most patients receiving quinine, in an increasing order of occurrence were; vomiting, dizziness, hypoglycaemia and tinnitus, which were all relatively rare with artemisinin. Some patients treated with artemisinin showed tenesmus which was not observed in any patient treated with quinine. CONCLUSION: The rectal artemisinin is more efficacious and safer than the intravenous quinine. Thus, artemisinin may be considered a potential drug which can replace quinine in the treatment of severe malaria in Ethiopia provided it is made available at affordable prices.

12802828
Birku Y, Mekonnen E, Bjorkman A, Wolday D
Delayed clearance of Plasmodium falciparum in patients with human immunodeficiency virus co-infection treated with artemisinin.
Ethiop Med J. 2002 Apr;40 Suppl 1:17-26.
We investigated the effect of artemisinin on the rate of clearance of Plasmodium falciparum in patients with or without human immunodeficiency virus (HIV) co-infection. Initial mean (+/- SEM) parasite density was not different between HIV-infected and HIV-uninfected groups (27,486 +/- 2,643 versus 32,892 +/- 6,583, respectively; P = 0.55). The mean (+/- SEM) time to clear 75% and 90% of the parasites was 23.1 hr +/- 1.8 and 29.3 hr +/- 1.9, respectively, for the HIV seropositive patients compared with 16.0 hr +/- 1.4 and 20.8 hr +/- 1.4, respectively for the HIV seronegative patients (P = 0.0075 and 0.0026, respectively). By 32 hr, almost all (6/7) HIV positive patients remained parasitemic in contrast with 2/12 HIV seronegative patients. Moreover, the mean parasite density was almost 12-fold higher in the HIV seropositive patients than in the HIV seronegative patients at the same period (1789 +/- 616 versus 150 +/- 118, respectively; P = 0.0037). Overall, the mean parasite clearance time was 37.7 hr +/- 2.1 in the HIV seropositive group and 30.0 hr +/- 2.1 in those who were HIV seronegative (P = 0.0284). Whereas mean fever clearance time was 40.6 hr +/- 2.4 for the HIV seropositive group, it was 28.7 hr +/- 1.2 for those who were HIV seronegative (P = 0.0001). These observations are compatible with the hypothesis that the host's immunity affects the activity of antimalarial drugs, and our data suggest for the first time that clearance of P. falciparum after administration of artemisinin is delayed in patients with HIV co-infection.

15893289
Bjorkman A, Bhattarai A
Public health impact of drug resistant Plasmodium falciparum malaria.
Acta Trop. 2005 Jun;94(3):163-9.

The alarming increase in Plasmodium falciparum resistance to commonly used anti-malarial drugs represents a major public health threat. The impact is however difficult to quantify. In low transmission areas, an increase in acute manifestations ("epidemic") is often quickly apparent and resistance is rapidly propagated due to high drug pressure on existing parasite populations. In high transmission areas, the clinical effects are mainly prolonged/chronic infections with increasing risk of severe anemia. Mortality estimates from public health records in Africa generally suggest significant increases (from 2- to 11-fold) in malaria-associated mortality among children when resistance develops and spreads. Hospital attendances and admissions show similar trends. Change of policy to alternative efficacious treatment with radical cure is necessary at an earlier stage (from 10% treatment failure) than previously assumed in order to prevent deaths in millions of African children. Early switch to artemisinin based combination therapy (ACT) represents such a critical and urgent strategy.

16504002
Blair S, Carmona-Fonseca J, Pineros JG, Rios A, Alvarez T, Alvarez G, Tobon A
Therapeutic efficacy test in malaria falciparum in Antioquia, Colombia.
Malar J. 2006 Feb 20;5:14.
OBJECTIVE: Evaluate the frequency of failure of eight treatments for non-complicated malaria caused by Plasmodium falciparum in patients from Turbo (Uraba region), El Bagre and Zaragoza (Bajo Cauca region), applying the 1998 protocol of the World Health Organization (WHO). Monotherapies using chloroquine (CQ), amodiaquine (AQ), mefloquine (MQ) and sulphadoxine-pyrimethamine (SP), and combinations using chloroquine-sulphadoxine-pyrimethamine (CQ-SP), amodiaquine-sulphadoxine-pyrimethamine (AQ-SP), mefloquine-sulphadoxine-pyrimethamine (MQ-SP) and artesunate-sulphadoxine-pyrimethamine (AS-SP), were examined. METHODOLOGY: A balanced experimental design with eight groups. Samples were selected based on statistical and epidemiological criteria. Patients were followed for 21 to 28 days, including seven or eight parasitological and clinical evaluations, with an active search for defaulting patients. A non-blinded evaluation of the antimalarial treatment response (early failure, late failure, adequate response) was performed. RESULTS: Initially, the loss of patients to follow-up was higher than 40%, but the immediate active search for the cases and the monetary help for transportation expenses of patients, reduced the loss to 6%. The treatment failure was: CQ 82%, AQ 30%, MQ 4%, SP 24%, CQ-SP 17%, AQ-SP 2%, MQ-S-P 0%, AS-SP 3%. CONCLUSION: The characteristics of an optimal epidemiological monitoring system of antimalarial treatment response in Colombia are discussed. It is proposed to focus this on early failure detection, by applying a screening test every two to three years, based on a seven to 14-day follow-up. Clinical and parasitological assessment would be carried out by a general physician and a field microscopist from the local hospital, with active measures to search for defaulter patients at follow-up.

11196485
Bloland PB, Ettling M, Meek S
Combination therapy for malaria in Africa: hype or hope?
Bull World Health Organ. 2000;78(12):1378-88. Epub 2003 Nov 17.
The development of resistance to drugs poses one of the greatest threats to malaria control. In Africa, the efficacy of readily affordable antimalarial drugs is declining rapidly, while highly efficacious drugs tend to be too expensive. Cost-effective strategies are needed to extend the useful life spans of antimalarial drugs. Observations in South-East Asia on combination therapy with artemisinin derivatives and mefloquine indicate that the development of resistance to both components is slowed down. This suggests the possibility of a solution to the problem of drug resistance in Africa, where, however, there are major obstacles in the way of deploying combination therapy effectively. The rates of transmission are relatively high, a large proportion of asymptomatic infection occurs in semi-immune persons, the use of drugs is frequently inappropriate and ill-informed, there is a general lack of laboratory diagnoses, and public health systems in sub-Saharan Africa are generally weak. Furthermore, the cost of combination therapy is comparatively high. We review combination therapy as used in South-East Asia and outline the problems that have to be overcome in order to adopt it successfully in sub-Saharan Africa.

11512657
Blum PG, Stephens D
Severe falciparum malaria in five soldiers from East Timor: a case series and literature review.
Anaesth Intensive Care. 2001 Aug;29(4):426-34.
Despite chemoprophylaxis, malaria remains a serious threat for large numbers of non-immune soldiers deployed in endemic areas. Five adult cases of severe falciparum malaria are reported. Three cases were complicated by multiorgan failure and one of these patients died from cerebral malaria. These cases serve to highlight issues, in an Australian intensive care unit, associated with the management of severe malaria, an uncommon disease in our country. The need for rapid diagnosis and commencement of appropriate treatment is paramount in preventing further morbidity and mortality. Understanding and management of malaria continues to evolve rapidly. The pathophysiology of acute lung injury, shock and brain injury

associated with malaria are examined in light of recent research. This article discusses the current controversies of exchange blood transfusion and the use of the new artemisinin derivatives.

10784269
Bodeker G
Searching for antimalarials in plants.
J Altern Complement Med. 2000 Apr;6(2):127-9.

10212901
Boele van Hensbroek M
The role of the qinghaosu derivatives in the treatment of severe malaria.
Med Trop (Mars). 1998;58(3 Suppl):59-60.
Over the past years, several studies have been published comparing artemisinin (qinghaosu) derivatives with quinine in the treatment of children and adults with severe malaria. Due to a lower than expected mortality rate in the control (quinine) groups and a small difference in mortality between the artemether and quinine treated groups, none of the studies has reached statistic significance. An attempt to combine the various studies in an overview (meta-analysis) using the raw individual patient data is in process. This paper summarises the differences between artemether and quinine with respect to important outcome measurements in severe malaria using the published studies.

16456051
Bohannon J
Arata Kochi profile. Fighting words from WHO's new malaria chief.
Science. 2006 Feb 3;311(5761):599.

7477532
Bont L, Schepel N, de Vries P, Kager PA
[Malaria in a changed health care system in Vietnam]
Ned Tijdschr Geneeskd. 1995 Sep 23;139(38):1928-31.
OBJECTIVE. To determine how and where malaria was diagnosed in a forestry area in South-Vietnam and how it was treated. DESIGN. Descriptive. SETTING. Hieu Liem, Dong Nai province, Vietnam. METHOD. In the government hospital and health posts malaria diagnosis and treatment were free of charge while treatment had to be paid for in four private clinics. A population survey was carried out in the forestry area and outside this area: the people were examined for splenic enlargement and a blood sample was analysed. RESULTS. Most patients went to private clinics and it was here that malaria was most frequently diagnosed. In 7.5% of the population in the forest area parasites were found while 1.8% of those living outside the forest appeared to have parasites in the blood. None of the persons with parasitaemia had splenomegaly. Splenomegaly was found in 2.9% of the population, 6.7% in and 0.9% outside the forest area. CONCLUSION. Recent changes in the health sector in Vietnam have liberalized malaria treatment, possibly control. The wide distribution and extensive use of effective drugs like artesunate and mefloquine have probably contributed to reduction of (severe) malaria, but development of resistance to these drugs is to be feared. Control of drug distribution and of prescription practices is urgently needed.

12604519
Borrmann S, Adegnika AA, Missinou MA, Binder RK, Issifou S, Schindler A, Matsiegui PB, Kun JF, Krishna S, Lell B, Kremsner PG
Short-course artesunate treatment of uncomplicated Plasmodium falciparum malaria in Gabon.
Antimicrob Agents Chemother. 2003 Mar;47(3):901-4.
Artesunate is one of the most important antimalarial agents available, since it is effective against parasites that have developed resistance to conventional antimalarials in sub-Saharan Africa. Antimalarial combination chemotherapies with artesunate (4 mg/kg of body weight once daily for 3 days) as one partner have been proposed. However, the efficacy of a 3-day course of artesunate alone has never been evaluated in individuals in Africa (which has 90% of the worldwide malaria burden) living in regions of hyperendemicity, where a considerable degree of immunity might substantially enhance the efficacy of short courses of artesunate compared to those in regions where the levels of endemicity are low. This lack of information does not permit a systematic assessment of the value of artesunate-based combination chemotherapies in Africa. Therefore, we studied the efficacy and safety of a 3-day course of artesunate (4 mg/kg of body weight, orally, once daily) for the treatment of uncomplicated Plasmodium falciparum malaria in Gabonese patients aged 4 to 15 years (n = 50). Artesunate was well tolerated, and no severe adverse event was reported. Parasite elimination was rapid and was achieved in all patients within < or =72 h (geometric mean

time to elimination, 34 h). The PCR-corrected cure rate by day 14 was 92% (46 of 50 patients), but it dropped to 72% (36 of 50 patients) by day 28. We conclude that a 3-day course of artesunate fails to achieve sufficiently high cure rates for uncomplicated falciparum malaria in Gabonese children.

16127049
Borrmann S, Adegnika AA, Moussavou F, Oyakhirome S, Esser G, Matsiegui PB, Ramharter M, Lundgren I, Kombila M, Issifou S, Hutchinson D, Wiesner J, Jomaa H, Kremsner PG
Short-course regimens of artesunate-fosmidomycin in treatment of uncomplicated Plasmodium falciparum malaria.
Antimicrob Agents Chemother. 2005 Sep;49(9):3749-54.
Fosmidomycin is effective against malaria, but it needs to be given for > or =4 days when used alone. We conducted a study of 50 children with Plasmodium falciparum malaria to evaluate the safety and efficacy of consecutively shortened regimens of artesunate-fosmidomycin (1 to 2 mg/kg of body weight and 30 mg/kg of body weight, respectively; doses given every 12 hours). All dosing regimens were well tolerated. Artesunate-fosmidomycin acted rapidly, resulting in consolidated geometric mean parasite and fever clearance times of 24 h and 15 h, respectively. Treatment regimens of > or =2 days led to cure ratios of 100% by day 14 (39/39; 95% confidence interval [95% CI], 91% to 100%). Most importantly, the 3-day regimen achieved 100% cure on day 28 (10/10; 95% CI, 69% to 100%). Treatment with artesunate-fosmidomycin was associated with transient grade I or II neutropenia (absolute neutrophil counts of 750 to 1,200/microl and 400 to 749/microl, respectively) in six or two patients, respectively. Artesunate-fosmidomycin demonstrates the feasibility and potential value of short-course artemisinin-based combination chemotherapy with rapidly eliminated combination partners.

12407136
Borrmann S, Szlezak N, Binder RK, Missinou MA, Lell B, Kremsner PG
Evidence for the efficacy of artesunate in asymptomatic Plasmodium malariae infections.
J Antimicrob Chemother. 2002 Nov;50(5):751-4.
This study evaluated the efficacy and safety of a 3-day course of artesunate (4 mg/kg/day) for asymptomatic Plasmodium malariae infections. The parasitological cure rates on days 7 and 56 in the group treated with artesunate were 100% and 83%, respectively, compared with no cure in the placebo group (P < 0.0001).

12435451
Borstnik K, Paik IH, Shapiro TA, Posner GH
Antimalarial chemotherapeutic peroxides: artemisinin, yingzhaosu A and related compounds.
Int J Parasitol. 2002 Dec 4;32(13):1661-7.
Mechanism-based rational design and gram-scale chemical synthesis have produced some new trioxane and endoperoxide antimalarial drug candidates that are efficacious and safe. This review summarises recent achievements in this area of peroxide drug development for malaria chemotherapy.

11800303
Bounyasong S
Randomized trial of artesunate and mefloquine in comparison with quinine sulfate to treat P. falciparum malaria pregnant women.
J Med Assoc Thai. 2001 Sep;84(9):1289-99.
To compare the effectiveness and safety of quinine sulfate and artesunate with mefloquine for treating second trimester pregnancy in women who suffered from Plasmodium falciparum malaria. The prospective study was done in Srisangwal Hospital, Mae Hong Son, Thailand. Sixty, second to third trimester pregnant patients with P. falciparum infection, were recruited at random. They received either quinine sulfate 10 mg/kg/day for at least 7 days, 29 women (group I), or oral artesunate 2 mg/kg as the first dose, 1 mg/kg every 12 hours orally for at least 5 days together with split doses of mefloquine, 15 mg/kg and 6 hours later 10 mg/kg orally 1 day after artesunate was stopped, 28 women (group II). Three cases (5%) were lost to follow-up before delivery, one case in group I and two cases in group II. After treatment, the mean hematocrit of group I was significantly less than group II (p = 0.000). The PCT (parasite clearance time) and FCT (fever clearance time) of group II were significantly shorter than group I (p = 0.000). None of the patients in both groups had recrudescences within 28 days. Group I had more adverse effects than group II. No adverse neurological effects in pregnancy were found in both groups. The calcification of placenta and IUGR (Intrauterine growth retard) were not different between the two groups (p = 0.964, 0.363 respectively). The PCT was not different between the calcified placenta group and normal placenta group (p = 0.058), but the TTPP (Total time of parasite presentation) was (p = 0.000). TTPP related to low birth weight and low apgar score at 1 minute might be the cause (p = 0.000, 0.000 F = 5.261, 21.627 respectively). TTPP and PCT related to neonatal blood pH and caused low neonatal blood pH (p = 0.000, 0.001 F = 24.351, 11.162 respectively). The physical and neurological development of the babies at 2, 4, 6 and 12 months follow-up, were normal and there were no congenital abnormalities in either group. TTPP relating to fetal outcome, the

longer the TTPP, the worse the fetal outcome, so we should diagnose early and treat P. falciparum malaria in pregnancy to prevent fetal jeopardy. Artesunate with mefloquine could shorten the PCT more than quinine sulfate in pregnancy, so the fetal outcome was better than that of quinine sulfate. In cases of prolonged infection before treatment, artesunate might be the alternative treatment of P. falciparum malaria in pregnancy. However, its safety should be carefully studied further with a larger sample size.

10078393
Bourgeade A, Delmont J
[The proper use of antimalarial drugs currently available]
Bull Soc Pathol Exot. 1998;91(5 Pt 1-2):493-6.
French medical practitioners have at their disposal several antimalarial drugs for giving chemoprophylaxis to people travelling to a malaria endemic country or treating an imported malaria case in a patient. The choice depends on the contre-indications and indications of each drug, essentially subordinated to the presence and level of Plasmodium falciparum chemosensitivity in the visited area. For prevention, chloroquine alone can be taken in the areas where P. falciparum is absent or not chloroquine resistant; elsewhere, the choice between chloroquine/proguanil or mefloquine depends on knowing the prevalence and level of falciparum chloroquine resistance in these areas. For treatment, the only indications of chloroquine are imported malaria cases either due to P. vivax, P. ovale or P. malariae, or caused by P. falciparum contracted in one of the rare countries where the species is still sensitive to chloroquine. For uncomplicated falciparum malaria cases acquired in a chemoresistance area, mefloquine, halofantrine, sulfadoxine-pyrimethamine or oral quinine is selected, depending on the observed chemoprophylaxis, the contra-indications and the suspicion of chemoresistance type. Whatever the provenance area, P. falciparum in a patient with one or several serious symptoms or possibly profuse vomiting is treated by intravenous quinine, associated with tetracycline if the patient comes from an area known for a low quinine sensitivity of this species. The spectrum of falciparum malaria treatment has recently broadened to include new drugs such as artemisinin, artemether or atovaquone/proguanil, the latter being as yet unauthorized in France.

10626375
Bouwmeester HJ, Wallaart TE, Janssen MH, van Loo B, Jansen BJ, Posthumus MA, Schmidt CO, De Kraker JW, Konig WA, Franssen MC
Amorpha-4,11-diene synthase catalyses the first probable step in artemisinin biosynthesis.
Phytochemistry. 1999 Nov;52(5):843-54.
The endoperoxide sesquiterpene lactone artemisinin and its derivatives are a promising new group of drugs against malaria. Artemisinin is a constituent of the annual herb Artemisia annua L. So far only the later steps in artemisinin biosynthesis--from artemisinic acid--have been elucidated and the expected olefinic sesquiterpene intermediate has never been demonstrated. In pentane extracts of A. annua leaves we detected a sesquiterpene with the mass spectrum of amorpha-4,11-diene. Synthesis of amorpha-4,11-diene from artemisinic acid confirmed the identity. In addition we identified several sesquiterpene synthases of which one of the major activities catalysed the formation of amorpha-4,11-diene from farnesyl diphosphate. This enzyme was partially purified and shows the typical characteristics of sesquiterpene synthases, such as a broad pH optimum around 6.5-7.0, a molecular mass of 56 kDa, and a K(m) of 0.6 microM. The structure and configuration of amorpha-4,11-diene, its low content in A. annua and the high activity of amorpha-4,11-diene synthase all support that amorpha-4,11-diene is the likely olefinic sesquiterpene intermediate in the biosynthesis of artemisinin.

15470761
Bradbury J
Synthetic antimalaria drug enters clinical trials.
Lancet Infect Dis. 2004 Oct;4(10):598.

16265885
Bray PG, Ward SA, O'Neill PM
Quinolines and artemisinin: chemistry, biology and history.
Curr Top Microbiol Immunol. 2005;295:3-38.
Plasmodium falciparum is the most important parasitic pathogen in humans, causing hundreds of millions of malaria infections and millions of deaths each year. At present there is no effective malaria vaccine and malaria therapy is totally reliant on the use of drugs. New drugs are urgently needed because of the rapid evolution and spread of parasite resistance to the current therapies. Drug resistance is one of the major factors contributing to the resurgence of malaria, especially resistance to the most affordable drugs such as chloroquine. We need to fully understand the antimalarial mode of action of the existing drugs and the way that the parasite becomes resistant to them in order to design and develop the new therapies that are so

urgently needed. In respect of the quinolines and artemisinins, great progress has been made recently in studying the mechanisms of drug action and drug resistance in malaria parasites. Here we summarize from a historical, biological and chemical, perspective the exciting new advances that have been made in the study of these important antimalarial drugs.

15331814
Breman JG, Alilio MS, Mills A
Conquering the intolerable burden of malaria: what's new, what's needed: a summary.
Am J Trop Med Hyg. 2004 Aug;71(2 Suppl):1-15.
Each year, up to three million deaths due to malaria and close to five billion episodes of clinical illness possibly meriting antimalarial therapy occur throughout the world, with Africa having more than 90% of this burden. Almost 3% of disability adjusted life years are due to malaria mortality globally, 10% in Africa. New information is presented in this supplement on malaria-related perinatal mortality, occurrence of human immunodeficiency virus in pregnancy, undernutrition, and neurologic, cognitive, and developmental sequelae. The entomologic determinants of transmission and uses of modeling for program planning and disease prediction and prevention are discussed. New data are presented from the Democratic Republic of the Congo, Tanzania, Ethiopia, and Zimbabwe on the increasing urban malaria problem and on epidemic malaria. Between 6% and 28% of the malaria burden may occur in cities, which comprise less than 2% of the African surface. Macroeconomic projections show that the costs are far greater than the costs of individual cases, with a substantial deleterious impact of malaria on schooling of patients, external investments into endemic countries, and tourism. Poor populations are at greatest risk; 58% of the cases occur in the poorest 20% of the world's population and these patients receive the worst care and have catastrophic economic consequences from their illness. This social vulnerability requires better understanding for improving deployment, access, quality, and use of effective interventions. Studies from Ghana and elsewhere indicate that for every patient with febrile illness assumed to be malaria seen in health facilities, 4-5 episodes occur in the community. Effective actions for malaria control mandate rational public policies; market forces, which often drive sales and use of drugs and other interventions, are unlikely to guarantee their use. Artemisinin-based combination therapy (ACT) for malaria is rapidly gaining acceptance as an effective approach for countering the spread and intensity of Plasmodium falciparum resistance to chloroquine, sulfadoxine/pyrimethamine, and other antimalarial drugs. Although costly, ACT ($1.20-2.50 per adult treatment) becomes more cost-effective as resistance to alternative drugs increases; early use of ACT may delay development of resistance to these drugs and prevent the medical toll associated with use of ineffective drugs. The burden of malaria in one district in Tanzania has not decreased since the primary health care approach replaced the vertical malaria control efforts of the 1960s. Despite decentralization, this situation resulted, in part, from weak district management capacity, poor coordination, inadequate monitoring, and lack of training of key staff. Experience in the Solomon Islands showed that spraying with DDT, use of insecticide-treated bed nets (ITNs), and health education were all associated with disease reduction. The use of nets permitted a reduction in DDT spraying, but could not replace it without an increased malaria incidence. Baseline data and reliable monitoring of key outcome indicators are needed to measure whether the ambitious goals for the control of malaria and other diseases has occurred. Such systems are being used for evidence-based decision making in Tanzania and several other countries. Baseline cluster sampling surveys in several countries across Africa indicate that only 53% of the children with febrile illness in malarious areas are being treated; chloroquine (CQ) is used 84% of the time, even where the drug may be ineffective. Insecticide-treated bed nets were used only 2% of the time by children less than five years of age. Progress in malaria vaccine research has been substantial over the past five years; 35 candidate malaria vaccines are in development, many of which are in clinical trials. Development of new vaccines and drugs has been the result of increased investments and formation of public-private partnerships. Before malaria vaccine becomes deployed, consideration must be given to disease burden, cost-effectiveness, financing, delivery systems, and approval by regulatory agencies. Key to evaluation of vaccine effectiveness will be collection and prompt analysis of epidemiologic information. Training of persons in every aspect of malaria research and control is essential for programs to succeed. The Multilateral Initiative on Malaria (MIM) is actively promoting research capacity strengthening and has established networks of institutions and scientists throughout the African continent, most of whom are now linked by modern information-sharing networks. Evidence over the past century is that successful control malaria programs have been linked to strong research activities. To ensure effective coordination and cooperation between the growing number of research and control coalitions forming in support of malaria activities, an umbrella group is needed. With continued support for scientists and control workers globally, particularly in low-income malarious countries, the long-deferred dream of malaria elimination can become a reality.

11132385
Brockman A, Price RN, van Vugt M, Heppner DG, Walsh D, Sookto P, Wimonwattrawatee T, Looareesuwan S, White NJ, Nosten F

Plasmodium falciparum antimalarial drug susceptibility on the north-western border of Thailand during five years of extensive use of artesunate-mefloquine.
Trans R Soc Trop Med Hyg. 2000 Sep-Oct;94(5):537-44.
Following a marked decline in the efficacy in vivo of mefloquine between 1990 and 1994, a combination of artesunate (4 mg/kg/d for 3 d) and mefloquine (25 mg/kg) has been used as first line treatment of uncomplicated falciparum malaria in camps for displaced persons located along the north-western border of Thailand. Antimalarial drug susceptibility of fresh isolates of Plasmodium falciparum from this population was evaluated using a radioisotope microdilution assay between 1995 and 1999. In total, 268 isolates were collected, of which 189 were from primary infections and 79 from recrudescent infections. The geometric mean 50% inhibitory concentration (IC50) values from primary infections were: dihydroartemisinin 1.2 ng/mL, artesunate 1.6 ng/mL, artemether 4.8 ng/mL, atovaquone 0.4 ng/mL, lumefantrine 32 ng/mL, chloroquine 149 ng/mL, quinine 354 ng/mL, mefloquine 27 ng/mL and halofantrine 4.1 ng/mL. A significant positive correlation was found between the susceptibility in vitro to artesunate and quinine ($r = 0.43$, $P < 0.001$), mefloquine ($r = 0.46$, $P < 0.001$), and halofantrine ($r = 0.51$, $P < 0.001$). These levels of resistance in vitro are among the highest reported and confirm continuing high level multidrug resistance in this area. Despite intensive use of the combination between 1995 and 1999 there has been a significant improvement in mefloquine sensitivity ($P < 0.001$) and artesunate sensitivity ($P < 0.001$). This supports observations in vivo that the combination of artesunate and mefloquine has reversed the previous decline in mefloquine sensitivity.

3279208
Brossi A, Venugopalan B, Dominguez Gerpe L, Yeh HJ, Flippen-Anderson JL, Buchs P, Luo XD, Milhous W, Peters W
Arteether, a new antimalarial drug: synthesis and antimalarial properties.
J Med Chem. 1988 Mar;31(3):645-50.
Arteether (6) has been prepared from dihydroquinghaosu (3) by etherification with ethanol in the presence of Lewis acid and separated from its chromatographically slower moving alpha-dihydroqinghaosu ethyl ether (7). The absolute stereochemistry at C-12 has been determined by 1H NMR data (J11,12, NOESY). Ethyl ethers 6 and 7 showed potent in vitro inhibition of Plasmodium falciparum, and both compounds were highly potent antimalarials in mice infected with a drug-sensitive strain of Plasmodium berghei. Crystalline arteether (6) and its oily epimer 7 were 2-3 times more potent schizontocides than quinghaosu (1), but deoxy compounds 8, 9, and 11 were 100-300 times less potent in vitro than their corresponding peroxy precursors. Pharmacological studies have shown arteether(6) to have antimalarial activity in animals comparable to artesunate (2) and artemether (4), both of which are fast-acting blood schizontocides in humans. Arteether (6) has now been chosen for a clinical evaluation in high-risk malaria patients.

16384927
Buffet PA, Milon G, Brousse V, Correas JM, Dousset B, Couvelard A, Kianmanesh R, Farges O, Sauvanet A, Paye F, Ungeheuer MN, Ottone C, Khun H, Fiette L, Guigon G, Huerre M, Mercereau-Puijalon O, David PH
Ex-vivo perfusion of human spleens maintains clearing and processing functions.
Blood. 2005 Dec 29;.
The spleen plays a central role in the pathophysiology of several potentially severe diseases such as inherited red cell membrane disorders, hemolytic anemias and malaria. Research on these diseases is hampered by ethical constraints that limit human spleen tissue explorations. We identified a surgical situation - left spleno-pancreatectomy for benign pancreas tumours - allowing spleen retrieval at no risk for patients. Ex-vivo perfusion of retrieved intact spleens during 4-6 hours preserved parenchymal structure, vascular flow and metabolic activity. Function preservation was assessed by testing the ability of isolated-perfused spleens to retain Plasmodium falciparum - infected erythrocytes pre-exposed to the antimalarial drug artesunate (Art-iRBCs). More than 95% of Art-iRBCs were cleared from the perfusate in 2 hours. At each transit through isolated-perfused spleens, parasite remnants were removed from 0.2% - 0.23% of Art-iRBCs, a proportion consistent with the 0.02% - 1% pitting rate previously established in artesunate-treated patients. Histological analysis showed that > 90% of Art-iRBCs were retained and processed in the red pulp, providing the first direct evidence of a zone-dependent parasite clearance by the human spleen. Human-specific physiological or pathophysiological mechanisms involving clearing or processing functions of the spleen can now be experimentally explored in a human tissue context.

16437507
Bukirwa H, Critchley J
Sulfadoxine-pyrimethamine plus artesunate versus sulfadoxine-pyrimethamine plus amodiaquine for treating uncomplicated malaria.
Cochrane Database Syst Rev. 2006 Jan 25;(1):CD004966.

BACKGROUND: Artemisinin-based combination treatments are strongly advocated, but supplies are limited. Sulfadoxine combined with amodiaquine is an alternative non-artemisinin combination. OBJECTIVES: To compare sulfadoxine-pyrimethamine plus amodiaquine (SP plus AQ) with sulfadoxine-pyrimethamine plus artesunate (SP plus AS) for treating uncomplicated Plasmodium falciparum malaria. SEARCH STRATEGY: We searched the Cochrane Infectious Diseases Group Specialized Register (October 2005), CENTRAL (The Cochrane Library 2005, Issue 4), MEDLINE (1966 to October 2005), EMBASE (1988 to October 2005), LILACS (October 2005), and reference lists. We also contacted researchers and organizations working in this field. SELECTION CRITERIA: Randomized controlled trials comparing SP plus AS with SP plus AQ for treating uncomplicated P. falciparum malaria. DATA COLLECTION AND ANALYSIS: Two authors independently applied the inclusion criteria, extracted data, and assessed methodological quality. The primary outcome measure was treatment failure (parasitological or clinical evidence of treatment failure between start of treatment and day 28). We calculated the relative risk (RR) with 95% confidence intervals (CI) for dichotomous data. MAIN RESULTS: Four trials (775 participants) met the inclusion criteria. All were from areas of high and seasonal malaria transmission in Africa. Fewer participants using SP plus AQ failed treatment by day 28 (RR 0.59, 95% CI 0.42 to 0.83; 652 participants, 3 trials). Even excluding new infections, SP plus AQ performed better (RR 0.62, 95% CI 0.40 to 0.96; 649 participants, 3 trials). There was no statistically significant difference between the two treatments for treatment failure at day 14 (RR 1.14, 95% CI 0.47 to 2.78; 775 participants, 4 trials). SP plus AS was more effective at reducing gametocyte carriage at day seven (RR 2.31, 95% CI 1.36 to 3.92; 220 participants, 1 trial). One trial reported that one person - in the SP plus AQ group - developed severe malaria. Adverse events were poorly reported, but did not seem to differ in type and number between the two treatment combinations. AUTHORS' CONCLUSIONS: SP plus AQ performed better at controlling treatment failure at day 28, but was not as good as SP plus AS at reducing gametocyte carriage at day seven. Careful consideration of local resistance patterns is required because resistance to sulfadoxine-pyrimethamine and amodiaquine are high in many areas. In order to delay development of resistance to artesunate, the combination with sulfadoxine-pyrimethamine should only be considered where both drugs are known to be effective. Data on adverse events are still lacking.

16235367
Bukirwa H, Orton L
Artesunate plus mefloquine versus mefloquine for treating uncomplicated malaria.
Cochrane Database Syst Rev. 2005 Oct 19;(4):CD004531.
BACKGROUND: Multiple-drug-resistant malaria is widespread, and in South-East Asia resistance is high against nearly all single therapy antimalarial drugs. Here, and in other areas with low malaria transmission, the combination of artesunate and mefloquine may provide an effective alternative. OBJECTIVES: To compare artesunate plus mefloquine with mefloquine alone for treating uncomplicated Plasmodium falciparum malaria. SEARCH STRATEGY: We searched the Cochrane Infectious Diseases Group Specialized Register (May 2005), CENTRAL (The Cochrane Library Issue 2, 2005), MEDLINE (1966 to May 2005), EMBASE (1988 to May 2005), LILACS (May 2005), BIOSIS (1985 to June 2005), conference proceedings, and reference lists. We also contacted researchers, organizations, and pharmaceutical companies. SELECTION CRITERIA: Randomized and quasi-randomized controlled trials comparing artesunate plus mefloquine with mefloquine alone for treating uncomplicated malaria. DATA COLLECTION AND ANALYSIS: Two authors independently applied the inclusion criteria, extracted data, and assessed methodological quality. The primary outcome was treatment failure by day 28, defined as evidence of parasitaemia with or without clinical failure between days zero (start of treatment) and 28. For dichotomous data we calculated relative risks (RR) and 95% confidence intervals (CI). MAIN RESULTS: Eight trials involving 1996 participants met the inclusion criteria. All were conducted in areas with low malaria transmission, seven in South-East Asia and one in the Peruvian Amazon. The doses and dosing regimens of artesunate and mefloquine varied across trials. The trials using a total dose of 25 mg/kg mefloquine and 10 mg artesunate reported fewer treatment failures with the combination at all time points: day 28 (RR 0.17, 95% CI 0.06 to 0.47; 824 participants, 4 trials), day 42 (RR 0.23, 95% CI 0.14 to 0.39; 298 participants, 1 trial), and day 63 (RR 0.26, 95% CI 0.09 to 0.77; 501 participants, 2 trials). The results for parasitaemia showed a similar trend. Trials using a lower dose of artesunate tended to favour the artesunate plus mefloquine combination. Overall, adverse events were similar across treatment arms. AUTHORS' CONCLUSIONS: Artesunate plus mefloquine performs better than mefloquine alone for treating uncomplicated falciparum malaria in areas with low malaria transmission. A total dose of 25 mg/kg mefloquine and at least 10 mg artesunate leads to higher cure rates. Better reporting of methods and standardisation of outcomes would help the interpretation of future trials.

8882193
Bunnag D, Kanda T, Karbwang J, Thimasarn K, Pungpak S, Harinasuta T
Artemether or artesunate followed by mefloquine as a possible treatment for multidrug resistant falciparum malaria.

Trans R Soc Trop Med Hyg. 1996 Jul-Aug;90(4):415-7.
Plasmodium falciparum in south-east Asia is highly resistant to chloroquine and sulfadoxine-pyrimethamine. Mefloquine used to be the chemosuppressant drug of choice in areas with chloroquine resistance. However, sensitivity to this drug has recently decreased in Thailand, Cambodia and Myanmar, and there is no suitable single alternative drug. We therefore investigated possible alternative combination therapies for multidrug resistant falciparum malaria. 120 male Thai patients at Makarm Malaria Clinic, Chantaburi, in eastern Thailand were allocated at random to receive either oral artemether (group A) or artesunate (group B) at a single dose of 300 mg on day 1, both followed by mefloquine, 750 and 500 mg at 24 and 30 h, respectively. Follow-up was on days 1, 2, 7, 14, 21, 28, 35 and 42. Patients in both groups had a rapid initial response to treatment; in most cases parasitaemia was cleared within 24 h, and fever was cleared within 24 h in 62% and 76.7% of the patients in groups A and B, respectively. 58 patients in group A and 57 in group B completed follow-up and cure rates were 98% and 97%, respectively. Reinfection could not be excluded for the 3 patients with recrudescences; all were cured with a repeated course of treatment. No serious adverse effect was observed in either group, only mild and transient nausea, vomiting and loss of appetite, with no significant difference between the 2 groups. These results suggest that a single oral dose of 300 mg of either artemether or artesunate followed by 1250 mg of mefloquine in 2 divided doses is effective against multiple drug resistant falciparum malaria. Either regimen can be considered as a suitable 'stand-by' in endemic areas of multiple drug resistant falciparum malaria.

9656393
Bunnag D, Kanda T, Karbwang J, Thimasarn K, Pungpak S, Harinasuta T
Two doses of artemether/mefloquine or artesunate/mefloquine combination for multidrug resistant falciparum Malaria.
Southeast Asian J Trop Med Public Health. 1997 Dec;28(4):727-30.
Plasmodium falciparum in Southeast Asia is highly resistant to chloroquine, sulfadoxine/ pyrimethamine, quinine and even mefloquine. The use of two doses of short course artemether/mefloquine combination has been shown to be effective in a recent study. In the present study, we have assessed the efficacy of short course treatment with artesunate/mefloquine, in comparison with artemether/mefloquine in patients with multidrug resistant falciparum malaria. Ninety-nine Thai male patients who sought consultation at Makham Malaria Clinic, Chantaburi (eastern part of Thailand), were randomized to receive either the combination of artemether (150 and 100 mg; group A) or artesunate (150 and 100 mg; group B) with mefloquine (750 and 500 mg) at 24 hours apart. The follow-up was on days 1, 2, 7, 14, 21, 28, 35 and 42. Patients in both groups showed a rapid initial response to treatment; fever and parasite were cleared within 48 hours in 100 and 100% vs 91.8 and 96%, for group A vs B, respectively. All patients in group A had completed the 42 day-follow up; however, two patients in group B did not finish the 42-day follow-up. The cure rate was 100% in either group. No serious adverse effects were found. Artemether or artesunate with mefloquine given two doses at 24 hours apart can be used as effective alternative treatment regimens for multidrug resistant falciparum malaria.

1818389
Bunnag D, Viravan C, Looareesuwan S, Karbwang J, Harinasuta T
Clinical trial of artesunate and artemether on multidrug resistant falciparum malaria in Thailand. A preliminary report.
Southeast Asian J Trop Med Public Health. 1991 Sep;22(3):380-5.
A 5-day course of oral artesunate at total doses of 1200, 600, 650 mg and intramuscular artemether 480 mg proved effective (90-100% cured) in the treatment of multidrug resistant falciparum malaria in Thailand. Shorter courses yielded high recrudescence rates. The fever clearance and parasite clearance times were short. The side effects were mild and transient including occasional abnormal electrocardiograms and pain at the injection site. Slight reduction of neutrophil leucocytes and reticulocytes was observed. Further studies of artesunate and artemether should be carried out to find the optimum dosage regimen and to clarify the hematological effects.

1820641
Bunnag D, Viravan C, Looareesuwan S, Karbwang J, Harinasuta T
Double blind randomised clinical trial of oral artesunate at once or twice daily dose in falciparum malaria.
Southeast Asian J Trop Med Public Health. 1991 Dec;22(4):539-43.
A double blind randomised comparative trial of the efficacy of daily dose (200 mg as an initial dose followed by 100 mg daily for another 4 days) and twice daily dose (100 mg 12 hourly for 2 doses on the first day, followed by 50 mg 12 hourly for another 8 doses) regimens of oral artesunate at 600 mg was studied in 59 Thai patients with uncomplicated falciparum malaria. Fifty patients had a complete 28-day follow-up period. Both regimens produced similar efficacy with no difference in adverse effects. The patients with the daily artesunate regimen had mean fever and parasite clearance times of 20 and 40 hours, respectively. The cure rate was 72%. Eight patients had recrudescence during days 15 to 28 while 8 showed P. vivax in their

peripheral blood between days 12 and 21. The patients with the twice daily regimen had mean fever and parasite clearance time of 28 and 40 hours, respectively. The cure rate was 76%. Six patients had recrudescence during days 15 and 27 while 7 showed P. vivax during days 12 and 23. We suggest that the duration of the treatment may be a more important factor determining the efficacy of artesunate rather than the frequency of the doses. Further studies based on pharmacokinetics are therefore needed to improve the cure rate to 100% to prevent the spread of P. falciparum, particularly in areas where there are high numbers of multi-drug resistant strains.

1820640
Bunnag D, Viravan C, Looareesuwan S, Karbwang J, Harinasuta T
Double blind randomised clinical trial of two different regimens of oral artesunate in falciparum malaria.
Southeast Asian J Trop Med Public Health. 1991 Dec;22(4):534-8.
A double blind randomized comparative trial of the efficacy of 7-day and 5-day courses of oral artesunate at 600 mg was studied in 89 Thai patients with uncomplicated falciparum malaria. Eighty patients completed the 28-day follow-up period. Artesunate was found to be well tolerated in either regimen. There was an increase of 7% in the cure rate obtained from a 7-day regimen. In 43 patients with a 7-day regimen, the cure rate was 92.5% and 15 patients showed P. vivax in their peripheral blood between days 12 and 34. The mean fever and parasite clearance times were 20 and 40 hours, respectively. In 46 patients with a 5-day regimen, the cure rate was 85% and 8 patients showed P. vivax during days 13 and 24. The mean fever and parasite clearance times were 29 and 40 hours, respectively. Although the cure rates of oral artesunate were high in both regimens, the efficacy was considered unsatisfactory since the aim of the treatment is to achieve 100% cure rate. We suggest however that the extension of the duration of treatment to 7 days together with the increase in total dose may improve therapeutic efficacy of artesunate in falciparum malaria.

7606866
Burgmann H, Hollenstein U, Wenisch C, Thalhammer F, Looareesuwan S, Graninger W
Serum concentrations of MIP-1 alpha and interleukin-8 in patients suffering from acute Plasmodium falciparum malaria.
Clin Immunol Immunopathol. 1995 Jul;76(1 Pt 1):32-6.
The chemokines are a superfamily of small proteins secreted primarily by leukocytes and related by a conserved four-cystein motif. In the present study we investigated the serum levels of macrophage inflammatory protein 1 alpha (MIP-1 alpha) and interleukin-8 (IL-8). MIP-1 alpha is a neutrophil chemotactic protein important in acute and chronic inflammation. Recent studies demonstrated that MIP-1 alpha may also act as potent inhibitor of hemopoetic stem cell proliferation, which may be important in the development of prolonged anemia in patients suffering from Plasmodium falciparum malaria. IL-8 serum concentrations correlate with severity and outcome of infectious diseases. Moreover, recent reports indicate that IL-8 plays a major role in fatal gram-negative sepsis. It was the aim of this study to investigate the time course of MIP-1 alpha and IL-8 concentrations in patients suffering from acute P. falciparum infection. Blood samples of 20 patients suffering from severe P. falciparum malaria were investigated. MIP-1 alpha and IL-8 concentrations were determined using ELISA technique at admission, on Days 7, 14, 21, and 28. Maximal concentrations of MIP-1 alpha and IL-8 were found on Day 14, at a time when parasites were not detected in the smears. The serum levels of IL-8 on the day of admission were correlated to the parasite count. No correlation was seen between the hematokrit values and the MIP-1 alpha concentrations at any time.

8886997
Burgmann H, Looareesuwan S, Viravan C, Vanijanonta S, Zedwitz-Liebenstein K, Vorbach H, Graninger W
Serum laminin and basic fibroblast growth factor concentrations in patients with complicated Plasmodium falciparum malaria.
J Clin Immunol. 1996 Sep;16(5):278-82.
Serum concentrations of laminin and basic fibroblast growth factor (FGF) were measured in 20 patients suffering from complicated Plasmodium falciparum malaria in Bangkok. Significant higher mean serum concentrations of laminin were determined prior to treatment (1973 ng/ml) and 7 days after starting medication (1025 ng/ml) in comparison to the control (412 ng/ml). The values remained numerically higher for at least 21 days. With regard to serum basic FGF concentrations, a peak was found 7 day after starting treatment (35.61 pg/ml). In addition, a significant correlation was found for parasite clearance time and basic FGF concentration on day 7 ($P < 0.01$). These increased values of laminin and basic FGF may be the consequence of endothelial and basement membrane damage induced by sequestration of the parasites. Furthermore, basic FGF might play a role in endothelial repair mechanisms after the clearance of the parasites.

15761118

Burk O, Arnold KA, Nussler AK, Schaeffeler E, Efimova E, Avery BA, Avery MA, Fromm MF, Eichelbaum M
Antimalarial artemisinin drugs induce cytochrome P450 and MDR1 expression by activation of xenosensors pregnane X receptor and constitutive androstane receptor.
Mol Pharmacol. 2005 Jun;67(6):1954-65. Epub 2005 Mar 10.
Artemisinin drugs are of utmost importance in the treatment of malaria, because they represent the sole class of therapeutically used antimalarial drugs to which malaria parasites have not yet developed resistance. The major disadvantage of these medicines is the comparatively high recrudescence rate, which has been attributed to the remarkable decrease of artemisinin plasma concentrations during multiple dosing. Autoinduction of CYP2B6-mediated metabolism has been implicated as the underlying mechanism. So far, the molecular mechanism of induction by artemisinin has not been resolved. Because the xenosensors pregnane X receptor (PXR) and constitutive androstane receptor (CAR) have been shown to mediate induction of drug-metabolizing enzymes and drug transporters, we investigated the hypothesis that artemisinin induces cytochrome P450 expression by activating PXR and/or CAR. By combining in vitro transfection methods and quantitative analyses of gene expression in cell lines and primary human hepatocytes, we here show that artemisinin drugs activate human PXR as well as human and mouse CAR and induce the expression of CYP2B6, CYP3A4, and MDR1 in primary human hepatocytes and in the human intestinal cell line LS174T. Furthermore, we demonstrate that artemisinin acts as a ligand of both nuclear receptors, because it modulates the interaction of the receptors with coregulators. In conclusion, activation of PXR and CAR and especially the resulting induction of CYP3A4 and MDR1 demonstrate that artemisinin has a higher risk of potential drug interactions than anticipated previously.

15190315
Butler D
Global fund changes tack on malaria therapy.
Nature. 2004 Jun 10;429(6992):588.

16289651
Campbell P, Baruah S, Narain K, Rogers CC
A randomized trial comparing the efficacy of four treatment regimens for uncomplicated falciparum malaria in Assam state, India.
Trans R Soc Trop Med Hyg. 2006 Feb;100(2):108-18. Epub 2005 Nov 14.
A four-arm drug sensitivity study compared chloroquine, sulfadoxine-pyrimethamine (SP), mefloquine and mefloquine-artesunate in Sonitpur and Karbi Anglong districts in Assam state, India. Two criteria were used to ascertain outcome: success of clinical treatment and parasitologic cure. In Sonitpur, at 14 days, there were 36/56 early and late treatment failures plus late parasitologic failures to chloroquine and 16/56 for SP. In Karbi Anglong, combined treatment failure at 14 days was 16/56 to chloroquine and 8/60 to SP. Mefloquine and mefloquine-artesunate demonstrated 93.9% and 93.6% sustained responses respectively at 42 days. High failure rates to both chloroquine and SP preclude the use of these drugs as first-line treatment for uncomplicated falciparum malaria in this region. A mefloquine-artesunate combination presents an effective alternative utilizing the currently recommended higher dose of mefloquine.

11231359
Campos SB, Rouch LH, Seguro AC
Effects of sodium artesunate, a new antimalarial drug, on renal function.
Kidney Int. 2001 Mar;59(3):1044-51.
BACKGROUND: Sodium artesunate is currently used in malaria treatment. Adverse effects of this drug have not been described, probably because they cannot be differentiated from malaria-related effects. METHODS: The effects on renal function of an acute infusion of sodium artesunate (12 mg/kg body weight) were studied in the rat with clearance techniques. We also evaluate the effect of sodium artesunate on chloride lumen-bath flux (Cl Jlb) in the isolated thick ascending limb of the loop of Henle (TALH) microperfused in vitro. RESULTS: Acute infusion of artesunate to the rat decreased inulin clearance, despite an increase in renal blood flow. These effects were associated with an increase in urinary excretion of sodium, chloride, potassium, and nitric oxide metabolites (NO(2)/NO(3)). In water-loaded animals, artesunate increased sodium and water distal delivery and decreased free water clearance (C(H(2)O)) factored for sodium and water delivery. Following hypertonic NaCl infusion, artesunate decreased free water excretion (Tc(H(2)O)) corrected by clearance of osmolarity (C(Osm)). In vitro, artesunate 10(-6) and 10(-3) mol/L added to bath solution decreased chloride lumen-bath flux in isolated rabbit TALH in a dose-dependent manner, with the threshold effect at 10(-4) mol/L. This effect was completely blocked by N(G)-nitroL-arginine-metilester (L-NAME) 5 mmol/L. Artesunate 10(-4) mol/L added to the perfusion solution did not change Cl Jlb. CONCLUSION: These findings suggest that artesunate decreases glomerular filtration rate and increases

renal blood flow and urinary excretion of Na, Cl, and K. These effects were due, at least in part, to the inhibition of Cl transport across cortical and medullary TALH, and were mediated by local production of nitric oxide, since it is associated with an increase in NO(2)/NO(3) urinary excretion and it is blocked by L-NAME in vitro.

9231212
Cao XT, Bethell DB, Pham TP, Ta TT, Tran TN, Nguyen TT, Pham TT, Nguyen TT, Day NP, White NJ
Comparison of artemisinin suppositories, intramuscular artesunate and intravenous quinine for the treatment of severe childhood malaria.
Trans R Soc Trop Med Hyg. 1997 May-Jun;91(3):335-42.
Severe malaria remains a major cause of mortality and morbidity for children living in many tropical regions. With the emergence of strains of Plasmodium falciparum resistant to both chloroquine and quinine, alternative antimalarial agents are required. The artemisinin group of compounds are rapidly effective in severe disease when given by intramuscular or intravenous injection. However, these routes of administration are not always available in rural areas. In an open, randomized comparison 109 Vietnamese children, aged between 3 months and 14 years, with severe P.falciparum malaria, were allocated at random to receive artemisinin suppositories followed by mefloquine (n = 37), intramuscular artesunate followed by mefloquine (n = 37), or intravenous quinine followed by pyrimethamine/sulfadoxine (n = 35). There were 9 deaths: 2 artemisinin, 4 artesunate and 5 quinine-treated children. There was no difference in fever clearance time, coma recovery, or length of hospital stay among the 3 groups. However, parasite clearance times were significantly faster in artemisinin and artesunate-treated patients than in those who received quinine ($P < 0.0001$). Both artemisinin and artesunate were very well tolerated, but children receiving these drugs had lower peripheral reticulocyte counts by day 5 of treatment than those in the quinine group ($P = 0.011$). No other adverse effect or toxicity was found. There was no treatment failure in these 2 groups, but 4 patients in the quinine group failed to clear their parasites within 7 d of starting treatment and required alternative antimalarial therapy. Artemisinin suppositories are easy to administer, cheap, and very effective for treating children with severe malaria. In rural areas where medical facilities are lacking these drugs will allow antimalarial therapy to be instituted earlier in the course of the disease and may therefore save lives.

8701045
Cardoso Bda S, Dourado HV, Pinheiro Mda C, Crescente JA, Amoras WW, Baena J, Saraty S
[An efficacy and tolerance study of oral artesunate alone and in combination with mefloquine in the treatment of uncomplicated falciparum malaria in an endemic area of Para, Brazil]
Rev Soc Bras Med Trop. 1996 May-Jun;29(3):251-7.
With the objective to evaluate the efficacy and tolerance of artesunate in the treatment of noncomplicated falciparum malaria in endemic area of the State of Para, 153 patients were randomized and studied in three groups, distributed by therapeutical scheme (I received mefloquine 1000 mg, II used artesunate 600 mg followed by mefloquine 500 mg). Evaluation was made by daily clinical and parasitological examination, in the first 7 days, and weekly until the 35th day of the follow-up. Biochemical and hematological analysts previously done and on the 7th day, targeting cure control and identification of possible effects related to drugs administration. As to sex, parasitemia and fever, studied groups were homogeneous. Time for parasitemia disappearance was shorter in the groups II and III respectively, whose therapeutical schemes had artesunate. Fever disappearance was quicker in the group treated with the combination of drugs. Clinical and biochemical alterations associated with drugs administration did not show significant differences among the studied groups. Early disappearance of fever and parasitemia, and absence of important side effects suggest that artesunate, isolated or administrated in combination with mefloquine, constitutes an able therapeutical procedure to constitutes and able therapeutical procedure to contribute for disease control in that region.

12807291
Carson CF, Riley TV
Non-antibiotic therapies for infectious diseases.
Commun Dis Intell. 2003;27 Suppl:S143-6.
The emergence of multiple antibiotic resistant organisms in the general community is a potentially serious threat to public health. The emergence of antibiotic resistance has not yet prompted a radical revision of antibiotic utilisation. Instead it has prompted the development of additional antibiotics. Unfortunately, this does not relieve the underlying selection pressure that drives the development of resistance. A paradigm shift in the treatment of infectious disease is necessary to prevent antibiotics becoming obsolete and, where appropriate, alternatives to antibiotics ought to be considered. There are already several non-antibiotic approaches to the treatment and prevention of infection including probiotics, phages and phytomedicines. There is some evidence that probiotics such as Lactobacillus spp. or Saccharomyces boulardii are useful in the prevention and treatment of diarrhoea, including Clostridium difficile-associated diarrhoea that can be difficult to treat and recurs frequently. Bacteriophages have received renewed attention for the control of both

staphylococcal and gastrointestinal infections. Phytomedicines that have been utilised in the treatment of infections include artesunate for malaria, tea tree oil for skin infections, honey for wound infections, mastic gum for Helicobacter pylori gastric ulcers and cranberry juice for urinary tract infections. Many infections may prove amenable to safe and effective treatment with non-antibiotics.

12641400
Cattamanchi A, Kyabayinze D, Hubbard A, Rosenthal PJ, Dorsey G
Distinguishing recrudescence from reinfection in a longitudinal antimalarial drug efficacy study: comparison of results based on genotyping of msp-1, msp-2, and glurp.
Am J Trop Med Hyg. 2003 Feb;68(2):133-9.
Genotyping frequently is used to distinguish recrudescent from new infections in antimalarial drug efficacy trials, but methodology and interpretation of results have not been standardized. We compared the utility of polymorphisms within 3 Plasmodium falciparum genes during a longitudinal trial in Kampala, Uganda. Merozoite surface protein-1 (msp-1) and merozoite surface protein-2 (msp-2) revealed greater diversity than glutamate-rich protein. Genotypes based on msp-1, msp-2, and all 3 genes combined were compared for 394 initial and subsequent isolates. Classification of most episodes as due to recrudescence or reinfection was straightforward. In 24% (msp-1), 16% (msp-2), and 62% (3 genes combined) of samples, subsequent episodes contained identical and new alleles, however. Our analysis suggested that such episodes should be classified as reinfections and not recrudescence. Comparing the 3 studied genes, msp-2 results were most accurate, and analysis of this single gene effectively distinguished recrudescence from reinfection in our study population.

15906639
Chanthap L, Tsuyuoka R, Na-Bangchang K, Nivanna N, Suksom D, Sovannarith T, Socheat D
Investigation of bioavailability, pharmacokinetics and safety of new pediatric formulations of artesunate and mefloquine.
Southeast Asian J Trop Med Public Health. 2005 Jan;36(1):34-43.
The bioavailability/pharmacokinetics of dihydroartemisinin and mefloquine following the oral doses of 4 mg/kg body weight artesunate (Cambodian Pharmaceutical Enterprise) given concurrently with 10 mg/kg body weight oral mefloquine artesunate (Cambodian Pharmaceutical Enterprise) were investigated in 15 healthy Cambodian male volunteers. Both formulations were generally well tolerated. Both produced satisfactory plasma/blood concentration-time profiles. Oral artesunate and mefloquine were rapidly absorbed from gastrointestinal tract with marked inter-individual variation. For the dihydroartemisinin, the median (95% CI) Cmax of 748 (304-1,470) ng/ml was observed at 1.5 (0.3-3.0) hours (tmax) after drug administration. The median (95% CI) values for AUC0-infinity, lambda(z) and tl/2z were 1.673 (1.08-2.88) microg.h/ml, 0.54(0.24-1.1)/hour and 1.3 (0.6-2.9) hours, respectively. For mefloquine, a median (95% CI) Cmax of 1,000 (591-1,500) ng/ml was observed at 4 (2-6) hours (tmax) after drug administration. The median (95% CI) value for AUC0-168h was 3.92 (2.88-7.02) microg.h/ml.

15324729
Charlwood D
The paradox of home management of malaria with artemisinin combinations.
Trends Parasitol. 2004 Sep;20(9):405-6.

8705840
Chaudhury RR
A closer look at malaria in India.
Nat Med. 1996 Aug;2(8):833.

3541309
Chawira AN, Warhurst DC, Peters W
Qinghaosu resistance in rodent malaria.
Trans R Soc Trop Med Hyg. 1986;80(3):477-80.
Resistance to qinghaosu (artemisinin) developed rapidly in a chloroquine-resistant line of Plasmodium yoelii (NS) passaged in mice, but was not produced in chloroquine-sensitive P. berghei. Development of resistance took place in an apparently stepwise fashion. After removal of drug selection pressure some resistance was lost which was regained rapidly within three passages when drug pressure was reapplied. The resistant QS line was cross-resistant to two reduced derivatives of artemisinin but not to propoxycarbonyl dihydroartemisinin or artesunate. No significant resistance was shown against primaquine, pyrimethamine, cycloguanil or pyrimethamine-sulphadoxine, but resistance to chloroquine was enhanced

and marked resistance to quinine, mefloquine and amodiaquine was noted. It is suggested that the unusual cross-resistance pattern of the strain relates to changes in membrane characteristics.

3328341
Chawira AN, Warhurst DC, Robinson BL, Peters W
The effect of combinations of qinghaosu (artemisinin) with standard antimalarial drugs in the suppressive treatment of malaria in mice.
Trans R Soc Trop Med Hyg. 1987;81(4):554-8.
Artemisinin is a novel antimalarial drug isolated in China from the wormwood plant Artemisia annua L. Studies with rodent malaria were carried out to detect antagonism and synergism with a variety of antimalarial drugs. Isobolograms of drug interaction were plotted at the ED90 level. With a normally susceptible strain of Plasmodium berghei, marked potentiative synergism was found with mefloquine, tetracycline and spiramycin. There was some synergism also with primaquine. Combinations of artemisinin with dapsone, sulfadiazine, sulfadoxine, pyrimethamine, pyrimethamine/sulfadoxine and cycloguanil showed antagonism. A high degree of potentiation was shown between artemisinin and primaquine with a primaquine-resistant strain, whilst the combination with mefloquine showed enhanced potentiation with a mefloquine-resistant strain. Combinations of artemisinin with mefloquine, primaquine, tetracycline or clindamycin showed marked potentiation with an artemisinin-resistant strain. The mechanisms underlying the drug interactions observed are discussed.

12625148
Checchi F, Balkan S, Vonhm BT, Massaquoi M, Biberson P, Eldin de Pecoulas P, Brasseur P, Guthmann JP
Efficacy of amodiaquine for uncomplicated Plasmodium falciparum malaria in Harper, Liberia.
Trans R Soc Trop Med Hyg. 2002 Nov-Dec;96(6):670-3.
In the face of spreading chloroquine and sulfadoxine-pyrimethamine (SP) resistance, amodiaquine remains a cheap and efficacious alternative for treating uncomplicated Plasmodium falciparum malaria in many settings. In Harper, south-eastern Liberia, a previous study we conducted showed very high levels of resistance to both chloroquine and SP. In 2001, in an effort to look for possible alternatives, we measured in the same setting the efficacy of amodiaquine in a 28-d study in vivo, with results corrected by polymerase chain reaction genotyping to distinguish recrudescences from reinfections. In total, 107 children were included in the study and received a 3-d supervised course of 25 mg/kg amodiaquine. Of these, 81 were analysable at day 28. The overall failure rate was 19.8% (95% CI 11.7-30.1%) considering both parasitological and clinical outcomes. These results provide hitherto missing data on amodiaquine in Liberia, and confirm that the drug may still be efficacious in settings where chloroquine and SP are failing. We recommend the introduction of amodiaquine in association with artesunate as a first-line antimalarial in Harper.

15078262
Checchi F, Piola P, Kosack C, Ardizzoni E, Klarkowski D, Kwezi E, Priotto G, Balkan S, Bakyaita N, Brockman A, Guthmann JP
Antimalarial efficacy of sulfadoxine-pyrimethamine, amodiaquine and a combination of chloroquine plus sulfadoxine-pyrimethamine in Bundi Bugyo, western Uganda.
Trop Med Int Health. 2004 Apr;9(4):445-50.
We report below an in vivo antimalarial efficacy study conducted in 2002 in Bundi Bugyo, a district of western Uganda housing a large displaced population. We tested sulfadoxine-pyrimethamine (SP), amodiaquine (AQ) and the combination chloroquine plus SP (CQ + SP). A total of 268 children with uncomplicated Plasmodium falciparum malaria were followed-up for 28 days according to WHO recommendations, with PCR genotyping to distinguish late recrudescences from re-infections. PCR-adjusted failure proportions at day 28 were 37.0% (34/92, 95% CI 27.1-47.7) in the SP group, 20.6% (14/68, 95% CI 11.7-32.1) in the AQ group and 22.8% (18/79, 95% CI 14.1-33.6) in the CQ + SP group. Early failures were particularly frequent in the SP group (15.2%). Clearance of gametocytes was slower in the SP and CQ + SP groups than in the AQ group. This study suggests that, in Bundi Bugyo, CQ + SP (Uganda's first-line regimen) will need to be replaced by a more efficacious regimen. Across Uganda, the deployment of SP containing combinations may not be a feasible long-term strategy. For Bundi Bugyo, we recommend a combination of artesunate and AQ. Our study also confirms previous findings that resistance is considerably underestimated by 14-day follow-ups. Antimalarial policy decisions should therefore be based on 28-day studies, with PCR adjustment to distinguish re-infections.

15679557
Checchi F, Roddy P, Kamara S, Williams A, Morineau G, Wurie AR, Hora B, Lamotte N, Baerwaldt T, Heinzelmann A, Danks A, Pinoges L, Oloo A, Durand R, Ranford-Cartwright L, Smet M

Evidence basis for antimalarial policy change in Sierra Leone: five in vivo efficacy studies of chloroquine, sulphadoxine-pyrimethamine and amodiaquine.
Trop Med Int Health. 2005 Feb;10(2):146-53.
OBJECTIVES: To provide nationally relevant information on the antimalarial efficacy of chloroquine (CQ), sulphadoxine-pyrimethamine (SP) and amodiaquine (AQ) in Sierra Leone, with a view to updating antimalarial policy in the country. METHODS: Between October 2002 and May 2003, standard WHO methodology for in vivo efficacy assessment was used in five sites to study the therapeutic response of 6-59 months old uncomplicated Plasmodium falciparum malaria cases treated with CQ (n = 247), SP (n = 353) or AQ (n = 434). Follow-up was of 28 days, with polymerase chain reaction genotyping to distinguish late recrudescences from re-infections. RESULTS: Overall 85.3% of patients reached an analysable endpoint. CQ failure proportions were very high, ranging from 39.5% (95% CI: 25.0-55.6) in Kabala to 78.8% (65.3-88.9) in Kailahun. Early failures under CQ were frequent. SP efficacy was also disappointing, with failure from 23.2% (13.9-34.9) in Kabala to 46.1% (35.4-57.0) in Kailahun. AQ resistance was more moderate, ranging from 5.4% (1.8-12.1) in Makeni to 29.8% (20.3-40.8) in Kailahun, with almost no early failures. AQ also provided more rapid fever and parasite clearance. CONCLUSION: In a consensus meeting organized by the Ministry of Health and Sanitation, and based on these findings, artesunate (AS) + AQ and artemether-lumefantrine (Coartemtrade mark) were identified as the only options to rapidly replace CQ. The choice fell on AS + AQ because of expected high efficacy, lower cost in a blister presentation, and the absence of safety data on artemether-lumefantrine in pregnancy. Donor support is required to support this policy change. Throughout Africa, as SP resistance increases, these two regimens are probably the only options available while newer combinations are developed. Efficacy studies should focus on testing AQ and AS + AQ.

11677770
Chen L, Li G, Lu Y, Luo Z
Histopathological changes of Macaca mulatta infected with Plasmodium knowlesi.
Chin Med J (Engl). 2001 Oct;114(10):1073-7.
OBJECTIVE: To study the histopathological changes of relevant internal organs of Macaca mulatta infected with Plasmodium knowlesi (P. knowlesi). METHODS: Histopathological examination of 3 monkeys who died of P. knowlesi infection, 2 P. knowlesi infected monkeys who died of treatment failure with artesunate suppository and 1 P. knowlesi infected monkey that was cured by piperaquine phosphate (PQP) but died of trauma and necrosis of the fore limb. RESULTS: The heart, liver, spleen, lung, kidney, brain, pancreas, parathyroid, pituitary and lymph nodes showed severe pathological changes in 3 monkeys (No. 1, 7 and 12) who died of P. knowlesi infection and 1 infected monkey (No. 72) who died of treatment failure with artesunate suppository. Red blood cells containing malarial parasites and pigments were concentrated in the capillaries of these organs. Malarial pigments were deposited in many organs or phagocytized by macrophages in 1 monkey (No. 131), it was cured by piperaquine phosphate but died of trauma and necrosis of the fore limb; cellular atrophy and disappearance of pancreatic islets, parathyroid and pituitary cells were also observed. One monkey (No. 33) treated with artesunate suppository, showed that blood parasites became negative but recrudesced and pituitary later died from a gavage accident. Its organs showed a significant difference to those of the infected monkeys receiving no treatment. Only the liver Kupffer cells and cerebral matrix contained malarial parasites and pigments; many relevant internal organs showed repair. CONCLUSION: The pathological changes of relevant internal organs of Macaca mulatta infected with P. knowlesi were examined in detail, especially cellular atrophy and the disappearance of pancreatic islets, parathyroid and pituitary cells and myolysis of cardiac muscles. These changes have not previously been reported elsewhere.

12110308
Cheng F, Shen J, Luo X, Zhu W, Gu J, Ji R, Jiang H, Chen K
Molecular docking and 3-D-QSAR studies on the possible antimalarial mechanism of artemisinin analogues.
Bioorg Med Chem. 2002 Sep;10(9):2883-91.
Artemisinin (Qinghaosu) is a natural constituent found in Artemisia annua L, which is an effective drug against chloroquine-resistant Plasmodium falciparum strains and cerebral malaria. The antimalarial activities of artemisinin and its analogues appear to be mediated by the interactions of the drugs with hemin. In order to understand the antimalarial mechanism and the relationship between the physicochemical properties and the antimalarial activities of artemisinin analogues, we performed molecular docking simulations to probe the interactions of these analogues with hemin, and then performed three-dimensional quantitative structure-activity relationship (3-D-QSAR) studies on the basis of the docking models employing comparative molecular force fields analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA). Molecular docking simulations generated probable 'bioactive' conformations of artemisinin analogues and provided a new insight into the antimalarial mechanism. The subsequent partial least squares (PLS) analysis indicates that the calculate binding energies correlate well with the experimental activity values. The CoMFA and CoMSIA models based on the bioactive conformations proved to have good predictive ability and in turn

match well with the docking result, which further testified the reliability of the docking model. Combining these results, that is molecular docking and 3-D-QSAR, together, the binding model and activity of new synthesized artemisinin derivatives were well explained.

15228723
Chim P, Lim P, Sem R, Nhem S, Maciejewski L, Fandeur T
The in-vitro antimalarial activity of ferrochloroquine, measured against Cambodian isolates of Plasmodium falciparum.
Ann Trop Med Parasitol. 2004 Jun;98(4):419-24.

12932087
Chippaux JP, Le Hesran JY, Garcia A, Brasseur P
Recent studies have reported significant toxicity of artemisinin and its derivatives for schistosomula in various Schistosoma species.
Am J Trop Med Hyg. 2003 Jul;69(1):1; author reply 1-2.

15100453
Chotivanich K, Udomsangpetch R, Chierakul W, Newton PN, Ruangveerayuth R, Pukrittayakamee S, Looareesuwan S, White NJ
In vitro efficacy of antimalarial drugs against Plasmodium vivax on the western border of Thailand.
Am J Trop Med Hyg. 2004 Apr;70(4):395-7.
The susceptibility of 20 isolates of Plasmodium vivax on the Thailand-Myanmar border to seven antimalarial drugs was evaluated using the schizont maturation inhibition technique. The geometric mean 50% inhibition concentration (IC(50)) values were quinine = 308 ng/mL, amodiaquine =14 ng/mL, chloroquine =50 ng/mL, mefloquine = 127 ng/mL, sulfadoxine/pyrimethamine (80:1) = 800/10 ng/mL, pyrimethamine = 8 ng/mL, and artesunate = 0.5 ng/mL. Compared with P. falciparum in this area, P. vivax was more sensitive to chloroquine and artesunate, equally sensitive to quinine, and more resistant to mefloquine.

10915102
Chotivanich K, Udomsangpetch R, Dondorp A, Williams T, Angus B, Simpson JA, Pukrittayakamee S, Looareesuwan S, Newbold CI, White NJ
The mechanisms of parasite clearance after antimalarial treatment of Plasmodium falciparum malaria.
J Infect Dis. 2000 Aug;182(2):629-33. Epub 2000 Jul 28.
Studies were conducted to determine how malaria parasites are cleared from the blood after antimalarial treatment. Neither artesunate nor quinine decreased parasitized red cell deformability or increased antibody binding. In acute falciparum malaria, ring-infected erythrocyte surface antigen (RESA) was observed in erythrocytes without malaria parasites (RESA-red blood cell [RBC]), indicating prior parasitization. In uncomplicated malaria, RESA-RBC numbers increased significantly (P=.002) within 24 h of starting artesunate but rose much more slowly (7 days) after quinine treatment. In severe malaria, RESA-RBC increased significantly (P=. 001) within hours of starting artesunate but not with quinine treatment (P=.43). RESA-RBCs were not produced after drug treatment of malaria parasite cultures in vitro. Rapid malaria parasite clearance after treatment with artemisinin derivatives results mainly from the extraction of drug-affected parasites from host erythrocytes-presumably by the spleen. This explains why the fall in hematocrit after treatment of hyperparasitemia is often less than that predicted from loss of parasitized cells.

11992295
Chotivanich K, Udomsangpetch R, McGready R, Proux S, Newton P, Pukrittayakamee S, Looareesuwan S, White NJ
Central role of the spleen in malaria parasite clearance.
J Infect Dis. 2002 May 15;185(10):1538-41. Epub 2002 Apr 22.
In acute malaria, red blood cells (RBCs) that have been parasitized, but no longer contain a malaria parasite, are found in the circulation (ring-infected erythrocyte surface antigen [RESA]-RBCs). These are thought to arise by splenic removal of dead or damaged intraerythrocytic parasites and return of the intact RBCs to the circulation. In a study of 5 patients with acute falciparum malaria who had previously undergone splenectomy, it was found that none of these 5 patients had any circulating RESA-RBCs, in contrast to the uniform finding of RESA-RBCs in all patients with acute malaria and intact spleens. Parasite clearance after artesunate treatment was markedly prolonged, although the parasites appeared to be dead and could not be cultured ex vivo. These observations confirm the central role of the spleen in the clearance of parasitized RBCs after antimalarial treatment with an artemisinin derivative. Current criteria for high-grade antimalarial drug resistance that are based on changes in parasitemia are not appropriate for asplenic patients.

9614453
Chotivanich KT, Udomsangpetch R, Pipitaporn B, Angus B, Suputtamongkol Y, Pukrittayakamee S, White NJ
Rosetting characteristics of uninfected erythrocytes from healthy individuals and malaria patients.
Ann Trop Med Parasitol. 1998 Jan;92(1):45-56.
Rosetting, defined as the binding of two or more uninfected red blood cells (rbc) to an infected rbc, occurs when malarial parasites mature, to trophozoites and schizonts, in the second half of their asexual development. Rosetting is believed to be an important factor in the development of cerebral malaria. In a series of studies to examine the characteristics of the uninfected rbc which contribute to rosetting, the ability of rbc from healthy donors to form rosettes was found to be greater in the cells of group A and B than in those of group O (P = 0.05), and to decrease during storage under blood-blank conditions. Normal rbc exposed for > or = 30 min to quinine, artesunate or artemether (each at 0.25 microgram/ml) in vitro showed significantly decreased rosetting. This effect could not be reversed by extensive washing followed by cultivation for another 24 h in drug-free medium. Mefloquine and pyrimethamine had no effect. Uninfected rbc from patients with uncomplicated or severe falciparum malaria exhibited a lower rosetting ability than rbc from healthy donors (P = 0.01). The rosetting of uninfected rbc of all blood groups from patients with uncomplicated malaria decreased significantly within 2 h of the patients starting treatment with qinghaosu derivatives (artesunate or artemether) and within 8 h of them starting quinine treatment. Similar effects were observed with uninfected rbc from patients with severe malaria after treatment with artesunate but not after quinine. The mechanisms underlying this potentially beneficial effect on rbc adherence are not known.

9713226
Chung SY, Das R, Oon CT
Treatment of severe falciparum malaria with artesunate and mefloquine.
Singapore Med J. 1998 May;39(5):208-10.
AIM: To study the therapeutic efficacy of low dose intravenous artesunate followed by oral mefloquine in severe falciparum malaria in Singapore. METHODOLOGY: Retrospective review of 4 cases of severe falciparum malaria admitted for treatment in a private hospital in the first six months of this year. Patients were considered cured when no malaria parasites were detected in the blood film on discharge and remained afebrile at 28 days. RESULTS: This drug regimen was well tolerated, rapidly reduced parasitaemia and achieved 100% cure in all four patients. CONCLUSION: Low dose intravenous artesunate followed by mefloquine was found to be well tolerated and rapidly effective in treating severe falciparum malaria contracted in Indonesia and India. There was no relapse of clinical disease in all four cases after 28 days.

11105128
Cimerman S, Barata LC, Pignatari AC, Di Santi SM, Branquinho MS, Tubaki RM, Kirschgatter K, Burattini MN
Malaria Transmission Associated with Airplane Travel.
Braz J Infect Dis. 1997 Jun;1(3):135-137.
Plasmodium falciparum malaria was diagnosed in 3 patients in Sa o Paulo during a 5 day period between August 31, and September 4, 1996, at a time and place where malaria transmission does not occur. After investigation of the 3 cases it was determined that the infections were acquired as a result of an international airplane flight from Lebanon to Sao Paulo on August 16, which included a 30 minute stop-over in Abidjan, Ivory Coast, Africa. During the epidemiological evaluation, it was found that each of the 3 patients had been seated in the first class cabin. Entomological investigation at the airport revealed the presence of 4 specimens of Anopheles gambiae in airplanes (3 in the first class cabin and 1 in the luggage compartment) used on this route. The species of mosquito identified is predominant in Africa. Two of the patients were seriously ill, but all recovered after treatment with either mefloquine (1 patient) or artesunate (2 patients). A survey of other passengers on the same flight or on similar Aights did not reveal any other eases of malaria. Malaria was not considered during initial evaluation by the attending physicians at the three different hospitals where the patients were admitted. These cases reveal the existence of vector borne disease transmission during airplane travel, and emphasize the importance of obtaining a travel history during the evaluation of an ill patient. In addition, the cases reinforce the need for vigilance in the control of vectors of disease around seaports, airports and hospitals.

16503464
Cisse B, Sokhna C, Boulanger D, Milet J, Ba el H, Richardson K, Hallett R, Sutherland C, Simondon K, Simondon F, Alexander N, Gaye O, Targett G, Lines J, Greenwood B, Trape JF
Seasonal intermittent preventive treatment with artesunate and sulfadoxine-pyrimethamine for prevention of malaria in Senegalese children: a randomised, placebo-controlled, double-blind trial.
Lancet. 2006 Feb 25;367(9511):659-67.

BACKGROUND: In the Sahel and sub-Sahelian regions of Africa, malaria transmission is highly seasonal. During a short period of high malaria transmission, mortality and morbidity are high in children under age 5 years. We assessed the efficacy of seasonal intermittent preventive treatment-a full dose of antimalarial treatment given at defined times without previous testing for malaria infection. METHODS: We did a randomised, placebo-controlled, double-blind trial of the effect of intermittent preventive treatment on morbidity from malaria in three health-care centres in Niakhar, a rural area of Senegal. 1136 children aged 2-59 months received either one dose of artesunate plus one dose of sulfadoxine-pyrimethamine or two placebos on three occasions during the malaria transmission season. The primary outcome was a first or single episode of clinical malaria detected through active or passive case detection. Primary analysis was by intention-to-treat. This study is registered with , number NCT00132561. FINDINGS: During 13 weeks of follow-up, the intervention led to an 86% (95% CI 80-90) reduction in the occurrence of clinical episodes of malaria. With passive case detection, protective efficacy against malaria was 86% (77-92), and when detected actively was 86% (78-91). The incidence of malaria in children on active drugs was 308 episodes per 1000 person-years at risk, whereas in those on placebo it was 2250 episodes per 1000 person-years at risk. 13 children were not included in the intention-to-treat analysis, which was restricted to children who received a first dose of antimalarial or placebo. There was an increase in vomiting in children who received the active drugs, but generally the intervention was well tolerated. INTERPRETATION: Intermittent preventive treatment could be highly effective for prevention of malaria in children under 5 years of age living in areas of seasonal malaria infection.

15617018
Clark RL, White TE, A Clode S, Gaunt I, Winstanley P, Ward SA
Developmental toxicity of artesunate and an artesunate combination in the rat and rabbit.
Birth Defects Res B Dev Reprod Toxicol. 2004 Dec;71(6):380-94.
The artemisinins are playing an increasingly important role in treating multidrug-resistant malaria. The artemisinin, artesunate, is currently in use in Southeast Asia and is advocated for use in Africa. In these areas, more than one million people die of malaria each year, with the highest mortality occurring in children and pregnant women. To test the developmental toxicity in ICH-compliant animal studies, embryofetal development studies were conducted in rats and rabbits treated with artesunate alone or a three-drug combination (CDA) consisting of chlorproguanil hydrochloride, Dapsone, and artesunate in the ratio 1.00:1.25:2.00. Developmental toxicity seen with CDA could be attributed to the administered dose of artesunate. The hallmark effect of artesunate exposure was a dramatic induction of embryo loss, apparent as abortions in rabbits and resorptions in both rats and rabbits. In addition, low incidences of cardiovascular malformations and a syndrome of skeletal defects were induced at or close to embryolethal doses of artesunate in both rats and rabbits. The cardiovascular malformations consisted of ventricular septal and vessel defects. The skeletal syndrome consisted of shortened and/or bent long bones and scapulae, misshapen ribs, cleft sternebrae, and incompletely ossified pelvic bones. These developmental effects were observed largely in the absence of any apparent maternal toxicity. The no or low adverse effect levels were in the range of 5 to 7 mg/kg/day artesunate. Encouragingly, no adverse drug-related developmental effects have been observed in a limited number of pregnant women (more than 100 first trimester and 600 second and third trimester) treated with artemisinins, primarily artesunate. Investigations of the mechanism of developmental toxicity are ongoing to attempt to determine whether rats and rabbits are more sensitive to artemisinins than humans.

15331838
Coleman PG, Morel C, Shillcutt S, Goodman C, Mills AJ
A threshold analysis of the cost-effectiveness of artemisinin-based combination therapies in sub-saharan Africa.
Am J Trop Med Hyg. 2004 Aug;71(2 Suppl):196-204.
Artemisinin-based combination therapies (ACTs) are generally regarded as vital in addressing the growing problem posed by the development of antimalarial resistance across sub-Saharan Africa. However, the costs of the new ACTs are likely to be significantly higher than current therapies. Therefore, it is important to examine formally the cost-effectiveness of the more effective yet more expensive ACTs before advocating a switch in policy. Importantly, any such economic evaluation must consider the temporal dynamics of drug resistance, and not just focus on the static question of whether switching today would be cost-effective at current levels of resistance, particularly since the development of new antimalarials in the future is so uncertain. However, predicting the future changes in drug resistance is a major difficulty in accurately quantifying the relative costs and health outcomes associated with different drug therapies over time. Here, we use a simple decision tree model to estimate the incremental cost-effectiveness of using ACTs, compared with persisting with current therapies, over 5-, 10-, and 15-year periods. We describe the dynamics of drug resistance using a general logistic growth function, in which the starting frequency of resistance and maximum growth may be altered. However, rather than make assumptions about the absolute rate at which resistance to ACTs will progress, we allow the ratio of the growth rate of resistance to

ACTs relative to that of current therapies to vary. Defining the growth rate of ACT resistance in this manner allows us to calculate the threshold ratio at which ACTs would no longer appear cost-effective, for any starting conditions of resistance to current therapies and ACTs, and over any time period. The influence of uncertainty in other decision tree parameters on the threshold ratio values is also quantified, using Monte Carlo simulation techniques. This analysis shows that ACTs are more than 95% likely to be cost-effective under most conditions, other than very low levels of initial resistance to sulfadoxine/pyrimethamine and a five-year time frame. These predictions are conservative in that 95% certainty is a stringent decision rule favoring the rejection of new policies. The importance of other variables not included in the analysis for the robustness of the findings are discussed (e.g., consideration of the entire population at risk for malaria, the affordability of ACTs in specific settings, and the growth of resistance modeled according to population genetic parameters).

9692163
Congpuong K, Sirtichaisinthop J, Tippawangkosol P, Suprakrob K, Na-Bangchang K, Tan-ariya P, Karbwang J
Incidence of antimalarial pretreatment and drug sensitivity in vitro in multidrug-resistant Plasmodium falciparum infection in Thailand.
Trans R Soc Trop Med Hyg. 1998 Jan-Feb;92(1):84-6.
Blood samples for determination of baseline antimalarial levels and sensitivity testing in vitro were collected from 411 patients with uncomplicated multidrug-resistant Plasmodium falciparum malaria (365 males, 46 females) before starting antimalarial treatment (62 in hospital and 349 as out-patients). Three hundred and eighty-two were successfully tested, and 110 (28.8%) and 20 (5.2%) patients, respectively, had detectable baseline blood mefloquine and quinine levels. Thirty-nine (10.2%), 44 (11.5%), 23 (6.0%) and 4 (1.1%) cases, respectively, had mefloquine concentrations in whole blood of < 100, 100-500, > 500-1000 and > 1000 ng/mL; the corresponding values for baseline plasma quinine levels were 0 (0%), 9 (2.4%), 3 (0.8%) and 9 (2.4%). None had detectable baseline artemether or artesunate. Sensitivity tests in vitro of pretreatment P. falciparum isolates showed the median IC50, IC90 and IC99 values (ranges in parentheses) for mefloquine, quinine and artemisinin to be 0.121 (0.046-0.715), 0.333 (0.085-3.0) and 0.64 (0.16-1.28) microM, 0.256 (0.064-1.315), 1.10 (0.154-20.49) and 2.56 (0.64-5.12) microM, and 0.02 (0.003-0.382), 0.112 (0.015-4.3) and 0.3 (0.03-3.0) microM, respectively. There was no difference in the sensitivity of P. falciparum isolates to these antimalarial compounds, regardless of the areas where patients had contracted the infection. Previous treatment with mefloquine or quinine was not statistically associated with a high incidence of resistance to these compounds.

15032633
Cooper RA, Carucci DJ
Proteomic approaches to studying drug targets and resistance in Plasmodium.
Curr Drug Targets Infect Disord. 2004 Mar;4(1):41-51.
Ever increasing drug resistance by Plasmodium falciparum, the most virulent of human malaria parasites, is creating new challenges in malaria chemotherapy. The entire genome sequences of P. falciparum and the rodent malaria parasite, P. yoelii yoelii are now available. Extensive genome sequence data from other Plasmodium species including another important human malaria parasite, P. vivax are also available. Powerful research techniques coupled to genomic resources are needed to help identify new drug and vaccine targets against malaria. Applied to Plasmodium, proteomics combines high-resolution protein or peptide separation with mass spectrometry and computer software to rapidly identify large numbers of proteins expressed from various stages of parasite development. Proteomic methods can be applied to study sub-cellular localization, cell function, organelle composition, changes in protein expression patterns in response to drug exposure, drug-protein binding and validation of data from genomic annotation and transcript expression studies. Recent high-throughput proteomic approaches have provided a wealth of protein expression data on P. falciparum, while smaller-scale studies examining specific drug-related hypotheses are also appearing. Of particular interest is the study of mechanisms of action and resistance of drugs such as the quinolines, whose targets currently may not be predictable from genomic data. Coupling the Plasmodium sequence data with bioinformatics, proteomics and RNA transcript expression profiling opens unprecedented opportunities for exploring new malaria control strategies. This review will focus on pharmacological research in malaria and other intracellular parasites using proteomic techniques, emphasizing resources and strategies available for Plasmodium.

8891104
Cumming JN, Ploypradith P, Posner GH
Antimalarial activity of artemisinin (qinghaosu) and related trioxanes: mechanism(s) of action.
Adv Pharmacol. 1997;37:253-97.

15549057
Cyranoski D
Campaign to fight malaria hit by surge in demand for medicine.
Nature. 2004 Nov 18;432(7015):259.

12806460
da Silva Rdo S, Pinto AY, Calvosa VS, de Souza JM
[Short course schemes for vivax malaria treatment]
Rev Soc Bras Med Trop. 2003 Mar-Apr;36(2):235-9. Epub 2003 Jun 10.
with the objective of evaluating shortened therapeutic outlines effective in vivax malaria treatment, we accomplished an open, prospective study allocating 234 patients with vivax malaria distributed at random into eight therapeutic groups. Six groups used oral arthemisin as blood esquizonticide at different doses for one day and the other two groups received chloroquine in a single dose. The primaquine was used as a hypnozoiticide in all groups. They received a daily dose of 30mg in the course of five or seven days in all groups. The clearance of parasitaemia in patients treated with arthemisin (independent of dosage) was faster than the chloroquine group (p

15655007
D'Alessandro U, Talisuna A, Boelaert M
Editorial: Should artemisinin-based combination treatment be used in the home-based management of malaria?
Trop Med Int Health. 2005 Jan;10(1):1-2.

16143357
Dao NV, Quoc NP, Ngoa ND, Thuy le T, The ND, Dai B, Binh VQ, Rieckmann KH, Edstein MD
Fatty food does not alter blood mefloquine concentrations in the treatment of falciparum malaria.
Trans R Soc Trop Med Hyg. 2005 Dec;99(12):927-31. Epub 2005 Sep 6.
Food has been reported to increase the bioavailability of mefloquine in healthy volunteers, but its role in increasing blood mefloquine concentrations in malaria patients treated with mefloquine is unclear. In this study, we compared blood mefloquine concentrations after the administration of artesunate (8 mg/kg) and mefloquine (15 mg/kg) over 12h with either a low-fat (approximately 3g of fat) or high-fat (approximately 30 g of fat) meal for the treatment of Plasmodium falciparum malaria in 12 Vietnamese patients. No statistical differences were detected in the following kinetic parameters between the low-fat (n=6) and high-fat (n=6) groups, respectively: maximum blood mefloquine concentrations (2838+/-531 ng/ml and 2556+/-657 ng/ml, 95% CI -486 to 1050 ng/ml, P=0.43) and the area under the blood mefloquine concentration versus time curves (246.8+/-58.3 microg.h/ml and 238.3+/-28.4 microg.h/ml, 95% CI -50.5 to 67.5 microg.h/ml, P=0.75). A fatty meal does not appear to increase the bioavailability of mefloquine in malaria patients and should not affect the response of malaria infections to treatment.

11273187
Das B, Jena RK, Swain KP, Parida P
Emerging resistance of Plasmodium falciparum to artemisinine and related compounds.
J Assoc Physicians India. 2000 Apr;48(4):443-4.

15889476
Das P
New combination drug to treat malaria.
Lancet Infect Dis. 2005 May;5(5):267.

12499215
Davis TM, Binh TQ, Ilett KF, Batty KT, Phuong HL, Chiswell GM, Phuong VD, Agus C
Penetration of dihydroartemisinin into cerebrospinal fluid after administration of intravenous artesunate in severe falciparum malaria.
Antimicrob Agents Chemother. 2003 Jan;47(1):368-70.
Penetration of cerebrospinal fluid (CSF) by artesunate and DHA was assessed in six adults with cerebral or severe malaria. Lumbar punctures were performed on admission and during convalescence, at 15 min

(patient 1), 30 min (patient 2), 45 min (patient 3), 60 min (patient 4), 90 min (patient 5), and 120 min (patient 6) after intravenous administration of 120 mg of artesunate. No artesunate was detectable in CSF. In both studies, DHA levels in CSF increased with time while dihydroartemisinin levels in plasma fell. Dihydroartemisinin might accumulate in CSF during frequent artesunate dosing.

12497978
Davis TM, Binh TQ, Thu le TA, Long TT, Johnston W, Robertson K, Barrett PH
Glucose and lactate turnover in adults with falciparum malaria: effect of complications and antimalarial therapy.
Trans R Soc Trop Med Hyg. 2002 Jul-Aug;96(4):411-7.
Hypoglycaemia and lactic acidosis are potentially life-threatening, poorly understood sequelae of Plasmodium falciparum infections. We investigated relationships between clinical status, treatment, and glucose and lactate kinetics during management of falciparum malaria in 14 Vietnamese adults. Nine had severe malaria, of whom 4 were administered quinine (Group 1a) and 5 artesunate (Group 1b). Five uncomplicated cases received artesunate (Group 2). Glucose and lactate turnover were studied on 3 occasions: (i) immediately after initial antimalarial treatment, (ii) at parasite clearance a median of 3 days later, and (iii) at discharge from hospital a median of 9 days post-admission. Steady-state glucose and lactate kinetics were derived from plasma isotopic enrichment during a primed-continuous infusion of D-[6,6-D2]glucose and a parallel infusion of L-[1-13C]lactate. Group 1a patients had the lowest plasma glucose concentrations in the admission study (median [range] 3.9 [3.6-5.1] vs 6.3 [4.9-7.1] and 4.5 [4.3-5.5] mmol/L in Groups 1b and 2 respectively; $P < 0.05$ vs Group 1b), but glucose production rates and serum insulin concentrations that were similar to those in the other groups ($P > 0.17$). This was also the case at parasite clearance and suggested an inappropriate beta cell response. Group 1a patients had the highest admission lactate production (60 [36-77] vs 26 [21-47] and 22 [4-31] mumol/kg.min in Group 1b and 2 respectively; $P < 0.05$ vs Group 2). Amongst the 9 severe cases, there was an inverse association between plasma glucose and lactate production at admission and parasite clearance ($P < 0.05$), but no correlation between admission lactate production and serum bicarbonate ($P = 0.73$). The present data confirm previous studies showing that quinine depresses plasma glucose through stimulation of insulin secretion. It is hypothesized that the low plasma glucose activates Na+,K(+)-ATPase through increased plasma catecholamine concentrations, leading to accelerated glycolysis and increased lactate production in well-oxygenated tissues. In some severely ill patients with falciparum malaria, a raised plasma lactate on its own may, therefore, be an unreliable index of a developing acidosis.

9140347
Davis TM, Breheny FX, Kendall PA, Daly F, Batty KT, Singh A, Ilett KF
Severe falciparum malaria with hyperparasitaemia treated with intravenous artesunate.
Med J Aust. 1997 Apr 21;166(8):416-8.
We report a 57-year-old man with falciparum malaria contracted in Kenya who presented with a three-day history of symptoms. Despite prompt treatment with quinine and artesunate and rapid clearing of the parasitaemia, he developed multiple complications and died 28 days after presentation. This case illustrates the potential for malaria to be fatal despite appropriate treatment and is one of the first reports of the use of artesunate in a hospital in a developed country.

9289650
Davis TM, Edwards GO, McCarthy JS
Artesunate and cerebellar dysfunction in falciparum malaria.
N Engl J Med. 1997 Sep 11;337(11):792; author reply 793.

15610051
Davis TM, Hung TY, Sim IK, Karunajeewa HA, Ilett KF
Piperaquine: a resurgent antimalarial drug.
Drugs. 2005;65(1):75-87.
Piperaquine is a bisquinoline antimalarial drug that was first synthesised in the 1960s, and used extensively in China and Indochina as prophylaxis and treatment during the next 20 years. A number of Chinese research groups documented that it was at least as effective as, and better tolerated than, chloroquine against falciparum and vivax malaria, but no pharmacokinetic characterisation was undertaken. With the development of piperaquine-resistant strains of Plasmodium falciparum and the emergence of the artemisinin derivatives, its use declined during the 1980s. However, during the next decade, piperaquine was rediscovered by Chinese scientists as one of a number of compounds suitable for combination with an artemisinin derivative. The rationale for such artemisinin combination therapies (ACTs) was to provide an inexpensive, short-course treatment regimen with a high cure rate and good tolerability that would reduce

transmission and protect against the development of parasite resistance. This approach has now been endorsed by the WHO. Piperaquine-based ACT began as China-Vietnam 4 (CV4): dihydroartemisinin [DHA], trimethoprim, piperaquine phosphate and primaquine phosphate), which was followed by CV8 (the same components as CV4 but in increased quantities), Artecom (in which primaquine was omitted) and Artekin or Duo-Cotecxin (DHA and piperaquine phosphate only). Recent Indochinese studies have confirmed the excellent clinical efficacy of piperaquine-DHA combinations (28-day cure rates >95%), and have demonstrated that currently recommended regimens are not associated with significant cardiotoxicity or other adverse effects. The pharmacokinetic properties of piperaquine have also been characterised recently, revealing that it is a highly lipid-soluble drug with a large volume of distribution at steady state/bioavailability, long elimination half-life and a clearance that is markedly higher in children than in adults. The tolerability, efficacy, pharmacokinetic profile and low cost of piperaquine make it a promising partner drug for use as part of an ACT.

15720175
Davis TM, Karunajeewa HA, Ilett KF
Artemisinin-based combination therapies for uncomplicated malaria.
Med J Aust. 2005 Feb 21;182(4):181-5.
There has been a relentless increase in resistance of malaria parasites to conventional antimalarial drugs, including chloroquine, sulfadoxine-pyrimethamine and mefloquine. In response to this situation, short-course artemisinin-based combination therapies (ACTs) have been developed. The World Health Organization has endorsed ACT as first-line treatment where the potentially life-threatening parasite Plasmodium falciparum is the predominant infecting species. ACTs combine the rapid schizontocidal activity of an artemisinin derivative (artesunate, artemether or dihydroartemisinin) with a longer-half-life partner drug. Although the use of chloroquine and sulfadoxine-pyrimethamine as partners in ACT improves their efficacy, this may only have value as a short-term measure in patients with a degree of immunity to malaria. Alternative currently available partner drugs include mefloquine, lumefantrine and piperaquine. Artesunate-mefloquine is highly effective but is expensive and side effects (mainly neurotoxicity) can be problematic. Artemether-lumefantrine, the only ACT available in Australia, appears less effective than artesunate-mefloquine and needs to be administered with food to ensure adequate bioavailability. Dihydroartemisinin-piperaquine is highly effective, well tolerated and relatively inexpensive. The goal of potent, safe, easy-to-administer and inexpensive ACTs may see trioxolanes in place of artemisinin derivatives, as well as novel partner drugs such as pyronaridine or naphthoquine, in the future.

11120963
Davis TM, Phuong HL, Ilett KF, Hung NC, Batty KT, Phuong VD, Powell SM, Thien HV, Binh TQ
Pharmacokinetics and pharmacodynamics of intravenous artesunate in severe falciparum malaria.
Antimicrob Agents Chemother. 2001 Jan;45(1):181-6.
To provide novel data relating to the dispositions, effects, and toxicities of the artemisinin derivatives in severe malaria, we studied 30 Vietnamese adults with slide-positive falciparum malaria treated with intravenous artesunate. Twelve patients with complications (severe; group 1) and 8 patients without complications but requiring parenteral therapy (moderately severe; group 2) received 120 mg of artesunate by injection, and 10 patients with moderately severe complications (group 3) were given 240 mg by infusion. Serial concentrations of artesunate and its active metabolite dihydroartemisinin in plasma were measured by high-performance liquid chromatography. The time to 50% parasite clearance (PCT(50)) was determined from serial parasite densities. Full clinical (including neurological) assessments were performed at least daily. In noncompartmental pharmacokinetic analyses, group mean artesunate half-lives (t(1/2)) were short (range, 2.3 to 4.3 min). The dihydroartemisinin t(1/2) (range, 40 to 64 min), clearance (range, 0.73 to 1.01 liters/h/kg), and volume of distribution (range, 0.77 to 1.01 liters/kg) were also similar both across the three patient groups ($P > 0.1$) and to previously reported values for patients with uncomplicated malaria. Parasite clearance was prompt (group median PCT(50) range 6 to 9 h) and clinical recovery was complete under all three regimens. These data indicate that the pharmacokinetics of artesunate and dihydroartemisinin are not influenced by the severity of malaria. Since the pharmacokinetic parameters for both artesunate and dihydroartemisinin were similar regardless of whether injection or infusion was used, artesunate can be considered a prodrug that is converted stoichiometrically to dhydroartemisinin. Conventional doses of artesunate are safe and effective when given to patients with complications of falciparum malaria.

10212895
Dayan AD
Neurotoxicity and artemisinin compounds do the observations in animals justify limitation of clinical use?
Med Trop (Mars). 1998;58(3 Suppl):32-7.
High parenteral doses of certain artemisinin derivatives can produce a limited and unique, selective brain stem neuronopathy in laboratory animals. There is necrosis of a small number of nerve cells in certain brain stem nuclei and more extensive chromatolysis of neurons in the same nuclei a few days after intramuscular

or intravenous injection of dihydroqinghaosu, artemether and arteether in doses exceeding about 6mg/kg/d intramuscular or intravenous for about 3-5 days (in an oily solvent) in the dog, or after a single parenteral dose exceeding about 100 mg/kg. The limited information available about the monkey suggests that it is only affected after doses several times higher. The probable order of sensitivity of species is dog > rat > monkey, but this is based on only few results. No lesions have been reported after various intramuscular and oral dosages of artesunate and artelinate. The limited reports of clinical observations have not suggested any specific pattern of abnormalities. The lesion is unique in its distribution, in the small number of neurons that become necrotic and the occurrence in nearby cells of chromatolysis. The latter is almost certainly reversible because more prolonged or higher dose studies have not shown more extensive neuronal damage. As the pathogenesis of this toxic response is not known, evaluation of the risk to man must be based on conventional assessment of active doses in animals versus those employed in the treatment of cerebral malaria. It is argued that there is no reason to anticipate a particular risk of conventional regimes employing up to artemether 3-6mg/kg/d intramuscular or other regimes involving artesunate per rectum for a few days.

11904104
De Clercq D, Vercruysse J, Kongs A, Verle P, Dompnier JP, Faye PC
Efficacy of artesunate and praziquantel in Schistosoma haematobium infected schoolchildren.
Acta Trop. 2002 Apr;82(1):61-6.
Praziquantel is the current mainstay for morbidity control of schistosomiasis. Artemisinin and its derivatives, widely used for the treatment of malaria, also display antischistosomal properties. The present study is an effort to assess the therapeutic efficacy of artesunate, an artemisinin derivative, in Schistosoma haematobium infections in a human population. The efficacy of artesunate and praziquantel were comparatively studied in primary schoolchildren from two villages, Lampsar (n=180) and Makhana (n=108), located along the Lampsar river in the delta of the Senegal River Basin in Northern Senegal (West Africa). In each village, half of the infected children were treated with a single oral dose of 40 mg/kg praziquantel and half with artesunate following the recommended malaria monotherapy regimen. For both drugs, cure and egg count reduction rates were, without apparent explanation, higher in Makhana than in Lampsar. In both villages, high and nearly comparable egg count reduction rates were obtained with both drugs at each follow-up after treatment (5, 12 and 24 weeks) in the heavy infected group of children (>50 eggs/10 ml of urine). No major adverse effects were observed. The results demonstrate that artesunate is effective against S. haematobium, but the results obtained with praziquantel were consistently better.

11422958
De Martin S, von Seidlein L, Deen JL, Pinder M, Walraven G, Greenwood B
Community perceptions of a mass administration of an antimalarial drug combination in The Gambia.
Trop Med Int Health. 2001 Jun;6(6):442-8.
To test the hypothesis that widespread treatment with artemisinin derivatives can reduce malaria transmission, a mass drug administration (MDA) campaign was undertaken in an area of The Gambia in 1999. Coverage of 85% of the target population was achieved, but the intervention did not reduce overall malaria transmission. We studied the perceptions, knowledge and attitudes of the community to the MDA campaign. A validated questionnaire was administered to randomly selected MDA participants (n = 90) and MDA refusers (n = 71). Individuals who believed in the importance of the MDA (adjusted OR 58.3%; 95% CI 17.4-195.8) and those who were aware that a high level of participation was needed for the MDA to be successful (adjusted OR 28.1; 95% CI 10.3-75.9) were more likely to participate. Understanding that the purpose of the MDA was to reduce malaria (adjusted OR 13.9; 95% CI 5.5-35.1) and knowledge of the fact that malaria is transmitted by mosquitoes and of the clinical signs of malaria (adjusted OR 3.4; 95% CI 3.1-9.0) were associated with participation. Individuals who discussed the MDA with other villagers (adjusted OR 5.5; 95% CI 2.2-13.5) and those who attended the sensitization meeting (adjusted OR 2.6; 95% CI 1.1-6.0) were also more likely to participate. Women were significantly more likely to participate in the MDA than men (adjusted OR 3.1; 95% CI 1.5-6.2). Individuals who refused to participate were unlikely to plan participation in future MDAs. One of the most difficult challenges in the implementation of a malaria control strategy such as an MDA is to convince villagers to participate and to make them aware that a high level of participation by the community is needed for success. We found that our sensitization meetings could be improved by giving more information on how the MDA works and finding means to generate small group discussions after the meeting.

10402979
de Vries PI, Le NH, Le TD, Ho PL, Nguyen VN, Trinh KA, Kager PA
Short course of azithromycin/artesunate against falciparum malaria: no full protection against recrudescence.
Trop Med Int Health. 1999 May;4(5):407-8.

10770766
de Vries PJ, Bich NN, Van Thien H, Hung LN, Anh TK, Kager PA, Heisterkamp SH
Combinations of artemisinin and quinine for uncomplicated falciparum malaria: efficacy and pharmacodynamics.
Antimicrob Agents Chemother. 2000 May;44(5):1302-8.
Combinations of artemisinin and quinine for uncomplicated falciparum malaria were studied. A total of 268 patients were randomized to 7 days of quinine at 10 mg/kg of body weight three times a day (Q) or to artemisinin at 20 mg/kg of body weight followed by 3 (AQ3) or 5 (AQ5) days of quinine. Recrudescence rates were 16, 38, and 15% for the Q, AQ3, and AQ5 groups, respectively (P < 0.001). Recrudescence was associated with shorter parasite clearance time (PCT) and longer treatment after the blood smear had become negative (eradication time). However, classification of patients to outcome-recrudescence or radical cure-was correct in only 77% of patients. The population kinetics of the parasitemia was estimated with nonlinear mixed-effect models. Several models were tested, but the best model was a monoexponential decline of the parasitemia in which the mean parasite elimination half-life was shorter after artemisinin (5.1 h; 95% confidence interval [CI], 4.9 to 5.2 h) than after quinine (8.0 h [95% CI, 7.5 to 8.3 h]). Attempts to simulate the initial increase of the parasitemia did not result in better models with a biologically plausible interpretation. Recrudescence was associated with slower parasite clearance and a higher simulated terminal parasitemia (P(term)). The classification of patients to outcome groups based on P(term) was correct in 78% of patients. The data suggest that parasite strains with reduced sensitivity to quinine are prevalent in Vietnam, with slower parasite clearance and consequent recrudescence. A single dose of artemisinin induces rapid parasite reduction and lowers the value of P(term), but to prevent recrudescence, this should be followed by quinine for at least 3 days after parasite clearance, or 5 days in total.

8957153
de Vries PJ, Dien TK
Clinical pharmacology and therapeutic potential of artemisinin and its derivatives in the treatment of malaria.
Drugs. 1996 Dec;52(6):818-36.
Artemisinin and its derivatives are renowned for their potent antimalarial activity. They have found their way into clinical use in many areas where malaria is endemic. The in vitro concentration at which artemisinin can inhibit 50% of the growth of Plasmodium falciparum ranges from 3 to 30 micrograms/L. The fat-soluble derivatives artemether and arteether are approximately twice as active. The water-soluble dihydro-artemisinin and artesunate are 4 to 5 times more active in vitro. Artemisinin is available only for oral and rectal administration. Absorption is incomplete and elimination is fast, with and elimination half-life of 2 to 5 hours. Plasma concentrations after a single 500 mg oral dose most often exceed 200 micrograms/L. Artesunate and artemether can be considered as prodrugs. Biotransformation into the active metabolite dihydro-artemisinin occurs rapidly--almost immediately for artesunate. The reported elimination half-life of artesunate is less than 1 hour, and for artemether the figure is 3 to 11 hours. The pharmacokinetics of dihydro-artemisinin are not yet completely clear. Elimination is probably also rapid, with an elimination half-life of a few hours. Arteether, dissolved in oil for intramuscular administration, has a much longer elimination half-life of over 20 hours. The clinical efficacy of this group of drugs is characterised by an almost immediate onset and rapid reduction of parasitaemia, with complete clearance in most cases within 48 hours. Efficacy is high even in areas with multidrug-resistant parasite strains. To prevent recrudescence with monotherapy of these compounds, treatment needs to be extended beyond the disappearance of parasites. After 5 days of therapy the rate of recrudescence is approximately 10%. Alternatively, combination with other drugs can be used. Combination with mefloquine is recommended for areas with multidrug-resistant P. falciparum.

9180598
De Vries PJ, Tran KD, Nguyen XK, Le Nguyen B, Pham TY, Dao DD, Van Boxtel CJ, Kager PA
The pharmacokinetics of a single dose of artemisinin in patients with uncomplicated falciparum malaria.
Am J Trop Med Hyg. 1997 May;56(5):503-7.
The pharmacokinetics of artemisinin was studied in 11 Vietnamese patients with uncomplicated falciparum malaria after a single 500 mg oral dose. Curative treatment with mefloquine (15 mg/kg) was provided 24 hr after the artemisinin dose. Artemisinin concentrations were measured by high-performance liquid chromatography with electrochemical detection. The following pharmacokinetic results were found (all mean +/- SD); calculated volume of distribution/bioavailability = 22.8 +/- 16.6 L.kg-1, mean absorption time = 1.16 +/- 0.92 hr, calculated maximum concentration = 364 +/- 250 micrograms.L-1 occurring at 2.88 +/- 1.71 hr after drug intake, and an elimination half-life of 2.72 +/- 1.76 hr. Bioavailability was low. These results do not differ from results in healthy subjects. Parasites disappeared rapidly, with a mean parasite clearance time of 36 hr. No relationship was found between pharmacokinetics and the parasite elimination rate. Tolerance to the single dose of artemisinin was good. No adverse effects were detected. In conclusion, pharmacokinetics of a single dose of artemisinin for uncomplicated falciparum malaria is not different from findings in healthy subjects. A single dose of 500 mg of artemisinin is effective in reducing parasitemia in nonsevere lalciparum malaria and is well-tolerated.

11320331
Debaert M
[Developments in anti-malaria agents: chemical data, structure-activity relationships]
Ann Pharm Fr. 2001 Apr;59(2):75-84.
Various features of the evolution of a few antimalarial drugs including amodiaquine, dihydrofolate-reductase inhibitors, and artemisinin are described. The mechanism of action of artemisinin is detailed to explain the information of the main metabolites and drug design of certain compounds. Structure-activity and structure-neurotoxicity relations are reported. A few examples of cyclic peroxycetal synthesis are given. Finally, trends in new and novel compounds are presented.

11579889
Deen JL, von Seidlein L, Pinder M, Walraven GE, Greenwood BM
The safety of the combination artesunate and pyrimethamine-sulfadoxine given during pregnancy.
Trans R Soc Trop Med Hyg. 2001 Jul-Aug;95(4):424-8.
Malaria during pregnancy is associated with an increased risk of severe anaemia and low-birthweight babies. Effective intermittent therapy with pyrimethamine-sulfadoxine (PSD) decreases parasitaemia and severe anaemia and improves birthweight in areas where Plasmodium falciparum is sensitive to this drug. Increasing resistance to PSD is a concern and alternative antimalarial regimens during pregnancy are needed. Artesunate with PSD is a promising antimalarial combination but few data are available on the safety of artemisinins when taken during pregnancy. Outcome of pregnancy was evaluated for 287 women in The Gambia who were exposed in June 1999 to a single dose of the combination artesunate and PSD during a mass drug administration and 172 women who were not exposed. Women who received placebo (40) and those who did not participate in the mass drug administration (132) comprised the non-exposed group. There was no difference in the proportion of abortions, stillbirths, or infant deaths among those exposed or not exposed to the drugs. The mean weight of 18 infants born to mothers who had received artesunate and PSD during the third trimester was 3.10 kg compared to a mean weight of 2.62 kg of the 10 infants of untreated mothers (adjusted P value = 0.05). We found no evidence of a teratogenic or otherwise harmful effect of gestational exposure to artesunate and PSD. Treatment of a self-selected group of pregnant women with PSD and artesunate during pregnancy was associated with a greater birthweight, which may have resulted from clearance of malaria parasites. However, the influence of confounding factors cannot be excluded.

9766094
Delfosse M
[Artemisia annua for the treatment of malaria]
J Pharm Belg. 1998 Jul-Aug;53(4):276-7.

12861472
Delhaes L, Benoit-Vical F, Camus D, Capron M, Meunier B
Chloroquine and artemisinin: six decades of research--what next?
IDrugs. 2003 Jul;6(7):674-80.
Over the next decade drugs will remain the focus of continuous efforts to control malaria, with a contribution from pharmacogenomic development. Quinine, extracted from Cinchona bark, has been the source for aminoquinoline drugs such as chloroquine; more recently, artemisinin extracted from Artemisia allowed the design of artemisinin mimics containing a trioxane structure. Here, we examine parallels between chloroquine and artemisinin in terms of pharmacological target discovery, mechanism of action and parasite resistance. The widespread use of chloroquine has dramatically reduced its therapeutic response, thus recent strategies are based on artemisinin combinations.

15548382
Dell'Eva R, Pfeffer U, Vene R, Anfosso L, Forlani A, Albini A, Efferth T
Inhibition of angiogenesis in vivo and growth of Kaposi's sarcoma xenograft tumors by the anti-malarial artesunate.
Biochem Pharmacol. 2004 Dec 15;68(12):2359-66.
Artesunate (ART) is a semi-synthetic derivative of the sesquiterpene artemisinin used for the second line therapy of malaria infections with Plasmodium falciparum. ART also inhibits growth of many transformed cell lines. In the present investigation, we show that ART inhibited the growth of normal human umbilical endothelial cells and of KS-IMM cells that we have established from a Kaposi's sarcoma lesion obtained from a renal transplant patient. The growth inhibitory activity correlated with the induction of apoptosis in KS-IMM cells. Apoptosis was not observed in normal endothelial cells, which, however, showed drastically increased

cell doubling times upon ART treatment. ART strongly reduced angiogenesis in vivo in terms of vascularization of Matrigel plugs injected subcutaneously into syngenic mice. We conclude that ART represents a promising candidate drug for the treatment of the highly angiogenic Kaposi's sarcoma. As a low-cost drug, it might be of particular interest for areas of Kaposi's sarcoma endemics. ART could be useful for the prevention of tumor angiogenesis.

15679556
Depoortere E, Guthmann JP, Presse J, Sipilanyambe N, Nkandu E, Balkan S, de Pecoulas PE, Legros D
Efficacy and effectiveness of the combination of sulfadoxine/pyrimethamine and a 3-day course of artesunate for the treatment of uncomplicated falciparum malaria in a refugee settlement in Zambia.
Trop Med Int Health. 2005 Feb;10(2):139-45.
In the Maheba Refugee Settlement, in the clinics supported by Medecins Sans Frontieres, all children aged up to 5 years with a confirmed diagnosis of uncomplicated falciparum malaria are treated with the combination of sulfadoxine/pyrimethamine (SP) and artesunate (AS). We compared the treatment's efficacy and effectiveness. Patients were randomized in order to receive the treatment supervised (efficacy) or unsupervised (effectiveness). Therapeutic response was determined after 28 days of follow up. The difference between recrudescence and re-infection was ascertained by polymerase chain reaction (PCR). We also assessed genetic markers associated to SP resistance (dhfr and dhps). Eighty-five patients received treatment under supervision and 84 received it unsupervised. On day 28, and after PCR adjustment, efficacy was found to be 83.5% (95% CI: 74.1-90.5), and effectiveness 63.4% (95% CI: 52.6-73.3) ($P < 0.01$). Point mutations on dhfr (108) and dhps (437) were found for 92.0% and 44.2% respectively of the PCR samples analysed. The significant difference in therapeutic response after supervised and unsupervised treatment intake can only be explained by insufficient patient adherence. When implementing new malaria treatment policies, serious investment in ensuring patient adherence is essential to ascertain the effectiveness of the new treatment schedules.

14728608
Depoortere E, Guthmann JP, Sipilanyambe N, Nkandu E, Fermon F, Balkan S, Legros D
Adherence to the combination of sulphadoxine-pyrimethamine and artesunate in the Maheba refugee settlement, Zambia.
Trop Med Int Health. 2004 Jan;9(1):62-7.
Artemisinin-based combination therapy (ACT) is one strategy recommended to increase cure rates in malaria and to contain resistance to Plasmodium falciparum. In the Maheba refugee settlement, children aged 5 years or younger with a confirmed diagnosis of uncomplicated falciparum malaria are treated with the combination of sulphadoxine-pyrimethamine (1 day) and artesunate (3 days). To measure treatment adherence, home visits were carried out the day after the last treatment dose. Patients who had any treatment dose left were considered certainly non-adherent. Other patients' classification was based on the answers to the questionnaire: patients whose caretakers stated the child had received the treatment regimen exactly as prescribed were considered probably adherent; all other patients were considered probably non-adherent. Reasons for non-adherence were assessed. We found 21.2% (95% CI [15.0-28.4]) of the patients to be certainly non-adherent, 39.4% (95% CI [31.6-47.6]) probably non-adherent, and 39.4% (95% CI [31.6-47.6]) probably adherent. Insufficient explanation by the dispenser was identified as an important reason for non-adherence. When considering the use of ACT, the issue of patient adherence remains challenging. However, it should not be used as an argument against the introduction of ACT. For these treatment regimens to remain efficacious on a long-term basis, specific and locally adapted strategies need to be implemented to ensure completion of the treatment.

14710987
Deshpande A, Kalgutkar S, Udani S
Red cell exchange using cell separator (therapeutic erythrocytapheresis) in two children with acute severe malaria.
J Assoc Physicians India. 2003 Sep;51:925-6.
Red cell exchange using a cell separator (therapeutic erythrocytapheresis) has been used successfully in a large number of clinical conditions including acute severe cases of malaria. We report two children suffering from severe malaria (Plasmodium falciparum) with infestation rates of 75% and 67% respectively. They were treated successfully with erythrocytapheresis in combination with antimalarial treatment.

14754490
Dev V, Phookan S, Barman K
Therapeutic efficacies of antimalarial drugs in the treatment of uncomplicated, Plasmodium falciparum malaria in Assam, north-eastern India.
Ann Trop Med Parasitol. 2003 Dec;97(8):783-91.

In the Indian state of Assam, the current therapeutic efficacies of the drugs commonly used in the area for the treatment of uncomplicated, Plasmodium falciparum malaria were investigated. As is routine in this area, subjects found positive for P. falciparum malaria were initially treated with chloroquine (CQ). They were given sulfadoxine-pyrimethamine (SP) if this treatment failed, and subsequently quinine if the SP failed. The protocol of the World Health Organization's extended in-vivo test was used to follow parasite clearance and clinical cure. Therapeutic response was assessed by comparing the baseline (day-0) level of parasitaemia with that observed on day 3. Many (75.7%) of the 144 evaluable subjects were treatment successes after CQ, but six early (4.2%) and 29 (20.1%) late CQ-treatment failures were observed. Of the 34 CQ-treatment failures followed, 31 (91.2%) responded adequately to SP but the other three were early (one) or late (two) SP-treatment failures. Two (66.7%) of the SP-treatment failures responded adequately to parenteral quinine but the other (a late quinine-treatment failure) had to be given an artemisinin derivative to achieve a clinical cure. The foci in which multidrug-resistant cases of malaria are developing in India need to be identified quickly, so that such cases can be cured before the mutant strains of P. falciparum that are resistant to several drugs have a chance to become more widespread.

9653734
Dobson MJ
Bitter-sweet solutions for malaria: exploring natural remedies from the past.
Parassitologia. 1998 Jun;40(1-2):69-81.
This paper explores "a wonderful cure" for malaria used successfully by Robert Talbor, an apothecary's apprentice in the English marshes, to treat Essex smugglers and European Royalty in the seventeenth century. The basis of this cure is identified as "quinquina" from the bark of the South American Cinchona tree. The story of Robert Talbor and his secret remedy for malaria opens up a set of intriguing questions about the early history of "quinquina", the subsequent development of quinine, the use of higher plants for antimalarial drugs, including the Chinese plant Artemisia annua L., and the value of unlocking the secrets of the past in our search for strategies to control malaria.

10696418
Doherty JF, Sadiq AD, Bayo L, Alloueche A, Olliaro P, Milligan P, von Seidlein L, Pinder M
A randomized safety and tolerability trial of artesunate plus sulfadoxine--pyrimethamine versus sulfadoxine-pyrimethamine alone for the treatment of uncomplicated malaria in Gambian children.
Trans R Soc Trop Med Hyg. 1999 Sep-Oct;93(5):543-6.
Artemisinin derivatives, such as artesunate, have a short half-life and very rapid anti-malarial activity. Theoretically, using such agents in conjunction with well-established anti-malarial drugs such as sulfadoxine-pyrimethamine may reduce the rate of drug resistance. Such a combination has not previously been used in Africa. We have conducted a pilot safety trial of artesunate (4 mg/kg for 3 days) given with a single dose of sulfadoxine-pyrimethamine (25 mg/kg sulfadoxine) compared to sulfadoxine-pyrimethamine alone among 40 Gambian children with uncomplicated malaria. Both regimens were safe and well tolerated and there were no adverse experiences attributed to the combination. The addition of artesunate resulted in a higher proportion of afebrile children and children with a negative blood film on Day 2, and a reduction in the proportion of gametocyte carriers, when compared to sulfadoxine-pyrimethamine alone.

12171580
Dominguez JN
Chemotherapeutic agents against malaria: what next after chloroquine?
Curr Top Med Chem. 2002 Nov;2(11):1173-85.
This is a general review of currently available antimalarial drugs, these compounds are gathered according with its chemical structure and the biological targets. A great number of these new antimalarial agents are now moving actively in the pipeline from basic science to clinical studies.

16125588
Dondorp A, Nosten F, Stepniewska K, Day N, White N
Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial.
Lancet. 2005 Aug 27-Sep 2;366(9487):717-25.
BACKGROUND: In the treatment of severe malaria, intravenous artesunate is more rapidly acting than intravenous quinine in terms of parasite clearance, is safer, and is simpler to administer, but whether it can reduce mortality is uncertain. METHODS: We did an open-label randomised controlled trial in patients admitted to hospital with severe falciparum malaria in Bangladesh, India, Indonesia, and Myanmar. We assigned individuals intravenous artesunate 2.4 mg/kg bodyweight given as a bolus (n=730) at 0, 12, and 24 h, and then daily, or intravenous quinine (20 mg salt per kg loading dose infused over 4 h then 10 mg/kg infused over 2-8 h three times a day; n=731). Oral medication was substituted when possible to complete treatment. Our primary endpoint was death from severe malaria, and analysis was by intention to treat. FINDINGS: We assessed all patients randomised for the primary endpoint. Mortality in artesunate recipients

was 15% (107 of 730) compared with 22% (164 of 731) in quinine recipients; an absolute reduction of 34.7% (95% CI 18.5-47.6%; p=0.0002). Treatment with artesunate was well tolerated, whereas quinine was associated with hypoglycaemia (relative risk 3.2, 1.3-7.8; p=0.009). INTERPRETATION: Artesunate should become the treatment of choice for severe falciparum malaria in adults.

15598255
Dondorp AM, Newton PN, Mayxay M, Van Damme W, Smithuis FM, Yeung S, Petit A, Lynam AJ, Johnson A, Hien TT, McGready R, Farrar JJ, Looareesuwan S, Day NP, Green MD, White NJ
Fake antimalarials in Southeast Asia are a major impediment to malaria control: multinational cross-sectional survey on the prevalence of fake antimalarials.
Trop Med Int Health. 2004 Dec;9(12):1241-6.
OBJECTIVE: To assess the prevalence of counterfeit antimalarial drugs in Southeast (SE) Asia. DESIGN: Cross-sectional survey. SETTING: Pharmacies and shops selling antimalarial drugs in Myanmar (Burma), Lao PDR, Vietnam, Cambodia and Thailand. MAIN OUTCOME MEASURES: Proportion of artemisinin derivatives or mefloquine containing drugs of substandard quality. RESULTS: Of the 188 tablet packs purchased which were labelled as 'artesunate' 53% did not contain any artesunate. All counterfeit artesunate tablets were labelled as manufactured by 'Guilin Pharma', and refinements of the fake blisterpacks made them often hard to distinguish from their genuine counterparts. No other artemisinin derivatives were found to be counterfeited. Of the 44 mefloquine samples, 9% contained

16033274
Dong Y, Chollet J, Matile H, Charman SA, Chiu FC, Charman WN, Scorneaux B, Urwyler H, Santo Tomas J, Scheurer C, Snyder C, Dorn A, Wang X, Karle JM, Tang Y, Wittlin S, Brun R, Vennerstrom JL
Spiro and dispiro-1,2,4-trioxolanes as antimalarial peroxides: charting a workable structure-activity relationship using simple prototypes.
J Med Chem. 2005 Jul 28;48(15):4953-61.
This paper describes the discovery of synthetic 1,2,4-trioxolane antimalarials and how we established a workable structure-activity relationship in the context of physicochemical, biopharmaceutical, and toxicological profiling. An achiral dispiro-1,2,4-trioxolane (3) in which the trioxolane is flanked by a spiroadamantane and spirocyclohexane was rapidly identified as a lead compound. Nonperoxidic 1,3-dioxolane isosteres of 3 were inactive as were trioxolanes without the spiroadamantane. The trioxolanes were substantially less effective in a standard oral suspension formulation compared to a solubilizing formulation and were more active when administered subcutaneously than orally, both of which suggest substantial biopharmaceutical liabilities. Nonetheless, despite their limited oral bioavailability, the more lipophilic trioxolanes generally had better oral activity than their more polar counterparts. In pharmacokinetic experiments, four trioxolanes had high plasma clearance values, suggesting a potential metabolic instability. The toxicological profiles of two trioxolanes were comparable to that of artesunate.

10212135
Dong Y, Matile H, Chollet J, Kaminsky R, Wood JK, Vennerstrom JL
Synthesis and antimalarial activity of 11 dispiro-1,2,4,5-tetraoxane analogues of WR 148999. 7,8,15,16-Tetraoxadispiro[5.2.5.2]hexadecanes substituted at the 1 and 10 positions with unsaturated and polar functional groups.
J Med Chem. 1999 Apr 22;42(8):1477-80.
Eleven novel dispiro-1,2,4,5-tetraoxanes 3 bearing unsaturated and polar functional groups were designed to enhance the oral antimalarial activity of the prototype tetraoxane 2 (WR 148999). With the exception of 3g and 3h, tetraoxanes 3 were available via the peroxidation of corresponding cyclohexanone derivatives in H2SO4/CH3CN. Tetraoxanes 3g and 3h were prepared by hydrolysis of ester tetraoxanes 3e and 3i, respectively. Five of the 11 tetraoxanes were inactive, but six tetraoxanes had IC50 values of 6-26 nM against the K1 and NF54 strains of Plasmodium falciparum compared to corresponding IC50 values of 28 and 39 nM for 2, and 10 and 12 nM for artemisinin (1). Ester tetraoxane 3e was the most active in vitro, some 2-fold more potent than 1. However, none of the six tetraoxanes active in vitro were as effective as either 1 or 2 in vivo; at single doses of 100 mg/kg most possessed little to no vivo activity in mice infected with Plasmodium berghei. Unsaturated tetraoxane 3a was uniquely more active when administered per os (po) than subcutan (sc). For this series of tetraoxanes, the discrepancy between vitro and vivo activities underscores the limitations of conclusions drawn solely from in vitro antimalarial data and illustrates a practical benefit of complementary single-dose in vivo antimalarial screens.

14962366
Dong Y, Vennerstrom JL
Mechanisms of in situ activation for peroxidic antimalarials.
Redox Rep. 2003;8(5):284-8.

This review describes mechanisms of action of artemisinin-related antimalarials, emphasizing the site and target of activation, pathways of generating reactive species, and possible targets of free radicals with implications for antimalarial peroxide drug design. It also presents a useful link between the mode of action of artemisinin and that of chloroquine, and highlights redox cycles involved in the interaction between the drug and vital biomolecules.

15642967
Dorsey G, Dokomajilar C, Kiggundu M, Staedke SG, Kamya MR, Rosenthal PJ
Principal role of dihydropteroate synthase mutations in mediating resistance to sulfadoxine-pyrimethamine in single-drug and combination therapy of uncomplicated malaria in Uganda.
Am J Trop Med Hyg. 2004 Dec;71(6):758-63.
Antimalarial resistance to sulfadoxine-pyrimethamine (SP) is mediated by mutations in the dihydrofolate reductase (dhfr) and dihydropteroate synthase (dhps) genes. However, the relative importance of different mutations is incompletely understood and has not been studied with combination therapy. Samples from 812 patients treated for uncomplicated malaria in Kampala, Uganda were tested for the presence of mutations commonly found in Africa. The dhps Glu-540 mutation was the strongest independent predictor of treatment failure. The dhfr Arg-59 mutation was only predictive of treatment failure in the presence of the dhps Glu-540 mutation. Comparing combination regimens with SP monotherapy, the addition of chloroquine to SP did not improve efficacy, the addition of artesunate lowered the risk of treatment failure only for infections with both the dhfr Arg-59 and dhps Glu-540 mutations, and the addition of amodiaquine lowered this risk for all dhfr/dhps mutation patterns. The dhps Glu-540 mutation played a principal role and the dhfr Arg-59 mutation a secondary role in mediating resistance to SP alone and in combination.

12504399
Dorsey G, Njama D, Kamya MR, Cattamanchi A, Kyabayinze D, Staedke SG, Gasasira A, Rosenthal PJ
Sulfadoxine/pyrimethamine alone or with amodiaquine or artesunate for treatment of uncomplicated malaria: a longitudinal randomised trial.
Lancet. 2002 Dec 21-28;360(9350):2031-8.
BACKGROUND: New antimalarial treatments are urgently needed in sub-Saharan Africa. Improved therapies should decrease failure rates in the short term, but their effect on incidence of subsequent episodes of malaria is little studied. We aimed to compare the short-term and long-term effectiveness of three antimalarial regimens in children from Kampala, Uganda. METHODS: We randomly allocated healthy children aged 6 months to 5 years to receive 25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine plus either placebo, 25 mg/kg amodiaquine, or 12 mg/kg artesunate. Participants were followed up for 1 year and received the same preassigned treatment for every new episode of uncomplicated malaria diagnosed during follow-up. Recrudescent and new infections were distinguished by comparison of polymorphisms in merozoite surface protein 2 (MSP2). Our primary endpoint was the total number of treatments for malaria per time at risk. Analyses were done per protocol. FINDINGS: 183 (61%) of 316 participants were diagnosed with at least one episode of uncomplicated malaria. A total of 577 episodes of uncomplicated Plasmodium falciparum malaria were treated with study drugs; all regimens were safe and well tolerated. Clinical treatment failure after 14 days was significantly more frequent in the sulfadoxine/pyrimethamine group (38 of 215, 18%) compared with either the sulfadoxine/pyrimethamine plus amodiaquine group (two of 164, 1%; p

14551894
Dorsey G, Vlahos J, Kamya MR, Staedke SG, Rosenthal PJ
Prevention of increasing rates of treatment failure by combining sulfadoxine-pyrimethamine with artesunate or amodiaquine for the sequential treatment of malaria.
J Infect Dis. 2003 Oct 15;188(8):1231-8. Epub 2003 Oct 10.
Combination antimalarial therapy may delay the spread of drug resistance, but clinical data supporting this notion are limited. For 1 year, we studied Ugandan children who were treated for uncomplicated malaria with sulfadoxine-pyrimethamine (SP), SP + amodiaquine (AQ), or SP + artesunate (AS). We compared treatment responses and the prevalence of resistance-conferring mutations of new infections with those of recrudescent infections due to parasites that survived prior treatment. Recrudescent infections were associated with the selection of SP resistance-conferring mutations in all treatment groups, but responses to repeat therapy differed. Compared with initial treatments, treatment of recrudescent infections was associated with a higher rate of treatment failure (hazard ratio [HR], 2.44; P=.01), for the SP group, but with a lower rate of treatment failure (HR, 0.40; P=.08), for the SP + AS group. Treatment failure in the SP + AQ group was uncommon, limiting the analysis of recrudescent parasites. Our results suggest that the use of combination antimalarial therapy in Africa may slow the spread of drug-resistant malaria and prolong the therapeutic life span of available treatment regimens.

16495267
Dow G, Bauman R, Caridha D, Cabezas M, Du F, Gomez-Lobo R, Park M, Smith K, Cannard K

Mefloquine induces dose-related neurological effects in a rat model.
Antimicrob Agents Chemother. 2006 Mar;50(3):1045-53.
Mefloquine is one of the drugs approved by the FDA for malaria chemoprophylaxis. Mefloquine is also approved for the treatment of malaria and is widely used for this purpose in combination with artesunate. However, the clinical utility of the compound has been compromised by reports of adverse neurological effects in some patients. In the present study, the potential neurological effects of mefloquine were investigated with six 7-week-old female rats given a single oral dose of the compound. Potential mefloquine-induced neurological effects were monitored using a standard functional observational battery, automated open field tests, automated spontaneous activity monitoring, a beam traverse task, and histopathology. Plasma mefloquine concentrations were determined 72 h after dosing by using liquid chromatography-mass spectrometry. Mefloquine induced dose-related changes in endpoints associated with spontaneous activity and impairment of motor function and caused degeneration of specific brain stem nuclei (nucleus gracilis). Increased spontaneous motor activity was observed only during the rats' normal sleeping phase, suggesting a correlate to mefloquine-induced sleep disorders. The threshold dose for many of these effects was 187 mg/kg of body weight. This dose yielded plasma mefloquine concentrations after 72 h that are similar to those observed in humans after the treatment dose. Collectively, these data suggest that there may be a biological basis for some of the clinical neurological effects associated with mefloquine.

14728607
Drakeley CJ, Jawara M, Targett GA, Walraven G, Obisike U, Coleman R, Pinder M, Sutherland CJ
Addition of artesunate to chloroquine for treatment of Plasmodium falciparum malaria in Gambian children causes a significant but short-lived reduction in infectiousness for mosquitoes.
Trop Med Int Health. 2004 Jan;9(1):53-61.
OBJECTIVES: Combination therapy using existing anti-malarials together with artesunate (AS) has been advocated as a method to slow the spread of drug resistance. We assessed the effect on Plasmodium falciparum transmissibility of the addition of AS to chloroquine (CQ) in an area of The Gambia where resistance to CQ is increasing. METHODS: Gambian children with acute uncomplicated P. falciparum malaria were treated with either CQ monotherapy (n=120) or the combination of CQ plus three doses of AS (CQ/AS; n=352). Post-treatment sexual-stage parasitaemia was assessed during a 4-week follow-up period. Experimental infections of Anopheles gambiae s.s. mosquitoes were performed with blood from patients who were carrying gametocytes 7 days after starting treatment (n=69). RESULTS: The addition of AS significantly reduced post-treatment prevalence and mean density of gametocytes in the first 14 days (day 7: 43.7% vs. 12.4%, 62.4/microl vs. 6.2/microl; day 14: 32.9% vs. 3.7%; 21.9/microl vs. 5.2/microl; CQ vs. CQ/AS), although by day 28 the benefits of the combination were substantially less marked (40.5% vs. 21.8%; 23.0/microl vs. 63.1/microl; CQ vs. CQ/AS). The duration of gametocyte carriage over the study period was significantly lower in the CQ/AS group (5.2 days vs. 1.5 days; CQ vs. CQ/AS). The estimated infectious proportion of children at day 7 was also lower in the combination group (19.2% vs. 3.4%; CQ vs. CQ/AS), as were the proportion of mosquitoes infected and mean oocyst density (11.5% vs. 0.9%; 0.3 vs. 0.01; CQ vs. CQ/AS). Treatment failure was associated with threefold and twofold higher gametocyte carriage rates during follow-up in CQ and CQ/AS groups, respectively (P

8619447
Duarte EC, Fontes CJ, Gyorkos TW, Abrahamowicz M
Randomized controlled trial of artesunate plus tetracycline versus standard treatment (quinine plus tetracycline) for uncomplicated Plasmodium falciparum malaria in Brazil.
Am J Trop Med Hyg. 1996 Feb;54(2):197-202.
A triple-blind, randomized, clinical trial was undertaken in a Brazilian Amazon region to compare the effectiveness of oral artesunate (seven days, total dose = 0.75 g) plus tetracycline (seven days, total dose = 10.5 g) (AT) and oral quinine (three days, total dose = 6 g) plus tetracycline (seven days, total dose = 10.5 g) (QT) against uncomplicated Plasmodium falciparum malaria. Effectiveness was assessed by cure rates (World Health Organization [WHO]) and parasite clearance at day 2. Patients were randomized, 88 to each group. The groups had similar baseline clinical characteristics. The incidence of side effects was much higher in the QT group (82%) than in the AT group (50%) ($P < 0.001$). Cure rates were similar: 80% in the AT group and 77% in the QT group ($P = 0.68$). Parasitemia (by day 2) cleared faster in the AT group than in the QT group (98.5% versus 47.6%, respectively; $P < 0.001$). These results indicate that the combination of artesunate plus tetracycline is effective in the treatment of uncomplicated falciparum malaria and may provide a useful alternative to other treatment regimens.

14723982
Duffy PE, Mutabingwa TK
Drug combinations for malaria: time to ACT?
Lancet. 2004 Jan 3;363(9402):3-4.

16325683
Duffy PE, Sibley CH
Are we losing artemisinin combination therapy already?
Lancet. 2005 Dec 3;366(9501):1908-9.

15305692
Dupouy-Camet J
[New drugs for the treatment of human parasitic protozoa]
Parassitologia. 2004 Jun;46(1-2):81-4.
Whereas parasitic diseases are always a heavy burden for humanity, few are the new antiparasitic molecules marketed during the last 25 years. Thus on the 1393 new molecules marketed between 1975 and 1999, only 7 have antiprotozoan properties. This talk will detail the progress made in the treatment of the intestinal protozoa, malaria, visceral leishmaniasis and toxoplasmosis, problems with which are especially confronted the European parasitologists. The treatment of Giardia and intestinal amoebas is based on 5-nitro-imidazoles derivatives. Single-dose treatments can be used with tinidazole or secnidazole. Resistance to these compounds of Giardia were described and in these cases, treatment by quinacrine or nitazoxanide are possible alternatives. Nitazoxanide is marketed in the United States and in Australia. It seems to be a well tolerated antiparasitic agent with a broad spectrum because it is active on a lot of intestinal protozoa and helminths. It acts on the same metabolic way as the 5-nitro-imidazoles (inhibition of the ferredoxine reductase) but without synthesis of free radicals and DNA deterioration of the target cell. It is thus neither teratogenic nor mutagenic. Artemisinin derivatives allowed considerable progress in the treatment of malaria. They have short half-lifes, allowing a fast parasitic clearance and these derivatives do no provoke resistance. They are first line drugs for the treatment of malaria in areas of drug resistance. The arthemeter-lumefantrine association (Riamet, Coartem) ensures a rapid disappearance of the circulating parasites and is well tolerated. Atovaquone-proguanil (Malarone) is usable in the treatment of acute malaria but also in disease prevention with the advantage of continuing drug intake for only 7 days after having left the infected area. The treatment of leishmaniasis is always delicate and is characterized by the worrying development of antimony resistances, probably related in the European zones to the treatment of dogs. Liposomal amphotricin is an alternative of choice but remains very expensive. The heating of amphotericin to 70 degrees C during 20 minutes gives it experimental properties and efficacies comparable with that of liposomal amphotericin, but at a less cost. Miltefosine, an alkyl-phospholipide antimetabolite, is very active on visceral leishmaniasis resistant to antimonial treatment. However, its long half-life could induce the emergence of resistances. Miltefosine induces much less side effects than conventional amphotericin B. The commonly used anti-toxoplasmic drugs (sulphadiazine and pyrimethamine) were marketed some 50 years ago and are only active on the rapid forms in multiplication. No drug is really efficient on the cysts although preliminary tests with atovaquone are encouraging to treat ophthalmologic forms in immunocompetent patients. To conclude, it is important to continue to search for new antiprotozoan molecules because, for some parasites, drug resistance is an important problem. Moreover, the treatment of the pregnant women, particularly during the first trimester, is often impossible and there is a lack of galenic forms easily usable in children. A better knowledge of the metabolic pathways of protozoa (particularly the apicoplast of Apicomplexa parasites) would certainly open the posssibility to identify new drugs. To reduce and delay the appearance of resistances, mass-treatments of mass should be avoided and targeted treatments prefered as well as the use of associations of molecules having different modes of action.

15876420
Duraisingh MT, Cowman AF
Contribution of the pfmdr1 gene to antimalarial drug-resistance.
Acta Trop. 2005 Jun;94(3):181-90.
The emergence of drug-resistance poses a major obstacle to the control of malaria. A homolog of the major multidrug-transporter in mammalian cells was identified, Plasmodium falciparum multidrug resistance protein-1, pfmdr1, also known as the P-glycoprotein homolog 1, Pgh-1. Several studies have demonstrated strong, although incomplete, associations between resistance to the widely used antimalarial drug chloroquine and mutation of the pfmdr1 gene in both laboratory and field isolates. Genetic studies have confirmed a link between mutation of the pfmdr1 gene and chloroquine-resistance. Although not essential for chloroquine-resistance, pfmdr1 plays a role in modulating levels of resistance. At the same time it appears to be a significant component in resistance to the structurally related drug quinine. A strong association has been observed between possession of the wildtype form of pfmdr1, amplification of pfmdr1 and resistance to hydrophobic drugs such as the arylaminoalcohol mefloquine and the endoperoxide artemisinin derivatives in field isolates. This is supported by genetic studies. The arylaminoalcohol and endoperoxide drugs are structurally unrelated drugs and this resistance resembles true multidrug resistance. Polymorphism in pfmdr1

and gene amplification has been observed throughout the world and their usefulness in predicting resistance levels is influenced by the history of drug selection of each population.

10599075
Duraisingh MT, Jones P, Sambou I, von Seidlein L, Pinder M, Warhurst DC
Inoculum effect leads to overestimation of in vitro resistance for artemisinin derivatives and standard antimalarials: a Gambian field study.
Parasitology. 1999 Nov;119 (Pt 5):435-40.
Artemisinin (QHS) and its derivatives are new antimalarials which are effective against Plasmodium falciparum parasites resistant to chloroquine (CQ). As these drugs are introduced it is imperative that resistance is monitored. In this paper we demonstrate that the inoculum size used in in vitro testing influences the measured in vitro susceptibility to QHS and its derivative dihydroartemisinin (DHA) and to mefloquine (MEF) and CQ over the range of parasitaemias routinely used in testing with the WHO in vitro microtest. An increase in parasitaemia and/or haematocrit was accompanied by a decrease in the measured sensitivity of 2 laboratory lines. In the context of a field study testing in vitro susceptibility of parasite isolates from patients with uncomplicated malaria in Fajara, The Gambia we demonstrate that failure to control for inoculum size significantly overestimates the level of resistance to QHS and DHA as well as MEF, halofantrine (HAL) and quinine (QUIN). When controlling for the inoculum effect, cross-resistance was observed between QHS, MEF and HAL suggesting the presence of a multidrug resistance-like mechanism. These studies underline the importance of inoculum size in in vitro susceptibility testing.

10802315
Duraisingh MT, Jones P, Sambou I, von Seidlein L, Pinder M, Warhurst DC
The tyrosine-86 allele of the pfmdr1 gene of Plasmodium falciparum is associated with increased sensitivity to the anti-malarials mefloquine and artemisinin.
Mol Biochem Parasitol. 2000 Apr 30;108(1):13-23.
Although chloroquine-resistance (CQR) in Plasmodium falciparum is increasing and resistance to other blood schizonticidal anti-malarials has been reported, the molecular basis remains unclear. In this study fresh field isolates were obtained from The Gambia, an area of emerging CQR and tested for sensitivity to the anti-malarial drugs mefloquine, halofantrine, artemisinin, dihydroartemisinin, chloroquine and quinine. Sequence polymorphisms in the pfmdr1 gene and size polymorphisms in the cg2 gene were assessed using PCR-based systems. A strong association was observed between the presence of the tyr-86 allele of pfmdr1 and increased sensitivity to mefloquine and halofantrine, as well as the structurally unrelated drugs artemisinin and dihydroartemisinin. A weaker association was found between the presence of tyr-86 and increased resistance to chloroquine and quinine. The cg2 Dd2-like omega repeat size polymorphism was associated with increased resistance to chloroquine and increased sensitivity to mefloquine and halofantrine. An intragenic association was also found between a polymorphism in the polyasparagine linker region of pfmdr1 and the tyr-86 allele, which may be due to genetic hitchhiking, indicative of recent selection by chloroquine. Our data support a hypothesis where the pfmdr1 gene confers a true multidrug resistance phenotype which is lost by mutation.

16091030
Duraisingh MT, Refour P
Multiple drug resistance genes in malaria -- from epistasis to epidemiology.
Mol Microbiol. 2005 Aug;57(4):874-7.
A decline in our ability to successfully treat patients with malaria infections of the parasitic protozoan Plasmodium falciparum with cheap quinoline drugs has led to a huge escalation in morbidity and mortality in recent years. Many approaches have been taken, including classical genetics, reverse genetics and molecular epidemiology, to identify the molecular determinants underlying this resistance. The contribution of the P. falciparum multidrug resistance gene, pfmdr1, to antimalarial resistance has been a source of controversy for over a decade since it was first identified. In the current issue of Molecular Microbiology, Sidhu and colleagues use powerful reverse genetics to demonstrate the importance of commonly occurring alleles of pfmdr1 in conferring resistance to the second-line drugs quinine and sensitivity to the new alternatives mefloquine and artemisinin. They also elegantly highlight the importance of genetic background and epistasis between pfmdr1 and other potential modulators of drug resistance. Such molecular knowledge will facilitate surveillance/monitoring and aid the development of strategies for the reversal of resistance.

10844681
Duraisingh MT, Roper C, Walliker D, Warhurst DC
Increased sensitivity to the antimalarials mefloquine and artemisinin is conferred by mutations in the pfmdr1 gene of Plasmodium falciparum.
Mol Microbiol. 2000 May;36(4):955-61.

The declining efficacy of chloroquine and pyrimethamine/sulphadoxine in the treatment of human malaria has led to the use of newer antimalarials such as mefloquine and artemisinin. Sequence polymorphisms in the pfmdr1 gene, the gene encoding the plasmodial homologue of mammalian multidrug resistance transporters, have previously been linked to resistance to chloroquine in some, but not all, studies. In this study, we have used a genetic cross between the strains HB3 and 3D7 to study inheritance of sensitivity to the structurally unrelated drugs mefloquine and artemisinin, and to several other antimalarials. We find a complete allelic association between the HB3-like pfmdr1 allele and increased sensitivity to these drugs in the progeny. Different pfmdr1 sequence polymorphisms in other unrelated lines were also associated with increased sensitivity to these drugs. Our results indicate that the pfmdr1 gene is an important determinant of susceptibility to antimalarials, which has major implications for the future development of resistance.

15941414
Durrani N, Leslie T, Rahim S, Graham K, Ahmad F, Rowland M
Efficacy of combination therapy with artesunate plus amodiaquine compared to monotherapy with chloroquine, amodiaquine or sulfadoxine-pyrimethamine for treatment of uncomplicated Plasmodium falciparum in Afghanistan.
Trop Med Int Health. 2005 Jun;10(6):521-9.
INTRODUCTION: In South and Central Asia resistance to chloroquine (CQ) has reached unmanageable levels, and resistance to sulfadoxine-pyrimethamine (SP) is emerging. Amodiaquine (AQ) is widely used in the region, and elsewhere shows only partial resistance to CQ. In Afghanistan, one option for slowing the spread of resistance and improving treatment outcomes is the use of artemisinin combination therapy (ACT). METHODS: The efficacy of CQ, AQ, SP and amodiaquine plus artesunate (AQ/AS) in the treatment of uncomplicated falciparum malaria was investigated using standard World Health Organization (WHO) procedures. Malaria patients were randomized to four treatment groups: 268 were enrolled and 240 completed the trial. RESULTS: There was a high level of cross-resistance between CQ and AQ resistance: adequate clinical and parasitological response by day 42 was 11% after CQ treatment and 9% after AQ treatment. The trend of treatment failure between AQ and CQ was almost identical. Cure rates were considerably improved by the addition of artesunate to AQ or by use of SP; adequate clinical and parasitological response being 72% for AQ/AS and 92% for SP. The combination of AS/AQ substantially reduced the odds of treatment failure relative to AQ monotherapy by day 42 [odds ratio (OR) = 0.03, 95% confidence interval (CI) 0.01-0.1] in addition to reducing the proportion of patients with gametocytes throughout the 42-day period. Gametocyte carriage rate was only marginally higher in the SP than in the CQ- and AQ-treated groups. CONCLUSION: The therapeutic and parasitological cure rates with AS/AQ were inadequate, and the criteria for deploying ACT - namely to prevent further selection of drug resistance from a position of low frequency - was not met in the region. An alternative drug combination to AQ/AS is required for Afghanistan.

12931192
Eckstein-Ludwig U, Webb RJ, Van Goethem ID, East JM, Lee AG, Kimura M, O'Neill PM, Bray PG, Ward SA, Krishna S
Artemisinins target the SERCA of Plasmodium falciparum.
Nature. 2003 Aug 21;424(6951):957-61.
Artemisinins are extracted from sweet wormwood (Artemisia annua) and are the most potent antimalarials available, rapidly killing all asexual stages of Plasmodium falciparum. Artemisinins are sesquiterpene lactones widely used to treat multidrug-resistant malaria, a disease that annually claims 1 million lives. Despite extensive clinical and laboratory experience their molecular target is not yet identified. Activated artemisinins form adducts with a variety of biological macromolecules, including haem, translationally controlled tumour protein (TCTP) and other higher-molecular-weight proteins. Here we show that artemisinins, but not quinine or chloroquine, inhibit the SERCA orthologue (PfATP6) of Plasmodium falciparum in Xenopus oocytes with similar potency to thapsigargin (another sesquiterpene lactone and highly specific SERCA inhibitor). As predicted, thapsigargin also antagonizes the parasiticidal activity of artemisinin. Desoxyartemisinin lacks an endoperoxide bridge and is ineffective both as an inhibitor of PfATP6 and as an antimalarial. Chelation of iron by desferrioxamine abrogates the antiparasitic activity of artemisinins and correspondingly attenuates inhibition of PfATP6. Imaging of parasites with BODIPY-thapsigargin labels the cytosolic compartment and is competed by artemisinin. Fluorescent artemisinin labels parasites similarly and irreversibly in an Fe2+-dependent manner. These data provide compelling evidence that artemisinins act by inhibiting PfATP6 outside the food vacuole after activation by iron.

11736877
Edstein MD, Kocisko DA, Brewer TG, Walsh DS, Eamsila C, Charles BG
Population pharmacokinetics of the new antimalarial agent tafenoquine in Thai soldiers.
Br J Clin Pharmacol. 2001 Dec;52(6):663-70.

AIMS: To describe the population pharmacokinetics of tafenoquine in healthy volunteers after receiving tafenoquine for malaria prophylaxis. METHODS: The population consisted of 135 male Thai soldiers (mean age 28.9 years; weight 60.3 kg). All soldiers were presumptively treated with artesunate for 3 days plus doxycycline for 7 days to remove any pre-existing malaria infections. After the treatment regime, 104 soldiers (drug group) received a loading dose of 400 mg tafenoquine base daily for 3 days followed by 400 mg tafenoquine monthly for 5 consecutive months. In the placebo group, 31 soldiers were infected with malaria during the study period. They were re-treated with artesunate for 3 days plus doxycycline for 7 days followed by a loading dose of 400 mg tafenoquine daily for 3 days and then 400 mg tafenoquine weekly for prophylaxis. Blood samples were randomly collected from each soldier on monthly and weekly prophylaxis. Plasma tafenoquine concentrations were measured by h.p.l.c. Population pharmacokinetic modelling was performed using NONMEM. RESULTS: A one-compartment model was found best to describe the pharmacokinetics of tafenoquine after oral administration. Age and weight influenced volume of distribution (V/F), and subjects who contracted malaria had higher clearance (CL/F), but none of these factors was considered to have sufficient impact to warrant change in dosing. The population estimates of the first-order absorption rate constant (Ka), CL/F and V/F were 0.694 h(-1), 3.20 l h(-1) and 1820 l, respectively. The intersubject variability in these parameters (coefficient of variation, CV%) was 61.2%, 25.3% and 14.8%, respectively. The absorption and elimination half-lives were 1.0 h and 16.4 days, respectively. The residual (unexplained) variability was 17.9%. CONCLUSIONS: The population pharmacokinetics of orally administered tafenoquine have been determined in Thai soldiers under field conditions. This information, together with its known potent antimalarial activity, portends well for the application of tafenoquine as a useful prophylactic drug or for short-term radical treatment of vivax malaria.

14689348
Edstein MD, Kocisko DA, Walsh DS, Eamsila C, Charles BG, Rieckmann KH
Plasma concentrations of tafenoquine, a new long-acting antimalarial agent, in thai soldiers receiving monthly prophylaxis.
Clin Infect Dis. 2003 Dec 15;37(12):1654-8. Epub 2003 Nov 20.
We measured plasma tafenoquine concentrations in Thai soldiers given a monthly regimen of tafenoquine to determine whether these concentrations adequately suppressed malarial infections on the Thai-Cambodian border. After receiving a treatment course of artesunate and doxycycline, 104 male soldiers were administered a loading dose of tafenoquine (400 mg daily for 3 days), followed by tafenoquine monthly (400 mg every 4 weeks) for 5 months. Consecutive monthly mean (+/- standard deviation) trough plasma tafenoquine concentrations were 223+/-41, 127+/-29, 157+/-51, 120+/-24, and 88+/-20 ng/mL. Only 1 soldier developed malaria during the study. At the time of malaria diagnosis, his plasma tafenoquine concentration was 40 ng/mL, which was approximately 3-fold lower than the trough concentrations of the other soldiers. Although low tafenoquine concentrations appear to be uncommon, additional investigations are needed to determine the relationship between plasma tafenoquine concentrations and suppression of malaria.

15878303
Efferth T
Mechanistic perspectives for 1,2,4-trioxanes in anti-cancer therapy.
Drug Resist Updat. 2005 Feb-Apr;8(1-2):85-97.
In addition to their well-known anti-malarial activity, artemisinin and its derivatives (1,2,4-trioxanes) possess potent activity against tumor cells in the nano- to micromolar range. Candidate genes that may contribute to the sensitivity and resistance of tumor cells to artemisinins were identified by pharmacogenomic and molecular pharmacological approaches. Target validation was performed using cell lines transfected with candidate genes or corresponding knockout cells. These genes are from classes with different biological function; for example, regulation of proliferation (BUB3, cyclins, CDC25A), angiogenesis (vascular endothelial growth factor and its receptor, matrix metalloproteinase-9, angiostatin, thrombospondin-1) or apoptosis (BCL-2, BAX). Artesunate triggers apoptosis both by p53-dependent and -independent pathways. Anti-oxidant stress genes (thioredoxin, catalase, gamma-glutamyl-cysteine synthetase, glutathione S-transferases) as well as the epidermal growth factor receptor confer resistance to artesunate. Cell lines over-expressing genes that confer resistance to established anti-tumor drugs (MDR1, MRP1, BCRP, dihydrofolate reductase, ribonucleotide reductase) were not cross-resistant to artesunate, indicating that this drug has a different target and is not subject to multidrug resistance. The Plasmodium translationally controlled tumor protein (TCTP) represents a known target protein of artemisinin and its derivatives in the malaria parasite. The microarray-based mRNA expression of human TCTP correlated with sensitivity to artesunate in tumor cells, suggesting that human TCTP contributes to response of tumor cells to the drug. The multi-factorial nature of cellular response to artemisinin and its derivatives may be beneficial to treat otherwise drug-resistant tumors and may explain why resistance development has not been observed in either cancer or malaria.

11251172

Efferth T, Dunstan H, Sauerbrey A, Miyachi H, Chitambar CR
The anti-malarial artesunate is also active against cancer.
Int J Oncol. 2001 Apr;18(4):767-73.
Artesunate (ART) is a semi-synthetic derivative of artemisinin, the active principle of the Chinese herb Artemisia annua. ART reveals remarkable activity against otherwise multidrug-resistant Plasmodium falciparum and P. vivax malaria. ART has now been analyzed for its anti-cancer activity against 55 cell lines of the Developmental Therapeutics Program of the National Cancer Institute, USA. ART was most active against leukemia and colon cancer cell lines (mean GI50 values: 1.11+/-0.56 microM and 2.13+/-0.74 microM , respectively). Non-small cell lung cancer cell lines showed the highest mean GI50 value (25.62+/-14.95 microM) indicating the lowest sensitivity towards ART in this test panel. Intermediate GI50 values were obtained for melanomas, breast, ovarian, prostate, CNS, and renal cancer cell lines. Importantly, a comparison of ART's cytotoxicity with those of other standard cytostatic drugs showed that ART was active in molar ranges comparable to those of established anti-tumor drugs. Furthermore, we tested CEM leukemia sub-lines resistant to either doxorubicin, vincristine, methotrexate, or hydroxyurea which do not belong to the N.C.I. screening panel. None of these drug-resistant cell lines showed cross resistance to ART. To gain insight into the molecular mechanisms of ART's cytotoxicity, we used a panel of isogenic Saccaromyces cerevisiae strains with defined genetic mutations in DNA repair, DNA checkpoint and cell proliferation genes. A yeast strain with a defective mitosis regulating BUB3 gene showed increased ART sensitivity and another strain with a defective proliferation-regulating CLN2 gene showed increased ART resistance over the wild-type strain, wt644. None of the other DNA repair or DNA check-point deficient isogenic strains were different from the wild-type. These results and the known low toxicity of ART are clues that ART may be a promising novel candidate for cancer chemotherapy.

10497989
Eggelte TA, van Agtmael MA, Vuong TD, van Boxtel CJ
The development of an immunoassay for the detection of artemisinin compounds in urine.
Am J Trop Med Hyg. 1999 Sep;61(3):449-56.
We have produced monoclonal antibodies against artelinic acid and investigated the reactivity with artemisinin drugs and metabolites. Antibody F170-10 is fairly specific for artelinic acid but does bind artemisinin and artemether (3-5% cross-reactivity). Dihydroartemisinin, artesunate, and metabolites of artemisinin showed less reactivity. With this antibody, an inhibition ELISA has been set up to detect artemisinin compounds in urine. In healthy subjects who received a single oral dose of artemisinin, artemether, artesunate or dihydroartemisinin, ELISA reactivity in urine was found. This reactivity in urine paralleled the plasma concentrations of artemether and dihydroartemisinin. The results show that this immunoassay for artelinic acid can be used to detect artemisinin compounds in urine for about 8 hr after intake. With a more sensitive test, this simple method as a urine dipstick may be become useful for drug use and compliance studies in malaria-endemic areas where the artemisinin derivatives are increasingly used.

9182179
Ekvall H, Aust-Kettis A, Bjorkman A
[Severe falciparum malaria among travellers to Thailand. Blood exchange and artemisinine treatment are therapeutic alternatives]
Lakartidningen. 1997 Apr 30;94(18):1713-5.

9551823
El Menyawi I, Looareesuwan S, Knapp S, Thalhammer F, Stoiser B, Burgmann H
Measurement of serum nitrite/nitrate concentrations using high-performance liquid chromatography.
J Chromatogr B Biomed Sci Appl. 1998 Mar 20;706(2):347-51.
Previous studies have reported increased serum concentrations of nitrite/nitrate - the degradation products of nitric oxide - in Plasmodium vivax malaria and uncomplicated Plasmodium falciparum malaria. In all these studies, however, nitrite/nitrate has been measured spectrometrically using Griess reagent which carries major disadvantages in the determination of serum nitrite/nitrate. The method does not allow an exact differentiation of nitrite and biogenic amines that are physiologically present in plasma. In the present study we introduce high-performance liquid chromatography as a new, accurate and cost effective method for determination of serum nitrite/nitrate levels. Significantly increased nitrate concentrations were found in malaria patients and serum values remained above normal levels for at least 21 days. It could be shown that our HPLC method is a sensitive and cost-effective method for direct determination of nitrite/nitrate in serum samples, which is not influenced by the presence of biogenic amines.

11456797
El Sayed KA, Kelly M, Kara UA, Ang KK, Katsuyama I, Dunbar DC, Khan AA, Hamann MT

New manzamine alkaloids with potent activity against infectious diseases.
J Am Chem Soc. 2001 Mar 7;123(9):1804-8.
The isolation of the new enantiomers of 8-hydroxymanzamine A (1), manzamine F (2), along with the unprecedented manzamine dimer, neo-kauluamine from an undescribed genus of Indo-Pacific sponge (family Petrosiidae, order Haplosclerida) is reported. The relative stereochemistry of neo-kauluamine was established through detailed analysis of NOE-correlations combined with molecular modeling. The significance of the manzamines as in vivo antimalarial agents with superior activity to the clinically used drugs artemisinin and chloroquine is discussed along with the activity in vitro against the AIDS-opportunistic infectious diseases tuberculosis and toxoplasmosis. Reexamination of the sponges identified as Prianos, and Pachypellina, in earlier publications has confirmed that these are members of the same genus as the sponge described here, but differ at the species level.

16162284
Elamin SB, Malik EM, Abdelgadir T, Khamiss AH, Mohammed MM, Ahmed ES, Adam I
Artesunate plus sulfadoxine-pyrimethamine for treatment of uncomplicated Plasmodium falciparum malaria in Sudan.
Malar J. 2005 Sep 14;4:41.
BACKGROUND: Early diagnosis and effective treatment with an appropriate drug form the main components of the World Health Organization's strategy to reduce malaria related mortality. The few available drugs might be safeguarded if combined with artesunate. The addition of artesunate to a standard antimalarial treatment substantially reduces treatment failure, recrudescence and gametocyte carriage. METHODS: During late 2004, the efficacy of artesunate (4 mg/kg. day, on days 0-2) plus sulfadoxine-pyrimethamine (25 mg/kg, on day 0) for the treatment of uncomplicated Plasmodium falciparum malaria was investigated in four sentinel areas in Sudan, with different malaria transmission (Damazin, Kassala, Kosti, and Malakal). RESULTS: Two hundreds and sixty-nine patients completed the 28-day follow-up. On day one, 60 (22.3%) patients were febrile and 15 (5.5%) patients were parasitaemic. On day three, all the patients were afebrile and aparasitaemic. While two patients (0.7%, Kassala) showed late Clinical and Parasitological Failures, the rest (99.3%) of the patients demonstrated Adequate Clinical and Parasitological Response. A gametocytaemia were detected during the follow-up in one patient (0.37%, Kassala). Adverse drug effects were detected in 32 (11.9%) patients. CONCLUSION: The study showed that AS plus SP is an effective, safe drug in the treatment of uncomplicated P. falciparum malaria in Sudan.

15811526
Elandalloussi LM, Adams B, Smith PJ
ATPase activity of purified plasma membranes and digestive vacuoles from Plasmodium falciparum.
Mol Biochem Parasitol. 2005 May;141(1):49-56.
The ATPase activity of the human malaria parasite, Plasmodium falciparum was investigated using two experimental systems, (i) digestive vacuoles, and (ii) purified plasma membranes isolated from a chloroquine-sensitive and a chloroquine-resistant strain. No correlation between the level of ATPase activity and chloroquine sensitivity could be detected. In both systems, the ATPase activity of the chloroquine-resistant and -sensitive strain was decreased in the presence of the P-glycoprotein inhibitor vanadate. Susceptibility to inhibition by vanadate together with the lack of effect of ouabain implies a P-type ATPase activity in the plasma membrane. Furthermore, the inhibition of Fac8 ATPase activity by oligomycin both in the digestive vacuoles and the plasma membranes would be consistent with higher levels of Pgh1 in Fac8. Our data are consistent with the presence of a V-type H+-ATPase in the parasite food vacuole. Bafilomycin A1 and N-ethylmaleimide decreased the vacuolar ATPase activity in both chloroquine-resistant and -sensitive strains. Interestingly, a 30% decrease was observed between the ATPase activity of plasma membranes isolated from Fac8 and D10 in the presence of bafilomycin A1, suggesting the presence of a V-type ATPase in D10 plasma membrane that is underexpressed or altered in the plasma membrane of the chloroquine-resistant Fac8. The chemosensitisers tested had no effect on the ATPase activity of chloroquine-resistant P. falciparum in both systems suggesting that their activity is not mediated through an ATP-dependent mechanism. No effect was observed on the vacuolar ATPase activity in the presence of the antimalarials tested indicating that an ATP-dependent transport has not been activated.

3318019
Elford BC, Roberts MF, Phillipson JD, Wilson RJ
Potentiation of the antimalarial activity of qinghaosu by methoxylated flavones.
Trans R Soc Trop Med Hyg. 1987;81(3):434-6.
Interaction between the flavones casticin and artemetin and the antimalarial activity of chloroquine and qinghaosu (QHS) was examined using an in vitro growth assay based on [3H]hypoxanthine incorporation in synchronized cultures of a cloned line of Plasmodium falciparum. Casticin, and to a lesser extent artemetin, selectively enhanced the inhibition of growth by QHS, but had little effect on the activity of chloroquine. The

findings suggest that flavones indigenous to Artemisia annua, from which QHS is isolated, might significantly alter the clinical potential of this novel antimalarial drug in the treatment of chloroquine-resistant malaria.

12346557
Epstein D
Malaria: failure, puzzle, challenge.
Perspect Health. 1999;4(1):2-7.
Chloroquine-resistant Plasmodium vivax has not yet occurred in Vietnam. The efficacy of artemisinin for P. vivax was not established. We conducted a double-blind randomized study involving 240 inpatients with P. vivax malaria who received artemisinin (40 mg/kg over 3 days) plus placebo chloroquine (Art) or chloroquine (25 mg/kg over 3 days) plus placebo artemisinin (Chl). Patients were followed up with weekly blood smears for 28 days. In each group 113 cases were analysed. All patients recovered rapidly. The median (range) parasite clearance time of regimen Art was 24 h (8-72) and of Chl 24 h (8-64; P = 0.3). Parasites reappeared in two cases in each group on day 14, in eight cases in each group (7%) on day 16 and in 25 (23%) and 18 (16%) cases, respectively, at the end of 4-week follow-up (P = 0.3). The population parasite clearance curve followed a mono-exponential decline. The parasite reduction ratio per 48 h reproduction cycle was 2.3 x 104 for both regimens. We conclude that artemisinin and chloroquine are equally effective in the treatment of P. vivax infections in Vietnam. Reappearance of parasites before day 16 (7%) suggests the emergence of chloroquine resistance. Three days of artemisinin monotherapy does not prevent recrudescence.

16185239
Eriksen J, Nsimba SE, Minzi OM, Sanga AJ, Petzold M, Gustafsson LL, Warsame MY, Tomson G
Adoption of the new antimalarial drug policy in Tanzania--a cross-sectional study in the community.
Trop Med Int Health. 2005 Oct;10(10):1038-46.
OBJECTIVE: To assess the diffusion of the change of first line antimalarial drug from chloroquine (CQ) to sulphadoxine/pyrimethamine (SP) at household level in a rural district of Tanzania less than a year after the policy implementation. METHODS: Caretakers in 729 households were interviewed on knowledge of the new policy, home stocking of antimalarials, home-treatment practices of children younger than 5 years with fever, health-seeking behaviour and experience of SP. SP and CQ levels in blood were analysed from 328 children younger than 5 years in the households. Twelve focus group discussions (FGD) were performed with mothers, fathers and health workers. RESULTS: About 51% of the population knew that SP was the first line antimalarial. Only 8% of mothers stocked antimalarials, and only 4% stated self-treatment as the first action. We estimated that 84% of the children who had had fever during the last 4 weeks sought care at public health facilities. SP was detectable in 18% of the total child population and in 32% of those with reported fever, CQ in only 5% and 7%, respectively. The FGDs revealed negative perceptions of SP and fear of severe adverse reactions with mass media reported as key informant. CONCLUSION: The policy had diffused to the communities in the sense that CQ had been changed to SP, which was well known as first line treatment. Moreover, there was a reported dramatic change from self-treatment with CQ to seeking care at public health facilities where SP was given under observation.

11293628
Etchegorry MG, Matthys F, Galinski M, White NJ, Nosten F
Malaria epidemic in Burundi.
Lancet. 2001 Mar 31;357(9261):1046-7.

8791866
Ezedinachi E
In vivo efficacy of chloroquine, halofantrine, pyrimethamine-sulfadoxine and qinghaosu (artesunate) in the treatment of malaria in Calabar, Nigeria.
Cent Afr J Med. 1996 Apr;42(4):109-11.
We used the WHO in vivo seven day test, extended to 14 day follow up to evaluate the efficacy of the alternative antimalarial drugs in Nigeria (1992), where chloroquine resistant P. falciparum (CRPD) has been confirmed. One thousand and four patients were screened. Those fulfilling recruitment criteria were randomly treated with chloroquine (CQ), n = 50, halofantrine (H), n = 53, pyrimethamine-sulfadoxine (P-S), n = 52 and qinghaosu (Q), n = 53. Parasitological treatment failures were found with all drugs i.e. CQ-53.6pc, H-9.5pc, P-S-28.5pc and Q-2.0pc. H and Q were significantly more efficacious than CQ and P-S, $p < 0.003$ and $p < 0.006$, respectively. similarly symptom clearance after 48 hours by H and Q, was 76.3pc and 94pc respectively, better than CQ. P-S was not significantly better than CQ, 64.4pc and 63.3pc, respectively, $p > 0.05$. The symptom clearance rate of CQ has markedly reduced from 97.7pc to 67.7pc, and in increased proportion of RIII, from 5.9pc to 14.3pc, are signs of increase in chloroquine resistant Plasmodium falciparum. Drug resistant P. falciparum in Nigeria constitutes a serious problem to malaria chemotherapy.

15837358
Falade C, Makanga M, Premji Z, Ortmann CE, Stockmeyer M, de Palacios PI
Efficacy and safety of artemether-lumefantrine (Coartem) tablets (six-dose regimen) in African infants and children with acute, uncomplicated falciparum malaria.
Trans R Soc Trop Med Hyg. 2005 Jun;99(6):459-67.
Approximately one million children die from malaria each year. A recently approved artemisinin-based tablet, Coartem (co-artemether), comprising artemether 120 mg plus lumefantrine 20 mg, given in four doses, provides effective antimalarial treatment for children in many sub-Saharan countries. However, this regimen is considered insufficient for non-immune infants and in areas where multidrug-resistant Plasmodium falciparum predominates. This open-label study assessed the efficacy and safety of co-artemether administered to 310 African children weighing 5-25 kg, with acute, uncomplicated falciparum malaria. Six doses of co-artemether were given over 3 days, with follow-up at 7, 14 and 28 days. Treatment rapidly cleared parasitemia and fever. The overall 28-day cure rate was 86.5%, and 93.9% when corrected by PCR for reinfection. Cure rates at 7 and 14 days exceeded 97.0% (uncorrected) and, on day 28, were similar in infants (5-

12078295
Fan B, Zhao W, Ma X, Huang Z, Wen Y, Yang J, Yang Z
[In vitro sensitivity of Plasmodium falciparum to chloroquine, piperaquine, pyronaridine and artesunate in Yuxi prefecture of Yunnan province]
Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi. 1998;16(6):460-2.
AIM: To assess the sensitivity of Plasmodium falciparum to four antimalarials. METHODS: WHO standard in vitro microtest was used. RESULTS: The resistance rates of the malaria parasite to chloroquine, piperaquine pyronaridine and artesunate were 85.7%, 66.7%, 38.1% and 5.0%, respectively. CONCLUSION: Among the antimalarials tested in Yuxi Prefecture, Yunnan Province, high resistance of P. falciparum to chloroquine and piperaquine was found. The sensitivity of P. falciparum in part of the cases to pyronaridine decreased. However, most of the cases were relatively sensitive to artesunate.

10575838
Fang CT, Chang SC, Chang HL, Chen YC, Hsueh PR, Hung CC, Hsieh WC
Imported malaria: successful treatment of 31 patients in the era of chloroquine resistance.
J Formos Med Assoc. 1999 Oct;98(10):683-7.
The diagnosis and management of imported malaria presents a continuing challenge in developed countries, including Taiwan. We retrospectively analyzed the records of all 31 patients with imported malaria treated at National Taiwan University Hospital from January 1984 through December 1998. Plasmodium falciparum was identified as the causative malarial parasite in 18 patients, P. vivax in 12, and P. ovale in one. All 31 patients had fever, but only 13 presented with the characteristic fever pattern. The most common initial laboratory abnormalities were thrombocytopenia (20/31), mild hyperbilirubinemia (20/31), and leukopenia (7/31). The median time from the onset of fever to the correct diagnosis was 4 days for P. falciparum and 5 days for P. vivax. In 28 cases, the clue that led to early diagnosis was the patient's travel history. Quinine, but not chloroquine, was effective in 17 out of 18 cases of falciparum malaria. Three patients treated with intravenous quinine required a change of regimen because of life-threatening quinine toxicity; artesunate served as a safe and effective alternative in this situation. While most patients with tertian malaria were cured with the standard chloroquine and primaquine regimen, a higher dosage was required for one case acquired in Papua New Guinea. All patients, including two with severe malaria, survived. We conclude that, the mortality of imported malaria in the chloroquine resistance era can be minimized with early recognition by obtaining a thorough travel history, and instituting appropriate antimalarial chemotherapy based on precise identification of species. Quinine toxicity should be closely monitoried, especially when this drug is given intravenously.

15672556
Farooq U, Mahajan RC
Drug resistance in malaria.
J Vector Borne Dis. 2004 Sep-Dec;41(3-4):45-53.
Ever since the discovery of the first case of chloroquine resistance along the Thai-Combodian border in the late 1950s, Southeast Asia has played an important role as a focus for the development of drug resistance in Plasmodium falciparum. Although the first case of quinine resistance had been reported much earlier from South America, the onset of chloroquine resistance marked the beginning of a new chapter in the history of malaria in Southeast Asia and by 1973 chloroquine finally had to be replaced by the combination of sulphadoxine and pyrimethamine (SP) as first line drug for the treatment of uncomplicated malaria in Thailand and more than 10 African countries have also switched their first line drug to SP. In 1985, eventually SP was replaced by mefloquine. The rapid development of resistance to this new drug leads to

the introduction of artemisinin as a combination drug in the mid-1990s. It is mandatory to mention here that therapeutic regimens for prevention and treatment of chloroquine-resistant P. falciparum are associated with higher costs and side-effects compared to chloroquine. Additionally, some of these alternative treatments are associated with more side-effects, take longer time for cure and are more difficult to comply with than chloroquine. Urgent efforts are needed to identify effective, affordable, alternative antimalarial regimens. Molecular markers for antimalarial resistance have been identified, including pfmdr-1 and pfcrt polymorphisms associated with chloroquine resistance and dhfr and dhps polymorphisms associated with SP resistance. Polymorphisms in pfmdr-1 may also be associated with resistance to chloroquine, mefloquine and artemisinin. Use of such genetic information for the early detection of resistance foci and future monitoring of drug resistant malaria is a potentially useful epidemiological tool, in conjunction with the conventional in vitro and in vivo drug sensitivity assessments. The purpose of this review is to describe the state of knowledge regarding drug resistant malaria and to outline the changing patterns of drug resistance including its determinants, current status in diverse geographical areas, molecular markers and their implications to limit the advent, spread and intensification of drug resistant malaria.

12825544
Faucher JF, Ngomo R, Kremsner PG, Ngou-Milama E
[Hypertriglyceridemia related to falciparum malaria: the role played by glycerol]
Ann Biol Clin (Paris). 2003 May-Jun;61(3):363-4.

14628378
Feng XP, Liu DQ
[Factors affecting the in vitro microtest for drug sensitivity of Plasmodium falciparum]
Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi. 2003;21(4):234-7.
OBJECTIVE: To explore factors influencing the results of in vitro microtest for drug sensitivity of Plasmodium falciparum (Pf). METHODS: Handy media, microplates predisposed with antimalarial drug, cultured Pf parasites (FCC-1/HN isolate) and blood samples from patients were used to evaluate the factors influencing the in vitro determination of drug sensitivity of Pf. RESULTS: Liquid medium and lyophilized medium stored at 4 degrees C for 2 months and 1 year respectively could keep their effect unchanged. The effect of the drug-coated plates was not changed within the following period of storage: plates coated with chloroquine and piperaquine stored at 4 degrees C for 2 years and 6 months respectively; plates coated with pyronaridine and artesunate stored at 4 degrees C for 3 months. The adhesive paper of the sealed plate could be unsealed once only. The plastic plate must be harmless to the growing of parasites. The drug liquid should not be stored over 2 wk at 4 degrees C; otherwise the drug concentration was changed. Parasites tested were at synchronous ring stage, with a density of 1,000-80,000/microliter blood, stored at room temperature for 1 h, and at 4 degrees C for 48 h. Operation needed to follow strictly the standard technical procedure. CONCLUSION: Drug plates, media, adhesive paper, parasites and operation technique can affect the result of in vitro microtest for drug sensitivity of P. falciparum. Standardized materials and operational procedure should be used to guarantee a reliable result of the test.

15040683
Ferrer-Rodriguez I, Perez-Rosado J, Gervais GW, Peters W, Robinson BL, Serrano AE
Plasmodium yoelii: identification and partial characterization of an MDR1 gene in an artemisinin-resistant line.
J Parasitol. 2004 Feb;90(1):152-60.
The molecular mechanisms by which the malarial parasite has managed to develop resistance to many antimalarial drugs remain to be completely elucidated. Mutations in the pfmdr1 gene of Plasmodium falciparum, as well as an increase in pfmdr1 copy number, have been associated with resistance to the quinoline-containing antimalarial drugs. We investigated the mechanisms of drug resistance in Plasmodium using a collection of P. yoelii lines with different drug resistance profiles. The mdr1 gene of P. yoelii (pymdr1) was identified and characterized. A 2- to 3-fold increase in the pymdr1 gene copy number was observed in the P. yoelii ART line (artemisinin resistant) when compared with the NS parental line. The pymdr1 gene was mapped to a chromosome of 2.1 Mb in all lines analyzed. Reverse transcriptase-polymerase chain reaction and Western blot experiments confirmed the expression of the gene at the RNA and protein levels.

10450446
Fevre EM, Barnish G, Yamokgul P, Rooney W
Sensitivity in vitro of Plasmodium falciparum to three currently used antimalarial drugs on the western border of Thailand.
Trans R Soc Trop Med Hyg. 1999 Mar-Apr;93(2):180-4.

The sensitivity in vitro of Plasmodium falciparum to mefloquine, quinine and artemisinin was assessed in an area of multi-drug resistance on the Thai-Myanmar border, using the World Health Organization's microtest, based on schizont maturation inhibition. Participating individuals were exclusively those who had contracted their infections within Myanmar. A total of 34 successful tests were carried out for mefloquine and quinine, showing a marked decrease in sensitivity compared to previously published results. Ten artemisinin tests were successful, with many failures due to the poor storage stability of the test plates. The implications of the shelf-life of the artemisinin plates is discussed. These results contribute to setting a base line of sensitivity to artemisinin in vitro.

10674097
Fivelman QL, Walden JC, Smith PJ, Folb PI, Barnes KI
The effect of artesunate combined with standard antimalarials against chloroquine-sensitive and chloroquine-resistant strains of Plasmodium falciparum in vitro.
Trans R Soc Trop Med Hyg. 1999 Jul-Aug;93(4):429-32.
The interactions of artesunate with chloroquine, mefloquine, quinine, doxycycline and pyrimethamine were tested in vitro against chloroquine-sensitive (D10) and chloroquine-resistant (RSA11) strains of Plasmodium falciparum. Mefloquine and quinine both showed synergism of artesunate activity against each of the strains, whilst doxycycline showed an additive interaction. Pyrimethamine combinations were antagonistic, and the combination of artesunate with chloroquine was antagonistic against RSA11, and additive against D10. Although weak antagonism in vitro might not indicate any clinical significance, synergism with artesunate may increase the clinical usefulness of either drug, and could potentially be of value in delaying the emergence of resistance.

9093426
Fleck SL, Robinson BL, Peters W, Thevin F, Boulard Y, Glenat C, Caillard V, Landau I
The chemotherapy of rodent malaria. LIII. 'Fenozan B07' (Fenozan-50F), a difluorinated 3,3'-spirocyclopentane 1,2,4-trioxane: comparison with some compounds of the artemisinin series.
Ann Trop Med Parasitol. 1997 Jan;91(1):25-32.
Fenozan B07, a difluorinated 3,3'-spirocyclopentane, 1,2,4-trioxane, is a novel, second-generation antimalarial endoperoxide which is a potent blood schizontocide against strains of rodent malaria that are highly resistant to a wide spectrum of classical antimalarials. Like compounds of the artemisinin series, its action is limited to the intra-erythrocytic stages, both asexual and sexual, and it is devoid of causal prophylactic activity. Both Fenozan B07 and the artemisinins are potent gametocytocides. In contrast to arteether, in a model using synchronous infection with Plasmodium vinckei petteri, Fenozan B07 inhibits the development of all asexual stages except preschizonts, as well as gametocytes. The activity of the artemisinin series in rodent-malaria models is limited to the rings and young trophozoites. The combined effect of Fenozan B07 with artesunate against P. v. petteri was only additive. A slight degree of potentiation was found in mice infected with asynchronous, drug-sensitive P. berghei but the combination was only additive against CQ-resistant P. yoelli ssp. NS. On the other hand, a significant degree of synergism was observed when mice infected with the artemisinin-resistant ART line of P. yoelii ssp. NS received combinations of Fenozan B07 with artemisinin. The conclusion is drawn from these and other data that there are significant differences between the blood schizontocidal actions of Fenozan B07 and the artemisinins. The basis of these differences remains to be determined.

15022176
Francois G, Passreiter CM
Pseudoguaianolide sesquiterpene lactones with high activities against the human malaria parasite Plasmodium falciparum.
Phytother Res. 2004 Feb;18(2):184-6.
Four sesquiterpene lactones of the pseudo-guaianolide type (helenalin, dihydrohelenalin and their acetates), have shown activities against asexual blood forms of Plasmodium falciparum in vitro. Their IC(50) values were situated in the range of 0.23 to 7.41 micro M. The activity found for helenalin was high, even compared to the activity found for artemisinin.

12173975
Frederich M, Dogne JM, Angenot L, De Mol P
New trends in anti-malarial agents.
Curr Med Chem. 2002 Aug;9(15):1435-56.
Malaria is the major parasitic infection in many tropical and subtropical regions, leading to more than one million deaths (principally young African children) out of 400 million cases each year (WHO world health report 2000). More than half of the world's population live in areas where they remain at risk of malaria infection. During last years, the situation has worsened in many ways, mainly due to malarial parasites becoming increasingly resistant to several antimalarial drugs. Furthermore, the control of malaria is

becoming more complicated by the parallel spread of resistance of the mosquito vector to currently available insecticides. Discovering new drugs in this field is therefore a health priority. Several new molecules are under investigation. This review describes the classical treatments of malaria and the latest discoveries in antimalarial agents, especially artemisinin and its recent derivatives as well as the novel peroxidic compounds.

9763724
Fungladda W, Honrado ER, Thimasarn K, Kitayaporn D, Karbwang J, Kamolratanakul P, Masngammueng R
Compliance with artesunate and quinine + tetracycline treatment of uncomplicated falciparum malaria in Thailand.
Bull World Health Organ. 1998;76 Suppl 1:59-66.
A randomized, controlled, malaria-clinic-based field trial was conducted to compare compliance with a 7-day quinine + tetracycline regimen and a 5-day 700-mg artesunate regimen for the treatment of uncomplicated falciparum malaria in a community in Thailand. Of 137 patients, aged 15-60 years attending a malaria clinic, 77 received artesunate and 60 received quinine + tetracycline. Compliance and cure rates were evaluated on days 5 (artesunate) and 7 (quinine + tetracycline) using patient interview/residual pill counts and peripheral blood smear, respectively. Data were analysed using the intention-to-treat approach, and the reasons for compliance and noncompliance were investigated. Compliance was significantly higher (98.4%) with artesunate than with quinine + tetracycline (71.7%) (relative risk adjusted for sex (aRR) = 1.39 (95% C.I. = 1.15-1.68); referent: quinine + tetracycline). Cure rate (100%) was higher in those receiving artesunate than quinine + tetracycline (77.4%) (aRR = 1.32 (95% C.I. = 1.12-1.55)). Reasons for compliance included the desire to be cured and to follow the advice of malaria staff/employer, and the simple dosing regimen. Noncompliance was mostly due to adverse reactions and forgetting to take the drugs. These results can serve as a baseline for designing and evaluating new interventions to improve compliance, as well as for studying cost-effectiveness to help drug policy decision-making. We recommend a strategy which integrates a short-course, once-a-day regimen (with minimal adverse reactions), a better delivery system for antimalarial drugs and health education, and an enhanced advisory role of malaria staff. Considering the higher compliance rate and curative effectiveness of artesunate, we recommend its use instead of quinine + tetracycline for the treatment of uncomplicated malaria in clinics in Thailand.

15363498
Gabriels M, Plaizier-Vercammen J
Experimental designed optimisation and stability evaluation of dry suspensions with artemisinin derivatives for paediatric use.
Int J Pharm. 2004 Sep 28;283(1-2):19-34.
There is a great need for oral anti-malaria preparations especially for small children, which are easy to administer and keep their stability under tropical conditions. The purpose of this work was therefore to develop a dry suspension, containing one of the artemisinin derivatives, namely artesunate, artemether and dihydroartemisinin using fast wetting suspending agents, i.e. xanthan gum and Avicel CL611. For the optimisation of these two variables, namely the suspending agent's content, a Doehlert design was applied. Via preliminary tests on sedimentation behaviour, the limits of both products were determined, respectively 0.1-0.4% (w/v) and 1.0-2.5% (w/v). As responses, sedimentation as a function of time, viscosity and price of the suspension, were evaluated. The stability tests of the reconstituted suspensions showed bad results for artesunate, even when the pH was adapted. In contrast, dihydroartemisinin showed only 10% degradation within 10 days and artemether was stable at least 21 days. Practically the last one was able to foresee a chemically and physically stable suspension at least during the administration period (5 to 7 days) and was therefore selected for further optimisation concerning taste and appearance. Based on the results of selection tests for the colourant, sweetener and taste masking agent, the following composition was proposed for a suitable dry powder with artemether (AM) as active compound to prepare 100 ml reconstituted suspension: AM 300 mg, Avicel CL611 2 g, xanthan gum 200 mg, crystalline saccharose 35 g, citric acid monohydrate 150 mg, Nipagine 80 mg, Nipasol 20 mg, sodium saccharinate 250 mg, tutti-frutti 250 mg and Sunset yellow 10 mg.

12644192
Gabriels M, Plaizier-Vercammen J
Physical and chemical evaluation of liposomes, containing artesunate.
J Pharm Biomed Anal. 2003 Mar 26;31(4):655-67.
As artesunate has a rapid onset of therapeutic effect and quick elimination, frequent administration is required, especially in the treatment of malaria. Such treatment courses led to bad patients' compliance, leading to high recrudescence rate. Therefore, slow release preparations seemed to be a logical approach in artesunate monotherapies, as can be developed with liposomal suspensions, especially for parenteral administration. Thus, the aim of this study was to develop sterile liposomes. The suspension was evaluated

on its chemical/physical stability, including chemical degradation and crystallization of artesunate, and release capacities, by use of the dialysis technique. The maximal encapsulation degree of artesunate without crystals was 1.5 mg in 300 mg lipids per ml suspension, containing egg-phosphatidylcholine/cholesterol in a molar ratio of 4:3. The highest stability was obtained with a phosphate buffer of pH 5, which could be expected, as artesunate is almost totally encapsulated. But by reason of instability in water, the suspension containing artesunate 1 mg/ml was preferred, as the encapsulation efficiency is 100%. The in vitro release test proves that artesunate is reversibly encapsulated in liposomes. A method for sterile production of liposomes at lab-scale level is also presented.

9289651
Gachot B, Eliaszewicz M, Dupont B
Artesunate and cerebellar dysfunction in falciparum malaria.
N Engl J Med. 1997 Sep 11;337(11):792-3.

10778518
Garg MR, Gogtay NJ, Kotwani RN, Bodhe PV, Kshirsagar NA
Resurgence of malaria in Mumbai--is escalating chloroquine resistance a cause?
J Assoc Physicians India. 1999 Apr;47(4):377-9.
OBJECTIVES: Given the steep increase in the incidence of malaria in the city of Mumbai in the nineties, we decided to study the causes for the same as well as analyse the resistance pattern of P. falciparum in the city. METHODS: Smear positive cases of acute uncomplicated P. falciparum malaria who presented to us in 1994, 1995 and 1996 were analysed for their response to full dose chloroquine (25 mg/kg over 3 days). Samples of those patients who satisfied criteria for in vitro resistance testing to chloroquine and other antimalarials, were also studied. Chloroquine level in all patients was studied on Day 3 by HPLC. In vivo response to chloroquine was studied in 30, 71 and 78 patients while in vitro response was studied in 17, 35 and 30 patients respectively in the above years. RESULTS: We found in vivo chloroquine resistance figures of 36.78%, 45% and 53.8% in the years '94, '95 and '96 and the in vitro resistance figures of 41.17%, 54.28% and 66.6% in the same years. CONCLUSIONS: Our previous studies documenting 15% chloroquine resistance in 1993 and the increasing incidence in subsequent years suggests resistance to chloroquine as one of the causes of resurgence and maintenance of malaria in the city. If patients of uncomplicated P. falciparum malaria are to be treated with chloroquine, rigorous monitoring for nonresponse and timely rescue medication is necessary. Alternative antimalarial drugs such as mefloquine, artemisinin derivatives and sulfadoxine-pyrimethamine should be used in patients where this is not possible.

15839750
Garner P, Graves PM
The benefits of artemisinin combination therapy for malaria extend beyond the individual patient.
PLoS Med. 2005 Apr;2(4):e105. Epub 2005 Apr 26.

9129535
Gay F, Bustos D, Traore B, Jardinel C, Southammavong M, Ciceron L, Danis MM
In vitro response of Plasmodium falciparum to atovaquone and correlation with other antimalarials: comparison between African and Asian strains.
Am J Trop Med Hyg. 1997 Mar;56(3):315-7.
Atovaquone (dihydroxynaphthoquinone 566C80) is a broad-spectrum antiprotozoal compound demonstrating potent antimalarial activity against multidrug-resistant malaria. We present the results of in vitro drug sensitivity tests of 142 Plasmodium falciparum isolates, 108 from 14 countries of West and Central Africa, 32 from the Philippines, and one each from Laos and Myanmar. These were tested in vitro against nine drugs: the classic antimalarials chloroquine, quinine, mefloquine and halofantrine, the four qinghaosu derivatives, artemisinin, artemether, artesunate, and arteether, and the new compound atovaquone. Results showed the Asian strains have a higher median 50% inhibitory concentration (IC50) to almost all drugs compared with those from Africa. This was significantly different for chloroquine, halofantrine, and artemisinin. We used three different approaches to estimate the threshold for resistance of atovaquone to be approximately 5-7 nmol/L. The global median of 96 pooled strains is 1.4 nmol/L and the 90th percentile is 5.5 nmol/L for atovaquone. There were no correlations of atovaquone with the eight other antimalarials among African strains, but significant correlations, except for halofantrine, were observed among Asian strains. The absence of a correlation between atovaquone and the other available drugs indicates the potential of atovaquone as an alternative antimalarial in Africa. The correlation observed among Asian strains, however, suggests that atovaquone has to be used cautiously in Asia. Nevertheless, the association with proguanil in

recently concluded clinical trials in Europe, South America, Asia, and Africa has demonstrated its antimalarial efficacy.

9492419
Gera R, Khalil A
Artemisinine and its derivatives.
Indian Pediatr. 1997 Sep;34(9):813-6.

11791958
Giao PT, Binh TQ, Kager PA, Long HP, Van Thang N, Van Nam N, de Vries PJ
Artemisinin for treatment of uncomplicated falciparum malaria: is there a place for monotherapy?
Am J Trop Med Hyg. 2001 Dec;65(6):690-5.
The efficacy of artemisinin monotherapy was studied in 227 patients with uncomplicated falciparum malaria. They all received artemisinin at t = 0 hr, t = 8 hr, and thereafter once daily; treatment was extended at random until they had taken either 5 days of artemisinin followed by 2 days of placebo (A5), or 7 days (A7) of artemisinin. The adult artemisinin dose was 500 mg; children aged < 15 years received 10 mg/kg per dose. The median (range) parasite clearance time was 39 (8-112) hr for A5 and 43 (38-104) hr for A7 (P = 0.085). The recrudescence rates were similar between the groups. The lowest parasite count achieved during treatment (Pterm) was associated with the occurrence of recrudescence (P = 0.046, Cox regression model); it was lower for patients with a radical cure or late recrudescence than for early recrudescence (P = 0.034, t-test). Artemisinin monotherapy may offer rapid recovery and fast parasite clearance, but recrudescence is frequent. Extending the duration of monotherapy from 5 days to 7 days does not reduce recrudescence.

14511555
Giao PT, De Vries PJ, Hung LQ, Binh TQ, Nam NV, Kager PA
Atovaquone-proguanil for recrudescent Plasmodium falciparum in Vietnam.
Ann Trop Med Parasitol. 2003 Sep;97(6):575-80.
Malarone, a fixed combination of atovaquone with proguanil (AP), has recently been recognized as a promising treatment against multidrug-resistant Plasmodium falciparum. In Vietnam, the first-line treatment for P. falciparum malaria is currently a combination of mefloquine and an artemisinin derivative, and the use of AP has not been explored. The aim of the present study, based in Vietnam, was to assess the efficacy of AP when used to treat P. falciparum recrudescences that had occurred after primary treatment with mefloquine-artesunate. All but two of the 39 patients investigated completed follow-up. The mean parasite- and fever-clearance times [and 95% confidence intervals (CI)] after AP treatment were 36 (30-42) and 21 (18-24) h, respectively. Most (32) of the 37 infections that were followed adequately appeared to be eradicated by the AP, the other five recrudescing once more. The overall cure 'rate' and (CI) was 86% (76%-98%). All of the patients tolerated the AP well. Atovaquone-proguanil appears to be a safe and promising alternative treatment for P. falciparum infections in South-east Asia, although the combination is relatively expensive and may not clear some infections with multidrug-resistant parasites.

16135200
Giao PT, Vries PJ, Binh TQ, Nam NV, Kager PA
Early diagnosis and treatment of uncomplicated malaria and patterns of health seeking in Vietnam.
Trop Med Int Health. 2005 Sep;10(9):919-25.
Early diagnosis and treatment of malaria (EDTM) is a key component of malaria control. The success of EDTM depends on health seeking behaviour and the quality of the health service. This study assessed self-diagnosis, treatment and treatment delay after the introduction of EDTM in 1993. In southern Vietnam EDTM comprises microscopic diagnosis and free treatment with artemisinin derivatives at public health facilities. Until 2001, 1698 questionnaires had been completed by patients participating in randomized treatment trials of uncomplicated malaria. The presumptive self diagnosis 'malaria' increased from 68% in 1993 to 100% in 2001 and self-treatment decreased, from 74% to 8% in 2000 and 24% in 2001. The median (maximum) delay between first symptoms and seeking treatment at a public health facility decreased from 3 (23) to 1.3 (3) days (P

16117967
Gil VS, Ferreira MC, d'Alva FS, d'Abreu JA, Will IM, Gomes ML, Castelli F, Taylor WR, Olliaro P, D'Alessandro U
Efficacy of artesunate plus chloroquine for uncomplicated malaria in children in Sao Tome and Principe: a double-blind, randomized, controlled trial.
Trans R Soc Trop Med Hyg. 2003 Nov-Dec;97(6):703-6.

We conducted a double-blind, randomized, placebo-controlled trial in Sao Tome and Principe to investigate the safety, tolerability and efficacy of chloroquine (CQ) combined with artesunate (AS) over CQ monotherapy. Four hundred children, aged 6-59 months, with acute uncomplicated Plasmodium falciparum malaria were randomized to receive a standard dose of CQ (25 mg/kg bodyweight) over 3 d or CQ + AS (4 mg/kg bodyweight) daily for 3 d. Children were followed-up for 28 d. The combined treatment was well tolerated and there were no serious drug-related adverse events. By day 2 parasite clearance was significantly faster for children treated with CQ + AS compared with CQ alone (29/194 [14.9%] vs. 168/190 [88.4%] still parasitaemic, P< 0.0001). Day 14 parasitological failure rates were 153/191 (80.1%) for CQ alone compared with 32/193 (16.6%) in the CQ + AS group (odds ratio [OR] =20.2, 95% CI 11.7-35.4, P< 0.001). Corresponding clinical failure rates were 128/161 (67.0%) and 12/193 (6.2%) (OR = 30.6, 95% CI 15.3-62.7, P< 0.001). By day 28 the parasitological failure rates (new infections excluded) were 155/191 (81.1%) in the CQ group and 63/194 (32.4%) in the CQ + AS group (OR = 8.9, 95% CI 5.4-14.7, P< 0.001). Symptoms resolved faster in children who received AS. They were also less likely to be gametocytaemic after treatment. The combination treatment was well tolerated and considerably improved treatment efficacy. However, the current levels of CQ resistance preclude its use in Sao Tome where CQ should be abandoned as first-line drug. However, CQ + AS may be an option in areas where CQ resistance is lower.

11419681
Goka BQ, Adabayeri V, Ofori-Adjei E, Quarshie B, Asare-Odei G, Akanmori BD, Kurtzhals J, Ofori-Adjei D, Neequaye J
Comparison of chloroquine with artesunate in the treatment of cerebral malaria in Ghanaian children.
J Trop Pediatr. 2001 Jun;47(3):165-9.
Despite previously reported chloroquine-resistant forms of PF falciparum in Ghana, chloroquine remains the drug of choice in severe malaria. Artemisinin derivatives have been shown to be effective against chloroquine-resistant strains in other endemic areas. This open randomized study was conducted to compare the efficacy of chloroquine and artesunate in the treatment of childhood cerebral malaria. Out of 82 subjects that fulfilled the inclusion criteria, 36 were randomized to receive chloroquine and 46 to receive artemisinin. Blantyre coma scores, temperature and parasitaemia were monitored. Mortality and neurological deficits were documented. There was no difference in mortality rates (chloroquine, 16.7 per cent; artesunate, 21.7 per cent; p = 0.6), neurological deficit at day 14 (chloroquine, 0 per cent; artesunate, 4.3 per cent; p = 0.3), resolution of fever (p = 0.55), and coma recovery time (p = 0.8), between the two groups. The results suggest that syrup chloroquine and intramuscular/oral artesunate currently give comparable clinical responses in the treatment of cerebral malaria in Ghana. Possible reasons for this are discussed, and suggestions are made for future antimalarial drug policy.

10464415
Goldring JD, Padayachee T, Ismail I
Plasmodium falciparum malaria: rosettes are disrupted by quinine, artemisinin, mefloquine, primaquine, pyrimethamine, chloroquine and proguanil.
Mem Inst Oswaldo Cruz. 1999 Sep-Oct;94(5):667-74.
An assay was developed measuring the disruption of rosettes between Plasmodium falciparuminfected (trophozoites) and uninfected erythrocytes by the antimalarial drugs quinine, artemisinin mefloquine, primaquine, pyrimethamine, chloroquine and proguanil. At 4 hr incubation rosettes were disrupted by all the drugs in a dose dependent manner. Artemisinin and quinine were the most effective anti-malarials at disrupting rosettes at their therapeutic concentrations with South African RSA 14, 15, 17 and The Gambian FCR-3 P. falciparum strains. The least effective drugs were proguanil and chloroquine. A combination of artemisinin and mefloquine was more effective than each drug alone. The combinations of pyrimethamine or primaquine, with quinine disrupted more rosettes than quinine alone. Quinine may be an effective drug in the treatment of severe malaria because the drug efficiently reduces the number of rosettes.

10212912
Gomes M, Olliaro P, Folb P
What role can public health institutions play in drug development for the poor? A case study of artesunate.
Med Trop (Mars). 1998;58(3 Suppl):97-100.
Although the strategy of artesunate development was orchestrated from within WHO's Special Programme for Research and Training in Tropical Diseases, it relies heavily upon an alliance of scientist, laboratories, industry, regulators and ministries of health to ensure the public health outcome. This development strategy has transformed the way in which WHO does business, both within and outside the Organization. In essence, each and every player has rallied in the challenge to reduce the discrepancy between need and availability of a drug that can has the potential to reduce mortality form the disease.

9763718
Gomes M, Wayling S, Pang L

Interventions to improve the use of antimalarials in south-east Asia: an overview.
Bull World Health Organ. 1998;76 Suppl 1:9-19.
There are few drugs for malaria, and those which are available for use are subject to rapid development of resistance. Curiously, little effort has been made to improve drug use in malaria-endemic countries and to assess the benefits of such improvements. Advances can be made in public understanding of the value of ingesting a full regimen of antimalarials, in order to achieve complete cure, and in improving simple technologies (blister packaging) to achieve the same result. Better efforts can be made to reduce the availability of fake or substandard drugs in the marketplace. In this article, we describe the outcome of a concerted effort to improve drug compliance and drug quality in an area of multidrug resistance for malaria. These research efforts, guided by the Task Force for Improved Use of Antimalarials, characterized the problems in drug compliance in South-East Asia, and developed interventions to improve drug use in the various countries. Interventions involved drug packaging, public information campaigns, and assessments of drug quality. Results show that blister packaging worked best to improve drug compliance and that the increased cost of packaged medication did not limit its use. Drug quality was a major problem in unregulated countries and should be improved.

14636982
Gomez EA, Jurado MH, Cambon N
Randomised efficacy and safety study of two 3-day artesunate rectal capsule/mefloquine regimens versus artesunate alone for uncomplicated malaria in Ecuadorian children.
Acta Trop. 2003 Dec;89(1):47-53.
The combination of artesunate and mefloquine is one of the most effective treatments against multidrug-resistant falciparum malaria. Experience in children is however limited. The objective of this study was to compare the efficacy and safety of two artesunate/mefloquine combinations with artesunate monotherapy in Ecuadorian children. A total of 150 children with an age between 2 and 12 years, confirmed to have uncomplicated falciparum malaria, were randomly selected and divided in three treatment groups of 50 patients each. Group 1 received 50 mg rectal capsules alone (40 mg/kg total dose) administered over 6 days. Group 2 received 50 mg rectal capsules (30 mg/kg total dose) for 3 days combined with mefloquine (20 mg/kg total dose) on day 1. Group 3 was treated with 50 mg rectal capsules (30 mg/kg total dose) for 3 days, combined with mefloquine on days 1 and 3 (15-17 mg/kg total dose). Patients were continuously followed up and controlled by clinical and laboratory examinations for 7 days as well as on days 14, 21 and 28. An additional parasite examination was performed at 2 months following therapy. Clearance of parasitaemia was comparable between treatment groups. These were 9.2, 9.2 and 8.3 h for Groups 1, 2 and 3, respectively. Cure rates at day 28 were 76, 96 and 94% and after 2 months 60, 88 and 80%, respectively. There were no adverse events (AEs) reported during the study. Vital signs and laboratory examinations revealed no changes of clinical relevance. It can be concluded that the combination of artesunate rectal capsules with mefloquine is effective and safe. Starting concomitant administration already on day 1 is well tolerated. This combination significantly reduces the incidence of recrudescence compared to artesunate monotherapy. Comparing the two tested artesunate/mefloquine regimens, a total mefloquine dose of 20 mg/kg seems to be more effective compared to a total dose of 15-17 mg/kg. Further studies seem to be warranted.

11848324
Gopinathan VP, Jayraj PM, Rekha, Dejo R
Malaria as a cause of multi organ failure.
J Assoc Physicians India. 2001 Oct;49:1046.

11151745
Gordi T, Hai TN, Hoai NM, Thyberg M, Ashton M
Use of saliva and capillary blood samples as substitutes for venous blood sampling in pharmacokinetic investigations of artemisinin.
Eur J Clin Pharmacol. 2000 Nov;56(8):561-6.
OBJECTIVES: Artemisinin concentrations in venous plasma, capillary plasma and saliva were compared. METHODS: Eighteen Vietnamese adults with uncomplicated falciparum malaria were treated with artemisinin. Saliva, capillary and venous plasma were sampled and analysed for artemisinin using high-performance liquid chromatography with an ultraviolet detector (HPLC-UV). RESULTS: Artemisinin capillary plasma concentrations were highly correlated to its venous plasma levels (correlation coefficient r = 0.92). Capillary/venous concentration ratios were significantly higher than unity at 30 min and 60 min after drug intake, indicating an arterial-venous concentration difference. Artemisinin unbound fraction in plasma averaged 0.14 (SD = 0.03) and was independent of drug concentration (114-1001 ng/ml). Artemisinin concentrations in saliva were comparable to its unbound levels in plasma. Saliva levels were more highly

correlated to unbound capillary plasma (r = 0.85) than to unbound venous plasma concentrations (r = 0.77). No statistically significant differences were found between the saliva, unbound venous and unbound capillary area under the curve (AUC) values. CONCLUSIONS: Capillary plasma or saliva may replace venous plasma in pharmacokinetic investigations of artemisinin. Due to the ease of collection and handling, saliva sampling can be a simple approach in field studies of artemisinin, although the lower saliva concentrations require more sensitive analytical methods.

11897585
Gordi T, Huong DX, Hai TN, Nieu NT, Ashton M
Artemisinin pharmacokinetics and efficacy in uncomplicated-malaria patients treated with two different dosage regimens.
Antimicrob Agents Chemother. 2002 Apr;46(4):1026-31.
The immediate efficacies of two oral dosage regimens of artemisinin were investigated in 77 male and female adult Vietnamese falciparum malaria patients randomly assigned to treatment with either 500 mg of artemisinin daily for 5 days (group A; n = 40) or artemisinin at a dose of 100 mg per day for 2 days, with the dose increased to 250 mg per day for 2 consecutive days and with a final dose of 500 mg on the fifth day (group B; n = 37). Parasitemia was monitored every 4 h. The average parasite clearance time was longer in group B than in group A (means +/- standard deviations, 50 +/- 23 and 34 +/- 14 h, respectively; P < 0.01). Artemisinin concentrations in saliva samples obtained on days 1 and 5 were quantified by high-performance liquid chromatography. The average oral clearance, based on saliva drug concentrations in group B patients, was twofold higher than that in group A patients on day 1 (P < 0.01), with no differences in drug half-lives (P = 0.40), indicating a saturable first-pass metabolism. Female patients had higher oral clearance values on day 1. Artemisinin's pharmacokinetic parameters were similar on day 5 in both groups, although a significant increase in oral clearance from day 1 to day 5 was evident. Thus, artemisinin exhibited both dose- and time-dependent pharmacokinetics. The escalating dose studied did not result in higher artemisinin concentrations toward the end of the treatment period.

14757313
Gordi T, Lepist EI
Artemisinin derivatives: toxic for laboratory animals, safe for humans?
Toxicol Lett. 2004 Mar 1;147(2):99-107.
A discrepancy seems to prevail with regard to the toxicity and safety of the artemisinin family of antimalarials. While these compounds have been found to be virtually void of any serious side effects in humans, their neurotoxicity in animal models has raised concerns about their use. In this paper, we present selected examples of both pre-clinical and clinical studies dealing with adverse effects of artemisinin drugs. We suggest that the prolonged presence of artemisinins upon slow release from oil-based intramuscular formulations is the main cause of the observed toxicity in laboratory animals. In contrast, oral intake of these compounds, which is by far the most common formulation used for treatment of malaria patients, results in rapid clearance of these drugs and is thus unlikely to cause any toxicity in human subjects. Another plausible factor may be the relatively high doses of artemisinin compounds used in animal studies. In conclusion, the observation of the toxicity of artemisinin compounds in animals, but not in humans, is most likely due to different pharmacokinetic profiles after different routes of administrations.

16305583
Gordi T, Xie R, Jusko WJ
Semi-mechanistic pharmacokinetic/pharmacodynamic modelling of the antimalarial effect of artemisinin.
Br J Clin Pharmacol. 2005 Dec;60(6):594-604.
PURPOSE: To characterize artemisinin pharmacokinetics (PK) and its antimalarial activity in vivo. METHODS: Artemisinin salivary concentration and parasite count data were obtained from Vietnamese malaria patients receiving two different dosage regimens. PK data were analysed using a previously developed semiphysiological model incorporating autoinduction of eliminating enzymes. A pharmacodynamic (PD) model reflecting different stages of the parasite life-cycle was developed and fitted to the data. The model included visible and invisible compartments as well as sensitive, insensitive, and injured parasite stages. Salivary artemisinin concentrations functioned as the driving force for the observed decrease in the number of parasites. RESULTS: Large interindividual variability was observed in both PK and PD data. The PK model described reasonably well the observed decrease in salivary concentrations after repeated drug administration. The preinduction hepatic extraction ratio of artemisinin was estimated to be 0.87 with a volume of distribution of 27 L. Artemisinin half-life averaged 0.7 h. Incorporation of a saturable hepatic elimination affecting the first-pass extraction as well as a higher intrinsic clearance in female patients resulted in the best fit of the model to the data. The PD model described the decrease in the number of parasites during the course of treatment well. The longest mean transit time of parasites from sensitive, visible to invisible to insensitive visible stages was found to be 34.5 h through one life-cycle. The half-life of injured parasites was 2.7 h. CONCLUSIONS: The proposed semimechanistic PK/PD model successfully

described the time course of both salivary artemisinin concentrations after repeated dosing and the number of parasites in patients treated with the drug.

10456689
Grace JM, Skanchy DJ, Aguilar AJ
Metabolism of artelinic acid to dihydroqinqhaosu by human liver cytochrome P4503A.
Xenobiotica. 1999 Jul;29(7):703-17.
1. Artelinic acid (AL), a water-soluble artemisinin analogue for treatment of multidrug resistant malaria, is metabolized to the active metabolite dihydroqinghaosu (DQHS) solely by CYP3A4/5. Although AL is not metabolized by CYP2C9, it does inhibit diclofenac 4-hydroxylase activity with an IC50 = 115 microM. Interestingly, AL activates CYP2D6-mediated bufuralol metabolism in human liver microsomes but not recombinant CYP2D6-Val by approximately 30% at AL concentrations up to 100 microM. 2. In human liver microsomes, AL is metabolized to DQHS with a Km = 157 +/- 44 microM and Vmax = 0.77 +/- 0.56 nmol DQHS/min/mg protein. Human recombinant CYP3A4 catalysed the conversion of AL to DQHS with a Km = 102 +/- 23 microM and a Vmax = 1.96 +/- 0.38 nmol DQHS/min/nmol P450. The kinetic parameters (Km and Vmax) for DQHS formation from CYP3A5 were 189 +/- 19 microM and 3.60 +/- 0.42 nmol DQHS/min/nmol P450 respectively. 3. Inhibition studies suggest that azole antifungals and calcium channel blockers may present clinically significant drug drug interactions. In human liver microsomes, ketoconazole and miconazole were potent competitive inhibitors of DQHS formation with a Ki = 0.028 and 0.124 microM respectively. Verapamil is a non-competitive inhibitor of DQHS formation in human liver microsomes with a Ki = 15 microM.

16297419
Grandesso F, Bachy C, Donam I, Ntambi J, Habimana J, D'Alessandro U, Maikere J, Vanlerberghe V, Kerah CH, Guthmann JP
Efficacy of chloroquine, sulfadoxine-pyrimethamine and amodiaquine for treatment of uncomplicated Plasmodium falciparum malaria among children under five in Bongor and Koumra, Chad.
Trans R Soc Trop Med Hyg. 2006 May;100(5):419-26. Epub 2005 Nov 16.
We report two 28-day in-vivo antimalarial efficacy studies carried out in the urban centres of Bongor and Koumra, southern Chad. We assess chloroquine (CQ), sulfadoxine-pyrimethamine (SP) and amodiaquine (AQ) to treat Plasmodium falciparum uncomplicated malaria. Methods and outcome classification complied with latest WHO guidelines. Out of the 301 and 318 children aged 6-59 months included in Bongor and Koumra, respectively, 246 (81.7%) and 257 (80.8%) were eligible for analysis. In Bongor and Koumra, the 28-day PCR-adjusted failure rates for CQ were 23.7% (95% CI 14.7-34.8%) and 32.9% (95% CI 22.1-45.1%), respectively, and those for SP were 16.3% (95% CI 9.4-25.5%) and 4.3% (95% CI 1.2-10.5%). AQ failure rates were 6.4% (95% CI 2.1-14.3%) and 2.2% (95% CI 0.3-7.6%). The current use of CQ in Bongor and Koumra is questionable, and a more efficacious treatment is needed. Considering the reduced efficacy of SP in Bongor, AQ seems to be the best option for the time being. Following WHO recommendations that prioritize the use of artemisinin-based combinations, artesunate plus amodiaquine could be a potential first-line treatment. Nevertheless, the efficacy of this combination should be evaluated and the change carefully prepared, implemented and monitored.

11108540
Green MD, Mount DL, Wirtz RA, White NJ
A colorimetric field method to assess the authenticity of drugs sold as the antimalarial artesunate.
J Pharm Biomed Anal. 2000 Dec;24(1):65-70.
Artesunate is the most widely used of the artemisinin derivatives. These drugs are being used increasingly throughout the tropical world, and are an essential component of the treatment of multi-drug resistant malaria. The recent and widespread appearance of counterfeit artesunate tablets in several countries in Southeast Asia poses a serious threat to health in this region. We have developed a simple, inexpensive colorimetric test to determine artesunate authenticity in tablets. The test is based on a reaction between an alkali decomposition product of artesunate and a diazonium salt, fast red TR (FRTR). The appearance of a yellow color indicates the presence of artesunate. The specificity of the test is dependent on the pH of the reaction. Among other antimalarials tested, (i.e. artemisinin, artemether, chloroquine, quinine, primaquine, sulfadoxine, and pyrimethamine) only artesunate produced a positive color reaction at pH 4. The assay requires only 1% of the total weight of a standard tablet containing 50 mg of artesunate and can be completed within 10 min. The method was tested on six genuine artesunate tablets and six counterfeit artesunate tablets obtained in Southeast Asia. The average amount of artesunate in the genuine tablets was determined to be 50.8 +/- 2.9 mg while the counterfeit tablets were found to contain no artesunate.

14998331
Grellepois F, Chorki F, Ourevitch M, Charneau S, Grellier P, McIntosh KA, Charman WN, Pradines B, Crousse B, Bonnet-Delpon D, Begue JP

Orally active antimalarials: hydrolytically stable derivatives of 10-trifluoromethyl anhydrodihydroartemisinin.
J Med Chem. 2004 Mar 11;47(6):1423-33.
New fluoroartemisinin derivatives containing polar or water-soluble functionalities at C-16 (11a-j, 12a-g) were synthesized using the key intermediate 16-bromo-10-trifluoromethyl anhydrodihydroartemisinin 10. The substitution reaction from 10 was more selective than that from the nonfluorinated parent bromide; the allylic bromide 10 underwent no allylic rearrangement and provided only nucleophilic substitution products in high yields with N-, O-, and C-nucleophiles. Among them, amines 11a-c appeared to be highly in vivo efficient antimalarials on mice infected with Plasmodium berghei, more than the reference sodium artesunate 1d. In particular, the most effective piperazinoethanol derivative 11b cured all mice after oral treatment at a dose lower than 10 mg/kg. Further pharmacokinetic studies showed that the bioavailability in rats following oral administration was 25 times greater for 11b than for artemether 1b.

9025258
Grigorov M, Weber J, Tronchet JM, Jefford CW, Milhous WK, Maric D
A QSAR study of the antimalarial activity of some synthetic 1,2,4-trioxanes.
J Chem Inf Comput Sci. 1997 Jan-Feb;37(1):124-30.
The antimalarial activity of a series of synthetic 1,2,4-trioxanes is correlated with molecular structure by using a pharmacophore search method (CATALYST). The technique is shown to have predictive accuracy and confirms that docking between an active trioxane and the receptor, heme, is the crucial step for drug action.

12658914
Grobusch MP, Borrmann S, Omva J, Issifou S, Kremsner PG
Severe malaria in a splenectomised Gabonese woman.
Wien Klin Wochenschr. 2003 Jan 31;115(1-2):63-5.
BACKGROUND: The intact splenic function is of utmost importance for the host's defence capacity against Plasmodium spp. not only by limiting the acute infection through the removal of parasites from the blood stream, but also by modulating parasite antigen expression on the surface of infected red blood cells as well as cellular and humoral immune response. Splenectomised individuals are at high risk to develop a more severe and prolonged disease, even if they had acquired semi-immunity prior to their loss of splenic tissue. CASE REPORT: We report on a 37 year old splenectomised Gabonese woman who developed severe falciparum malaria with hyperparasitaemia, profound anaemia, and an overwhelming gametocytaemia, recovering very slowly following quinine therapy. Whereas the clinical course is not at odds with previous descriptions, the massive occurrence of mature gametocytes as documented here has not been reported before. Whether the high gametocyte count observed in our patient was primarily due to the impaired clearance of asexual forms or to the induction of gametocytogenesis remains unclear. Regarding the optimal drug regimen for treating malaria in splenectomized patients, a combination of an aminoquinoline with an artemisinin derivative might be the optimal choice.

12206972
Guerin PJ, Olliaro P, Nosten F, Druilhe P, Laxminarayan R, Binka F, Kilama WL, Ford N, White NJ
Malaria: current status of control, diagnosis, treatment, and a proposed agenda for research and development.
Lancet Infect Dis. 2002 Sep;2(9):564-73.
Rolling back malaria is possible. Tools are available but they are not used. Several countries deploy, as their national malaria control treatment policy, drugs that are no longer effective. New and innovative methods of vector control, diagnosis, and treatment should be developed, and work towards development of new drugs and a vaccine should receive much greater support. But the pressing need, in the face of increasing global mortality and general lack of progress in malaria control, is research into the best methods of deploying and using existing approaches, particularly insecticide-treated mosquito nets, rapid methods of diagnosis, and artemisinin-based combination treatments. Evidence on these approaches should provide national governments and international donors with the cost-benefit information that would justify much-needed increases in global support for appropriate and effective malaria control.

12543147
Gumede B, Folb P, Ryffel B
Oral artesunate prevents Plasmodium berghei Anka infection in mice.
Parasitol Int. 2003 Mar;52(1):53-9.
Artesunate, a semi-synthetic derivative of a naturally occurring anti-malarial artemisinin was compared with chloroquine in C57BL/6 mice infected with Plasmodium berghei Anka (PbA). A 7-day oral administration of artesunate prevented parasitaemia at 10 mg/kg/day. However, recrudescence of parasitaemia and cerebral malaria occurred upon cessation of treatment followed by death within 28 days. However, a 14-day course of artesunate (100 mg/kg/day) prevented completely the development of parasitaemia and cerebral malaria with a survival of more than 60-days as did 10 mg/kg/day chloroquine. These data demonstrate that oral

artesunate inhibits PbA and prevents cerebral malaria, but needs to be administered at high dose and for prolonged time to eradicate PbA infection in mice.

14521743
Guo WZ, Guo XB, Zheng QJ, Tan B, Chen RJ, Ou FZ, Fu LC
[A randomized comparative study of naphtoquine, mefloquine and artsunate in the treatment of falciparum malaria]
Zhonghua Yi Xue Za Zhi. 2003 Aug 25;83(16):1406-8.
OBJECTIVE: To evaluate the efficacy and safety of naphtoquine, compared with mefloquine and artesunate in the treatment of falciparum malaria. METHOD: Ninety patients with falciparum malaria were randomly allocated to 3 groups, including naphtoquine, mefloquine and artesunate group. In the naphtoquine group, thirty patients were prescribed single daily dosage of 1,000 mg for one day. In the mefloquine group, equal patients were treated with single dosage of 750 mg. Another thirty patients in the artesunate group were given total dosage of 600 mg for five days and doubling dosage on the first day. RESULT: In all three groups, symptoms were well controlled. The average fever-subsidence time in naphtoquine group was 30 h +/- 16 h and approximate that in mefloquine group (24 h +/- 15 h, P>0.05), but was longer than that in naphtoquine group (18 h +/- 9 h, P

2698257
Guo XB
[Clinical observations on 100 cases of malignant malaria treated with artesunate tablets]
Zhonghua Yi Xue Za Zhi. 1989 Sep;69(9):515-6.

16103586
Gupta RK, Van Vugt M, Paiphun L, Slight T, Looareesuwan S, White NJ, Nosten F
Short report: no evidence of cardiotoxicity of atovaquone-proguanil alone or in combination with artesunate.
Am J Trop Med Hyg. 2005 Aug;73(2):267-8.
Combinations are set to become the mainstay in treatment and prophylaxis of malaria due to Plasmodium falciparum. Various antimalarials have been implicated in cardiotoxicity via prolongation of the QTc interval. Atovaquone-proguanil is an effective and increasingly popular antimalarial choice when used alone or with artesunate in areas of drug resistance. We report the results of an investigation carried out on the Thai-Burmese border in 42 patients randomized to receive either atovaquone-proguanil or atovaquone-proguanil-artesunate for three days. Electrocardiographic recordings were made at baseline and one hour after each dose. There was no statistically significant change in QTc interval between baseline and any subsequent readings in either treatment group or the cohort as a whole. We conclude that atovaquone-proguanil shows no evidence of cardiotoxicity either alone or when combined with artesunate.

11971651
Gupta S, Thapar MM, Mariga ST, Wernsdorfer WH, Bjorkman A
Plasmodium falciparum: in vitro interactions of artemisinin with amodiaquine, pyronaridine, and chloroquine.
Exp Parasitol. 2002 Jan;100(1):28-35.
In the scenario of drug-resistant Plasmodium falciparum malaria combination therapy represents an effective approach. Artemisinin and its derivatives are of special interest because they represent the most effective group of compounds against multidrug-resistant malaria with a rapid onset of action and a short half-life. Interactions of artemisinin with amodiaquine, pyronaridine, and chloroquine were therefore investigated against three strains of P. falciparum using a 48-h in vitro culture assay. Two of the strains were chloroquine sensitive and one was partially chloroquine resistant. Observed effective concentrations (O) of the combined compounds at different concentration ratios were calculated for different degrees of inhibition (EC50, EC90, EC99) and compared to expected calculated effective concentrations (E) using a probit method. Synergism with mean O/E EC90 values of 0.25 and 0.8 were found with the combination of artemisinin and the two Mannich bases, amodiaquine and pyronaridine, respectively, whereas chloroquine showed addition with a mean value of 1.2. Although both amodiaquine and chloroquine are 4-aminoquinolines, their interaction with artemisinin appears to be different. The combination of artemisinin with amodiaquine represents an important option for the treatment of falciparum malaria.

15876443
Guthmann JP, Ampuero J, Fortes F, van Overmeir C, Gaboulaud V, Tobback S, Dunand J, Saraiva N, Gillet P, Franco J, Denoncin A, van Herp M, Balkan S, Dujardin JC, D'Alessandro U, Legros D
Antimalarial efficacy of chloroquine, amodiaquine, sulfadoxine-pyrimethamine, and the combinations of amodiaquine + artesunate and sulfadoxine-pyrimethamine + artesunate in Huambo and Bie provinces, central Angola.

Trans R Soc Trop Med Hyg. 2005 Jul;99(7):485-92.
We studied three antimalarial treatments in Caala and Kuito, Angola, in 2002 and 2003. We tested chloroquine (CQ), amodiaquine (AQ) and sulfadoxine-pyrimethamine (SP) in Caala, and AQ, SP and the combinations AQ+artesunate (AQ+AS) and SP+artesunate (SP+AS) in Kuito. A total of 619 children (240 in Caala, 379 in Kuito) with uncomplicated Plasmodium falciparum malaria were followed-up for 28 days, with PCR genotyping to distinguish recrudescence from reinfection. PCR-corrected failure proportions at day 28 were very high in the CQ group (83.5%, 95% CI 74.1-90.5), high in the SP groups (Caala: 25.3%, 95% CI 16.7-35.8; Kuito: 38.8%, 95% CI 28.4-50.0), around 20% in the AQ groups (Caala: 17.3%, 95% CI 10.0-27.2; Kuito: 21.6%, 95% CI 14.3-30.6) and very low in the artemisinin-based combination groups (1.2%, 95% CI 0.0-6.4 for each combination AQ+AS and SP+AS). These results show that CQ and SP are no longer efficacious in Caala and Kuito and that the moderate efficacy of AQ is likely to be compromised in the short term if used as monotherapy. We recommend the use of AQ with AS, though this combination might not have a long useful therapeutic life because of AQ resistance.

9373657
Ha V, Nguyen NH, Tran TB, Bui MC, Nguyen HP, Tran TH, Phan TQ, Arnold K, Tran TH
Severe and complicated malaria treated with artemisinin, artesunate or artemether in Viet Nam.
Trans R Soc Trop Med Hyg. 1997 Jul-Aug;91(4):465-7.
One hundred and seventy five Vietnamese adults with severe and complicated malaria admitted to a rural district hospital were entered into an open randomized comparative study to compare 4 treatment regimens based on artemisinin and its derivatives. The median time of defervescence was 48 h (95% confident interval [CI] 38-58 h) in those given intramuscular (i.m.) artemether, 42 h (95% CI 36-48 h) in those given artemisinin suppositories, 36 h (95% CI 30-42 h) in those receiving artesunate (i.m.) and 30 h (95% CI 18-42 h) in those receiving intravenous artesunate (P = 0.13). The respective median parasite clearance times were 30 h (95% CI 26-34 h), 30 h (95% CI 24-36 h), 24 h (95% CI 15-33 h), and 24 h (95% CI 15-33 h) (P = 0.30); the median times for recovery of consciousness were 47 h (95% CI 31-63 h), 24 h (95% CI 18-30 h), 30 h (95% CI 18-42 h), and 24 h (95% CI 4-44 h) (P = 0.18); and the mortality rates were 11.1%, 17.6%, 10.2% and 16.6%, respectively (P = 0.64). There was no significant difference in efficacy between the 4 treatments.

9294540
Hall AJ
Report on the 8th European congress of Clinical Microbiology and Infectious Diseases, Lausanne, Switzerland May 25-28, 1997.
Trop Med Int Health. 1997 Aug;2(8):719-20.

15388456
Hallett RL, Sutherland CJ, Alexander N, Ord R, Jawara M, Drakeley CJ, Pinder M, Walraven G, Targett GA, Alloueche A
Combination therapy counteracts the enhanced transmission of drug-resistant malaria parasites to mosquitoes.
Antimicrob Agents Chemother. 2004 Oct;48(10):3940-3.
Malaria parasites carrying genes conferring resistance to antimalarials are thought to have a selective advantage which leads to higher rates of transmissibility from the drug-treated host. This is a likely mechanism for the increasing prevalence of parasites with resistance to chloroquine (CQ) and sulfadoxine-pyrimethamine in sub-Saharan Africa. Combination therapy is the key strategy being implemented to reduce the impact of resistance, but its effect on the transmission of genetically resistant parasites from treated patients to mosquito vectors has not been measured directly. In a trial comparing CQ monotherapy to the combination CQ plus artesunate (AS) in Gambian children with uncomplicated falciparum malaria, we measured transmissibility by feeding Anopheles gambiae mosquitoes with blood from 43 gametocyte-positive patients through a membrane. In the CQ-treated group, gametocytes from patients carrying parasites with the CQ resistance-associated allele pfcrt-76T prior to treatment produced infected mosquitoes with 38 times higher Plasmodium falciparum oocyst burdens than mosquitoes fed on gametocytes from patients infected with sensitive parasites (P < 0.001). Gametocytes from parasites carrying the resistance-associated allele pfmdr1-86Y produced 14-fold higher oocyst burdens than gametocytes from patients infected with sensitive parasites (P = 0.011). However, parasites carrying either of these resistance-associated alleles pretreatment were not associated with higher mosquito oocyst burdens in the CQ-AS-treated group. Thus, combination therapy overcomes the transmission advantage enjoyed by drug-resistant parasites.

9546420
Halpaap B, Ndjave M, Paris M, Benakis A, Kremsner PG

Plasma levels of artesunate and dihydroartemisinin in children with Plasmodium falciparum malaria in Gabon after administration of 50-milligram artesunate suppositories.
Am J Trop Med Hyg. 1998 Mar;58(3):365-8.
A thermostable suppository of artesunate (artesunic acid) has been developed. In Gabon, 12 children with Plasmodium falciparum malaria received two administrations of this suppository in a 4-hr interval. Parasitemia and fever were then measured and the plasma levels of artesunate and its active metabolite, dihydroartemisinin, were determined by means of a reversed phase high-pressure liquid chromatography method using reductive electrochemical detection. Substantial parasite clearance (97-100%) was noted 24 hr after the beginning of the treatment and body temperature had returned to normal. Absorption, metabolism, and elimination of artesunate were rapid. Mean values of maximum plasma levels (Cmax) and maximum concentration peak times (tmax) were evaluated. The Cmax of dihydroartemisinin (0.18 +/- 0.10 microg/ml [mean +/- SE]) was higher than the Cmax of artesunate (0.09 +/- 0.04 microg/ml) and the tmax of dihydroartemisinin (1.13 +/- 0.58 hr) was higher than the tmax of artesunate (0.58 +/- 0.19 hr). Plasma levels 30 min after the second suppository administration were not consistently higher than those found 30 min after the first administration.

11882006
Hamada Y, Tokuhara H, Masuyama A, Nojima M, Kim HS, Ono K, Ogura N, Wataya Y
Synthesis and notable antimalarial activity of acyclic peroxides, L-(alkyldioxy)-L-(methyldioxy)cyclododecanes.
J Med Chem. 2002 Mar 14;45(6):1374-8.
Of several bis(alkyldioxy)alkanes and the related acyclic peroxides prepared in this study, 1,1-bis(methyldioxy)cyclododecane showed the most notable antimalarial activity particularly in vivo (almost a half of that of artemisinin).

15689068
Hamedi Y, Safa O, Zare S, Tan-ariya P, Kojima S, Looareesuwan S
Therapeutic efficacy of artesunate in Plasmodium vivax malaria in Thailand.
Southeast Asian J Trop Med Public Health. 2004 Sep;35(3):570-4.
Our previous study showed that in vitro susceptibility of Plasmodium vivax to chloroquine has significantly decreased in Thailand within the past two decades. Thus, the evaluation of alternative antimalarials for treatment of vivax malaria is needed. The aim of this study was to examine parasitological and clinical efficacy of an artemisinin derivative (artesunate) for the treatment of vivax malaria in patients who were admitted to the Bangkok Hospital for Tropical Diseases. We randomly allocated patients aged 12-56 years to receive 3.3mg/kg (adult dose 200 mg) on the first day, and for the next four days each patient was given 1.65 mg/kg orally (adult dose 100 mg), total dose = 600 mg. After the five-day course of artesunate, primaquine was given: a single oral dose of 15mg for 14 days. A total number of 42 patients received treatment. All participants were followed up for 28 days. In all the cases, both parasitemia and fever were resolved rapidly; the mean fever clearance time and parasite clearance time, 14.6 and 36.7 hours, respectively, showed that therapeutic response to artesunate was better than that of chloroquine. The 14-day cure rate was 100%, but reappearance of parasitemia was seen in two patients on days 21 and 25 following treatment, respectively. These two cases of failure rate should be considered as true relapse rather than recrudescence, since the relapse interval in Southeast Asian vivax malaria according to recent findings seems to be 3 weeks after start of treatment, if primaquine is not given or an inadequate amount is given. In conclusion, artesunate might be useful in treatment of vivax malaria, causing a good blood schizontocidal effect. However, to prevent emerging resistance it should never be used alone.

15869770
Hamour S, Melaku Y, Keus K, Wambugu J, Atkin S, Montgomery J, Ford N, Hook C, Checchi F
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 Jul;99(7):548-54.
Both northern and southern Sudan are deploying artemisinin-based combinations against uncomplicated Plasmodium falciparum malaria (artesunate+sulfadoxine-pyrimethamine [AS+SP] in the north, artesunate+amodiaquine [AS+AQ] in the south). In 2003, we tested the efficacy of 3 day AS+SP and AS+AQ regimens in vivo in the isolated, seasonally endemic Nuba Mountains region (the first study of AS combinations in southern Sudan). We also analysed pre-treatment blood samples for mutations at the P. falciparum chloroquine transporter (Pfcrt) gene (associated with CQ resistance), and at the dihydrofolate reductase (Dhfr) gene (associated with pyrimethamine resistance). Among 161 randomized children under 5 years, PCR-corrected cure rates after 28 days were 91.2% (52/57, 95% CI 80.7-97.1) for AS+SP and 92.7% (51/55, 95% CI 82.4-98.0) for AS+AQ, with equally rapid parasite and fever clearance. The Pfcrt K76T mutation occurred in 90.0% (144/160) of infections, suggesting CQ would work poorly in this region. Overall, 82.5% (132/160) carried mutations at Dhfr (N51I, C59R or S108N, but not I164L), but triple mutants (more

predictive of in vivo SP failure) were rare (3.1%). CQ use should be rapidly discontinued in this region. SP resistance may propagate rapidly, and AS+AQ is likely to be a better long-term option, provided AQ use is limited to the combination.

15363939
Hamzah J, Davis TM, Skinner-Adams TS, Beilby J
Characterization of the effect of retinol on Plasmodium falciparum in vitro.
Exp Parasitol. 2004 Jul-Aug;107(3-4):136-44.
A preliminary study from our laboratory found retinol (vitamin A alcohol) to have in vitro activity against Plasmodium falciparum at concentrations close to those in normal human serum (1-3 microM). To characterize the antimalarial potential of retinol in more detail, the 3D7 and K1 laboratory strains of P. falciparum were maintained in continuous culture and [3H]hypoxanthine incorporation and microscopy were used to assess the effect of retinol against asexual stages of the parasite life-cycle. Losses of retinol and retinol-associated hemolysis were also quantified in the in vitro culture system. There were retinol losses of >50% but no hemolysis was observed with added retinol concentrations up to 100 microM. All stages of parasite development showed comparable sensitivity to retinol including merozoite invasion (range of mean IC50 values 10.1-21.4 microM after adjustment for losses). Retinol pre-treatment of uninfected RBC did not inhibit merozoite invasion. Retinol treatment was associated with increased vacuolization within the parasite food vacuole and evidence of parasite membrane rupture. These appearances were similar to those seen with quinoline and artemisinin compounds. Although these data do not support a role for acute retinol supplementation in the treatment of falciparum malaria, they add to knowledge regarding potential antimalarial therapies and justify assessment of more potent synthetic retinoids and their metabolites.

11570566
Harder A, Greif G, Haberkorn A
Chemotherapeutic approaches to protozoa: haemosporina--current level of knowledge and outlook.
Parasitol Res. 2001 Sep;87(9):781-4.
Chloroquine and mefloquine are available for prophylactic treatment in malaria, against a background of the burgeoning problem of resistance developing to chloroquine and related drugs (Mehlhorn and Schrevel 1995). For this reason, highly specific national recommendations are given out regarding prophylaxis. The option of a viable vaccine is currently not available. More new compounds are therefore urgently required, since 2-5 million of the 200 300 million infected people die each year. At the moment, atovaquone and artemisinin derivatives are of great interest, as are drug combinations such as atovaquone/proguanil (since 1997), artemether/ benflumetol (since 1998?; Ciba-Geigy, patent WO9202217) and chlorproguanil/dapsone (since 2000?), as these compounds are also effective against multi-resistant strains of Plasmodium falciparum (Tables 1, 2; Croft 1997; Wang 1997). Pyronaridin (since 2000?) has been discovered in a Chinese academy and is in clinical trials (Trouiller and Olliaro 1998; Pecoul et al. 1999).

8730315
Hassan Alin M, Ashton M, Kihamia CM, Mtey GJ, Bjorkman A
Multiple dose pharmacokinetics of oral artemisinin and comparison of its efficacy with that of oral artesunate in falciparum malaria patients.
Trans R Soc Trop Med Hyg. 1996 Jan-Feb;90(1):61-5.
The study compared the clinical efficacy and safety of oral artemisinin and oral artesunate as well as artemisinin pharmacokinetics during and after resolution of falciparum malaria. Forty adults with symptomatic falciparum malaria were allocated at random to treatment with either oral artemisinin (500 mg single dose on day 1 followed by 250 mg twice daily for 4 d and then another 500 mg single dose on day 6) or with oral artesunate (100 mg single dose on day 1 followed by 50 mg twice daily for 5 d). Patients were admitted to hospital at the Kibaha Designated District Hospital, Kibaha, Tanzania for the duration of treatment. The patients were seen once weekly for 3 more weeks. The time to parasite clearance (PCT) after oral artesunate (26.4 +/- 3.6 h) was shorter (P = 0.002) than after artemisinin (31 +/- 3.6 h). The fever subsidence time (FST) after oral artesunate (18.9 +/- 4.0 h) was also shorter (P = 0.04) than after artemisinin (21.8 +/- 4.6 h). Parasites were detected in 4 (20%) and 7 (35%) patients after completing treatment with artesunate and artemisinin respectively. In these patients the parasitaemia reappeared at the 3rd or 4th week of follow-up. Standard haematology, blood biochemistry and urinalysis, performed before drug intake and again on days 6 and 14, were normal. No clinical abnormality was observed during the study period. Artemisinin plasma concentrations, determined by high performance liquid chromatography with post-column derivatization and detection by ultraviolet light, were followed up to 8 h after drug administration on days 1 and 6. Artemisinin absorption was rapid, the maximum plasma concentrations (Cmax) being attained at about 3 h. Artemisinin areas under the plasma concentration-time curve (AUC) and the Cmax values were about 6 times higher after the first dose on day 1 than on day 6. This decrease in artemisinin plasma concentration is suggestive of an increase in metabolic capacity due to pronounced autoinduction.

12364772
Hastings IM, Bray PG, Ward SA
Parasitology. A requiem for chloroquine.
Science. 2002 Oct 4;298(5591):74-5.

15780339
Havlik I, Looareesuwan S, Vannaphan S, Wilairatana P, Krudsood S, Thuma PE, Kozbor D, Watanabe N, Kaneko Y
Curdlan sulphate in human severe/cerebral Plasmodium falciparum malaria.
Trans R Soc Trop Med Hyg. 2005 May;99(5):333-40.
Preclinical studies have shown that curdlan sulphate (CRDS), a sulphated 1-->3-beta-D glucan, inhibits Plasmodium falciparum in vitro and down-modulates the immune response. A direct, non-specific effect on cytoadherence and rosetting may be predicted, as has been described with other sulphated polysaccharides, e.g. heparin. The anticoagulant effect of CRDS is 10-fold lower than heparin. Curdlan sulphate has, therefore, emerged as a candidate for adjunct medication in the treatment of severe/cerebral malaria. Two clinical studies were conducted using CRDS as adjunct medication to conventional therapy (artesunate) in patients with severe and severe/cerebral malaria. Both studies were double-blind and placebo-controlled to evaluate the efficacy and safety of the combination. Curdlan sulphate appeared to reduce the severity of the disease process, e.g. fever clearance time was shortened. Due to the small number of patients, there was no difference in mortality. The two treatment arms in both studies showed similar results for all laboratory parameters. The only adverse event recorded during CRDS treatment was an increase in activated partial thromboplastin time. This can be monitored easily. It seems that the patients who may benefit most are severe/cerebral cases with no organ damage on admission.

11964891
Haynes RK
Artemisinin and derivatives: the future for malaria treatment?
Curr Opin Infect Dis. 2001 Dec;14(6):719-26.
The isolation in 1972 of artemisinin by Chinese scientists, and their development of all the derivatives now used in the treatment of malaria today, were of outstanding importance. The results which have accumulated both from the Chinese work and from that subsequently conducted on a worldwide basis provide for a relatively comprehensive understanding of the chemistry, pharmacological profiles, toxicology, metabolism, and effects on the malaria parasite. The optimal regimens for use in the field are also apparent, particularly in combinations with longer half-life quinoline antimalarials. Thus the future use of the artemisinin class of drug appears assured. However, the mechanism of action needs to be clarified. More importantly from a clinical viewpoint, problems inherent in the current derivatives must be addressed, particularly that of neurotoxicity, if new artemisinin derivatives are to be introduced in a normal drug regulatory environment. The application of established principles of modern drug design should indeed allow for the first truly rationally designed, in so far as the target is still unknown, derivatives to come to hand.

15812783
Haynes RK, Chan HW, Ho WY, Ko CK, Gerena L, Kyle DE, Peters W, Robinson BL
Convenient access both to highly antimalaria-active 10-arylaminoartemisinins, and to 10-alkyl ethers including artemether, arteether, and artelinate.
Chembiochem. 2005 Apr;6(4):659-67.
An economical phase-transfer method is used to prepare 10-arylaminoartemisinins from DHA and arylamines, and artemether, arteether, and artelinate from the corresponding alcohols. In vivo sc screens against Plasmodium berghei and P. yoelii in mice reveal that the p-fluorophenylamino derivative 5 g is some 13 and 70 times, respectively, more active than artesunate; this reflects the very high sc activity of 10-alkylaminoartemisinins. However, through the po route, the compounds are less active than the alkylaminoartemisinins, but still approximately equipotent with artesunate.

8053018
Haynes RK, Vonwiller SC
Extraction of artemisinin and artemisinic acid: preparation of artemether and new analogues.
Trans R Soc Trop Med Hyg. 1994 Jun;88 Suppl 1:S23-6.
The preparation of artemether from artemisinin is reviewed. Firstly, the extraction of artemisinin from Artemisia annua is described and an estimation of the yield per hectare based on literature data is given. Artemisinin is reduced with sodium borohydride to produce dihydroartemisinin as a mixture of epimers. The mixture is treated with methanol and an acid catalyst to provide artemether. Increasing demand for use of artemether places pressure on the supply of artemisinin, and an alternative means of preparing the drug

from artemisinic acid, an abundant constituent of A. annua, which could triple current yields, is described. In anticipation of problems of drug resistance emerging with the continued use of artemether and artesunate to treat malaria, development of new derivatives of artemisinin which have enhanced stability is required. Examples of such derivatives which have been prepared in our laboratories, or proposed, are described.

8053033
Hien TT
An overview of the clinical use of artemisinin and its derivatives in the treatment of falciparum malaria in Viet Nam.
Trans R Soc Trop Med Hyg. 1994 Jun;88 Suppl 1:S7-8.
In order to combat increasing problems with drug resistance in Plasmodium falciparum, Viet Nam has turned increasingly to the artemisinin derivatives. Oral and suppository formulations of artemisinin are produced from locally grown plants. These compounds have been rapidly effective in a large number of studies and have proved of particular value in severe malaria. Artemisinin suppositories are as effective as the parenteral drugs and offer the prospect of a simple, safe and inexpensive method of treating severe malaria in rural areas.

1287904
Hien TT, Arnold K, Vinh H, Cuong BM, Phu NH, Chau TT, Hoa NT, Chuong LV, Mai NT, Vinh NN, et al.
Comparison of artemisinin suppositories with intravenous artesunate and intravenous quinine in the treatment of cerebral malaria.
Trans R Soc Trop Med Hyg. 1992 Nov-Dec;86(6):582-3.
Seventy-nine comatose cerebral malaria patients given standard supportive treatment were randomized to receive specific antimalarial chemotherapy of intravenous quinine, intravenous artesunate, or artemisinin suppositories. Artesunate and artemisinin reduced peripheral asexual parasitaemia significantly more rapidly than quinine (90% clearance time 16 h, 18.9 h and 34.5 h respectively), but did not significantly reduce the duration of coma or mortality. The rapid lowering of peripheral parasitaemia may not ameliorate complications already present. These results demonstrate that artemisinin suppositories are as effective as artesunate and quinine given intravenously, and have economic and practical advantages for the treatment of severe malaria in areas remote from major medical centres. However, large numbers of patients will need to be studied if differences in mortality between the 3 treatment groups are to be demonstrated.

15504846
Hien TT, Davis TM, Chuong LV, Ilett KF, Sinh DX, Phu NH, Agus C, Chiswell GM, White NJ, Farrar J
Comparative pharmacokinetics of intramuscular artesunate and artemether in patients with severe falciparum malaria.
Antimicrob Agents Chemother. 2004 Nov;48(11):4234-9.
The first-dose pharmacokinetic properties of intramuscular (i.m.) artesunate (ARTS; 2.4 mg/kg immediately [stat], followed by 1.2 mg/kg i.m. daily) and artemether (ARM; 3.2 mg/kg i.m. stat, followed by 1.6 mg/kg i.m. daily) were compared in Vietnamese adults with severe falciparum malaria. A total of 19 patients were studied; 9 received ARTS, and 10 received ARM. ARTS was absorbed very rapidly; concentrations in plasma peaked between 1,362 and 8,388 nmol/liter (median, 5,710 nmol/liter) within 20 min of injection and then declined with a median (range) half-life (t(1/2)) of 30 (3 to 67) min. ARTS was hydrolyzed rapidly and completely to the biologically active metabolite dihydroartemisinin (DHA). Peak DHA concentrations in plasma ranged between 1,718 and 7,080 nmol/liter (median, 3,060 nmol/liter) and declined with a t(1/2) of 52 (26 to 69) min. In contrast, ARM was slowly and erratically absorbed. The absorption profile appeared biphasic. Maximum ARM concentrations in plasma ranged between 67 nmol/liter (a value close to the 50% inhibitory concentration for some Plasmodium falciparum isolates) and 1,631 nmol/liter (median, 574 nmol/liter) and occurred at a median (range) of 10 (1.5 to 24) h. There was relatively little conversion to DHA. After i.m. injection in cases of severe malaria, absorption of the water-soluble ARTS is rapid and extensive, whereas the oil-based ARM is slowly and erratically absorbed, with relatively little conversion to the more active DHA. On the basis of this pharmacological study, parenteral ARTS is preferable to ARM as an initial antimalarial therapy, particularly in the most seriously ill patients. These findings should be formally assessed by a randomized clinical trial.

1287905
Hien TT, Phu NH, Mai NT, Chau TT, Trang TT, Loc PP, Cuong BM, Dung NT, Vinh H, Waller DJ, et al.
An open randomized comparison of intravenous and intramuscular artesunate in severe falciparum malaria.
Trans R Soc Trop Med Hyg. 1992 Nov-Dec;86(6):584-5.
An open paired randomized comparison of intramuscular and intravenous artesunate was conducted in 28 adult patients with severe falciparum malaria. The dose regimen in both groups was 2 mg/kg given immediately followed by 1 mg/kg at 12 and 24 h, and then daily until the patient could swallow. Both routes of administration were well tolerated and there was no evidence of toxicity. One patient in each treatment

group died. Clinical and parasitological measures of recovery in survivors were similar in the 2 groups with mean fever clearance times of 37.3 h (standard deviation [SD] = 26.1 h) and 31.5 h (SD = 24.2 h) and mean parasite clearance times of 33.4 h (SD = 13.9 h) and 29.4 h (SD = 12.7 h) in the intravenous and intramuscular groups respectively. Artesunate is equally effective and well tolerated when given by the intravenous or intramuscular routes.

9494675
Hien TT, VinhChau NV, Vinh NN, Hung NT, Phung MQ, Toan LM, Mai PP, Dung NT, HoaiTam DT, Arnold K
Management of multiple drug-resistant malaria in Viet Nam.
Ann Acad Med Singapore. 1997 Sep;26(5):659-63.
Malaria is still the most common infectious cause of mortality and morbidity in Viet Nam as it is in many developing countries in the tropics. The presence of resistance to available antimalarials and compliance in the target population are factors that influence the choice of drugs and regimens. In order to develop an ideal treatment for malaria, we conducted several clinical trials in patients with the disease in different settings. The results of these trials suggest that a combination of single dose artemisinin (or its derivatives) and mefloquine is the most effective, safe and practical treatment for acute non-complicated malaria due to multidrug-resistant Plasmodium falciparum. Concerning severe and complicated malaria, parenteral or rectal multi-doses of artemisinin or analogues are recommended due to their rapid parasite clearance time and other possible anti-cytoadherence effects. With its rapid parasite clearance, very early treatment of uncomplicated cases with artemisinin (and derivatives), especially at a health post level may help to prevent the development of complications, consequently reducing the number of severe cases and the malaria mortality rate.

11855985
Hindley S, Ward SA, Storr RC, Searle NL, Bray PG, Park BK, Davies J, O'Neill PM
Mechanism-based design of parasite-targeted artemisinin derivatives: synthesis and antimalarial activity of new diamine containing analogues.
J Med Chem. 2002 Feb 28;45(5):1052-63.
The potent antimalarial activity of chloroquine against chloroquine-sensitive strains can be attributed, in part, to its high accumulation in the acidic environment of the heme-rich parasite food vacuole. A key component of this intraparasitic chloroquine accumulation mechanism is a weak base "ion-trapping" effect whereupon the basic drug is concentrated in the acidic food vacuole in its membrane-impermeable diprotonated form. By the incorporation of amino functionality into target artemisinin analogues, we hoped to prepare a new series of analogues that, by virtue of increased accumulation into the ferrous-rich vacuole, would display enhanced antimalarial potency. The initial part of the project focused on the preparation of piperazine-linked analogues (series 1 (7-16)). Antimalarial evaluation of these derivatives demonstrated potent activity versus both chloroquine-sensitive and chloroquine-resistant parasites. On the basis of these observations, we then set about preparing a series of C-10 carba-linked amino derivatives. Optimization of the key synthetic step using a newly developed coupling protocol provided a key intermediate, allyldeoxoartemisinin (17) in 90% yield. Further elaboration, in three steps, provided nine target C-10 carba analogues (series 2 (21-29)) in good overall yields. Antimalarial assessment demonstrated that these compounds were 4-fold more potent than artemisinin and about twice as active as artemether in vitro versus chloroquine-resistant parasites. On the basis of the products obtained from biomimetic Fe(II) degradation of the C-10 carba analogue (23), we propose that these analogues may have a mode of action subtly different from that of the parent drug artemisinin (series 1 (7-16)) and other C-10 ether derivatives such as artemether. Preliminary in vivo testing by the WHO demonstrated that four of these compounds are active orally at doses of less than 10 mg/kg. Since these analogues are available as water-soluble salts and cannot form dihydroartemisinin by P450-catalyzed oxidation, they represent useful leads that might prove to be superior to the currently used derivatives, artemether and artesunate.

9715663
Hogh B
[New drugs in the treatment of malaria]
Ugeskr Laeger. 1998 Aug 10;160(33):4783-6.

9886189
Hollenstein U, Looareesuwan S, Aichelburg A, Thalhammer F, Stoiser B, Amradee S, Chullawichit S, El Menyawi I, Burgmann H
Serum procalcitonin levels in severe Plasmodium falciparum malaria.
Am J Trop Med Hyg. 1998 Dec;59(6):860-3.

Levels of procalcitonin (ProCT) have been found to be elevated in individuals with severe bacterial infections such as sepsis and peritonitis, and this correlates well with the severity of the disease. Recently, increased levels have been described in melioidosis and Plasmodium falciparum malaria. In this study ProCT levels were measured in 27 Thai patients with complicated malaria before and during/after treatment with artesunate and mefloquine. Initial parasite counts averaged 290,680/microl (range = 533-1,147,040). On admission, ProCT levels were elevated in all but one patient (median = 40 ng/ml, range = 0.04-662, normal values < 0.5 ng/ml). With treatment, levels decreased to 1.3 ng/ml (range = 0.01-6.5). Nitrite/nitrate levels in patients were higher than in controls throughout the study. The ProCT levels correlated with initial parasite density (P < 0.05), which is a marker of disease severity, and with nitrite/nitrate levels (P < 0.05). Based on the changes of ProCT levels over the course of the disease a possible role in the acute-phase reaction seems likely.

16271310
Holmgren G, Gil JP, Ferreira PM, Veiga MI, Obonyo CO, Bjorkman A
Amodiaquine resistant Plasmodium falciparum malaria in vivo is associated with selection of pfcrt 76T and pfmdr1 86Y.
Infect Genet Evol. 2005 Oct 31;.
The choice of partner drug is critical for artemisinine-based combination therapy (ACT) to remain effective and amodiaquine (AQ) is one important candidate to evaluate. We treated 81 children

15803790
Holzgrabe U
[Artemisinin and successors]
Pharm Unserer Zeit. 2005;34(2):95.

10212514
Honrado ER, Fungladda W, Kamoiratanaku P, Kitayaporn D, Karbwang J, Thimasarn K, Masngammueng R
Cost-effectiveness analysis of artesunate and quinine + tetracycline for the treatment of uncomplicated falciparum malaria in Chanthaburi, Thailand.
Bull World Health Organ. 1999;77(3):235-43.
A randomized, controlled, malaria-clinic-based field trial was carried out to compare the cost-effectiveness of a 5-day 700-mg oral artesunate and a 7-day quinine + tetracycline regimen for the treatment of uncomplicated falciparum malaria in Thailand. Cost-effectiveness was determined from the providers' perspective and based on curative effectiveness. A total of 137 patients, aged 15-60 years, attending a malaria clinic were followed for 28 days, 60 of them received quinine + tetracycline and 77 received artesunate. Cure rates were assessed on day 5 (artesunate) and day 7 (quinine + tetracycline), using the intention-to-treat approach. Cost-effectiveness and sensitivity analyses were performed by varying the day 5/day 7 curative effectiveness and cost of artesunate. The cure rate with artesunate (100%) was significantly higher than with quinine + tetracycline (77.4%) (relative risk adjusted for sex (aRR) = 1.32, 95% confidence interval (CI) = 1.12-1.55; referent quinine + tetracycline). Artesunate was more cost-effective than quinine + tetracycline at the following costs: artesunate, < or = US$0.36 per 50-mg tablet; quinine, US$0.06 per 300-mg tablet; tetracycline, US$0.02 per 250-mg capsule; and services per case found, < or = US$11.49. Because of the higher cure rate and higher cost-effectiveness of the artesunate regimen compared with quinine + tetracycline, we recommend its use for the treatment of uncomplicated falciparum malaria in malaria clinics in Thailand.

15712565
Hook C
Combination drug policy for malaria.
Trop Doct. 2005 Jan;35(1):59-60.

15215083
Hoppe HC, van Schalkwyk DA, Wiehart UI, Meredith SA, Egan J, Weber BW
Antimalarial quinolines and artemisinin inhibit endocytosis in Plasmodium falciparum.
Antimicrob Agents Chemother. 2004 Jul;48(7):2370-8.
Endocytosis is a fundamental process of eukaryotic cells and fulfills numerous functions, most notably, that of macromolecular nutrient uptake. Malaria parasites invade red blood cells and during their intracellular development endocytose large amounts of host cytoplasm for digestion in a specialized lysosomal compartment, the food vacuole. In the present study we have examined the effects of artemisinin and the

quinoline drugs chloroquine and mefloquine on endocytosis in Plasmodium falciparum. By using novel assays we found that mefloquine and artemisinin inhibit endocytosis of macromolecular tracers by up to 85%, while the latter drug also leads to an accumulation of undigested hemoglobin in the parasite. During 5-h incubations, chloroquine inhibited hemoglobin digestion but had no other significant effect on the endocytic pathway of the parasite, as assessed by electron microscopy, the immunofluorescence localization of hemoglobin, and the distribution of fluorescent and biotinylated dextran tracers. By contrast, when chloroquine was added to late ring stage parasites, followed by a 12-h incubation, macromolecule endocytosis was inhibited by more than 40%. Moreover, there is an accumulation of transport vesicles in the parasite cytosol, possibly due to a disruption in vacuole-vesicle fusion. This fusion block is not observed with mefloquine, artemisinin, quinine, or primaquine but is mimicked by the vacuole alkalinizing agents ammonium chloride and monensin. These results are discussed in the light of present theories regarding the mechanisms of action of the antimalarials and highlight the potential use of drugs in manipulating and studying the endocytic pathway of malaria parasites.

15001342
Hoshen M
Artesunate combinations for malaria.
Lancet. 2004 Feb 28;363(9410):737.

11085244
Hoshen MB, Na-Bangchang K, Stein WD, Ginsburg H
Mathematical modelling of the chemotherapy of Plasmodium falciparum malaria with artesunate: postulation of 'dormancy', a partial cytostatic effect of the drug, and its implication for treatment regimens.
Parasitology. 2000 Sep;121 (Pt 3):237-46.
Although artesunate, one of the potent derivatives of the qinghaosu family of drugs for treating falciparum malaria, is already in use in the field, its therapeutic protocol has only been developed empirically by hit-or-miss. A pharmacokinetic-pharmacodynamic (PK-PD) model, required for creating such a protocol, is not straightforward. Artesunate presents extremely fast pharmacokinetics. As a result the stage specificity of its action must be treated explicitly. Also, use of standard PK-PD modelling fails to explain the clinical results. Our PK-PD modelling of its activity leads us to the postulation of the existence of a novel effect: a small fraction of the parasites, as a result of chemotherapeutic pressure, become cytostatic, or 'dormant'. At this stage, the parasite cycle is halted, making them unsusceptible to further dosing until wakening. This slows down the antimalarial activity of the drug, entailing either many frequent doses or an extended period of treatment and surveillance. Based on our modelling, we suggest a method for deciding on rational models of chemotherapy against falciparum malaria.

11811806
Hoshen MB, Stein WD, Ginsburg H
Mathematical modelling of malaria chemotherapy: combining artesunate and mefloquine.
Parasitology. 2002 Jan;124(Pt 1):9-15.
Clinical data on the use of artesunate combined with mefloquine in a variety of treatment regimens and parasite loads in Thailand were modelled on the basis of experimentally determined pharmacokinetic data. The model assumed no pharmacodynamic interaction between artesunate and mefloquine, but that the parasites were already resistant to mefloquine. Predictions of the model accorded well with the data. In articular, in accordance with clinical observations, the model showed that monotherapy with either drug failed to cure at moderate parasitaemia, yet such patients could be treated effectively with the combination of 3 days of artesunate + mefloquine. For high levels of parasitaemia, 5 days of artesunate + mefloquine were needed. Simulations were also performed for situations of lower resistance to mefloquine and for the immune human populations found in Africa. The importance of mathematical modelling of combination therapy is borne out by this study and suggests its wider application for other drug combinations.

15306704
Hung le Q, de Vries PJ, Binh TQ, Giao PT, Nam NV, Holman R, Kager PA
Artesunate with mefloquine at various intervals for non-severe Plasmodium falciparum malaria.
Am J Trop Med Hyg. 2004 Aug;71(2):160-6.
To study the efficacy, tolerance, population pharmacokinetics and pharmacodynamics of artesunate followed by mefloquine at various intervals, 360 patients with Plasmodium falciparum malaria received 4 mg/kg of artesunate and thereafter 15 mg/kg of mefloquine simultaneously (group A), after 8 hours (after group B), and after 24 hours (group C). Three dosages were completed with placebo. Follow-up was 28 days. All patients recovered rapidly except one case of failure within the first 24 hours. Mefloquine pharmacokinetics was similar in the three regimens. Parasites reappeared in 26%, 26%, and 33% of the patients in groups A,

B, and C, respectively. Early recrudescence was associated with high initial parasite density, slow parasite clearance, and rapid mefloquine clearance and low plasma concentrations at day 28. Mefloquine plasma concentrations all reached therapeutic ranges, suggesting reduced parasite sensitivity. In conclusion, there is no interaction between artesunate and mefloquine with respect to tolerance, efficacy, and pharmacokinetics. Single-dose combination therapy with artemisinin drugs and 15 mg/kg of mefloquine does not completely prevent parasite recurrence and may not prevent mefloquine resistance.

12219158
Hung le Q, Vries PJ, Giao PT, Nam NV, Binh TQ, Chong MT, Quoc NT, Thanh TN, Hung LN, Kager PA
Control of malaria: a successful experience from Viet Nam.
Bull World Health Organ. 2002;80(8):660-6.
OBJECTIVE: To follow malaria prospectively in an ethnic minority commune in the south of Viet Nam with high malaria transmission and seasonal fluctuation, during malaria control interventions using insecticide-treated bednets (ITBNs) and early diagnosis and treatment (EDT) of symptomatic patients. METHODS: From 1994 onwards the following interventions were used: distribution of ITBNs to all households with biannual reimpregnation; construction of a health post and appointment of staff trained in microscopic diagnosis and treatment of malaria; regular supply of materials and drugs; annual cross-sectional malaria surveys with treatment of all parasitaemic subjects, and a programme of community involvement and health education. Surveys were held yearly at the end of the rainy season. During the surveys, demographic data were updated. Diagnosis and treatment of malaria were free of charge. Plasmodium falciparum infection was treated with artesunate and P. vivax infection with chloroquine plus primaquine. FINDINGS: The baseline survey in 1994 recorded 716 inhabitants. Of the children under 2 years of age, 37% were parasitaemic; 56% of children aged 2-10 years, and 35% of the remaining population were parasitaemic. P. falciparum accounted for 73-79% of these infections. The respective splenomegaly rates for the above-mentioned age groups were 20%, 56%, and 32%. In 1999, the proportion of parasitaemic subjects was 4%, 7% and 1%, respectively, of which P.falciparum contributed 56%. The splenomegaly rate was 0%, 5% and 2%, respectively. CONCLUSIONS: A combination of ITBNs and EDT, provided free of charge, complemented by annual diagnosis and treatment during malaria surveys and community involvement with health education successfully brought malaria under control. This approach could be applied to other regions in the south of Viet Nam and provides a sound basis for further studies in other areas with different epidemiological patterns of malaria.

12798169
Hung TY, Davis TM, Ilett KF
Measurement of piperaquine in plasma by liquid chromatography with ultraviolet absorbance detection.
J Chromatogr B Analyt Technol Biomed Life Sci. 2003 Jul 5;791(1-2):93-101.
Piperaquine (PQ) is an antimalarial drug enjoying a resurgence of use in combination with an artemisinin derivative because of parasite resistance to standard treatments. Its pharmacokinetic properties have not been characterised. An assay for PQ in plasma was developed using solvent extraction and liquid chromatographic separation on a Waters XTerra RP(18) column, with a mobile phase of 7% acetonitrile in water (containing 0.025% trifluoroacetic acid, 0.1% NaCl and 0.008% triethylamine) and UV detection at 340 nm. The assay was linear up to 1000 microg/l. Intra- and inter-day relative standard deviations were

11952945
Huong NM, Davis TM, Hewitt S, Huong NV, Uyen TT, Nhan DH, Cong le D
Comparison of three antigen detection methods for diagnosis and therapeutic monitoring of malaria: a field study from southern Vietnam.
Trop Med Int Health. 2002 Apr;7(4):304-8.
OBJECTIVES: To compare the sensitivity, specificity and post-treatment persistence of three commonly used rapid antigen detection methods. METHOD: We studied 252 Vietnamese patients aged from 4 to 60 years, 157 with falciparum and 95 with vivax malaria and 160 healthy volunteers. An initial blood sample was taken for microscopy, and OptiMAL, immunochromatographic test (ICT) malaria P.f./P.v. and Paracheck-Pf tests. Patients with falciparum malaria were treated with an artesunate-based combination regimen and those with vivax malaria received chloroquine. Eighty-seven patients with falciparum malaria who were initially positive for one of the antigen tests and who remained blood smear-negative underwent follow-up testing over 28 days. RESULTS: Paracheck-Pf was the most sensitive test for Plasmodium falciparum (95.8% vs. 82.6% for ICT malaria P.f./P.v. and 49.7% for OptiMAL). Specificities were all 100%. For vivax malaria, OptiMAL performed better than ICT malaria P.f./P.v. (sensitivities 73.7% and 20.0%, respectively), with 100% specificity in both cases. All tests had low sensitivities (< or = 75.0%) at parasitaemias < 1000/microl regardless of malaria species. During follow-up, Paracheck-Pf remained positive in the greatest proportion of patients, especially at higher parasitaemias (> 10,000/microl). Residual OptiMAL positivity occurred only in a relatively small proportion of patients (< 10%) with parasitaemias > 10,000/microl during the first 2 weeks after treatment. CONCLUSIONS: Although microscopy remains the gold standard for

malaria diagnosis, Paracheck-Pf may prove a useful adjunctive test in uncomplicated falciparum malaria in southern Vietnam. OptiMAL had the lowest sensitivity for P. falciparum but it might have a use in the diagnosis of vivax malaria and perhaps to monitor efficacy of treatment for falciparum malaria where microscopy is unavailable.

11491008
Huong NM, Hewitt S, Davis TM, Dao LD, Toan TQ, Kim TB, Hanh NT, Phuong VN, Nhan DH, Cong LD
Resistance of Plasmodium falciparum to antimalarial drugs in a highly endemic area of southern Viet Nam: a study in vivo and in vitro.
Trans R Soc Trop Med Hyg. 2001 May-Jun;95(3):325-9.
To assess the antimalarial sensitivity of Plasmodium falciparum in vivo and in vitro in a highly endemic area of southern Viet Nam, a field study was conducted (in 1999) at a rubber plantation in Binh Phuoc Province north of Ho Chi Minh City. Fifty patients were treated with either artesunate (4 mg/kg on day 0, then 2 mg/kg on day 1 to 4) or mefloquine (10 mg/kg at 0 h, then 5 mg/kg at 6 h), and their progress was followed for 28 days under standard WHO protocols. Blood spots were taken at baseline from all patients, as well as from those who redeveloped parasitaemia during follow-up, for polymerase chain reaction (PCR) determination of parasite genotypes to assist differentiation of re-infection from recrudescence. Both treatments cleared parasites within 5 days. Of the 25 mefloquine-treated patients, 2 (8%) re-presented with probable re-infections. For artesunate, 4 patients (16%) had re-infections and 5 (20%) had recrudescences. Sensitivity tests in vitro of pre-treatment P. falciparum isolates showed geometric mean IC50 values of 29, 38, 209 and 15 nmol/L for chloroquine (n = 32), mefloquine (n = 33), quinine (n = 31) and artemisinin (n = 31), respectively. There were significant correlations between IC50s for artemisinin and mefloquine (r = 0.72, P = 0.004), and chloroquine and quinine (r = 0.44, P = 0.05). These data show that, although mefloquine has been used for 10 years in Binh Phuoc Province, it remains fully effective, perhaps because an artemisinin derivative is commonly given at the same time. The recrudescence rate for artesunate is similar to those reported in other epidemiological contexts. The present in-vitro data imply that quinine remains effective and that reduced drug pressure has been associated with increased sensitivity of local strains of P. falciparum to chloroquine. Although from one hyperendemic area, these results may have implications for antimalarial prophylaxis and treatment strategies for residents and travellers to southern Viet Nam.

16179089
Hutagalung R, Paiphun L, Ashley EA, McGready R, Brockman A, Thwai KL, Singhasivanon P, Jelinek T, White NJ, Nosten FH
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 Sep 22;4:46.
BACKGROUND: The use of antimalarial drug combinations with artemisinin derivatives is recommended to overcome drug resistance in Plasmodium falciparum. The fixed combination of oral artemether-lumefantrine, an artemisinin combination therapy (ACT) is highly effective and well tolerated. It is the only registered fixed combination containing an artemisinin. The trial presented here was conducted to monitor the efficacy of the six-dose regimen of artemether-lumefantrine (ALN) in an area of multi-drug resistance, along the Thai-Myanmar border. METHODS: The trial was an open-label, two-arm, randomized study comparing artemether-lumefantrine and mefloquine-artesunate for the treatment of uncomplicated falciparum malaria with 42 days of follow up. Parasite genotyping by polymerase chain reaction (PCR) was used to distinguish recrudescent from newly acquired P. falciparum infections. The PCR adjusted cure rates were evaluated by survival analysis. RESULTS: In 2001-2002 a total of 490 patients with slide confirmed uncomplicated P. falciparum malaria were randomly assigned to receive artemether-lumefantrine (n = 245) or artesunate and mefloquine (n = 245) and were followed for 42 days. All patients had rapid initial clinical and parasitological responses. In both groups, the PCR adjusted cure rates by day 42 were high: 98.8% (95% CI 96.4, 99.6%) for artemether-lumefantrine and 96.3% (95% CI 93.1, 98.0%) for artesunate-mefloquine. Both regimens were very well tolerated with no serious adverse events observed attributable to either combination. CONCLUSION: Overall, this study confirms that these two artemisinin-based combinations remain highly effective and result in equivalent therapeutic responses in the treatment of highly drug-resistant falciparum malaria.

10762587
Hutagalung R, Wilairatana P, Looareesuwan S, Brittenham GM, Gordeuk VR
Influence of hemoglobin E trait on the antimalarial effect of artemisinin derivatives.
J Infect Dis. 2000 Apr;181(4):1513-6. Epub 2000 Apr 13.
To determine whether hemoglobin E trait influences the antimalarial effect of artemisinin derivatives, we retrospectively compared 32 case patients with hemoglobin E trait to 32 control patients who did not have hemoglobin E, beta-thalassemia, glucose-6-phosphate dehydrogenase deficiency, or alpha-thalassemia trait on the basis of a mean corpuscular volume > or =78 femtoliters. All patients were admitted to the Hospital for

Tropical Diseases in Bangkok, Thailand, with acute falciparum malaria. Control patients were matched to case patients with hemoglobin E trait by treatment with artemisinin derivatives versus other antimalarial drugs, by ethnic group, and by parasite count. Among 38 patients treated with artemisinin derivatives, the presence of hemoglobin E trait was associated with significantly faster parasite clearance (2.9-fold; 95% confidence interval [CI], 1.4-6.3; P=.006). Among 26 patients treated only with other antimalarial drugs, hemoglobin E trait did not significantly enhance parasite clearance (hazards ratio, 1.1; 95% CI, 0.5-2.5; P=. 8). Hemoglobin E trait may potentiate the antimalarial effect of artemisinin derivatives.

11849191
Ilett KF, Batty KT, Powell SM, Binh TQ, Thu le TA, Phuong HL, Hung NC, Davis TM
The pharmacokinetic properties of intramuscular artesunate and rectal dihydroartemisinin in uncomplicated falciparum malaria.
Br J Clin Pharmacol. 2002 Jan;53(1):23-30.
AIMS: To obtain pharmacokinetic data for artesunate (ARTS) and its active metabolite dihydroartemisinin (DHA) following i.m. ARTS and rectal DHA administration. METHODS: Twelve Vietnamese patients with uncomplicated falciparum malaria were randomized to receive either i.v. or i.m. ARTS (120 mg), with the alternative preparation given 8 h later in an open crossover design. A further 12 patients were given i.v. ARTS (120 mg) at 0 h and rectal DHA (160 mg) 8 h later. RESULTS: Following i.v. bolus, ARTS had a peak concentration of 42 microm (16 mg l(-1), elimination t1/2 = 3.2 min, CL = 2.8 l h(-1) kg(-1) and V = 0.22 l kg(-1) . The Cmax for DHA was 9.7 microm (2.7 mg l(-1)), t1/2 = 59 min, CL = 0.64 l h(-1) kg(-1) and V = 0.8 l kg(-1) . Following i.m. ARTS, Cmax was 2.3 microm (3.7 mg l(-1)), the apparent t1/2 = 41 min, CL = 2.9 l h(-1) kg(-1) and V = 2.6 l kg(-1). The relative bioavailability of DHA was 88%, Cmax was 4.1 microm (1.16 mg l(-1)) and t1/2 = 64 min. In the rectal DHA study, relative bioavailability of DHA was 16%. CONCLUSIONS: For patients with uncomplicated falciparum malaria i.m. ARTS is a suitable alternative to i.v. ARTS, at equal doses. To achieve plasma DHA concentrations equivalent to parenteral administration of ARTS, rectal DHA should be given at approximately four-fold higher milligram doses. Further studies are needed to determine whether these recommendations can be applied to patients with severe malaria.

12167566
Ilett KF, Ethell BT, Maggs JL, Davis TM, Batty KT, Burchell B, Binh TQ, Thu le TA, Hung NC, Pirmohamed M, Park BK, Edwards G
Glucuronidation of dihydroartemisinin in vivo and by human liver microsomes and expressed UDP-glucuronosyltransferases.
Drug Metab Dispos. 2002 Sep;30(9):1005-12.
The aim of this study was to elucidate the metabolic pathways for dihydroartemisinin (DHA), the active metabolite of the artemisinin derivative artesunate (ARTS). Urine was collected from 17 Vietnamese adults with falciparum malaria who had received 120 mg of ARTS i.v., and metabolites were analyzed by high-performance liquid chromatography-mass spectrometry (HPLC-MS). Human liver microsomes were incubated with [12-(3)H]DHA and cofactors for either glucuronidation or cytochrome P450-catalyzed oxidation. Human liver cytosol was incubated with cofactor for sulfation. Metabolites were detected by HPLC-MS and/or HPLC with radiochemical detection. Metabolism of DHA by recombinant human UDP-glucuronosyltransferases (UGTs) was studied. HPLC-MS analysis of urine identified alpha-DHA-beta-glucuronide (alpha-DHA-G) and a product characterized as the tetrahydrofuran isomer of alpha-DHA-G. DHA was present only in very small amounts. The ratio of the tetrahydrofuran isomer, alpha-DHA-G, was highly variable (median 0.75; range 0.09-64). Nevertheless, alpha-DHA-G was generally the major urinary product of DHA glucuronidation in patients. The tetrahydrofuran isomer appeared to be at least partly a product of nonenzymic reactions occurring in urine and was readily formed from alpha-DHA-G by iron-mediated isomerization. In human liver microsomal incubations, DHA-G (diastereomer unspecified) was the only metabolite found (V(max) 177 +/- 47 pmol min(-1) mg(-1), K(m) 90 +/- 16 microM). Alpha-DHA-G was formed in incubations of DHA with expressed UGT1A9 (K(m) 32 microM, V(max) 8.9 pmol min(-1) mg(-1)) or UGT2B7 (K(m) 438 microM, V(max) 10.9 pmol mg(-1) min(-1)) but not with UGT1A1 or UGT1A6. There was no significant metabolism of DHA by cytochrome-P450 oxidation or by cytosolic sulfotransferases. We conclude that alpha-DHA-G is an important metabolite of DHA in humans and that its formation is catalyzed by UGT1A9 and UGT2B7.

12731315
Imbert P, Gendrel D
[Malaria treatment in children. 2. Severe malaria]
Med Trop (Mars). 2002;62(6):657-64.
Severe forms of Plasmodium falciparum malaria are one of the world's leading causes of infection-related death in children. The World Health Organization (WHO) has defined a set of severity criteria to improve diagnosis and speed antimalarial treatment. Although the pertinence of these criteria has not been documented in France, child travelers presenting such features require hospitalization in intensive care. The

gold standard therapy is intravenous administration of quinine. According WHO recommendations, quinine therapy should begin with a loading dose barring contraindications. However French recommendations do not include the loading dose due to potentially dangerous side-effects in young children and lack of proven life-saving effect. Artemisinin derivatives have been shown to be as effective as quinine and are increasingly used in endemic zones due to good tolerance and convenience of use. However due to concerns about neurotoxicity, artemisinin derivatives are rarely used in France, except in patients with contraindications or resistance to quinine. Management of specific complications is also necessary to reduce the high mortality of severe malaria, even in Western countries, and to prevent neurological damage.

12638260
Ishizaki A, Kikuchi Y, Hatabu T, Kano S, Yasuoka A, Oka S
[An imported case of falciparum malaria successfully treated with Artemether-Lumefantrine in Japan]
Kansenshogaku Zasshi. 2003 Jan;77(1):34-7.
Spread of multi-drug resistant malaria in the endemic areas has made malaria control more difficult. Thus, WHO recommends combination therapy for the treatment of malaria. The aim of combination therapy is to improve efficacy and to reduce the incidence of resistance development to the each component of the combination. Particularly, the combination with artemisinin derivatives shows good outcome in Thailand where high resistance for mefloquine has already been found. We report the first case of falciparum malaria, successfully treated with Artemether-Lumefantrine in Japan. Artemether-Lumefantrine is a newly developed artemisinin-based combination agent for the treatment of uncomplicated multi-drug resistant malaria. This drug has proved highly effective and well tolerated by some clinical trials abroad. This Japanese female case showed a good clinical course without any side effect.

12325318
Itoda I, Yasunami T, Kikuchi K, Yamaura H, Totsuka K, Yoshinaga K, Teramura M, Mizoguchi H, Hatabu T, Kano S
[Severe falciparum malaria with prolonged hemolytic anemia after successful treatment with intravenous artesunate]
Kansenshogaku Zasshi. 2002 Aug;76(8):600-3.
We report a 68-year-old woman with severe falciparum malaria contracted in Tanzania. She presented high parasitemia and was treated successfully with intravenous artesunate, a qinghaosu derivative, and aggressive supportive therapy. She developed hemolytic anemia and jaundice on day 11 and blood transfusion was required. This case illustrates that intravenous artesunate has excellent antimalarial activity with rapid efficacy and that no severe adverse effect but conventional aggressive supportive therapy is still important in the treatment of severe falciparum malaria.

9736558
Ittarat W, Looareesuwan S, Pootrakul P, Sumpunsirikul P, Vattanavibool P, Meshnick SR
Effects of alpha-thalassemia on pharmacokinetics of the antimalarial agent artesunate.
Antimicrob Agents Chemother. 1998 Sep;42(9):2332-5.
Thalassemia is common in Southeast Asia, where artemisinin derivatives are frequently used in the treatment of malaria. It has been previously reported that artemisinin derivatives can be concentrated by uninfected thalassemic erythrocytes in vitro but not by normal erythrocytes. As a follow-up to this report, we studied the antimalarial kinetics of intravascular artesunate (2.4 mg/kg of body weight) in 10 persons with normal hemoglobins and in 10 patients with thalassemia (2 with alpha-thalassemia type 1-hemoglobin Constant Spring and 8 with alpha-thalassemia type 1-alpha-thalassemia type 2). Concentrations of artesunate and its active metabolites in plasma were measured by bioassay and expressed relative to those of dihydroartemisinin, the major biologically active metabolite. Concentrations of intravascular artesunate in plasma peaked in both the normal individuals and the thalassemic individuals 15 min after injection (the first time point). Plasma drug concentrations at all time intervals, except that at 1 h, were significantly higher in thalassemic subjects than in normal subjects ($P < 0.05$). The area under the concentration-time curve was 9-fold higher ($P < 0.001$) and the volume of distribution at steady state was 15-fold lower ($P < 0.001$) in thalassemic than in normal subjects. In light of the potential neurotoxicity of artemisinin derivatives, these results suggest that thalassemic subjects may need a drug administration regimen different from that of normal patients.

12641403
Ittarat W, Pickard AL, Rattanasinganchan P, Wilairatana P, Looareesuwan S, Emery K, Low J, Udomsangpetch R, Meshnick SR
Recrudescence in artesunate-treated patients with falciparum malaria is dependent on parasite burden not on parasite factors.
Am J Trop Med Hyg. 2003 Feb;68(2):147-52.

Artemisinin derivatives are first-line antimalarial drugs in Thailand. No firm evidence of clinically relevant artemisinin resistance exists. When used as monotherapy, artesunate has been associated with a high treatment failure (recrudescence) rate, which could be due to low-level artemisinin resistance. To understand the causes of recrudescence, we retrospectively studied a cohort of 104 malaria patients treated with artesunate monotherapy, 32 of whom recrudesced. There was no difference in in vitro artesunate sensitivities between 6 nonrecrudescent isolates and 16 paired admission and recrudescent isolates. Paired admission and recrudescent isolates from 10 patients were genotyped; only 3 had pfmdr1 mutations. Patients with admission parasitemias >10,000 per microl had a 9-fold higher likelihood of recrudescence (adjusted odds ratio) compared with patients with lower parasitemias. This study suggests (1) recrudescence after treatment with artesunate is not the result of inherent parasite resistance, and (2) admission parasitemia may be useful in choosing therapeutic options.

15115082
Ittarat W, Sreepian A, Srisarin A, Pathepchotivong K
Effect of dihydroartemisinin on the antioxidant capacity of P. falciparum-infected erythrocytes.
Southeast Asian J Trop Med Public Health. 2003 Dec;34(4):744-50.
Many lines of evidence reveal that artemisinin, an antimalarial containing endoperoxide, generates free radicals to kill malaria parasites. The present study re-evaluated the antioxidants of P. falciparum-infected erythrocytes in the absence and presence of 0.25, 0.5 and 1.0 ng/ml of dihydroartemisinin (DHA), the active metabolite of artemisinin. The ratio of reduced to oxidized glutathione (GSH/GSSG) and activities of superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx) were determined. The data indicated that malaria infection induced oxidative stress in erythrocytes that resulted in a significant lower GSH in parasitized cells compared to the non-parasitized. DHA showed no effect on the antioxidant levels of non-parasitized erythrocytes treated under similar conditions as P. falciparum-infected erythrocytes. However, significantly lower GSH as well as catalase and GPx activities in parasitized cells were seen at drug concentrations of 0.5 and 1.0 ng/ml ($p < 0.05$). GSH is the most sensitive indicator of oxidative stress in malaria-infected erythrocytes both in the absence and in the presence of DHA. Parasite GPx might play a more important role than catalase in the elimination of peroxide. Parasite viabilities in the presence of DHA were analyzed simultaneously and were affected to a greater extent than the antioxidant levels. The present observation showed that although DHA killed malaria parasites by generating free radicals from the endoperoxide bridge causing the reduction of antioxidants, but the depletion of parasite antioxidants is not a prerequisite for the parasite death.

10695778
Ittarat W, Udomsangpetch R, Chotivanich KT, Looareesuwan S
The effects of quinine and artesunate treatment on plasma tumor necrosis factor levels in malaria-infected patients.
Southeast Asian J Trop Med Public Health. 1999 Mar;30(1):7-10.
Tumor necrosis factor-alpha (TNF-alpha) is an endogenous mediator of shock and inflammation including malaria. Many lines of evidence suggest that cytoadherence, the life-threatening pathology associated with complicated and cerebral malaria, results from the overproduction of TNF in response to malarial parasite. Quinine has been shown to inhibit TNF synthesis and cytoadherence in vitro suggesting an additional beneficial effect of quinine on its anti-TNF action. On the other hand, artesunate inhibits cytoadherence better than quinine does not suppress TNF production in vitro. The present study compares the effect of artesunate and quinine on TNF levels of malaria-infected patients. Surprisingly, plasma TNF levels increased dramatically after quinine administration but did not increase after artesunate administration. This difference may be explained by previous observations showing that artesunate kills parasites in vitro and clears parasitemias in vivo for more rapidly than quinine. The rapid clearance of plasma TNF in quinine treated patients might be due to the drug's TNF-suppressive activity.

16325698
Jambou R, Legrand E, Niang M, Khim N, Lim P, Volney B, Ekala MT, Bouchier C, Esterre P, Fandeur T, Mercereau-Puijalon O
Resistance of Plasmodium falciparum field isolates to in-vitro artemether and point mutations of the SERCA-type PfATPase6.
Lancet. 2005 Dec 3;366(9501):1960-3.
Artemisinin derivatives are an essential component of treatment against multidrug-resistant Plasmodium falciparum malaria. We aimed to investigate in-vitro resistance to artemisinin derivatives in field isolates. In-vitro susceptibility of 530 P falciparum isolates from three countries (Cambodia, French Guiana, and Senegal) with different artemisinin use was assessed with an isotopic microtest. Artemether IC50 up to 117 and 45 nmol/L was seen in French Guiana and Senegal, respectively. DNA sequencing in a subsample of 60 isolates lends support to SERCA-PfATPase6 as the target for artemisinins. The S769N PfATPase6 mutation, noted exclusively in French Guiana, was associated with raised (>30 nmol/L) artemether IC50s (p

8082988
Janse CJ, Waters AP, Kos J, Lugt CB
Comparison of in vivo and in vitro antimalarial activity of artemisinin, dihydroartemisinin and sodium artesunate in the Plasmodium berghei-rodent model.
Int J Parasitol. 1994 Jul;24(4):589-94.
The in vitro and in vivo antimalarial activity of artemisinin, artesunate and dihydroartemisinin has been compared using the Plasmodium berghei-rodent model. Drugs were added to synchronized short-term in vitro cultures of the erythrocytic stages and inhibition of parasite development was determined by measuring DNA synthesis by flow cytometry. Dihydroartemisinin was the most effective drug. IC50 values of artemisinin, artesunate and dihydroartemisinin were 1.9, 1.1 and 0.3 x 10(-8) M, respectively, when drugs were present during the complete 24 h developmental cycle. IC50 values increased significantly when drugs were added to old trophozoites, indicating that the older stages are less sensitive. To determine the in vivo antimalarial activity, mice with a parasitaemia between 1% and 3% were injected intramuscularly on 3 consecutive days with a single dose of the drugs dissolved in Miglyol 812. Again dihydroartemisinin was the most effective drug in vivo, showing a cure rate of 47% at 10 mg/kg bodyweight, while with both other drugs the recrudescence rate was 100% at the same dosage. This study showed that the P. berghei-rodent model is a useful tool for accurate comparisons of the in vivo and in vitro antimalarial activity of drugs.

16274712
Jansen FH
The herbal tea approach for artemisinin as a therapy for malaria?
Trans R Soc Trop Med Hyg. 2006 Mar;100(3):285-6. Epub 2005 Nov 4.

15600243
Jefford CW
Synthetic peroxides as antimalarials.
Curr Opin Investig Drugs. 2004 Aug;5(8):866-72.
This review describes the present status of purely synthetic peroxides and 1,2,4-trioxanes and how they perform in various preclinical tests as potential antimalarial drug candidates. The literature is reviewed from 1986 onwards, comprising mostly articles published in the last ten years. As several papers on antimalarial peroxides have already been published, this review focuses on more recent studies detailing the novelty and potential of synthetic peroxides.

11772352
Jefford CW
Why artemisinin and certain synthetic peroxides are potent antimalarials. Implications for the mode of action.
Curr Med Chem. 2001 Dec;8(15):1803-26.
The discovery that the sesquiterpene peroxide yingzhaosu A (13) and 1,2,4-trioxane artemisinin (14) are active against chloroquine-resistant strains of Plasmodium falciparum, has opened a new era in the chemotherapy of malaria. In vitro and in vivo tests with synthetic structurally simpler trioxanes clearly demonstrate that much of the skeleton of 14 is redundant and that chirality is not required for activity. In addition, structure-activity relations and the search for the pharmacophore reveal that high antimalarial activity can be displayed by molecules which do not resemble the geometry of 13 and 14 at all. The possible mode of action of 13, 14, and synthetic peroxides is examined. They are believed to kill intraerythrocytic Plasmodium by interacting with the heme discarded by proteolysis of ingested hemoglobin. Complexation of heme with the peroxide bond followed by electron transfer generates an oxy radical that evolves to the ultimate parasiticidal agent. Experiments with ferrous reagents indicate that active peroxides including 14 and its congeners kill the parasite by alkylation with a sterically non-encumbered C-centered radical. However, another possibility is the involvement of a Fe(IV)=O species as the toxic agent. The review covers our own and other contributions to this timely topic and evaluates the different mechanisms proposed for the mode of action of peroxidic antimalarials.

14971909
Jeyadevan JP, Bray PG, Chadwick J, Mercer AE, Byrne A, Ward SA, Park BK, Williams DP, Cosstick R, Davies J, Higson AP, Irving E, Posner GH, O'Neill PM
Antimalarial and antitumor evaluation of novel C-10 non-acetal dimers of 10beta-(2-hydroxyethyl)deoxoartemisinin.
J Med Chem. 2004 Feb 26;47(5):1290-8.
Four series of C-10 non-acetal dimers were prepared from key trioxane alcohol 10beta-(2-hydroxyethyl)deoxoartemisinin (9b). All of the dimers prepared displayed potent low nanomolar antimalarial

activity versus the K1 and HB3 strains of Plasmodium falciparum. The most potent compound assayed was phosphate dimer 14a, which was greater than 50 times more potent than the parent drug artemisinin and about 15 times more potent than the clinically used acetal artemether. In contrast to their potent activity versus malaria parasites, virtually all of the dimers expressed poor anticancer activity apart from the trioxane phosphate ester dimers 14a and 14b, which expressed nanomolar growth inhibitory (GI50) values versus a range of cancer cell lines in the NCI 60 human cell line screen. Further detailed studies on these dimers in vitro in HL60 cells demonstrate that both phosphate ester dimers (14a and 14b) are more potent than the anticancer agent doxorubicin. Interestingly, phosphate ester monomers 9c and 9d, antimalarially active in the low nanomolar region versus P. falciparum, are inactive as anticancer agents even at concentrations in the millimolar region. This observation emphasizes the importance of two trioxane units for high antiproliferative activity, and we propose that the nature of the linker in dimers of this type plays a crucial role in imparting potent anticancer activity.

16261913
Jima D, Tesfaye G, Medhin A, Kebede A, Argaw D, Babaniyi O
Safety and efficacy of artemether-lumefantrine in the treatment of uncomplicated falciparum malaria in Ethiopia.
East Afr Med J. 2005 Aug;82(8):387-90.
OBJECTIVE: To document baseline data on the efficacy and safety of artemether-lumefantrine for the treatment of uncomplicated falciparum malaria in Ethiopia. DESIGN: Patients diagnosed for P. falciparum, who were treated with six doses of artemether-lumefantrine over three days, were followed for 28 days and treatment outcomes classified based on the WHO (2003) protocol. SETTING: Four health facilities located in malarious areas in two regions: Alamata and Humera hospitals in Tigray region and Assendabo and Nazareth in Oromia region. Subjects: Patients with body weight of more than 10 kgs, excluding pregnant women, who or their guardians consented to participate in the study after fulfilling the inclusion criteria were enrolled in the study for a follow-up period of 28 days. Main outcome measures: Proportion of treatment success and adverse drug effects that required discontinuation of treatment and/or follow-up. RESULTS: A total of 213 patients who fulfilled the enrolment criteria completed the 28 days follow-up after treatment with artemether-lumefantrine. A treatment success rate of 99.1% (95% confidence interval [CI] 96.9, 99.8) and no adverse effects or complaints related to the drug that required discontinuation of treatment or withdrawal from follow-up was reported. Treatment success was not achieved in 213 (0.9%) subjects for whom fever and peripheral parasitaemia was demonstrated on day 21 and 28. The day 21 and day 28 blood samples of the treatment failure cases were not PCR corrected. CONCLUSION: The artemisinin based combination drug artemether-lumefantrine has shown very high (99.1%) clinical and parasitological cure for the treatment of uncomplicated falciparum malaria with no reports of adverse reaction that required withdrawal of treatment or discontinuation of follow-up. In the presence of the low efficacy of sulfadoxine-pyrimethamine, chloroquine and amodiaquine, the use of artemether-lumefantrine for the treatment of uncomplicated falciparum malaria is the best choice for Ethiopia.

12802771
Johann-Liang R, Albrecht R
Safety evaluations of drugs containing artemisinin derivatives for the treatment of malaria.
Clin Infect Dis. 2003 Jun 15;36(12):1626-7; author reply 1627-8.

12383020
Jung M, Lee K, Kendrick H, Robinson BL, Croft SL
Synthesis, stability, and antimalarial activity of new hydrolytically stable and water-soluble (+)-deoxoartelinic acid.
J Med Chem. 2002 Oct 24;45(22):4940-4.
(+)-Deoxoartelinic acid (13), a new hydrolytically stable, water-soluble, and potent non-acetal-type antimalarial drug candidate, was successfully prepared from artemisinic acid by using sulfur ylide and photooxygenative cyclization in seven steps. This compound showed superior in vitro antimalarial activity against the chloroquine-resistant K1 strain of Plasmodium falciparum and higher suppression (98.7%) than arteether in vivo against Plasmodium chabaudi infected mice. (+)-Deoxoartelinic acid also showed remarkable stability with a half-life of 258.66 h, 23 times more stable than clinically useful arteether in simulated stomach acid, and improved solubility, 4 times more soluble than artemisinin in water.

11348524
Kachur SP, Abdulla S, Barnes K, Mshinda H, Durrheim D, Kitua A, Bloland P
Re.: Complex, and large, trials of pragmatic malaria interventions.
Trop Med Int Health. 2001 Apr;6(4):324-5.

15642960
Kachur SP, Khatib RA, Kaizer E, Fox SS, Abdulla SM, Bloland PB
Adherence to antimalarial combination therapy with sulfadoxine-pyrimethamine and artesunate in rural Tanzania.
Am J Trop Med Hyg. 2004 Dec;71(6):715-22.
Artemisinin-containing antimalarial combination therapies are recommended to confront drug-resistant Plasmodium falciparum malaria. Among the questions surrounding whether these complex multidose treatments will be practical is to what extent patients complete the recommended doses. Combination therapy through coadministration of sulfadoxine-pyrimethamine plus artesunate was introduced as a first-line treatment for uncomplicated malaria in one district in Tanzania. Interventions to optimize correct use were also implemented. We observed 453 patient encounters at one health facility and recorded key practices as health workers dispensed the combination. A total of 253 patients were followed-up at 24 or 48 hours. Complete adherence measured at 48 hours reached 75.0%, based on self-report and tablet counts. This is substantially better than reported elsewhere and compares favorably with intervention studies to optimize adherence to chloroquine. Counseling about what to do if a patient vomits appears to have been an independent risk factor for nonadherence.

10703586
Kager PA, de Vries PJ
[Why is malaria in Vietnam under control, but Africa is threatened with a malaria disaster?]
Ned Tijdschr Geneeskd. 2000 Feb 19;144(8):357-61.
In Africa malaria parasites are increasingly developing resistance to the 3 affordable and tolerable drugs: chloroquine, amodiaquine and sulfadoxine-pyrimethamine. Alternative products are much more expensive and more toxic. A malaria disaster is looming. On the contrary, in Vietnam a disaster appears to have been averted. Data on malaria epidemiology, on the mosquito, the parasite and the host, man, give insight into the differences and the possibilities of control. Artemisinin derivatives can play an important role in malaria control, also in Africa. Without improvement of care which will require considerable investment and attention, the prospects are bleak.

11219150
Kager PA, Schipper HG
[Acute schistosomiasis: fever and eosinophilia, with or without urticaria, after a trip to Africa]
Ned Tijdschr Geneeskd. 2001 Feb 3;145(5):220-5.
Despite treatment for malaria two travellers who acquired fever in Africa continued to have complaints: a 25-year-old Dutch woman and a 25-year-old Australian man. On questioning they appeared to have swum in Lake Malawi and a diagnosis of acute schistosomiasis was made, confirmed by serological tests. This syndrome, also called Katayama fever, is characterized by fever, oedema, urticaria and eosinophilia. The aetiology is not fully elucidated but it is supposed to be caused by immune complexes initiated by maturing worms and eggs. Patients who acquired fever in an endemic area must be questioned about contact with fresh water. Serological tests are important for the diagnosis. Treatment is with praziquantel but it is advised to treat only after the acute phase. During the acute manifestations corticosteroids may be necessary. Prevention is by avoiding contact with infected water. There is no vaccine. The role of artemisinin drugs in prevention is currently being studied.

12611273
Kaiser A, Gottwald A, Wiersch C, Maier W, Seitz HM
The necessity to develop drugs against parasitic diseases.
Pharmazie. 2002 Nov;57(11):723-8.
This review focuses on the most significant trends in the development of drugs for the treatment of malaria, African sleeping sickness and toxoplasmosis. In the case of malaria, those include new fixed-dose artemisinin combinations, antifolates and new targets in the apicoplast of Plasmodium falciparum. Targets in the treatment of trypanosomiasis are the biosynthesis of glycosylphosphatidylinositol and enzymes involved in the biosynthesis of trypanothione. Efforts to develop a vaccine against toxoplasmosis are discussed as well.

16403595
Kamat VR
"I thought it was only ordinary fever!" cultural knowledge and the micropolitics of therapy seeking for childhood febrile illness in Tanzania.
Soc Sci Med. 2006 Jan 3;.

Economic considerations are often cited as important determinants of health-seeking behavior. This paper describes a situation in peri-urban Tanzania where user fees do not constitute the primary reason why mothers delay seeking prompt treatment at a public health facility for their young, febrile children. Mothers commonly believe that they are dealing with an ordinary fever and not malaria or any other serious illness complicated by fever. Hence, they engage in extended home-based treatment. Drawing upon an ethnographic study, this paper illustrates how cultural knowledge about disease symptomatology, cultural meanings associated with febrile illness, gender relations, and patterns of communication between health care providers and mothers significantly influence outcomes for childhood febrile illnesses. It is argued that an overemphasis on the correlation between user fees and treatment delays with regard to childhood illnesses tends to divert attention from other significant cultural factors and existing structural constraints that influence the dynamics of health care seeking and health outcomes. At a time when calls to implement artemisinine-based combination therapy as one of the front-line strategies in Tanzania are increasingly frequent, there is a need to pay closer attention to the contextual factors and socio-cultural dynamics that influence patterns of treatment-seeking for childhood malaria.

9063352
Kamchonwongpaisan S, McKeever P, Hossler P, Ziffer H, Meshnick SR
Artemisinin neurotoxicity: neuropathology in rats and mechanistic studies in vitro.
Am J Trop Med Hyg. 1997 Jan;56(1):7-12.
Despite the wide use of artermisinin and its derivatives, concerns have been raised about their potential neurotoxicity. Accordingly, studies were undertaken on rats treated with high doses of arteether and on mouse neuroblastoma cells (Neu2a) treated with 3H-dihydroartemisinin. Rats uniformly developed neurologic symptoms following intramuscular administration of 50 mg/kg/day of arteether for 5-6 days. Acute neuronal necrosis associated with vacuolization and focal axonal swelling in the neuropil was observed in specific areas of the brain, especially the vestibular nuclei and red nuclei. Scattered swollen neurons were also evident in the cerebellar nuclei and the reticular formation. No neurologic symptoms, neuronal nuclei necrosis, nor gliosis was observed in rats administered 25 or 30 mg/kg/day for six or eight days. In vitro, Neu2a cells took up much less 3H-dihydroartemisinin than Plasmodium falciparum-infected red blood cells when incubated under identical conditions for 4 hr with 4.2 microM 3H-dihydroartemisinin. This selective uptake may explain why the artemisinin derivatives are selectively toxic to malaria parasites. Autoradiograms of sodium dodecyl sulfate-polyacrylamide gels run from 3H-dihydroartemisinin-treated cells showed that neuronal proteins with molecular weights of 27, 32, 40, and 81 kD were alkylated, although not nearly as strongly or rapidly as the P. falciparum proteins. The results indicate that while artemisinin derivatives have neurotoxic effects in rats and alkylate proteins in neuroblastoma cells, these effects only occur at high doses or after prolonged exposure.

8853288
Kamchonwongpaisan S, Meshnick SR
The mode of action of the antimalarial artemisinin and its derivatives.
Gen Pharmacol. 1996 Jun;27(4):587-92.
1. Atremisinin (qinghaosu) is a sesquiterpene endoperoxide derived from a plant which was used in Chinese herbal medicine for thousands of years. 2. Artemisinin and its derivatives have potent antimalarial activity, and are now being used clinically in much of the world. 3. The artemisinin derivatives have an unusual mode of action involving the iron-catalyzed generation of a carbon-centered free radical followed by the alkylation of malaria-specific proteins.

15619037
Kanda E, Kida Y, Suzuki H, Ando M, Negishi M, Sasaki S, Saito H
A female patient with malarial nephropathy.
Clin Exp Nephrol. 2004 Dec;8(4):359-62.
Malaria remains one of the world's major health problems, particularly in developing tropical countries. Imported malaria is reportedly increasing in Western countries. Acute renal failure (ARF) is the most common cause of death in severe malaria. We report the case of a 63-year-old female patient with a history of travel to a rural area in South Africa who was in coma and had a high fever on admission. Thirty percent of her erythrocytes were infected with Plasmodium falciparum. She had cerebral malaria, malarial nephropathy, anemia, hepatic dysfunction, and disseminated intravenous coagulation (DIC). Quinine and artesunate treatment decreased the number of parasites in the blood. To manage renal failure, hemodialysis was performed for 11 days. A relationship between ARF and hepatic dysfunction was suggested. This relationship is an indication of the clinical course of the disease. In this article, we discuss the mechanism underlying the development of malarial nephropathy and its management, particularly the usefulness of hemodialysis.

15361062

Kannan R, Kumar K, Sahal D, Kukreti S, Chauhan VS
Reaction of artemisinin with haemoglobin: implications for antimalarial activity.
Biochem J. 2005 Jan 15;385(Pt 2):409-18.
Elucidation of the principal targets of the action of the antimalarial drug artemisinin is an ongoing pursuit that is important for understanding the action of this drug and for the development of more potent analogues. We have examined the chemical reaction of Hb with artemisinin. The protein-bound haem in Hb has been found to react with artemisinin much faster than is the case with free haem. It appears that the uptake of Hb and the accumulation of artemisinin into the food vacuole, together with the preferred reactivity of artemisinin with haem in Hb, may make Hb the primary target of artemisinin's antimalarial action. Both monoalkylated (HA) and dialkylated (HAA) haem derivatives of artemisinin have been isolated. These 'haemarts' bind to PfHRP II (Plasmodium falciparum histidine-rich protein II), inhibiting haemozoin formation, and possess a significantly decreased ability to oxidize ascorbic acid. The accelerated formation of HAA from Hb is expected to decrease the ratio of haem to its alkylated derivatives. The haemarts that are generated from 'haemartoglobins' may bring about the death of malaria parasite by a two-pronged effect of stalling the formation of haemozoin by the competitive inhibition of haem binding to its templates and creating a more reducing environment that is not conducive to the formation of haemozoin.

11927257
Kannan R, Sahal D, Chauhan VS
Heme-artemisinin adducts are crucial mediators of the ability of artemisinin to inhibit heme polymerization.
Chem Biol. 2002 Mar;9(3):321-32.
A lack of molecular understanding of the targets and mechanisms of artemisinin action has impeded the improvisation of more efficient antimalarials based on this class of endoperoxide drugs. We have synthesized a heme-artemisinin adduct designated as "hemart" to discover if it mediates the ability of artemisinin to inhibit heme polymerization. Hemart mimics heme in binding to Plasmodium falciparum histidine-rich protein II (PfHRP II) but cannot self-polymerize. Instead, it inhibits all heme polymerizations, including basal and those triggered by PfHRP II, Monooleoyl glycerol (MOG), or P. yoelii extract. Hemart has an edge over heme in displacing heme from PfHRP II, and either low pH or chloroquine dissociates heme but not hemart from PfHRP II. Our results suggest that hemart, by mimicking heme, stalls all mechanisms of heme polymerization, resulting in the death of the malaria parasite.

15792501
Kaona FA, Tuba M
A qualitative study to identify community structures for management of severe malaria: a basis for introducing rectal artesunate in the under five years children in Nakonde District of Zambia.
BMC Public Health. 2005 Mar 25;5(1):28.
BACKGROUND: Malaria is a serious illness among children aged 5 years and below in Zambia, which carries with it many adverse effects including anemia and high parasites exposure that lead to infant and childhood mortality. Due to poor accessibility to modern health facilities, malaria is normally managed at home using indigenous and cosmopolitan medicines. In view of problems and implications associated with management of severe malaria at home, rectal artesunate is being proposed as a first aid drug to slow down multiplication of parasites in children before accessing appropriate treatment. METHODS: A qualitative study using standardised in-depth and Focus Group Discussions (FGDs) guides to collect information from four (4) villages in Nakonde district, was conducted between February and March 2004. The guides were administered on 29 key informants living in the community and those whose children were admitted in the health facility. Participants in the 12 FGDs came from the 4 participating villages. Participants and key informants were fathers, younger and older mothers including grandmothers and other influential people at household level. Others were traditional healers, headmen, village secretaries, traditional birth attendants, church leaders and blacksmiths. FGDs and interview transcriptions were coded to identify common themes that were related to recognition, classification and naming of malaria illness, care-seeking behaviour and community treatment practices for severe malaria. RESULTS: Parental prior knowledge of the disease was important as the majority of informants (23 out of 29) and participants (69 out of 97) mentioned four combined symptoms that were used to recognise severe malaria. The symptoms were excessive body hotness, convulsions, vomiting yellow things and bulging of the fontanelle. On the other hand, all informants mentioned two or more of symptoms associated with severe malaria. In all 12 FGDs, participants reported that treatment of severe malaria commenced with the family and moved into the community as the illness progressed. Although treatment of severe diarrheal effects, were common among the Winamwanga, no rectal medicines to treat severe malaria were identified. Apart from the anti-malarial fansidar, which was mentioned by 23 in IDIs and 40 in FGDs, participants and informants also frequently mentioned indigenous medicines provided by healers and other respectable herbalists for repelling evil spirits, once a child had severe malaria. Mothers were the important arms for administration of ant-malarial drugs in the villages. Referrals began with healers to CHWs, where no CHWs existed healers directly referred sick children to the health facility. CONCLUSION: Our findings showed that there is a precedent for rectal application of

traditional medicine for childhood illness. Therefore rectal artesunate may be a well-received intervention in Nakonde District, provided effective sensitisation, to mothers and CHWs is given which will strengthen the health care delivery system at community level.

16325931
Kaptein SJ, Efferth T, Leis M, Rechter S, Auerochs S, Kalmer M, Bruggeman CA, Vink C, Stamminger T, Marschall M
The anti-malaria drug artesunate inhibits replication of cytomegalovirus in vitro and in vivo.
Antiviral Res. 2006 Feb;69(2):60-9. Epub 2005 Nov 21.
Treatment of human cytomegalovirus (HCMV) infections with any of the currently available antiviral agents is frequently associated with the occurrence of severe complications, seriously threatening the successful outcome of treatment. Therefore, the development of novel antiviral strategies is a challenging goal of current investigations. Previously, we reported that artesunate (ART) is an effective, non-cytotoxic inhibitor of HCMV in vitro. Here, we demonstrate that the efficacy of the antiviral effect of ART is augmented by co-treatment of HCMV-infected fibroblasts with ferrous iron, i.e. Ferrosanol, and/or the iron transfer-mediating molecule holo-transferrin. This could alleviate the HCMV-induced modulation of cell surface expression of adhesion molecule Thy-1, suggesting that ART might be able to prevent pro-inflammatory effects of infection. The iron-enhanced, antiviral effect of ART could also be demonstrated in cultured cells infected with rat cytomegalovirus. Experiments using the RCMV/rat model showed that both the viral DNA load and virus titers in the salivary glands from infected rats were significantly reduced upon treatment with ART. Furthermore, an additive antiviral effect for ART together with each one of conventional anti-HCMV drugs, i.e. ganciclovir, cidofovir or foscarnet, was detected in HCMV-infected fibroblasts. These findings might open new perspectives regarding the use of ART in clinical trials.

9763725
Karbwang J, Fungladda W, Pickard CE, Shires S, Hay A, Feely M
Initial evaluation of low-dose phenobarbital as an indicator of compliance with antimalarial drug treatment.
Bull World Health Organ. 1998;76 Suppl 1:67-73.
Since poor compliance with antimalarial therapy is often suspected but difficult to prove, this study attempted to establish a model for predicting the plasma concentration of phenobarbital (given in low doses in conjunction with the drug) as an indicator of compliance. Phenobarbital was chosen because its value had been demonstrated as a marker of compliance in long-course therapies, any significant departure from steady-state concentrations (achieved with full compliance) indicating one or more missed doses. Therapy for uncomplicated malaria varies from 5 days with artesunate to 7 days with quinine + tetracycline. Volunteers with confirmed falciparum malaria were randomized into 5 groups and given malaria therapy as well as phenobarbital daily for 3-7 days. Plasma samples for determination of phenobarbital concentrations were taken just prior to the daily dose of phenobarbital. Although there was a clear and predictable individual pattern of blood concentrations following each dose of phenobarbital, inter-individual variation in blood levels was significant and reduced their predictive value beyond the second day's dose. The cause of the variations is not clear; it could be attributable to different sources of the drug, previous intake of phenobarbital by the patient, or differences in drug absorption and disposition in malaria patients. Results for the 5-day artesunate regimen suggest that phenobarbital may be useful as a marker of compliance if the patient stops medication after 3 days; clear differences were evident at the end of the course of treatment between plasma phenobarbital concentrations in individuals completing the 5-day course and those who stopped after 3 days. For the quinine-tetracycline regimen, results suggest that it may be possible to discriminate between subjects where there is a 3-day difference in treatment. Phenobarbital is a better discriminant when dosing is every 24 hours as with artesunate, rather than the 8-hourly regimen for quinine-tetracycline. When measuring compliance for malaria treatment, if it is important to know what proportion of patients reach 3, 5 or 7 days of compliance, then phenobarbital might have a role to play in this assessment, but further investigations in more patients would be required. Alternatively, different markers could be used for the doses to be given on these days and, as long as the patient does not mix the doses for the different days, sequential doses and determination of compliance could be based on an "all or none" detection of the marker rather than on drug levels.

8131255
Karbwang J, Na Bangchang K, Thanavibul A, Back DJ, Bunnag D, Harinasuta T
Pharmacokinetics of mefloquine alone or in combination with artesunate.
Bull World Health Organ. 1994;72(1):83-7.
A randomized comparative trial of the pharmacokinetics and pharmacodynamics of oral doses of mefloquine and of mefloquine in combination with artesunate was carried out on 20 Thai male patients with acute, uncomplicated falciparum malaria. The patients were randomized to receive either mefloquine alone (8 patients; 1250 mg of mefloquine--initial dose, 750 mg; followed 6 hours later by 500 mg), or in combination with oral artesunate (12 patients--initial dose, 200 mg of artesunate; followed by 750 mg and 500 mg of

mefloquine 6 hours and 12 hours later, respectively). The patients who received mefloquine alone all showed initially good responses to the treatment, with mean +/- SD values for the fever clearance time (FCT) and parasite clearance time (PCT) of 44.7 +/- 43.1 hours and 82.3 +/- 52.3 hours, respectively. Two patients had recrudescences on day 20 and day 31 (RI response). The cure rate was 75%, and one patient had Plasmodium vivax in his peripheral blood on day 52. The patients who received the combination treatment were clinically markedly improved, with a relatively shorter FCT (31.2 +/- 12.4 hours) and significantly shorter PCT (47.5 +/- 19.6 hours). Four had recrudescences on days 12, 18, 26 and 33; the cure rate was 66%. Artesunate caused three significant changes in mefloquine pharmacokinetics: a decrease in the maximum concentration (Cmax: 1623 ng.ml-1 versus 2212 ng.ml-1); an increase in the clearance rate (Cl/f:2.9 ml.min-1.kg-1 versus 1.1 ml.min-1.kg-1); and an expansion of the volume of distribution (Vdz/f: 31.8 l.kg-1 versus 25.0 l.kg-1).

7721226
Karbwang J, Na-Bangchang K
Clinical application of mefloquine pharmacokinetics in the treatment of P falciparum malaria.
Fundam Clin Pharmacol. 1994;8(6):491-502.
Malaria remains a major public health problem in large areas of the world. One of the major factors responsible for the resurgence is the emergence of Plasmodium falciparum, resistant to available antimalarials. An antimalarial, mefloquine, has been considered since its introduction as a promising alternative antimalarial drug to overcome the situation of widespread multidrug resistant P falciparum. Pharmacokinetic studies of mefloquine have been investigated in several groups of subjects either as mefloquine alone or as combined regimens. The oral absorption of mefloquine is relatively rapid, reaching peak concentrations within 24 hours. Metabolism takes place in the liver, with carboxymefloquine as a major metabolite. Mefloquine has a large apparent volume of distribution of 200 L and is highly bound (98%) to plasma proteins. The elimination is slow; the terminal half-life is 13 10 to 14 days in Thai patients with falciparum malaria. Vomiting within 1 hour of drug administration has an influence on blood concentrations of mefloquine and this may result in treatment failure. The whole blood concentrations of mefloquine on the first two days of treatment are important determinants of parasitological response. There appear to be no pharmacokinetic interactions between mefloquine and the other two components of Fansimef in patients with uncomplicated falciparum malaria. The advantage of this combination over mefloquine alone in multidrug resistant P falciparum is still debatable. However, recent data seem to support the higher efficacy of Fansimef over mefloquine alone. Concurrent administration of antibiotics, ie ampicillin and tetracycline with mefloquine results in a significant increase in maximum concentration, reduction of the apparent volume of distribution and shortening of the terminal elimination half-life of mefloquine. An antiemetic drug metoclopramide accelerates the absorption of mefloquine and increases the maximum concentration. In contrast, mefloquine concentrations are decreased in the presence of an antimalarial, artesunate. Primaquine has no effect on the pharmacokinetics of mefloquine when given concurrently.

8205643
Karbwang J, Na-Bangchang K, Thanavibul A, Bunnag D, Chongsuphajaisiddhi T, Harinasuta T
Comparison of oral artesunate and quinine plus tetracycline in acute uncomplicated falciparum malaria.
Bull World Health Organ. 1994;72(2):233-8.
In Thailand Plasmodium falciparum malaria is highly resistant to available antimalarials. Investigations on the efficacy of existing antimalarials and of alternative drugs are urgently needed. Artesunate has been shown to be effective against falciparum malaria, but is associated with a high recrudescence rate. We have carried out a comparative clinical trial of the standard regimen of quinine + tetracycline versus oral artesunate at a 700-mg total dose given over 5 days to patients with acute uncomplicated falciparum malaria. The 64 male patients who took part in the study were randomized to receive either quinine-tetracycline (33 patients) or oral artesunate (31 patients). All the patients were admitted to the Bangkok Hospital for Tropical Diseases for 28 days. Oral artesunate had faster parasite and fever clearance times than the combination quinine-tetracycline, but the cure rate was not significantly different for the two regimens. However, the occurrence of adverse effects, such as tinnitus, was significantly higher in the quinine-tetracycline group. Surprisingly nausea and dizziness were rather common with artesunate. The possibility of neurological adverse effects for artesunate should also be borne in mind. Oral artesunate (700 mg given over 5 days) is effective and better tolerated than the combination quinine-tetracycline. The cure rate we obtained is higher than that reported in previous studies with 600 mg of oral artesunate given over 5 days. Oral artesunate can be considered as an alternative drug for multiple-drug-resistant falciparum malaria; however, adverse effects, particularly neurotoxicity, should be closely monitored before its widespread use can be recommended.(ABSTRACT TRUNCATED AT 250 WORDS)

15273107
Karunajeewa HA, Ilett KF, Dufall K, Kemiki A, Bockarie M, Alpers MP, Barrett PH, Vicini P, Davis TM

Disposition of artesunate and dihydroartemisinin after administration of artesunate suppositories in children from Papua New Guinea with uncomplicated malaria.
Antimicrob Agents Chemother. 2004 Aug;48(8):2966-72.
A detailed pharmacokinetic analysis was performed with 47 children from Papua New Guinea with uncomplicated falciparum or vivax malaria treated with artesunate (ARTS) suppositories (Rectocaps) given in two doses of approximately 13 mg/kg of body weight 12 h apart. Following an intensive sampling protocol, samples were assayed for ARTS and its primary active metabolite, dihydroartemisinin (DHA), by liquid chromatography-mass spectrometry. A population pharmacokinetic model was developed to describe the data. Following administration of the first dose, the mean maximal concentrations of ARTS and DHA were 1,085 nmol/liter at 0.9 h and 2,525 nmol/liter at 2.3 h, respectively. The absorption half-life for ARTS was 2.3 h, and the conversion half-life (ARTS to DHA) was 0.27 h, while the elimination half-life of DHA was 0.71 h. The mean common volumes of distribution for ARTS and DHA relative to bioavailability were 42.8 and 2.04 liters/kg, respectively, and the mean clearance values relative to bioavailability were 6 and 2.2 liters/h/kg for ARTS and DHA, respectively. Substantial interpatient variability was observed, and the bioavailability of the second dose relative to that of the first was estimated to be 0.72. The covariates age, sex, and alpha-thalassemia genotype were not influential in the pharmacokinetic model development; but the inclusion of weight as a covariate significantly improved the performance of the model. An ARTS suppositories dose of 10 of 20 mg/kg is appropriate for use in children with uncomplicated malaria.

12634587
Karunajeewa HA, Kemiki A, Alpers MP, Lorry K, Batty KT, Ilett KF, Davis TM
Safety and therapeutic efficacy of artesunate suppositories for treatment of malaria in children in Papua New Guinea.
Pediatr Infect Dis J. 2003 Mar;22(3):251-6.
BACKGROUND: Although suppositories of artemisinin derivatives may be a valuable option for treatment of malaria in children when circumstances prevent oral and parenteral therapy, few confirmatory data have been published. METHODS: We assessed the safety and efficacy of rectal artesunate in 47 children ages 5 to 10 years with uncomplicated malaria acquired in a hyperendemic area of Papua New Guinea. Thirty were symptomatic and had Plasmodium falciparum parasitemia >2000/microl (Group 1), 12 had and either a parasitemia or =10 mg/kg rectal artesunate within the first 24 h.

16495259
Karunajeewa HA, Reeder J, Lorry K, Dabod E, Hamzah J, Page-Sharp M, Chiswell GM, Ilett KF, Davis TM
Artesunate Suppositories versus Intramuscular Artemether for Treatment of Severe Malaria in Children in Papua New Guinea.
Antimicrob Agents Chemother. 2006 Mar;50(3):968-74.
Drug treatment of severe malaria must be rapidly effective. Suppositories may be valuable for childhood malaria when circumstances prevent oral or parenteral therapy. We compared artesunate suppositories (n = 41; 8 to 16 mg/kg of body weight at 0 and 12 h and then daily) with intramuscular (i.m.) artemether (n = 38; 3.2 mg/kg at 0 h and then 1.6 mg/kg daily) in an open-label, randomized trial with children with severe Plasmodium falciparum malaria in Papua New Guinea (PNG). Parasite density and temperature were measured every 6 h for >/=72 h. Primary endpoints included times to 50% and 90% parasite clearance (PCT(50) and PCT(90)) and the time to per os status. In a subset of 29 patients, plasma levels of artemether, artesunate, and their common active metabolite dihydroartemisinin were measured during the first 12 h. One suppository-treated patient with multiple complications died within 2 h of admission, but the remaining 78 recovered uneventfully. Compared to the artemether-treated children, those receiving artesunate suppositories had a significantly earlier mean PCT(50) (9.1 versus 13.8 h; P = 0.008) and PCT(90) (15.6 versus 20.4 h; P = 0.011). Mean time to per os status was similar for each group. Plasma concentrations of primary drug plus active metabolite were significantly higher in the artesunate suppository group at 2 h postdose. The earlier initial fall in parasitemia with artesunate is clinically advantageous and mirrors higher initial plasma concentrations of active drug/metabolite. In severely ill children with malaria in PNG, artesunate suppositories were at least as effective as i.m. artemether and may, therefore, be useful in settings where parenteral therapy cannot be given.

15225468
Khan MA, Smego RA Jr, Razi ST, Beg MA
Emerging drug--resistance and guidelines for treatment of malaria.
J Coll Physicians Surg Pak. 2004 May;14(5):319-24.
The increasing prevalence of multi-resistant Plasmodium falciparum malaria worldwide is a serious public health threat to the global control of malaria, especially in poor countries like Pakistan. In many countries choloroquine-resistance is a huge problem, accounting for more than 90% of malaria cases. In Pakistan, resistance to choloroquin is on the rise and reported in up to 16- 62% of Plasmodium falciparum. four to 25%

of Plasmodium falciparum also reported to be resistant to sulfadoxine-pyrimethamine and several cases of delayed parasite clearance have been observed in patients with Plasmodium falciparum malaria treated with quinine. In this article we have introduced the concept of artemisinin- based combination therapy (ACT) and emphasize the use of empiric combination therapy for all patients with Plasmodium falciparum malaria to prevent development of drug resistance and to obtain additive and synergistic killing of parasite.

10049291
Khanh NX, de Vries PJ, Ha LD, van Boxtel CJ, Koopmans R, Kager PA
Declining concentrations of dihydroartemisinin in plasma during 5-day oral treatment with artesunate for Falciparum malaria.
Antimicrob Agents Chemother. 1999 Mar;43(3):690-2.
Six patients with uncomplicated falciparum malaria received artesunate for 5 days. Plasma concentrations of artesunate and dihydroartemisinin were determined by high-performance liquid chromatography with electrochemical detection. The concentrations of dihydroartemisinin in plasma 2 h after a dose showed a time-dependent decline. Concentrations of artesunate in plasma especially after the last dose, were very low. Despite this, all patients responded with a fast recovery.

16048916
Khim N, Bouchier C, Ekala MT, Incardona S, Lim P, Legrand E, Jambou R, Doung S, Puijalon OM, Fandeur T
Countrywide survey shows very high prevalence of Plasmodium falciparum multilocus resistance genotypes in Cambodia.
Antimicrob Agents Chemother. 2005 Aug;49(8):3147-52.
Cambodia is located in an area of resistance to multiple antimalarials and has been the first country to implement the systematic use of an artesunate-mefloquine combination as first-line treatment for Plasmodium falciparum malaria. Little is known, however, about the prevalence of resistance mutations within the natural parasite populations, impeding rational drug policy in this context. Using direct sequencing of PCR products, we have analyzed sequence polymorphism of the dihydrofolate reductase-thymidylate synthase, dihydropteroate synthetase, and multidrug resistance 1 genes in a large number of clinical P. falciparum isolates collected in various areas of Cambodia. This highlighted a 100% prevalence of haplotypes with multiple mutations in the target genes of antifolates after more than a decade without use of antifolates for malaria therapy. A high prevalence of mutations in Pfmdr1, including mutations associated with decreased in vitro susceptibility to mefloquine and quinine, was also observed. In addition, novel, low-frequency mutations were detected in Pfmdr1. Our findings show an alarming rate of multilocus resistance genotypes in Cambodia, requiring diligent surveillance and imposing limitations on possible future drug combinations.

11227768
Kim HS, Shibata Y, Ko N, Ikemoto N, Ishizuka Y, Murakami N, Sugimoto M, Kobayashi M, Wataya Y
Potent in vivo antimalarial activity of 3,15-di-O-acetylbruceolide against Plasmodium berghei infection in mice.
Parasitol Int. 2000 Jan;48(3):271-4.
The antimalarial activity of the O-acylated bruceolide derivative, 3,15-di-O-acetylbruceolide, was evaluated against Plasmodium berghei in vivo. The concentration of 3,15-di-O-acetylbruceolide required for 50% suppression (ED50) of P. berghei in mice was 0.46 +/- 0.06 mg/kg/day, whereas bruceolide was only half as effective as 3,15-di-O-acetylbruceolide. Two antimalarial drugs used clinically, chloroquine and artemisinin, demonstrated only low activity corresponding to 1/4 and 1/12 of the ED50 value of 3,15-di-O-acetylbruceolide, respectively. These results may be helpful in the design of better chemotherapeutic bruceolides against falciparum malaria.

8594702
Kirby GC
The use of chloroquine in combination with artemisinin derivatives.
Trans R Soc Trop Med Hyg. 1995 Nov-Dec;89(6):699.

11357994
Kissinger E, Hien TT, Hung NT, Nam ND, Tuyen NL, Dinh BV, Mann C, Phu NH, Loc PP, Simpson JA, White NJ, Farrar JJ
Clinical and neurophysiological study of the effects of multiple doses of artemisinin on brain-stem function in Vietnamese patients.
Am J Trop Med Hyg. 2000 Jul-Aug;63(1-2):48-55.

The qinghaosu (artemisinin) group of drugs is the most important new class of antimalarials developed in the last fifty years. Although there has been no clinical evidence of neurotoxicity, an unusual pattern of damage to specific brain-stem nuclei has been reported in experimental animals receiving high doses of arteether or artemether. Detailed clinical examinations, audiometry, and brain stem auditory evoked potentials (BSAEPs) were assessed in 242 Vietnamese subjects who had previously received up to 21 antimalarial treatment courses of artemisinin or artesunate alone and 108 controls from the same location who had not received these drugs. There was no evidence of a drug effect on the clinical or neurophysiological parameters assessed. In this population there was no clinical or neurophysiological evidence of brain-stem toxicity that could be attributed to exposure to artemisinin or artesunate.

3887571
Klayman DL
Qinghaosu (artemisinin): an antimalarial drug from China.
Science. 1985 May 31;228(4703):1049-55.
The herb Artemisia annua has been used for many centuries in Chinese traditional medicine as a treatment for fever and malaria. In 1971, Chinese chemists isolated from the leafy portions of the plant the substance responsible for its reputed medicinal action. This compound, called qinghaosu (QHS, artemisinin), is a sesquiterpene lactone that bears a peroxide grouping and, unlike most other antimalarials, lacks a nitrogen-containing heterocyclic ring system. The compound has been used successfully in several thousand malaria patients in China, including those with both chloroquine-sensitive and chloroquine-resistant strains of Plasmodium falciparum. Derivatives of QHS, such as dihydroqinghaosu, artemether, and the water-soluble sodium artesunate, appear to be more potent than QHS itself. Sodium artesunate acts rapidly in restoring to consciousness comatose patients with cerebral malaria. Thus QHS and its derivatives offer promise as a totally new class of antimalarials.

16458301
Kocken CH, van der Wel A, Arbe-Barnes S, Brun R, Matile H, Scheurer C, Wittlin S, Thomas AW
Plasmodium vivax: In vitro susceptibility of blood stages to synthetic trioxolane compounds and the diamidine DB75.
Exp Parasitol. 2006 Feb 1;.
Plasmodium vivax is an important human pathogen causing malaria in more temperate climates of the world. Similar to Plasmodium falciparum, the causative agent for malaria tropica, drug resistance is beginning to emerge for this parasite species and this hampers adequate treatment of infection. We have used a short-term ex vivo drug assay to monitor activity of OZ277 (RBx-11160), a fully synthetic anti-malarial peroxide, and the diamidine DB75 against P. vivax. For both compounds as well as the anti-malarial reference compounds artesunate, artemether, and chloroquine, the in vitro IC(50) values were determined in one-cycle hypoxanthine incorporation assays. Results from such assays were found to be very similar compared to IC(50) values obtained from one-cycle P. falciparum hypoxanthine assays. We demonstrate the anti-parasite activity of OZ277 and the reference compounds to be faster than that of DB75. These data warrant clinical testing of OZ277 against P. vivax malaria and support recent data on clinical activity against P. vivax for DB75.

15259473
Kofoed PE, Poulsen A, Co F, Hedegaard K, Aaby P, Rombo L
No benefits from combining chloroquine with artesunate for three days for treatment of Plasmodium falciparum in Guinea-Bissau.
Trans R Soc Trop Med Hyg. 2003 Jul-Aug;97(4):429-33.
The use of a combination of chloroquine and artesunate has been suggested for treatment of malaria in Africa. We used concomitant as well as sequential medication with these 2 drugs in relation to each drug separately for children infected with Plasmodium falciparum in Guinea-Bissau from March 2000 to November 2001. By block-randomization, 474 children with symptomatic malaria were divided into 4 groups and given either a total of 8 mg artesunate per kg bodyweight for 3 d, a total of 25 mg chloroquine base per kg bodyweight for 3 d, both drugs concomitantly for 3 d, or both drugs in sequence. All children were followed weekly for 5 weeks. On day 28, parasites had been detected in 40% of the children who were treated with artesunate only compared with 21% treated with chloroquine, 20% treated with artesunate in combination with chloroquine, and 16% treated with artesunate and chloroquine in sequence; on day 35 the corresponding percentages were 48%, 29%, 27%, and 24%, respectively. The outcome of the combination of chloroquine and artesunate in the doses studied was similar to the outcome of chloroquine monotherapy regardless of whether the 2 drugs are given concomitantly (relative risk [RR] = 0.93, 95% CI 0.56-1.53, P = 0.76) or in sequence (RR = 0.78, 95% CI 0.47-1.28, P = 0.32). Thus, neither an antagonistic, an additive, or a synergistic effect of the 2 drugs was indicated.

9430519

Kombila M, Duong TH, Dufillot D, Koko J, Guiyedi V, Guiguen C, Ferrer A, Richard-Lenoble D
Light microscopic changes in Plasmodium falciparum from Gabonese children treated with artemether.
Am J Trop Med Hyg. 1997 Dec;57(6):643-5.
The changes in Plasmodium falciparum in four Gabonese children suffering from severe malaria and treated with pure artemether were observed in thin blood smears fixed and stained with Giemsa and examined by light microscopy. Peripheral blood samples were taken every 8 hr up to 72 hr from three children and every 3 hr up to 9 hr from the other child. The morphologic changes involved all development stages (trophozoites, schizonts, and gametocytes); they were first seen 3 hr after the start of treatment and all parasites were abnormal after 24 hr. After two days of treatment, all infected erythrocytes disappeared except for a few with necrotic trophozoites. The morphologic changes were similar to the ultrastructural changes previously described in vivo and in vitro in experimental models. They confirm the rapid effect of artemisinin derivatives on parasite clearance and clinical recovery, particularly in cases of cerebral malaria.

9291675
Kondrachine AV, Trigg PI
Global overview of malaria.
Indian J Med Res. 1997 Aug;106:39-52.
Malaria continues to be one of the main public health problems in the world, especially in the majority of African countries. It particularly affects young children, young adults engaged in economic development activities, pregnant women and international itinerant groups of population, moving into malaria endemic areas. Malaria epidemics became a regular feature in many parts of the world, including the highlands of Africa, being associated with the warming of the climate, disruption of health services and large scale uncontrolled population movement as a result of social disruption and civil wars. Further proliferation of drug resistance is closely related to massive population movements, inadequate health services, improper use of antimalarial drugs, limited resources and operational difficulties in implementing malaria control activities. The economic impact of malaria is felt by various social groups of the society particularly by the poorest countries of the world and among populations living under the most difficult conditions. To overcome the malaria challenge, there is a need for concerted efforts by the health services, the private sector, the communities themselves, including the international community. Much could be achieved through the research and development (the use of insecticide-impregnated materials) and disease management (the use of artemisinin and its derivatives in areas with multi-drug resistance) will facilitate the achievement of the global goal of malaria control-to eliminate mortality and to reduce morbidity due to malaria.

9850402
Koopmans R, Duc DD, Kager PA, Khanh NX, Dien TK, de Vries PJ, van Boxtel CJ
The pharmacokinetics of artemisinin suppositories in Vietnamese patients with malaria.
Trans R Soc Trop Med Hyg. 1998 Jul-Aug;92(4):434-6.
Eight male Vietnamese malaria patients received 600 mg of artemisinin in a single dose of 3 suppositories containing 200 mg each; 24 h later they received a single oral dose of mefloquine, 15 mg/kg. Plasma artemisinin concentrations were measured until 24 h after dosing, and parasites were counted until none could be detected. Artemisinin concentration versus time curves of all subjects were analysed with model-independent methods. Mean Cmax was 108 micrograms/L (SD = 60, range 29-169), mean tlag was 0.3 h (SD = 0), mean tmax was 6.5 h (SD = 3.9, range 2-14). By comparing the area under the concentration-time curve with that found in a previous study on oral artemisinin, average bioavailability relative to oral administration was estimated to be approximately 30%. Median parasite clearance time was 24 h (range 24-72). We concluded that therapeutic blood concentrations of artemisinin can be reached after rectal administration. There was a large inter-individual variation in blood concentrations attained. The dose given by rectal administration should probably be twice the usual oral dose, i.e., at least 20 mg/kg of body weight twice daily.

16054584
Koram KA, Abuaku B, Duah N, Quashie N
Comparative efficacy of antimalarial drugs including ACTs in the treatment of uncomplicated malaria among children under 5 years in Ghana.
Acta Trop. 2005 Sep;95(3):194-203.
The emergence and spread of Plasmodium falciparum resistance to commonly used antimalarials such as chloroquine and sulphadoxine/pyrimethamine poses major challenges to malaria control in sub-Saharan Africa. We undertook a study on the efficacy of some antimalarial drugs in 2003 with the view of supporting the National Malaria Control Programme in the review of the antimalarial drug treatment policy in Ghana. Children aged 6-59 months with signs/symptoms of uncomplicated malaria including axillary temperature > or =37.5 degrees C; mono infection with P. falciparum; and parent's willingness to give consent, were randomized into four treatment groups and followed up for a maximum of 28 days. The treatment groups were chloroquine (CHQ), sulphadoxine/pyrimethamine (SP), amodiaquine+artesunate (ADQ+ART)

combination, and artemether+lumefantrine (Coartem) combination. Clinical evaluation of 168 children studied showed that cumulative pcr-corrected cure rates on day 28 were 100% for ADQ+ART; 97.5% for coartem, 60% for SP and 25% for CHQ. The artemisinin-based combinations effected rapid fever and parasite clearance. Prevalence of gametocytaemia was highest in the SP group whilst the CHQ group did not show any significant changes in haemoglobin levels during the follow-up period. The findings are in agreement with current recommendations for using artemisinin-based combinations for treating uncomplicated malaria in areas of high CHQ failure such as Ghana.

12875931
Kotecka BM, Rieckmann KH, Davis TM, Batty KT, Ilett KF
Comparison of bioassay and high performance liquid chromatographic assay of artesunate and dihydroartemisinin in plasma.
Acta Trop. 2003 Aug;87(3):371-5.
The study was a comparison of bioassay and HPLC analysis of artesunate (ARTS) and dihydroartemisinin (DHA) in plasma. ARTS and DHA in plasma samples from patients treated with ARTS were quantified by HPLC and expressed as DHA. DHA-equivalents in the same plasma samples were measured using a standardised parasite culture technique. DHA concentrations estimated by both methods were highly correlated (bioassay=0.96 x HPLC+11.0; r2=0.92). At high concentrations (>12000 nmol/l) bioassay sometimes overestimated DHA. Bioassay of active drug in plasma correlates well with specific chemical analysis by HPLC. ARTS and DHA appear to account for the total antimalarial activity in plasma after ARTS administration.

10886200
Kreil A, Wenisch C, Brittenham G, Looareesuwan S, Peck-Radosavljevic M
Thrombopoietin in Plasmodium falciparum malaria.
Br J Haematol. 2000 Jun;109(3):534-6.
Thrombopoietin (TPO) is the key growth factor for platelet production and is elevated in states of platelet depletion. As thrombocytopenia is a common finding in malaria, we analysed TPO regulation before, during and after antimalarial treatment. Before treatment, TPO serum levels were significantly higher in patients with severe malaria (n = 35) than in patients with uncomplicated malaria (n = 44; P = 0.024), normalizing within 14-21 d of therapy. The rapid normalization of TPO levels and increase in low peripheral platelet counts after treatment indicate that the biosynthesis of TPO and its regulation in malaria patients are normal.

12504391
Kremsner PG, Krishna S
Antimalarial cocktails--tropical flavours of the month.
Lancet. 2002 Dec 21-28;360(9350):1998-9.

11158748
Krishna S, Planche T, Agbenyega T, Woodrow C, Agranoff D, Bedu-Addo G, Owusu-Ofori AK, Appiah JA, Ramanathan S, Mansor SM, Navaratnam V
Bioavailability and preliminary clinical efficacy of intrarectal artesunate in Ghanaian children with moderate malaria.
Antimicrob Agents Chemother. 2001 Feb;45(2):509-16.
We report the first detailed pharmacokinetic assessment of intrarectal (i.r.) artesunate (ARS) in African children. Artesunate was given intravenously (i.v.; 2.4 mg/kg of body weight) and i.r. (10 or 20 mg/kg formulated as 50- or 200-mg suppositories [Rectocaps]) in a crossover study design to 34 Ghanaian children with moderate falciparum malaria. The median relative bioavailability of dihydroartemisinin (DHA), the active antimalarial metabolite of ARS, was higher in the low-dose i.r. group (10 mg/kg) than in the high-dose i.r. group (20 mg/kg) (58 versus 23%; P = 0.018). There was wide interpatient variation in the area under the concentration-time curve after i.r. ARS administration (up to 9-fold in the high-dose group and 20-fold in the low-dose group). i.r. administered ARS was more rapidly absorbed in the low-dose group than the high-dose group (median [range] absorption half-lives, 0.7 h [0.3 to 1.24 h] versus 1.1 h [0.6 to 2.7 h] [P = 0.023]. i.r. administered ARS was eliminated with a median (range) half-life of 0.8 h (0.4 to 2.7 h) (low-dose group and 0.9 h (0.1 to 2.5 h) (high-dose group) (P = 1). The fractional clearances of DHA were 3.9, 2.6, and 1.5 liters/kg/h for the 20-mg/kg, 10-mg/kg and i.v. groups, respectively (P = 0.001 and P = 0.06 for the high-and low-dose i.r. groups compared with the i.v. groups, respectively). The median volumes of distribution for DHA were 1.5 liters kg (20 mg/kg, i.r. group), 1.8 liters/kg (10 mg/kg, i.r. group), and 0.6 liters/kg (i.v. group) (P < 0.05 for both i.r. groups compared with the i.v. group). Parasite clearance kinetics were comparable in all treatment groups. i.r. administered ARS may be a useful alternative to parenterally administered ARS in the management of moderate childhood malaria and should be studied further.

12971556
Krudsood S, Chalermrut K, Pengruksa C, Srivilairit S, Silachamroon U, Treeprasertsuk S, Kano S, Brittenham GM, Looareesuwan S
Comparative clinical trial of two-fixed combinations dihydroartemisinin-napthoquine-trimethoprim (DNP) and artemether-lumefantrine (Coartem/Riamet) in the treatment of acute uncomplicated falciparum malaria in Thailand.
Southeast Asian J Trop Med Public Health. 2003 Jun;34(2):316-21.
An open randomized comparison of two-fixed dose artemisinin derivative-containing combination regimens was conducted in adults with acute uncomplicated multidrug resistant falciparum malaria in Thailand. DNP, a combination of dihydroartemisinin with napthoquine and trimethoprim developed recently in China, has been evaluated in China, Vietnam, Cambodia and Thailand. This study was performed to compare the safety, tolerability and efficacy of DNP and artemether-lumefantrine/Coartem. One hundred and thirty eligible uncomplicated falciparum malaria patients were enrolled into the study. Patients were randomly assigned in a 2:1 ratio into group A, which received DNP one tablet twice a day for one day; and group B, which received Coartem/Riamet four tablets twice a day for 3 days. The cure rates at 28-day were 99% and 97% in group A and group B, respectively. No serious adverse events occurred. We concluded that both DNP and Coartem/ Riamet were safe, well tolerated and highly efficacious in the treatment of acute uncomplicated falciparum malaria in Thailand.

15607340
Krudsood S, Imwong M, Wilairatana P, Pukrittayakamee S, Nonprasert A, Snounou G, White NJ, Looareesuwan S
Artesunate-dapsone-proguanil treatment of falciparum malaria: genotypic determinants of therapeutic response.
Trans R Soc Trop Med Hyg. 2005 Feb;99(2):142-9.
The combination of chlorproguanil and dapsone is being considered as an alternative antimalarial to sulfadoxine-pyrimethamine in Africa, because of its greater efficacy against resistant parasites, and its shorter half-lives, which exert less selective pressure for the emergence of resistance. A triple artesunate-chlorproguanil-dapsone combination is under development. In a previous study of relatively low-dose chlorproguanil-dapsone in multidrug-resistant falciparum malaria in Thailand failure rates were high. Proguanil is inexpensive, widely available and very similar to chlorproguanil. The safety and efficacy of artesunate-dapsone-proguanil (artesunate 4 mg/kg, dapsone 2.5mg/kg, proguanil 8 mg/kg daily for three days), was studied prospectively in 48 Thai adult patients with acute falciparum malaria followed daily for 28 days. Eleven of these had a recrudescence of their infection. Genotyping of Plasmodium falciparum dihydrofolate reductase (dhfr) and dihydropteroate synthase (dhps) indicated that the Pfdhfr I164L mutation was the main determinant of therapeutic outcome; all 11 failures carried this mutation (failure rate 11/37; 30%) whereas none of the 11 infections with 'wild type' 164 genotypes failed. The addition of artesunate considerably augments the antimalarial activity of the biguanide-dapsone combination, but this is insufficient for infections with parasites carrying the highly antifol-resistant Pfdhfr I164L mutation.

12479545
Krudsood S, Looareesuwan S, Silachamroon U, Chalermrut K, Pittrow D, Cambon N, Mueller EA
Artesunate and mefloquine given simultaneously for three days via a prepacked blister is equally effective and tolerated as a standard sequential treatment of uncomplicated acute Plasmodium falciparum malaria: randomized, double-blind study in Thailand.
Am J Trop Med Hyg. 2002 Nov;67(5):465-72.
The combination of artesunate and mefloquine is currently one of the most effective treatments against multidrug-resistant Plasmodium falciparum malaria. To improve patient compliance to such a combination, the two agents have been combined in a prepacked single blister. Patients were instructed to simultaneously co-administer the drugs once a day for three days. In the present randomized, double-blind, parallel group, comparative, single center study in Thailand, this concept was investigated in 204 adults and children with acute, uncomplicated P. falciparum malaria. Patients were randomized into two treatment groups and received once a day over a three-day period the following: Group A received artesunate, 4-5 mg/kg/day, and mefloquine, total dose = 25 mg/kg, approximately 8.5 mg/kg/day, simultaneously. Group B received artesunate, 4-5 mg/kg/day, and mefloquine, total dose = 25 mg/kg, sequentially (i.e., no mefloquine dose on the first day, 15 mg/kg on the second day, and 10 mg/kg on the third day). Both treatment groups showed no relevant differences in baseline demographic and clinical characteristics. Intent-to-treat analysis revealed a cure rate at day 28 (primary endpoint) of 100% in group A and 99% in group B (difference not significant). The secondary endpoints of mean time to fever clearance (group A = 34 hours, group B = 31 hours) and mean time to parasite clearance (group A = 44 hours group B = 48 hours) were similar between groups (both differences not significant). Tolerability was good in both treatment groups, with no difference in the overall incidence of adverse events. There was a low incidence of nausea/vomiting (4.9% in both groups) and

central nervous system side effects (4.9% in group A versus 8.8% in group B). These were comparable between groups and generally of a mild nature. The three-day combination of artesunate and mefloquine (Artequin, Mepha, Ltd., Aesch, Switzerland) with the introduction of mefloquine on day 1 offers a practical dosing regimen that is highly effective and well tolerated in patients of different ages with uncomplicated P. falciparum malaria. It is likely that the prepacked blister approach translates clinically into a better patient compliance, thereby contributing to limit the development of drug resistance.

11414432
Krudsood S, Silachamroon U, Wilairatana P, Singhasivanon P, Phumratanaprapin W, Chalermrut K, Phophak N, Popa C
A randomized clinical trial of combinations of artesunate and azithromycin for treatment of uncomplicated Plasmodium falciparum malaria in Thailand.
Southeast Asian J Trop Med Public Health. 2000 Dec;31(4):801-7.
Recently, a combination of artesunate and mefloquine has proved effective, although is contraindicated in early pregnancy and young children. Azithromycin, a widely used antibiotic and has antimalarial effects, replace mefloquine as a new alternative antimalarial regimen. Two hundred and two uncomplicated falciparum malaria patients were randomly assigned to 1 of 3 regimens. Patients in group I (n = 68) received artesunate 200 mg once daily for 3 days, group II (n = 67) received artesunate 200 mg together with mefloquine 10 mg/kg on the first 2 days and artesunate 200 mg together with mefloquine 5 mg/kg on the third day, and group III (n = 67) received artesunate 200 mg together with azithromycin 50 mg once daily for 3 days. The 28 day cure rates were 44, 98 and 56%, respectively. The median time to recrudescence was significantly longer in group III. In conclusion, a combination of artesunate and azithromycin might be useful in treating children in whom bacterial and malarial infections may be concomitant. However, further work is required in order to enhance its clinical efficacy.

12971515
Krudsood S, Wilairatana P, Vannaphan S, Treeprasertsuk S, Silachamroon U, Phomrattanaprapin W, Gourdeuk VR, Brittenham GM, Looareesuwan S
Clinical experience with intravenous quinine, intramuscular artemether and intravenous artesunate for the treatment of severe malaria in Thailand.
Southeast Asian J Trop Med Public Health. 2003 Mar;34(1):54-61.
We prospectively studied 803 Thai patients admitted to the Bangkok Hospital for Tropical Diseases to assess the safety, tolerability and effectiveness of treatments for strictly defined P. falciparum malaria. Patients were assigned to one of five treatment groups: (i) a 5-day course of intravenous artesunate in a total dose of 600 mg, Group Aiv; (ii) intravenous artesunate as in Group Aiv followed by mefloquine, 25 mg/kg, Group Aiv+M; (iii) a 3-day course of intramuscular artemether in a total dose of 480 mg, Group Aim; (iv) intramuscular artemether as in Group Aim followed by mefloquine, 25 mg/kg, Group Aim+M, and (v) intravenous quinine, 200 mg/kg given in divided doses over seven days followed by oral tetracylcine, 10 mg/kg, for 7 days. When patients could take oral medications, the parenteral antimalarials were administered as oral agents. There were no major adverse effects observed with any of the five treatment regimens. With all regimens, 95 to 100% of the patients survived. Mean parasite clearance times were more rapid with the artemisinin regimens (53 to 62 hours) than with quinine (92 hours). The mean fever clearance times with intravenous artesunate (80 to 82 hours) were about a day shorter than those with intramuscular artemether (108 hours) or intravenous quinine (107 hours). Mefloquine reduced the recrudescence rate from 24 to 5% with intravenous artesunate but from 45 to 20% with intramuscular artemether; recrudescence was 4% with quinine and tetracycline. A dose and duration of therapy greater than those in this study are needed for optimal therapy with intramuscular artemether. Effective therapy for severe falciparum malaria can be provided by either intravenous artesunate followed by mefloquine or by intravenous quinine followed by tetracycline.

16340051
Kundu R, Ganguly N, Ghosh TK, Choudhury P, Shah RC
Diagnosis and management of malaria in children: recommendations and IAP plan of action.
Indian Pediatr. 2005 Nov;42(11):1101-14.

10212896
Kyle DE, Teja-Isavadharm P, Li Q, Leo K
Pharmacokinetics and pharmacodynamics of qinghaosu derivatives: how do they impact on the choice of drug and the dosage regimens?
Med Trop (Mars). 1998;58(3 Suppl):38-44.

The critical decisions of which artemisinin derivative(s) to use and by which route(s) of administration for falciparum malaria are complex scientifically and politically. Despite the need for additional pharmacokinetic, pharmacodynamic and toxicokinetic data, these drugs are too important to delay concise, rational recommendations any longer. These types of decisions must be made now, implemented on a multinational level with WHO leadership, and revised as new findings emerge. For acute, uncomplicated disease, per os dosing of artesunate or artemether for three days is recommended, but only in combination with other antimalarial drugs like mefloquine. For severe falciparum malaria, intravenous administration is the preferred route, yet current formulations for intravenous dosing are not optimal and should be an area for future development emphasis. Clearly intramuscular administration of artemether has proven effective for severe disease, yet dosing regimens shouldn't be designed with ultimate parasitological cure as the aim and the problem of bioavailability of the sesame oil formulations must be examined further. Once the life-saving reduction in parasitemia and pathophysiological sequelae have been achieved, the patient can be given oral medication to affect radical cure. Much more data will be required to define the role of per rectum dosing for the treatment of severe malaria, yet this approach holds great promise as a life-saving intervention in rural areas where this disease has it most dramatic impact.

11177733
Labbe AC, Loutfy MR, Kain KC
Recent Advances in the Prophylaxis and Treatment of Malaria.
Curr Infect Dis Rep. 2001 Feb;3(1):68-76.
Increases in international travel and escalating drug resistance are putting put a growing number of travelers at risk of contracting malaria. Resistance to chloroquine and proguanil and real and perceived intolerance to standard agents, such as mefloquine, has highlighted the need for new antimalarials to prevent and treat malaria. Promising new agents to prevent malaria include the combination of atovaquone and proguanil, primaquine, and a related 8-aminoquinoline, tafenoquine. These agents are active against the liver stage of the malaria parasite, and therefore can be discontinued shortly after the traveler leaves the malaria-endemic area; this offers a clear advantage, in terms of adherence to a treatment regimen. For treatment of multidrug-resistant Plasmodium falciparum malaria, the combination of artemisinin derivatives plus mefloquine, or atovaquone plus proguanil, are the most active drug regimens.

15331837
Laxminarayan R
Act now or later? Economics of malaria resistance.
Am J Trop Med Hyg. 2004 Aug;71(2 Suppl):187-95.
In the past, malaria control efforts in sub-Saharan Africa have relied on a combination of vector control with effective treatment using chloroquine. With increasing resistance to chloroquine, attention has now turned to alternative treatment strategies to replace this failing drug. Some countries have already changed their official first-line treatment to sulfadoxine-pyrimethamine, while others are contemplating a switch to artemisinin-based combination treatments (ACTs). Although there are strong theoretical arguments in favor of switching to ACTs, the validity of these arguments in the face of financial constraints has not been previously analyzed. In this report, we use a bioeconomic model of malaria transmission and evolution of drug resistance to examine questions of optimal treatment strategy and coverage when drug resistance places an additional constraint on choices available to the policymaker.

16522574
Laxminarayan R, Over M, Smith DL
Will a global subsidy of new antimalarials delay the emergence of resistance and save lives?
Health Aff (Millwood). 2006 Mar-Apr;25(2):325-36.
Artemisinin-based combination treatments (ACTs) are seen as an important tool in the global effort to roll back malaria. With parasite resistance to chloroquine increasing rapidly in many parts of the world, there is greater recognition of the need for a globally coordinated strategy to ensure that artemisinins are not used as monotherapy, which has the potential to cut short their useful therapeutic life. We find that even a partial subsidy could delay the emergence of resistance and that a delay in implementing a subsidy for ACTs could facilitate the emergence of resistance and lower the economic value of ACTs.

10212892
Le Bras J
In vitro susceptibility of African Plasmodium falciparum isolates to dihydroartemisinin and the risk factors for resistance to qinghaosu.
Med Trop (Mars). 1998;58(3 Suppl):18-21.
In vitro susceptibility to dihydroartemisinin (DHART) and to artemether of 476 Plasmodium falciparum fresh clinical isolates obtained from non immune travellers returning from Africa to France in 1993-1996 were analysed to search for natural resistance and cross resistance of these compounds with available

antimalarials. The mean median inhibitory concentration (IC50) values for artemether and DHART were 2.69 nM and 1.17 nM, respectively. Nineteen isolates presented with a decreased IC50 to artemether or DHART. Chloroquine-resistant isolates were more susceptible to artemether (2.15 versus 3.26 nM) and DHART (0.876 versus 1.51 nM) than chloroquine-susceptible ones. Artemether and DHART responses were correlated (r2 = 0.599). The isolates identified as resistant to DHART or artemether in this study had IC50's close to the cut-off and limited cross-resistant profiles.

9781071
Le Bras J, Longuet C, Charmot G
[Human transmission and plasmodium resistance]
Rev Prat. 1998 Feb 1;48(3):258-63.
There is no longer malaria transmission in Europe and North America, while the transmission decreases in sub-tropical areas and increases in tropical countries. Most of malarias are now due to Plasmodium falciparum and happen in Africa. In the regions where the transmission is high, malaria is stable, baby mortality is high, and protective immunity is achieved in early childhood. Falciparum resistant malaria originates from mutations on drug target decreasing affinity to antifols, or mutations preventing accumulation of chloroquine in parasitized red blood cells. Resistance is a rapid event following large use of antifols, even associated, while falciparum chloroquine resistance is now widespread. Resistance to quinine, mefloquine and halofantrine is still at low levels out of Thailand, as their use remains through medical hands. Non resistance was observed yet with artemisinin derivatives.

10695777
Le NB, Pham TY, Nguyen BN, Dang CT, Pham TL, Le DC
Efficacy and effectiveness of five day treatment of uncomplicated falciparum with artemisinin or artesunate in Vietnam.
Southeast Asian J Trop Med Public Health. 1999 Mar;30(1):3-6.
A study on efficacy and effectiveness of artemisinin (total dose of 60 mg/kg) and artesunate (total dose of 12 mg/kg over five days) in treatment of uncomplicated malaria was conducted in highly malaria transmitted areas in Vietnam. 126 uncomplicated malaria cases finished 14 day follow-up. 100% cure rate achieved at day 14 in patients of the efficacy groups received either artemisinin or artesunate, while it was 83% and 93% in patients treated respectively with artemisinin and artesunate of the effectiveness groups. Compliance of the treatment regimens was discussed.

9196767
Le NN, de Vries PJ, Le TD, Bich L, Ho PL, Tran NH, Nguyen VM, Trinh KA, Kager PA
Single dose artemisinin-mefloquine versus mefloquine alone for uncomplicated falciparum malaria.
Trans R Soc Trop Med Hyg. 1997 Mar-Apr;91(2):191-4.
The efficacy of the combination of a single oral dose of 500 mg artemisinin with a single 500 mg oral dose of mefloquine (AM) in the treatment of uncomplicated falciparum malaria was compared to mefloquine therapy alone (M) in a double-'blind' randomized study in an endemic area in the south of Viet Nam where single low dose treatment was employed and where mefloquine had been recently introduced. 231 patients, 117 AM and 114 M, were studied. Failure of therapy occurred in 1 AM patient and in 3 M patients. The radical cure rate was 84% for the AM regimen and 65% for the M regimen (P = 0.002). Recrudescence (including an unknown percentage of reinfections) occurred in 15% of AM patients and in 30% of M patients (P = 0.01). The mean parasite clearance time was 40 h (SD = 16) for AM and 60 h (SD = 27) for the M regimen (P = 0.0001). No effect of artemisinin was noted on gametocytes present on admission, but new gametocytes developed less frequently in the AM group. The addition of a single dose of 500 mg artemisinin to 500 mg mefloquine increased the efficacy and reduced the rate of recrudescence, but this regimen was not adequate and, for short course regimens, more doses of artemisinin as well as higher, doses of mefloquine should be studied.

9356813
Le TA, Davis TM, Tran QB, Nguyen VP, Trinh KA
Delayed parasite clearance in a splenectomized patient with falciparum malaria who was treated with artemisinin derivatives.
Clin Infect Dis. 1997 Oct;25(4):923-5.

12549510
Lee MR
Plants against malaria, part 2: Artemisia annua (Qinghaosu or the sweet wormwood).
J R Coll Physicians Edinb. 2002;32(4):300-5.

11463111
Lefevre G, Looareesuwan S, Treeprasertsuk S, Krudsood S, Silachamroon U, Gathmann I, Mull R, Bakshi R
A clinical and pharmacokinetic trial of six doses of artemether-lumefantrine for multidrug-resistant Plasmodium falciparum malaria in Thailand.
Am J Trop Med Hyg. 2001 May-Jun;64(5-6):247-56.
The efficacy-safety and pharmacokinetics of the six-dose regimen of artemether-lumefantrine (Coartem/Riamet; Novartis Pharma AG, Basel, Switzerland) were assessed in a randomized trial in 219 patients (> or = 12 years old) with acute, uncomplicated Plasmodium falciparum malaria in Thailand. One hundred and sixty-four patients received artemether-lumefantrine and 55 received the standard treatment combination of mefloquine-artesunate. Both drugs induced rapid clearance of parasites and malaria symptoms. The 28-day cure rates were 95.5% (90% confidence interval [CI] = 91.7, 97.9%) for artemether-lumefantrine and 100% (90% CI = 94.5, 100%) for mefloquine-artesunate. This high-dose regimen of artemether-lumefantrine was very well tolerated, with very good compliance. The most frequent adverse events were headache, dizziness, nausea, abdominal pain, dyspepsia, vomiting, and skin rash. Overall, only 2% of patients in both groups showed QTc prolongations but without any cardiac complication, and no differences were seen between patients with and without measurable baseline plasma levels of quinine or mefloquine. Plasma levels of artemether, dihydroartemisinin, and lumefantrine were consistent with historical data for the same dose regimen, and were higher, particularly for lumefantrine, than those previously observed with the four-dose regimen, explaining the greater efficacy of the six-dose regimen in a drug-resistant setting. These results confirm the excellent safety and efficacy of the six-dose regimen of artemether-lumefantrine in the treatment of multidrug-resistant P. falciparum malaria.

11355556
Leonardi E, Gilvary G, White NJ, Nosten F
Severe allergic reactions to oral artesunate: a report of two cases.
Trans R Soc Trop Med Hyg. 2001 Mar-Apr;95(2):182-3.

3296654
Li CS, Du YL, Jiang Q
[Development of a qinghaosu-resistant line of Plasmodium berghei ANKA and N strain]
Yao Xue Xue Bao. 1986 Nov;21(11):811-5.

3913275
Li GD
[Development of a piperaquine-resistant line of Plasmodium berghei K 173 strain]
Yao Xue Xue Bao. 1985 Jun;20(6):412-7.

9863077
Li GQ, Fu YX, Bian WX
[Comparison on treatment of falciparum malaria with different courses of artesunate tablet]
Zhongguo Zhong Xi Yi Jie He Za Zhi. 1997 Mar;17(3):143-4.
OBJECTIVE: To assess the efficacy of Artesunate on falciparum malaria. METHODS: A randomized controlled study on the treatment of 90 uncomplicated falciparum malaria patients was carried out with 400 mg of artesunate tablet as a total dose over 3 days, 600 mg over 5 days and 800 mg over 7 days. RESULTS: All patients were cured. Fever clearance time (FCT) and parasite clearance time(PCT) among the three groups were similar. Parasite recrudescence rate within 28 days was 39.3% (11/ 28) in 3 day group, 6.9% (2/29) in 5 day group and 3.4% (1/29) in 7 day group (comparing 5 day group with 3 day group, $P < 0.005$, comparing 7 day group with 3 day group, $P < 0.005$). CONCLUSION: It indicated that parasite recrudescence rate may be effectively decreased by prolonging treatment courses.

8053027
Li GQ, Guo XB, Fu LC, Jian HX, Wang XH
Clinical trials of artemisinin and its derivatives in the treatment of malaria in China.
Trans R Soc Trop Med Hyg. 1994 Jun;88 Suppl 1:S5-6.

Since 1979 several derivatives of artemisinin have been synthesized and studied in China. Artemisinin suppositories, artesunate (oral or parenteral), intramuscular artemether and dihydroartemisinin tablets have all proved rapidly effective. In all, 2352 patients (2150 with Plasmodium falciparum and 202 with P. vivax) have been included in clinical trials from our centre. All preparations have been well tolerated. These drugs have now replaced chloroquine and quinine for the treatment of malaria in China.

6765849
Li GQ, Guo XB, Jin R, Wang ZC, Jian HX, Li ZY
Clinical studies on treatment of cerebral malaria with qinghaosu and its derivatives.
J Tradit Chin Med. 1982 Jun;2(2):125-30.

15642961
Li Q, Lugt CB, Looareesuwan S, Krudsood S, Wilairatana P, Vannaphan S, Chalearmrult K, Milhous WK
Pharmacokinetic investigation on the therapeutic potential of artemotil (beta-arteether) in Thai patients with severe Plasmodium falciparum malaria.
Am J Trop Med Hyg. 2004 Dec;71(6):723-31.
Pharmacokinetic data were obtained to evaluate the therapeutic potential of Artemotil (beta-arteether) in 56 Thai patients with severe Plasmodium falciparum malaria. Intramuscular administration was given at 1) a low dose of 3.2 mg/kg on day 0 and 1.6 mg/kg/day on days 1-4 and 2) a high dose of 4.8 mg/kg on day 0 at 0 hours, 1.6 mg/kg at 6 hours, and 1.6 mg/kg/day on days 1-4. Cmax values of 63.7 ng/mL at 6.1 hours and 140.8 ng/mL at 5.7 hours were reached in low-dose and high-dose patients, respectively. Drug concentrations decreased slowly with half-lives of 12.5-22.4 hours on day 0 and 31.6-40.7 hours on day 4 for both dosage regimens. Although the maintaining dosage on the last day was much lower than the loading dose on day 0, the area under the curve (AUC) and Cmax on day 4 were significantly increased (2.85-4.55 fold), suggesting drug accumulation in the blood. Dihydroartemisinin (DHA), an active metabolite of Artemotil, was detected in most patients. The mean ratios of DHA and Artemotil were 0.16-0.19 in both dosage regimens for the entire study period. Similar to previous reports, all patients showed a slow response to treatment with mean values of 77.2 hours for the fever clearance time (FCT) and 75.8 hours for the parasite clearance time (PCT) (low dose) and 70.1 hours for the FCT and 64.4 hours for the PCT (high dose). Interestingly, a very rapid response to the treatment was exhibited in patient 151, with an FCT of 4 hours and a PCT of 36 hours, with different pharmacokinetic data from others on day 0. The patient had a very high Cmax (2,407 ng/mL) and AUC (12,259 ng.hr/mL) values without an intramuscular absorption phase on the first day. These values were approximately 21.9 (Cmax) and 2.6 (AUC) times higher than in other patients; this patient may have been to be injected through a vessel at first dosing. In conclusion, the patients treated with the high dosage regimen had higher AUC values and higher antimalarial efficiency (cure rate = 48%) than the low-dose subjects (cure rate = 23%). Despite the high accumulation and longer exposure time (9-11 days) when compared with other artemisinin agents, due to the slow prolonged absorption of Artemotil from injection sites, the two dosage regimens did not show a better therapeutic effects than other artemisinin drugs, including alpha/beta-arteether dissolved in peanut oil used in Indian patients.

16126618
Li Q, Xie LH, Si Y, Wong E, Upadhyay R, Yanez D, Weina PJ
Toxicokinetics and hydrolysis of artelinate and artesunate in malaria-infected rats.
Int J Toxicol. 2005 Jul-Aug;24(4):241-50.
Comparative toxicokinetic (TK) and hydrolysis studies of intravenously administered two new antimalarial agents, artelinate (AL) and artesunate (AS), were performed in malaria-infected rats using three daily equimolar doses (96 micromoles/kg). The TK evaluation was related to select one drug for severe malaria treatment in U.S. Army. Drug concentration of AS with daily dose of 36.7 mg/kg was one-third less on day 3 than on day 1, which resembled its active metabolite, dihydroartemisinin (DHA), suggesting an autoinduction of hepatic drug-metabolizing enzymes for AS. The results were similar to other artemisinin drugs, but not for AL. TK parameters of AL were very comparable from day 1 to day 3 at same AS molecular dose at 40.6 mg/kg. AS is the prodrug of DHA with the DHA/AS ratio of 5.26 compared to the ratio of 0.01 for DHA/AL. Other TK parameters revealed that the total AUC1-3 days (84.4 microg.h ml-1) of AL was fivefold higher than that of AS (15.7 microg.h ml-1 of AS plus DHA). The elimination half-life of AL (7.1 h) was much longer than that of AS (0.36 h) or DHA (0.72 h). The remarkable alteration of the TK shape of AL may be caused by poor conversion rates to DHA and an enterohepatic circulation, which is confirmed by the present TK and tissue distribution studies. Compared to AS, higher drug exposure levels and longer exposure time of AL in the rat blood may be the cause of its increased toxicity.

12741507

Li QG, Si YZ, Lee P, Wong E, Xie LH, Kyle DE, Dow GS
Efficacy comparison of intravenous artelinate and artesunate in Plasmodium berghei-infected Sprague-Dawley rats.
Parasitology. 2003 Apr;126(Pt 4):283-91.
This paper reports the comparative antimalarial efficacy of intravenous artelinate and artesunate in rats. Prior to efficacy experiments, a Plasmodium berghei-Sprague-Dawley rat model of malaria was developed, in which the clearance effects of intravenous drugs could be readily compared. In efficacy experiments, groups of P. berghei-infected rats were given 3 daily intravenous treatments of artelinate or artesunate at molar equivalent dose rates (total of 0-191.2 micromoles/kg). Artelinate was superior to artesunate in terms of clearance (100% clearance dose of 95.6 micromoles/kg (40 mg/kg) versus 191.2 micromoles/ kg for AS (73.4 mg/kg)) and parasite clearance time (1.7 +/- 0.5 days for AL versus 2.7 +/- 0.5 days for AS at a dose rate of 191.2 micromoles/kg, $P < 0.01$). No frank clinical toxicity was observed, though both artesunate and artelinate induced dose-related vascular necrosis at the site of injection. The necrosis was less severe and reversible when the drugs were administered via femoral, rather than tail/foot veins. The data suggest that the P. berghei-7-week-old Sprague-Dawley rat model of malaria is reproducible and useful for assessing the efficacy of antimalarials and that artelinate is at least as potent, and safe, as artesunate, the leading clinical treatment for severe malaria.

10212890
Li Y, Wu YL
How Chinese scientists discovered qinghaosu (artemisinin) and developed its derivatives? What are the future perspectives?
Med Trop (Mars). 1998;58(3 Suppl):9-12.
Since the middle of this century and especially since the 1960s and 1970s. Chinese scientists have put considerable effort and resources into the search for new antimalarial compounds extracted from Chinese traditional herbs. Archaeological findings indicate that qinghao (Artemisia annua L.) has been used as a traditional remedy in China for over two thousand years. Its antimalarial principle was finally isolated in 1971 and named artemisinin or qinghaosu (meaning the principle of qinghao in Chinese). Its rapid action, low toxicity and powerful effect against falciparum malaria made it a favored subject for research. In 1976, the unique structure of the molecule, characterized by an endoperoxide and an alternative O-C-O-C segment, was identified. The specific lactone reduction discovered during the determination of the structure opened the way for the synthesis of qinghaosu derivatives, and thereafter a series of more active and more oil- or water-soluble derivatives was developed. Subsequent studies of the structure/activity relationship led to the discovery of dihydroartemisinin, artemether and artesunate. Now qinghaosu and these three derivatives are being used around the world as effective new antimalarial drugs in the fight against falciparum malaria, including multi-drug-resistant Plasmodium falciparum. At the present time new qinghaosu analogues or derivatives are being developed and studies of their structure/activity relationships, their antimalarial mechanisms, their interaction with ferrous ions and the DNA damage associated with these processes are being actively pursued. In addition, recent studies also indicate that some qinghaosu derivatives have other bioactivities, including antiparasitic (against Schistosoma japonicum, Toxoplasma gondii and so on) and anticancer activities. Research into qinghaosu and its derivatives has already produced and will no doubt continue to produce results of the utmost importance in the fight against malaria and other diseases.

13129573
Li Y, Yang ZS, Zhang H, Cao BJ, Wang FD, Zhang Y, Shi YL, Yang JD, Wu BA
Artemisinin derivatives bearing Mannich base group: synthesis and antimalarial activity.
Bioorg Med Chem. 2003 Oct 1;11(20):4363-8.
Novel artemisinin derivatives bearing Mannich base group were prepared and tested for their antimalarial activity. These water-soluble artemisinin derivatives were more stable than sodium artesunate and few compounds were found to be more active against Plasmodium berghei in mice than artesunic acid by oral administration. Two most potent derivatives 17b and 17d were examined for their antimalarial activity against Plasmodium knowlesi in rhesus monkeys.

10780920
Li Y, Zhu YM, Jiang HJ, Pan JP, Wu GS, Wu JM, Shi YL, Yang JD, Wu BA
Synthesis and antimalarial activity of artemisinin derivatives containing an amino group.
J Med Chem. 2000 Apr 20;43(8):1635-40.
In search of water-soluble artemisinin derivatives that are more stable than sodium artesunate, over 30 derivatives containing an amino group (compounds 3-5) were synthesized and tested in mice. All products tested (except 5a and 5b) are the beta isomers. These basic compounds combined with organic acids (oxalic acid, maleic acid, etc.) to yield the corresponding salts. Generally, the maleates have better solubility in water than the corresponding oxalates. The aqueous solutions of these salts can be kept at room temperature for several weeks without any discernible decomposition. Compounds 3f, 3h, and 3r are much

more active against P. berghei than artesunic acid by oral administration and therefore were further tested in monkeys. However, their oral efficacies are poorer than that of artesunic acid against P. knowlesi in rhesus monkeys. It is interesting to note that 3f, 3h, and 3r showed much lower efficacies against P. berghei when they were administered subcutaneously than orally.

15589795
Lim P, Chim P, Sem R, Nemh S, Poravuth Y, Lim C, Seila S, Tsuyuoka R, Denis MB, Socheat D, Fandeur T
In vitro monitoring of Plasmodium falciparum susceptibility to artesunate, mefloquine, quinine and chloroquine in Cambodia: 2001-2002.
Acta Trop. 2005 Jan;93(1):31-40.
We used a classical isotopic microtest to assess the in vitro sensitivity of 352 Plasmodium falciparum isolates collected in Cambodia in 2001 and 2002 to chloroquine, mefloquine, quinine and artesunate. Our results confirm conclusions drawn from earlier studies conducted by the Cambodian national malaria centre. Chloroquine-resistant phenotypes were highly prevalent in Cambodia. Similarly, a high proportion of isolates displayed elevated IC50 to mefloquine. In contrast, only 0.67 and 1.7% of isolates presented decreased susceptibility to quinine and artesunate, respectively. Distributions of mean IC50 according to drug and geographic origin indicated that the parasites circulating to the west of Cambodia largely account for the global situation of drug resistances in Cambodia. Isolates with decreased susceptibility to chloroquine and mefloquine were common along the border with Thailand. In contrast, most of the isolates from eastern Cambodia were susceptible to these compounds. Isolates collected at the western and eastern borders did not respond differently to artesunate. No major differences in responses to antimalarial drugs were observed between 2001 and 2002, suggesting that the situation of drug resistance is now stabilized and under control in Cambodia. However, the decreased susceptibility of isolates collected in the western provinces of Cambodia to mefloquine and the correlation between susceptibility to artesunate and susceptibility to mefloquine and quinine justify the need for an improved international surveillance program for malaria drug resistance in the Mekong sub region.

3669021
Lin AJ, Klayman DL, Milhous WK
Antimalarial activity of new water-soluble dihydroartemisinin derivatives.
J Med Chem. 1987 Nov;30(11):2147-50.
The usefulness of sodium artesunate (3), a water-soluble derivative of artemisinin (1), is impaired by its poor stability in aqueous solution. To overcome the ease of hydrolysis of the ester group in 3, a new series of derivatives of dihydroartemisinin (2) was prepared in which the solubilizing moiety, which contains a carboxylate group, is joined to dihydroartemisinin by an ether rather than an ester linkage. The new derivatives were prepared in good yield by treatment of dihydroartemisinin with an appropriate alcohol under boron trifluoride etherate catalysis at room temperature. All major condensation products are the beta isomer. Hydrolysis of the esters with 2.5% KOH/MeOH gave the corresponding potassium salts, which were converted to free acids (8b-d) by acidification. The derivatives were tested in vitro against two clones of human malaria, Plasmodium falciparum D-6 (Sierra Leone clone) and W-2 (Indochina clone). No cross-resistance to the antimalarial agents mefloquine, chloroquine, pyrimethamine, sulfadoxine, and quinine was observed. In general, the new compounds are more effective against the W-2 than the D-6 strain. Esters (5a-d) possess activity comparable to that of the parent compounds 1 and 2; however, conversion of the esters to their corresponding carboxylates (7a-d) or acids (8b-d), with the exception of artelinic acid (8d), drastically decreases the antimalarial activities in both cell lines. Artelinic acid, which is both soluble and stable in 2.5% K2CO3 solution, possesses superior in vivo activity against Plasmodium berghei than artemisinin or artesunic acid.

9135037
Lin AJ, Zikry AB, Kyle DE
Antimalarial activity of new dihydroartemisinin derivatives. 7. 4-(p-substituted phenyl)-4(R or S)-[10(alpha or beta)-dihydroartemisininoxy]butyric acids.
J Med Chem. 1997 Apr 25;40(9):1396-400.
To search for water soluble dihydroartemisinin derivatives with higher efficacy and longer plasma half-life than artesunic or artelinic acid, a series of new stereoisomers of 4-(p-substituted phenyl)-4(R or S)-[10(alpha or beta)-dihydroartemisininoxy]butyric acids were synthesized as new potential antimalarial agents. Two approaches were taken in the design of these new molecules in an attempt to (a) increase the lipophilicity of the molecule and (b) decrease the rate of oxidative dealkylation of the target compounds. The new compounds showed a 2-10-fold increase in in vitro antimalarial activity against D-6 and W-2 clones of Plasmodium falciparum than artemisinin or artelinic acid. R-diastereomers are, in general, more potent than the corresponding S-diastereomers. p-Chlorophenyl and p-bromophenyl derivatives showed in vivo oral antimalarial activity against P. berghei (with 3/8 cured) superior to that of artelinic acid (1/8 cured), whereas

p-fluorophenyl and p-methoxyphenyl analogs demonstrated activity only comparable (1/8 cured) to that of artelinic acid at the same dosage level (64 mg/kg twice a day). The in vivo antimalarial activity of these new compounds correlates with their SD50 (50% parasitemia suppression dose). The biological results suggested that an electronic effect, besides the lipophylicity, may play a role in determining the efficacy of this class of compounds.

8701764
Lin PY, Feng ZM, Pan JQ, Zhang D, Xiao LY
Effects of artesunate on immune function in mice.
Zhongguo Yao Li Xue Bao. 1995 Sep;16(5):441-4.
AIM: To study the effects of artesunate (dihydroartemisinine-12-alpha-succinate, Art) on immune function in mice. METHODS: Hemolysin concentration was determined by colorimetric method. Serum IgG and C3 contents were measured by single immunodiffusion method. Percentage of lymphocyte transformation, phagocytosis percentage and phagocytic index were counted under microscope. RESULTS: Art im 75 mg kg-1 bid x 7 d decreased the humolysin-forming capacity and levels of serum IgG of mice sensitized with sheep red blood cell. The serum complement 3 level rose remarkably, when Art was given im to Plasmodium berghei-infected mice. Art enhanced the PHA-induced lymphocyte transformation rate (in vivo) in mice and increased the weight of spleen but reduced that of thymus in mice. Art elevated the DNFB-induced delayed-type hypersensitivity. Art im 75 mg kg-1 bid x 5 d reduced the percentage of phagocytosis of peritoneal macrophages and the phagocytic index. CONCLUSION: Art suppressed the humoral immune responses but enhanced the cell-mediated immunity.

12078213
Lin Y, Xu Z
[Chemotherapy of parasitic diseases: current status and new advance]
Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi. 1998;16(1):68-72.

12567719
Liu AR, Yu ZY, Lu LL, Sui ZY
[The synergistic action of guanghuoxiang volatile oil and sodium artesunate against Plasmodium berghei and reversal of SA-resistant Plasmodium berghei]
Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi. 2000;18(2):76-8.
OBJECTIVE: To study the synergistic action of a combination of guanghuoxiang volatile oil (B) and sodium artesunate (SA) against Plasmodium berghei (P. b) and the resistance-reversal activity against SA-resistant P. b (P. b SA-R). METHODS: Mice infected with P. b N or P. b R were treated with a combination of B and SA respectively by 4-day suppressive test method and linear regression to calculate the SD50 of B and SA for each drug alone and in combination (equally effective dose compatibility). RESULTS: B alone, N:SD50 = 87.64 +/- 19.58(GKD), R:SD50 = 43.24 +/- 7.71(GKD); SA alone, N:SD50 = 0.88 +/- 0.01(MGKD), R:SD50 = 27.69 +/- 0.93(MGKD). B and SA combination, N:B SD50 = 36.89 +/- 4.57(GKD), SA SD50 = 0.39 +/- 0.05 (MGKD); R:B SD50 = 7.40 +/- 1.30(GKD), SA SD50 = 4.21 +/- 0.74(MGKD). The synergistic indexes of B and SA in combination were 2.2 for N and 6.6 for R, respectivly. The multiple of resistance reversal of B vs SA was 6.6. The relative reversal rate was 87.6%. CONCLUSION: A combination of B and SA may enhance the antimalarial effect against P. b and reverse the SA-resistance of P. b and delay the occurrence of resistance to SA in N.

9206055
Liu Y
Chemotherapy of parasitic diseases. Current status and new directions.
Chin Med J (Engl). 1996 Aug;109(8):579-82.

8053034
Looareesuwan S
Overview of clinical studies on artemisinin derivatives in Thailand.
Trans R Soc Trop Med Hyg. 1994 Jun;88 Suppl 1:S9-11.
Over 1000 patients have been treated with artesunate or artemether in clinical trials in Thailand since 1988. These drugs have proved rapidly effective and safe. Combination regimens with mefloquine have proved highly effective against multi-drug resistant Plasmodium falciparum infections. Both drugs are now licensed in Thailand.

1471736

Looareesuwan S, Kyle DE, Viravan C, Vanijanonta S, Wilairatana P, Charoenlarp P, Canfield CJ, Webster HK
Treatment of patients with recrudescent falciparum malaria with a sequential combination of artesunate and mefloquine.
Am J Trop Med Hyg. 1992 Dec;47(6):794-9.
A sequential combination of artesunate followed by mefloquine was evaluated prospectively in 24 patients with acute recrudescent falciparum malaria. The sequential combination was used to minimize possible side effects and to take advantage of the ability of artesunate to rapidly clear parasitemia and the prolonged effect of mefloquine to clear residual parasites. All patients had experienced one or more treatment failures with one or more courses of the following drugs (administered alone or in combination): quinine, tetracycline, mefloquine, artesunate, and sulfadoxine/pyrimethamine. Sequential treatment with artesunate (600 mg over five days) followed by mefloquine (750 mg and 500 mg six hours apart) cured all 24 patients. Each patient was followed for 28 days and 10 were observed for at least 35 days without clinical or parasitologic evidence of recrudescence. Fever and parasite clearance times after treatment with the sequential combination were 32.8 +/- 19.3 hr (mean +/- SD) and 40.0 +/- 16.2 hr, respectively. Susceptibility testing of selected parasite isolates indicated that all of the isolates tested were resistant to one or more antimalarial drugs. These results suggest that sequential treatment with artesunate followed by mefloquine is effective and well-tolerated in patients with recrudescent falciparum malaria.

10432050
Looareesuwan S, Sjostrom L, Krudsood S, Wilairatana P, Porter RS, Hills F, Warrell DA
Polyclonal anti-tumor necrosis factor-alpha Fab used as an ancillary treatment for severe malaria.
Am J Trop Med Hyg. 1999 Jul;61(1):26-33.
Single doses (250, 500, 1,000, or 2,000 units/kg) of an ovine polyclonal-specific Fab fragment directed against tumor necrosis factor-alpha (TNF-alpha) were given to 17 adult patients with severe falciparum malaria immediately before treatment with artesunate in a pilot study to assess safety and optimal dosage with a view to future studies. Clinical and laboratory variables were compared with 11 controls. In the groups given Fab, there was a tendency for a faster resolution of clinical manifestations and reduction of fever but also a tendency towards longer parasite clearance times. Adverse events were more common in the control group and no early anaphylactic or late serum sickness reactions occurred in the Fab treated patients. On admission all patients had markedly elevated levels of TNF-alpha (85-1,532 ng/L) and interleukin-6 (IL-6) (30-27,500 ng/L). Also, 86% had elevated interferon-gamma (IFN-gamma) levels, 75% had increased IL-2 levels, 36% had increased IL-8 levels, and 21% had increased IL-1beta levels. Antibody treatment reduced IFN-gamma concentrations in a dose-related manner, but had no obvious effects on levels of other cytokines in this small study, although unbound TNF-alpha was undetectable after Fab treatment. Circulating concentrations of soluble E-selectin, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 were not affected by Fab treatment. The Fab exhibited a two-compartment, dose-proportional kinetics with an average elimination half-life of 12.0 hr, with about 20% being excreted renally. These results encourage a randomized, placebo-controlled trial in patients with cerebral malaria and provide some guidance about dosage.

8067808
Looareesuwan S, Vanijanonta S, Viravan C, Wilairatana P, Charoenlarp P, Andrial M
Randomized trial of mefloquine alone and artesunate followed by mefloquine for the treatment of acute uncomplicated falciparum malaria.
Ann Trop Med Parasitol. 1994 Apr;88(2):131-6.
Mefloquine is the main antimalarial used for treatment of falciparum malaria patients at the malaria clinics in Thailand. However, the cure rate with mefloquine alone has declined seriously in recent years. The efficacy and tolerability of a sequential treatment of artesunate followed by mefloquine was therefore compared with those of mefloquine alone, in a randomized therapeutic trial involving 125 patients with acute uncomplicated falciparum malaria. Sixty-three patients received mefloquine alone (750 mg given immediately, followed by 500 mg 6 h later) and 62 each received 800 mg artesunate over 2 days (200 mg every 12 h) followed 6 h later by a single, 750-mg dose of mefloquine. All patients were admitted to the hospital in Bangkok for 28 days to exclude re-infection. Most patients (107) completed the study; 18 left the hospital prior to completion of follow-up for reasons unrelated to their treatment. Cure rates for the two groups were 74% (42/57) for mefloquine alone and 92% (46/50) for artesunate followed by mefloquine. The mean parasite clearance time was significantly shorter ($P < 0.001$) in the group treated with the sequential combination than in the group treated with mefloquine alone, but the mean fever clearance times were not significantly different ($P = 0.26$). Most patients responded well to the treatment regimens and none suffered from serious toxic adverse reactions. Only four patients who were treated with mefloquine alone had parasitaemia persisting to day 7 (RII), thus requiring alternative follow-up treatment.(ABSTRACT TRUNCATED AT 250 WORDS)

8266223

Looareesuwan S, Viravan C, Vanijanonta S, Wilairatana P, Charoenlarp P, Canfield C, Kyle DE
Treatment of acute uncomplicated falciparum malaria with a short course of artesunate followed by mefloquine.
Southeast Asian J Trop Med Public Health. 1993 Jun;24(2):230-4.
The clinical results of this study indicate that a half-dose regimen of artesunate followed by mefloquine produces an acceptable cure rate when compared to other commonly available drugs for treating acute uncomplicated falciparum malaria in Thailand. The 90% cure rate was comparable to the results with either a full dose of artesunate (600 mg over 5 days) or mefloquine (25 mg/kg in divided doses six hours apart) as well as the combination of quinine-tetracycline administered for seven days. This abbreviated regimen, however was less effective than the full dose regimen of both drugs previously reported.

8024075
Looareesuwan S, Viravan C, Vanijanonta S, Wilairatana P, Charoenlarp P, Canfield CJ, Kyle DE
Randomized trial of mefloquine-doxycycline, and artesunate-doxycycline for treatment of acute uncomplicated falciparum malaria.
Am J Trop Med Hyg. 1994 Jun;50(6):784-9.
One hundred nine adult patients with acute uncomplicated falciparum malaria were randomly selected to receive combinations of either doxycycline plus mefloquine or doxycycline plus artesunate. Fifty-four patients received mefloquine (1,250 mg divided between two doses of 750 and 500 mg six hours apart) with doxycycline and 55 patients received artesunate (300 mg total for 2.5 days; 100 mg followed by 50 mg every 12 hr for 2.5 days) with doxycycline. Doxycycline was administered in doses of 200 mg once a day for seven days. All patients were admitted to the hospital for 28 days to exclude reinfection. Ninety-seven patients completed the study; 12 patients left prior to completion of follow-up for reasons unrelated to their treatment. Cure rates for the two groups were 96% (46 of 48) for mefloquine plus doxycycline and 80% (39 of 49) for artesunate plus doxycycline. Mean fever and parasite clearance times were significantly shorter in the group that received artesunate plus doxycycline (38.7 and 41.3 hr) than mefloquine plus doxycycline (64.3 and 69.0 hr), respectively. In vitro drug sensitivity testing of selected isolates obtained prior to treatment indicated that eight of nine admission isolates were resistant to mefloquine; all isolates were susceptible to artesunate. Recrudescent isolates failed to show a pattern of decreased sensitivity to the drugs to which the parasites had been exposed during treatment; the studies showed decreased sensitivity to doxycycline in only two of eight isolates tested.(ABSTRACT TRUNCATED AT 250 WORDS)

8619450
Looareesuwan S, Viravan C, Vanijanonta S, Wilairatana P, Pitisuttithum P, Andrial M
Comparative clinical trial of artesunate followed by mefloquine in the treatment of acute uncomplicated falciparum malaria: two- and three-day regimens.
Am J Trop Med Hyg. 1996 Feb;54(2):210-3.
The difficulties in treating drug-resistant falciparum malaria in Thailand are compounded by the necessity of giving antimalarials over long periods of time. The resultant decrease in patient compliance not only lowers cure rates but also predisposes to the further spread of drug resistance. We compared the efficacy of two sequential treatment regimens given over two and three days in 111 patients with acute uncomplicated falciparum malaria. Sixty-seven patients received two 400-mg doses of artesunate (total dose = 800 mg) followed by two doses of mefloquine (750 mg given immediately and 500 mg 12 hr later; total dose = 1,250 mg) in Group 1. Forty-four patients (Group II) received four 200-mg doses of artesunate (total dose = 800 mg) given 12 hr apart followed by a mefloquine regimen similar to that for Group I. All patients were admitted to hospital in Bangkok for 28 days to preclude reinfection. Ninety-six patients completed the study. Cure rates for the two groups were 84% (49 of 58) for Group I and 100% (38 of 38) for Group II. The mean parasite clearance time and fever clearance time were significantly shorter in Group II ($P < 0.02$). There were no serious adverse reactions. All nine of the treatment failures in Group I were of the RI types. The results indicate that the sequential treatment with artesunate followed by mefloquine given over three days is effective and well-tolerated in patients with acute, uncomplicated falciparum malaria and suitable as an alternative treatment for multidrug-resistant falciparum malaria.

1347854
Looareesuwan S, Viravan C, Vanijanonta S, Wilairatana P, Suntharasamai P, Charoenlarp P, Arnold K, Kyle D, Canfield C, Webster K
Randomised trial of artesunate and mefloquine alone and in sequence for acute uncomplicated falciparum malaria.
Lancet. 1992 Apr 4;339(8797):821-4.
The increasing frequency of therapeutic failures in falciparum malaria in Thailand shows an urgent need for effective drugs or drug combinations. Artesunate, a qinghaosu derivative, is effective in clearing parasitaemia rapidly, but the recrudescence rate can be as high as 50%. We have compared artesunate followed by mefloquine with each drug alone in acute, uncomplicated falciparum malaria. 127 patients were

randomly assigned treatment with artesunate (600 mg over 5 days), mefloquine (750 mg then 500 mg 6 h later), or artesunate followed by mefloquine. All patients were admitted to hospital for 28 days to exclude reinfection. Cure was defined as no recrudescence during the 28 days' follow-up. The cure rates for mefloquine and artesunate alone were 81% (30/37 patients) and 88% (35/40); the combination was effective in all of 39 patients. Fever and parasite clearance times were significantly shorter in the groups that received artesunate than in the mefloquine-only group. The frequency of nausea and vomiting was slightly, but not significantly, higher among patients who received both drugs than in the other groups. The combination of artesunate followed by mefloquine is highly effective and well tolerated in patients with acute, uncomplicated falciparum malaria in Thailand.

10212910
Looareesuwan S, Wilairatana P
The rational use of qinghaosu and its derivatives: what is the future of new compounds?
Med Trop (Mars). 1998;58(3 Suppl):89-92.
In Thailand, artesunate and artemether are the mainly used antimalarials for treatment of severe or multidrug resistant falciparum malaria. However, their availability (supply) and the registration requirements are the major limitations for their large-scale use. At Bangkok Hospital for Tropical Diseases, Thailand, we have studied the new artemisinin derivatives, dihydroartemisinin and arteether, and artesunate suppositories. We found that the three preparations are well tolerated, safe, and efficacious.

9886126
Looareesuwan S, Wilairatana P, Chokejindachai W, Viriyavejakul P, Krudsood S, Singhasivanon P
Research on new antimalarial drugs and the use of drugs in combination at the Bangkok Hospital for Tropical Diseases.
Southeast Asian J Trop Med Public Health. 1998 Jun;29(2):344-54.
With the emergence of multidrug resistant falciparum malaria in Thailand, various approaches have been taken. Research on new antimalarial drugs and the use of existing available drugs with modification are urgently needed. New drugs and drugs in combination such as pyronaridine, WR 238605, arteether, dihydroartemisinin, benflumetol atovaquone/proguanil are being evaluated. Drug combinations for the treatment of patients suffering from uncomplicated falciparum malaria include quinine-tetracycline for 7 days, or sequential treatment of artesunate (600 mg given over 5 days) followed by mefloquine (1,250 mg divided into 2 doses 6 hours apart) are recommended. The sequential treatment is highly recommended for those who failed other treatment regimens. Other combinations such as a short course sequential treatment of artesunate (300 mg given over 2.5 days) followed by a single dose of 750 mg mefloquine, or a combination of mefloquine 1,250 mg together with tetracycline 1 g per day or doxycycline 200 mg per day for 7 days are alternative treatment regimens with acceptable cure rates. The simultaneous administration of artesunate and mefloquine, in various doses and duration of treatment, is currently being investigated. Until proven otherwise, the drug combinations are still recommended for all adult patients suffering from acute uncomplicated falciparum malaria contracted in multidrug resistant areas. In severe malaria and malaria in children, the drug combinations need further investigation.

9311648
Looareesuwan S, Wilairatana P, Molunto W, Chalermrut K, Olliaro P, Andrial M
A comparative clinical trial of sequential treatments of severe malaria with artesunate suppository followed by mefloquine in Thailand.
Am J Trop Med Hyg. 1997 Sep;57(3):348-53.
Sixty-three patients with severe falciparum malaria were randomly administered one of the two regimens of a sequential combination of artesunate suppository followed by an oral mefloquine tablet. Thirty-two patients received artesunate suppositories (200 mg/capsule) given rectally at 0, 4, 8, 12, 24, 36, 48, and 60 hr (total = 1,600 mg: Group I). Thirty-one patients received the same artesunate suppositories given rectally at 0, 12, 24, 36, 48, and 60 hr (total = 1,200 mg: Group II). Both regimens were followed by two doses of oral mefloquine, 750 mg given at 72 hr and 500 mg at 84 hr. Patient baseline characteristics were comparable in the two groups. All patients were admitted for 28 days to the Bangkok Hospital for Tropical Diseases to assess efficacy, tolerability, and delayed neuropsychiatric effects. The mean [SD] parasite clearance time was significantly shorter in Group I than Group II (47.3 [12.4] hr versus 55.3 [17.4] hr; P = 0.05) and the rate of parasite reduction was significantly faster in Group I (P = 0.05, by log-rank test). Mean [SD] fever clearance times were similar in the two Groups (71.1 [41.2] hr and 76.9 [47.9] hr, respectively). Twenty-two patients with unrousable coma on admission (median Glasgow Coma Score = 9) regained consciousness after 1-4 days. No deaths occurred. Sixty of sixty-three patients were parasitologically and clinically cured within 3-4 days of treatment. Three patients (5%) with deteriorating conditions required rescue treatment (one patient in Group I was administered intravenous artesunate, and two patients in Group II required two extra doses of suppository). No patients had major adverse drug effects. The cure rates at 28 days of follow-up in Group I were 96% (26 of 27 patients) and 89% (24 of 27 patients) in Group II. Artesunate suppository

followed by mefloquine was well tolerated and effective. In severe malaria, the sequential treatment is a suitable alternative treatment to parenteral drugs. Further studies in a larger number of patients under field conditions are required.

9241384
Looareesuwan S, Wilairatana P, Vanijanonta S, Pitisuttithum P, Ratanapong Y, Andrial M
Monotherapy with sodium artesunate for uncomplicated falciparum malaria in Thailand: a comparison of 5- and 7-day regimens.
Acta Trop. 1997 Sep 30;67(3):197-205.
We compared the safety and efficacy of two treatment regimens using sodium artesunate in 91 randomized patients with uncomplicated falciparum malaria acquired in Thailand. One group of 45 patients received 400 mg of artesunate on the first day of treatment and then 200 mg daily for 4 days for a total of 1200 mg (group I: 5-day treatment). A second group of 46 patients received 400 mg of artesunate on the first day of treatment and then 200 mg daily for 6 days for a total of 1600 mg (group II: 7-day treatment). Both regimens were well tolerated. All patients were followed for a total of 28 days. By the third day of treatment, most patients were blood smear negative for parasites. Eighty-two patients completed the 28-day follow-up period and were used for describing the cure rate. All patients treated with the 5-day regimen were cured. In the 7-day treatment group, 98% (39 of 40) of the patients were cured; one patient developed late recrudescence (RI). There were no significant differences in fever clearance or parasite clearance between the two groups. However, 13 patients (five in group I and eight in group II) developed Plasmodium vivax infection during the follow-up period. We conclude that 5- or 7-day regimens of sodium artesunate with a total dose of 1200-1600 mg are effective and safe in treating falciparum malaria acquired in Thailand.

7495360
Looareesuwan S, Wilairatana P, Vanijanonta S, Viravan C, Andrial M
Efficacy and tolerability of a sequential, artesunate suppository plus mefloquine, treatment of severe falciparum malaria.
Ann Trop Med Parasitol. 1995 Oct;89(5):469-75.
Thirty patients with severe falciparum malaria were each given a total of 1600-mg artesunate suppository over three consecutive days followed by 1250 mg mefloquine per os, divided into two doses which were given 12 h apart. All patients were admitted for 28 days to the Bangkok Hospital for Tropical Diseases, so that the efficacy and tolerability of the treatment could be assessed. All the patients showed clinical improvement, with mean (S.D.) parasite and fever clearance times of 50.4 (13.0) and 70.7 (44.9) h, respectively. Two patients with unrousable coma (Glasgow coma score < or = 8) on admittance regained consciousness 46 and 48 h post-treatment. One other patient had acute renal failure and required dialysis. Most patients (80%) were initially hyperparasitaemic, with a mean density of 184,344 parasites/microliters blood. No deaths occurred. Efficacy was evaluated in 25 of the patients. The cure rate 28 days post-treatment was 92%. None of the patients had major adverse effects although two had tenesmus and passed stools immediately after each suppository was administered. A fresh suppository had to be inserted when this occurred. The results indicate that artesunate suppositories followed by oral mefloquine constitute a well-tolerated regimen with a high cure rate. The combination is suitable as an alternative treatment for severe malaria, particularly in children. Further, large-scale studies are required.

8915132
Looareesuwan S, Wilairatana P, Vannaphan S, Gordeuk VR, Taylor TE, Meshnick SR, Brittenham GM
Co-administration of desferrioxamine B with artesunate in malaria: an assessment of safety and tolerance.
Ann Trop Med Parasitol. 1996 Oct;90(5):551-4.

9546417
Looareesuwan S, Wilairatana P, Vannaphan S, Wanaratana V, Wenisch C, Aikawa M, Brittenham G, Graninger W, Wernsdorfer WH
Pentoxifylline as an ancillary treatment for severe falciparum malaria in Thailand.
Am J Trop Med Hyg. 1998 Mar;58(3):348-53.
Pentoxifylline, an inhibitor of tumor necrosis factor, has been evaluated as an antimalarial agent in combination with artesunate in 45 patients with severe falciparum malaria. Patients were admitted to the intensive care unit at the Hospital for Tropical Diseases in Bangkok, Thailand, and randomly assigned to treatment for 72 hr with a combination of intravenously administered artesunate and 1) placebo, 2) low-dose pentoxifylline (0.83 mg/kg/hr), or 3) high-dose pentoxifylline (1.67 mg/kg/hr). All 45 patients had one or more manifestations of severe malaria such as cerebral malaria (n = 18), renal failure requiring hemodialysis (n = 9), azotemia (n = 8), jaundice (n = 25), or hyperparasitemia (n = 30). The overall severity was comparable in the three groups. Clinical outcome was assessed with respect to the parasite clearance time and the fever

clearance time in all patients. In addition, a number of subsidiary outcome variables were examined in specific subgroups, including the recovery time from coma for patients with cerebral malaria, the duration of intubation in patients with respiratory distress, the number of hemodialysis treatments needed for patients with acute renal failure, and the number of units of blood administered to patients requiring transfusion. Concentrations of tumor necrosis factor were reduced in all three groups at 48 hr after treatment. No significant differences among the three treatment groups were found for any of the outcome variables examined. We conclude that the addition of pentoxifylline to artesunate therapy for severe malaria produced no evident clinical benefit.

10326118
Luxemburger C, Brockman A, Silamut K, Nosten F, van Vugt M, Gimenez F, Chongsuphajaisiddhi T, White NJ
Two patients with falciparum malaria and poor in vivo responses to artesunate.
Trans R Soc Trop Med Hyg. 1998 Nov-Dec;92(6):668-9.

7485711
Luxemburger C, Nosten F, Raimond SD, Chongsuphajaisiddhi T, White NJ
Oral artesunate in the treatment of uncomplicated hyperparasitemic falciparum malaria.
Am J Trop Med Hyg. 1995 Nov;53(5):522-5.
Patients with uncomplicated hyperparasitemic falciparum malaria are usually given parenteral antimalarial treatment to prevent a progression to vital organ dysfunction and death. Since the oral artemisinin derivatives are more rapidly effective than other antimalarial drugs, we compared oral artesunate (4 mg/kg/day for three days with mefloquine 25 mg/kg on the second day) with an intravenous quinine loading dose (20 mg of salt/kg initially then 10 mg/kg every 8 hr, followed by mefloquine 25 mg/kg) in an open paired randomized trial in 60 patients with acute falciparum malaria and greater than 4% parasitemia, but no evidence of vital organ dysfunction. There were no deaths and none of the patients progressed to develop severe malaria. Oral artesunate treatment resulted in shorter median [range] times to fever clearance (19 hr [4-45] versus 47 hr [4-107]) (P < 0.0001), parasite clearance (36 hr [18-61] versus 82 hr [36-104]) (P < 0.0001), and discharge from the hospital (25 hr [12-44] versus 58 hr [24-115]) (P < 0.0001). There was no toxicity attributable to artesunate. The cure rates by day 28 were 70% (19 of 27) and 39% (11 of 27) in the artesunate and quinine groups, respectively (relative risk = 1.7; 95% confidence interval = 1.0-3.0). Oral artesunate was simpler, cheaper, safer, and more effective than intravenous quinine for the treatment of uncomplicated hyperparasitemia.

8985524
Luxemburger C, Price RN, Nosten F, Ter Kuile FO, Chongsuphajaisiddhi T, White NJ
Mefloquine in infants and young children.
Ann Trop Paediatr. 1996 Dec;16(4):281-6.
In an area where multi-drug resistance in Plasmodium falciparum is a particular problem, more than 500 children under 5 years of age weighing > 5 kg were treated with mefloquine, either alone or combined with an artemisinin derivative, and followed up for a minimum of 28 days. The principal adverse effect was vomiting and this was associated with reduced efficacy of treatment (even when treatment was repeated). Later adverse effects occurred less frequently than in adults. There was no serious toxicity and, in particular, there were no neuropsychiatric side-effects. The high dose of mefloquine (25 mg/kg) required in this area is well tolerated by young children. It should be given in a divided dose of 15 mg/kg initially, followed by 10 mg/kg > or = 12 hours later.

8036679
Luxemburger C, ter Kuile FO, Nosten F, Dolan G, Bradol JH, Phaipun L, Chongsuphajaisiddhi T, White NJ
Single day mefloquine-artesunate combination in the treatment of multi-drug resistant falciparum malaria.
Trans R Soc Trop Med Hyg. 1994 Mar-Apr;88(2):213-7.
The therapeutic efficacy and toxicity of a combination of low dose mefloquine (15 mg/kg) plus artesunate 10 mg/kg in one day (MA) was compared with the currently used regimen of high dose mefloquine (25 mg/kg) (MQ) in 552 patients with uncomplicated falciparum malaria in an area of multi-drug resistance on the Thai-Burmese border. MA gave faster clinical and parasitological responses and prevented early treatment failure; 15 patients in the MQ group (6%) were early failures (< 9 d) compared with none receiving MA (P = 0.0001). Overall failure rates by day 28 were 19% in the MA group and 24% in with MQ group (relative risk (RR) = 0.78, 95% confidence interval (CI) 0.54-1.12). In the subgroup of patients who required re-treatment, MA proved significantly more effective than MQ; failure rates were 25% and 52% respectively (RR = 0.49, 95% CI = 0.29-0.83). Treatment failures were associated with mefloquine treatment in the previous month (RR =

1.72, 95% CI = 1.09-2.70) and diarrhoea (RR = 1.55, 95% CI = 1.05-2.28). Gastrointestinal side-effects and dizziness were more likely in the MQ group. There was no evident adverse effect associated with artesunate. A single day's treatment with artesunate augments the antimalarial efficacy of mefloquine.

9861381
Luxemburger C, van Vugt M, Slight T, Price RN, Chongsuphajaisiddhi T, Chanthavanich P, White NJ, Nosten F
Early vomiting of mefloquine in children with malaria is not modified by the timing of antipyretic treatment.
Trans R Soc Trop Med Hyg. 1998 Sep-Oct;92(5):562-3.

1755047
Lwin M, Maun C, Aye KH
Trial of antimalarial potential of extracts of Artemisia annua grown in Myanmar.
Trans R Soc Trop Med Hyg. 1991 Jul-Aug;85(4):449.

15931450
Mabuza A, Govere J, La Grange K, Mngomezulu N, Allen E, Zitha A, Mbokazi F, Durrheim D, Barnes K
Therapeutic efficacy of sulfadoxine-pyrimethamine for Plasmodium falciparum malaria.
S Afr Med J. 2005 May;95(5):346-9.
OBJECTIVES: To assess the therapeutic efficacy of sulfadoxinepyrimethamine (SP) after 5 years of use as first-line treatment of uncomplicated Plasmodium falciparum malaria, and thus guide the selection of artemisinin-based combination therapy in Mpumalanga, South Africa. DESIGN: An open-label, in vivo therapeutic efficacy study of patients with uncomplicated P. falciparum malaria treated with a single oral dose of SP, with response to treatment monitored clinically and parasitologically on days 1, 2, 3, 7, 14, 21, 28 and 42. SETTING: Mangweni and Naas public health care clinics, Tonga district in rural Mpumalanga. SUBJECTS, OUTCOME MEASURES AND RESULTS: Of 152 patients recruited sequentially, 149 (98%) were successfully followed up for 42 days. One hundred and thirty-four patients (90%) demonstrated adequate clinical and parasitological response. Of the 15 patients (10%) who failed treatment, 2 (1.3%) had an early treatment failure, and polymerase chain reaction confirmed recrudescent infection in all 13 patients (8.7%) who had late parasitological (N = 11) or clinical (N = 2) failure. Gametocyte carriage was prevalent following SP treatment (84/152) and this has increased significantly since implementation in 1998 (relative risk 2.77 (confidence interval 1.65 - 4.66); p = 0.00004). CONCLUSION: Asexual P. falciparum parasites in Mpumalanga remain sensitive to SP, with no significant difference between the baseline cure rate (94.5%) at introduction in 1998, and the present 90% cure rate (p = 0.14). However, since gametocyte carriage has increased significantly we recommend that SP be combined with artesunate in Mpumalanga to reduce gametocyte carriage and thus decrease malaria transmission and potentially delay antimalarial resistance.

7506497
Maeno Y, Brown AE, Smith CD, Tegoshi T, Toyoshima T, Ockenhouse CF, Corcoran KD, Ngampochjana M, Kyle DE, Webster HK, et al.
A nonhuman primate model for human cerebral malaria: effects of artesunate (qinghaosu derivative) on rhesus monkeys experimentally infected with Plasmodium coatneyi.
Am J Trop Med Hyg. 1993 Dec;49(6):726-34.
We studied the effects of artesunate on rhesus monkeys infected with Plasmodium coatneyi. Sixteen rhesus monkeys were divided in four groups. Group I consisted of three monkeys that were splenectomized and were treated with three doses (loading dose: 3.3 mg/kg, maintenance doses: 1.7 mg/kg) of artesunate, group II consisted of three monkeys that were treated with three doses of artesunate (same as group I), group III consisted of two monkeys that were treated with one dose (3.3 mg/kg) of artesunate, and group IV consisted of five untreated monkeys. Parasitemias of these groups ranged from 13.3% to 19.5% before treatment. Twenty-four hours after administration, the parasitemia was reduced to 2.2% in group I and to < 0.1% in group II; parasitemia was lowered to 10.6% in group III only 3 hr after drug administration. The rate of sequestration in the cerebral microvessels, which was 29.4% in untreated animals, was < 0.1% in groups I and II (24 hr after treatment), and 2.0% in group III (3 hr after treatment). These data clearly indicate that artesunate not only reduced parasitemia, but also reduced the rate of parasitized red blood cell (PRBC) sequestration in cerebral microvessels. In an immunohistologic study, endothelial-leukocyte adhesion molecule-1 (ELAM-1) was not detected in group I after treatment with artesunate, although the presence of CD36, thrombospondin, intercellular adhesion molecule-1, IgG, and C3 in the cerebral microvessels was not altered. This is the first in vivo study to show that artesunate interferes with continued PRBC sequestration in the cerebral microvessels in cerebral malaria.(ABSTRACT TRUNCATED AT 250 WORDS)

15115411
Magueur G, Crousse B, Charneau S, Grellier P, Begue JP, Bonnet-Delpon D
Fluoroartemisinin: trifluoromethyl analogues of artemether and artesunate.
J Med Chem. 2004 May 6;47(10):2694-9.
The synthesis of a series of C-10 trifluoromethyl ethers of artemisinin has been achieved from key bromide 8, itself carried out in two steps from artemisinin. The substitution of 8 with methanol, ethanol, or succinic acid allowed the access of C-10 CF(3) analogues of beta-artemether, beta-arteether, or artesunate, respectively, in good yields (up to 89%). The presence of the CF(3) group at C-10 of artemisinin clearly increased the chemical stability under simulated stomach acid conditions. For example, the CF(3) analogue of arteether was found to be around 45 times more stable than arteether itself. The influence of the CF(3) moiety on biological activity was also highlighted. CF(3) analogues of artemether and arteether exhibited a high in vivo antimalarial activity on mice infected with Plasmodium berghei NK173, with a complete clearance of the parasitemia during the entire observation period (25 days).

15305693
Majori G
[Combined antimalarial therapy using artemisinin]
Parassitologia. 2004 Jun;46(1-2):85-7.
The existing armamentarium of drugs for the treatment and prevention of malaria is limited primarily by resistance (and cross-resistance between closely related drugs). However, most of these drugs still have a place and their life-span could be prolonged if better deployed and used, and also by rationally combining them based on pharmacodynamic and pharmacokinetic properties. Newer compounds are also being developed. The nature of malaria disease and its prevalence in the developing world call for innovative approaches to develop new affordable drugs and to safeguard the available ones. According to WHO, the concept of combination therapy is based on the synergistic or additive potential of two or more drugs, to improve therapeutic efficacy and also delay the development of resistance to the individual components of the combination. Combination therapy (CT) with antimalarial drugs is the simultaneous use of two or more blood schizontocidal drugs with independent modes of action and different biochemical targets in the parasite. In the context of this definition, multiple-drug therapies that include a nonantimalarial drug to enhance the antimalarial effect of a blood schizontocidal drug are not considered combination therapy. Similarly, certain antimalarial drugs that fit the criteria of synergistic fixed-dose combinations are operationally considered as single products in that neither of the individual components would be given alone for anti-malarial therapy. An example is sulfadoxine-pyrimethamine. Artemisinin-based combination therapies have been shown to improve treatment efficacy and also contain drug resistance in South-East Asia. However, major challenges exist in the deployment and use of antimalarial drug combination therapies, particularly in Africa. These include: 1) the choice of drug combinations best suited for the different epidemiological situations; 2) the cost of combination therapy; 3) the timing of the introduction of combination therapy; 4) the operational obstacles to implementation, especially compliance. As a response to increasing levels of antimalarial resistance, the World Health Organization (WHO) recommends that all countries experiencing resistance to conventional monotherapies, such as chloroquine, amodiaquine or sulfadoxine/pyrimethamine, should use combination therapies, preferably those containing artemisinin derivatives (ACTs--artemisinin-based combination therapies) for malaria caused by Plasmodium falciparum. There is a promising role of such compounds in replacing or complementing current options. Since 1979, several different formulations of artemisinin and its derivatives have been produced and studied in China in several thousand patients for either P. falciparum or P. vivax malaria. To date, there is no evidence of drug resistance to these compounds. The use of artemisinin, artemether, arteether and artesunate for either uncomplicated or severe malaria is now spreading through almost all malarious areas of the world, although some of they have no patent protection, their development (with few exceptions) has not followed yet full international standards. Both artesunate, artemether and arteether are rapidly and extensively converted to their common bioactive metabolite, dihydroarte-misinin. WHO currently recommends the following therapeutic options: 1) artemether/lumefantrine; 2) artesunate plus amodiaquine; 3) artesunate plus sulfadoxine/pyrimethamine (in areas where SP efficacy remains high); 4) artesunate plus mefloquine (in areas with low to moderate transmission); and 5) amodiaquine plus sulfadoxine/pyrimethamine, in areas where efficacy of both amodiaquine and sulfadoxine/pyrimethamine remains high (mainly limited to countries in West Africa). This non artemisinin-based combination therapy is reserved as an interim option for countries, which, for whatever reason, are unable immediately to move to ACTs.

9419840
Malagon F, Vazquez J, Delgado G, Ruiz A
Antimalaric effect of an alcoholic extract of Artemisia ludoviciana mexicana in a rodent malaria model.
Parassitologia. 1997 Mar;39(1):3-7.
Chloroquine resistance of Plasmodium falciparum first and of P. vivax more recently, stimulated the search for new antimalarics. Chinese investigators have introduced new compounds obtained from extracts of

Artemisia annua which possess an antimalaric active principle different from those of the drugs in use. In Mexico eight species of Artemisia have been described and among them just A. ludoviciana has been empirically used in the treatment of intermittent fever. To know whether mexican Artemisia had antimalaric activity several in vivo experiments were performed. Different type of extracts from two Artemisia species were prepared and assayed in five different doses on mice infected by Plasmodium yoelii yoelii, in a four-day test scheme. Here, only the results of the assays on ethanolic extract of A. ludoviciana are presented. The results of the in vivo experiments showed that the parasite reproduction was inhibited up to 98.6% at the fifth day, as compared with the controls; the ED50 was of 29.2 mg/kg and the SM50 of 28.7. We looked after the presence of artemisinin in the ethanolic extract, without success.

16195260
Malenga G, Palmer A, Staedke S, Kazadi W, Mutabingwa T, Ansah E, Barnes KI, Whitty CJ
Antimalarial treatment with artemisinin combination therapy in Africa.
BMJ. 2005 Oct 1;331(7519):706-7.

8980761
Marley SE, Eberhard ML, Steurer FJ, Ellis WL, McGreevy PB, Ruebush TK 2nd
Evaluation of selected antiprotozoal drugs in the Babesia microti-hamster model.
Antimicrob Agents Chemother. 1997 Jan;41(1):91-4.
The presently used therapy for Babesia microti infections, a combination of quinine and clindamycin, does not always result in parasitologic cures. To identify possible alternative chemotherapeutic agents for such infections, we screened, in the hamster-B. microti system, 12 antiprotozoal drugs that have either recently been released for human use or were in experimental stages of development at the Walter Reed Army Institute of Research for the treatment of malaria and leishmaniasis. Several well-recognized antimalarial drugs, such as mefloquine, halofantrine, artesunate, and artelenic acid, exhibited little or no effect on parasitemia. Two 8-aminoquinolines, WR006026 [8-(6-diethylaminohexylamino)-6-methoxy-4-methylquinoline dihydrochloride] and WR238605 [8-[(4-amino-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5 -(3-trifluoromethylphenoxy-7) quinoline succinate], produced clearance of patent parasitemia. Furthermore, blood from infected hamsters treated with WR238605 via an intramuscular injection failed to infect naive hamsters on subpassage, thus producing a parasitologic cure. These two compounds merit further screening in other systems and may prove useful in treating human babesiosis.

12812355
Marquino W, Huilca M, Calampa C, Falconi E, Cabezas C, Naupay R, Ruebush TK 2nd
Efficacy of mefloquine and a mefloquine-artesunate combination therapy for the treatment of uncomplicated Plasmodium falciparum malaria in the Amazon Basin of Peru.
Am J Trop Med Hyg. 2003 May;68(5):608-12.
In the Amazon Basin of Peru, more than 50% of patients with uncomplicated Plasmodium falciparum malaria fail to respond to treatment with chloroquine or sulfadoxine-pyrimethamine. To assist the National Malaria Control Program in identifying an alternative first-line therapy for this region, we conducted a trial of the safety and efficacy of mefloquine (MQ) compared with mefloquine-artesunate (MQ-AS) combination therapy. Patients with uncomplicated P. falciparum infections between the ages of 5 and 50 years were randomly assigned to be treated with either MQ (15 mg/kg in a single oral dose) or MQ (15 mg/kg) plus AS (4 mg/kg/day for three days). A total of 98 patients were enrolled and followed for 28 days. None of the 47 patients who received MQ alone or the 51 patients who received MQ-AS combination therapy had recurrences of parasitemia during the 28-day follow-up period. Asexual parasite densities decreased significantly more rapidly and the proportion of patients with gametocytes was significantly lower on days 3-21 in the MQ-AS group than in patients treated with MQ alone. All patients tolerated the medication well. Based on the results of this study and with the objective of slowing the development of resistance, the Peruvian Ministry of Health has decided to revise its malaria treatment policy and recommend combination therapy with MO-AS as the new first-line treatment of uncomplicated P. falciparum malaria in the Amazon region.

12557836
Marquino W, MacArthur JR, Barat LM, Oblitas FE, Arrunategui M, Garavito G, Chafloque ML, Pardave B, Gutierrez S, Arrospide N, Carrillo C, Cabezas C, Ruebush TK 2nd
Efficacy of chloroquine, sulfadoxine-pyrimethamine, and mefloquine for the treatment of uncomplicated Plasmodium falciparum malaria on the north coast of Peru.
Am J Trop Med Hyg. 2003 Jan;68(1):120-3.
As part of an effort to assess antimalarial drug resistance in Peru, we carried out 14-day in vivo efficacy trials of chloroquine (CQ; 25 mg/kg) and sulfadoxine-pyrimethamine (SP; 25 mg/kg of the sulfadoxine component)

for the treatment of uncomplicated Plasmodium falciparum infections at three sites on the northern coast of Peru. Mefloquine (MQ; 15 mg/kg) also was evaluated at one site. The results from all three sites were similar. Of the 53 patients treated with CQ, 58.5% had RII/RIII responses. No RIII failures were observed among the 112 patients who received SP, but 4.5% and 1.8%, respectively, had RII and RI responses. All 33 patients treated with MQ showed a sensitive response. Early treatment failures were observed in 27.1% of the CQ patients but in no patients receiving SP or MQ. Late treatment failures were seen in 59.3% of the CQ patients and 6.4% of the SP patients but in none of those treated with MQ. Based on these findings and because of concern about the potential for development of resistance if SP were used alone, the National Malaria Control Program is planning a change in malaria treatment policy to SP-artesunate combination therapy for this region of the country.

15891131
Marquino W, Ylquimiche L, Hermenegildo Y, Palacios AM, Falconi E, Cabezas C, Arrospide N, Gutierrez S, Ruebush TK 2nd
Efficacy and tolerability of artesunate plus sulfadoxine-pyrimethamine and sulfadoxine-pyrimethamine alone for the treatment of uncomplicated Plasmodium falciparum malaria in Peru.
Am J Trop Med Hyg. 2005 May;72(5):568-72.
To assist the Peruvian Ministry of Health in modifying the malaria treatment policy for their north Pacific coastal region, we conducted an in vivo efficacy trial of sulfadoxine-pyrimethamine (SP) and SP plus artesunate (SP-AS) for the treatment for uncomplicated Plasmodium falciparum infections. A total of 197 patients were randomized to therapy with either SP (25 mg/kg of the sulfadoxine component in a single dose on day 0) or a combination of SP plus AS (4 mg/kg on days 0, 1, and 2) and were followed for 28 days for symptoms and recurrence of parasitemia. No statistically significant differences between the two groups were observed on enrollment with respect to age, sex, history of malaria, or geometric mean parasite density. A total of 185 subjects completed the 28-day follow-up. Of the 91 subjects treated with SP alone, two had recurrences of parasitemia on day 7 and one on day 21. Of the 94 subjects treated with SP-AS, one had a recurrence of parasitemia on day 21. Fever and asexual parasite density decreased significantly more rapidly and the proportion of patients with gametocytemia on days 3-28 was significantly lower in subjects treated with combination therapy than in those who received SP alone. No severe adverse drug reactions were observed; however, self-limited rash and pruritis were significantly more common and an exacerbation of nausea, vomiting, and abdominal pain were observed significantly more frequently among patients who had received SP-AS. These results have contributed to a National Malaria Control Program decision to change to SP-AS combination therapy as the first-line treatment for uncomplicated P. falciparum malaria in northern coastal Peru in November 2001, making Peru the first country in the Americas to recommend this combination therapy.

12678444
Marsh K
Artemesinins for severe malaria in Africa?
East Afr Med J. 2002 Dec;79(12):619-20.

11183758
Marshall E
Drugs. Reinventing an ancient cure for malaria.
Science. 2000 Oct 20;290(5491):437-9.

16163624
Martensson A, Stromberg J, Sisowath C, Msellem MI, Gil JP, Montgomery SM, Olliaro P, Ali AS, Bjorkman A
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 Oct 15;41(8):1079-86. Epub 2005 Sep 13.
BACKGROUND: This is the first clinical trial comparing the efficacy of artesunate plus amodiaquine (ASAQ) and artemether-lumefantrine (AL)--the major artemisinin-based combination therapy (ACT) candidates for treatment of malaria in Africa--that involved an extended, 42-day follow-up period, polymerase chain reaction-adjusted parasitological cure rates (PCR APCRs), and systematic analyses of genetic markers related to quinoline resistance. METHODS. A total of 408 children with uncomplicated Plasmodium falciparum malaria in Zanzibar, Tanzania, were enrolled. Children who were 6-8 months of age and/or who weighed 6-8 kg were assigned to receive ASAQ for 3 days. Children who were 9-59 months of age and who weighted > or =9 kg were randomly assigned to receive either ASAQ or AL for 3 days in standard doses.

Intention-to-treat analyses were performed. RESULTS: Age- and weight-adjusted PCR-APCRs by follow-up day 42 were 91% (188 of 206 patients) in the ASAQ group and 94% (185 of 197 patients) in the AL group (odds ratio [OR] for the likelihood of cure, 2.07; 95% confidence interval [CI], 0.84-5.10; P=.115). A total of 5 and 7 recrudescences occurred after day 28 in the ASAQ and AL groups, respectively. On the assumption that 10 malaria episodes with uncertain PCR results were recrudescences, PCR-APCRs decreased to 88% in the ASAQ group and to 92% in the AL group. Unadjusted cure rates by day 42 were 56% (116 of 206 patients) in the ASAQ group versus 77% (151 of 197 patients) in the AL group (OR, 2.55; 95% CI, 1.66-3.91; P

12625145
Massougbodji A, Kone M, Kinde-Gazard D, Same-Ekobo A, Cambon N, Mueller EA
A randomized, double-blind study on the efficacy and safety of a practical three-day regimen with artesunate and mefloquine for the treatment of uncomplicated Plasmodium falciparum malaria in Africa.
Trans R Soc Trop Med Hyg. 2002 Nov-Dec;96(6):655-9.
A randomized, double-blind, parallel-group study in 104 hospitalized patients with acute, uncomplicated Plasmodium falciparum malaria was performed in West and Central Africa from March to July 2001. Patients were randomized to receive simultaneous dosing (artesunate 200 mg/d plus mefloquine 250 mg/d from the first to the third day [investigational group]) or sequential dosing (artesunate 200 mg/d for 3 d plus mefloquine 250 mg on the second and 500 mg on the third day [reference group]). Patients were followed-up for 28 d, and clinical and parasitological outcomes were assessed. The 14-d cure rate was 100% in the investigational group and 98% in the reference group with no recrudescence until day 28. Mean times to fever and parasite clearance were similar between the 2 groups (32 h vs. 26 h and 45 h vs. 48 h) and tolerability was good in both groups. The number of patients with vomiting was statistically significantly lower in the investigational group compared to the reference group (3.8% vs. 19.2%, P = 0.014). A 3-d once-daily co-administration of artesunate and mefloquine starting on day one offers a practical dosing regimen, which is highly effective and well tolerated in patients with uncomplicated P. falciparum malaria.

15486837
Mayxay M, Khanthavong M, Lindegardh N, Keola S, Barends M, Pongvongsa T, Yapom R, Annerberg A, Phompida S, Phetsouvanh R, White NJ, Newton PN
Randomized comparison of chloroquine plus sulfadoxine-pyrimethamine versus artesunate plus mefloquine versus artemether-lumefantrine in the treatment of uncomplicated falciparum malaria in the Lao People's Democratic Republic.
Clin Infect Dis. 2004 Oct 15;39(8):1139-47. Epub 2004 Sep 27.
BACKGROUND: Recent clinical trials in the Lao People's Democratic Republic have demonstrated that chloroquine and sulfadoxine-pyrimethamine, which are national malaria treatment policy, are no longer effective in the treatment of uncomplicated Plasmodium falciparum malaria. METHODS: A randomized comparison of 3 oral antimalarial combinations--chloroquine plus sulfadoxine-pyrimethamine versus artesunate plus mefloquine versus artemether-lumefantrine--with 42-day follow-up period, was conducted among 330 patients with acute uncomplicated falciparum malaria in southern Laos. RESULTS: The 42-day cure rates, as determined by intention-to-treat analysis and adjusted for reinfection, were 100%, 97%, and 93% for the groups receiving artesunate plus mefloquine, artemether-lumefantrine, and chloroquine plus sulfadoxine-pyrimethamine, respectively. Of 8 patients receiving chloroquine plus sulfadoxine-pyrimethamine who experienced treatment failure, 6 had early treatment failure. The mean parasite clearance time was significantly longer in patients treated with chloroquine plus sulfadoxine-pyrimethamine (2.9 days; 95% confidence interval [CI], 2.8-3.0 days) than in those treated with artesunate plus mefloquine (2.07 days; 95% CI, 2.0-2.1 days; P

16492359
Mboera LE, Fanello CI, Malima RC, Talbert A, Fogliati P, Bobbio F, Molteni F
Comparison of the Paracheck-Pf test with microscopy, for the confirmation of Plasmodium falciparum malaria in Tanzania.
Ann Trop Med Parasitol. 2006 Mar;100(2):115-22.
Paracheck-Pf is a rapid, qualitative immuno-assay for the detection of Plasmodium falciparum-specific histidine-rich protein-2 in samples of human blood. The assay has now been evaluated, against the usual 'gold standard', microscopy, using blood samples from 1655 individuals in five districts of Tanzania, four of which experience frequent malaria outbreaks. The aim was to verify whether Paracheck-Pf could be a reliable tool for the confirmation of malaria outbreaks in such areas. The overall measurements of the assay's performance were good, with a sensitivity of 90.0%, a specificity of 96.6%, a positive predictive value of 88.9%, and a negative predictive value of 97.0% (with an estimated malaria prevalence of 23.3%). There was, however, marked variation between the study districts, the assay's performance being relatively poor where the test had been stored for 12 months at room temperature (23.5+/-3.5 degrees C). The assay was easy to perform in the field and could clearly be a valuable tool in remote areas and in emergency situations,

such as the early detection of malaria outbreaks. The cost of the assay (U.S.$0.62/test at the time of the present study) is sufficiently low that its routine use in the confirmation of P. falciparum malaria might also be cost-effective, particularly in areas where there are no facilities for microscopy and/or where the first-line treatment of malaria is based on relatively expensive artemisinin-based combinations.

16088834
McGready R, Ashley EA, Moo E, Cho T, Barends M, Hutagalung R, Looareesuwan S, White NJ, Nosten F
A randomized comparison of artesunate-atovaquone-proguanil versus quinine in treatment for uncomplicated falciparum malaria during pregnancy.
J Infect Dis. 2005 Sep 1;192(5):846-53. Epub 2005 Jul 27.
BACKGROUND: There is no safe, practical, and effective treatment for pregnant women infected with multidrug-resistant Plasmodium falciparum. METHODS: We recruited pregnant Karen women in the second or third trimesters of pregnancy who had uncomplicated falciparum malaria for a randomized, open-label trial with a restricted sequential trial design of 7 days of supervised quinine (SQ7) versus 3 days of artesunate-atovaquone-proguanil (AAP). RESULTS: Eight-one pregnant women entered the study between December 2001 and July 2003; 42 were treated with SQ7 and 39 were treated with AAP. Fever, parasite clearance, and duration of anemia were significantly better with AAP; the treatment failure rate was 7 times lower (5% [2/39] vs. 37% [15/41]; relative risk, 7.1 [95% confidence interval, 1.7-29.2]; P = .001). There were no significant differences in birth weight, duration of gestation, or congenital abnormality rates in newborns or in growth and developmental parameters of infants monitored for 1 year. CONCLUSION: AAP is a well-tolerated, effective, practical, but expensive treatment for multidrug-resistant falciparum malaria during the second or third trimesters of pregnancy. Despite the small number of subjects, our results add to the growing body of evidence that AAP is safe for the mother and the fetus.

11198658
McGready R, Brockman A, Cho T, Cho D, van Vugt M, Luxemburger C, Chongsuphajaisiddhi T, White NJ, Nosten F
Randomized comparison of mefloquine-artesunate versus quinine in the treatment of multidrug-resistant falciparum malaria in pregnancy.
Trans R Soc Trop Med Hyg. 2000 Nov-Dec;94(6):689-93.
Since no effective malaria prevention measures have been identified for pregnant women living on the western border of Thailand, prompt diagnosis and efficient treatment are paramount, although drug resistance in Plasmodium falciparum has narrowed the treatment options. An open randomized comparison of supervised quinine (10 mg salt/kg every 8 h) for 7 days (Q7) versus mefloquine 25 mg base/kg (total dose) plus artesunate 4 mg/kg per day for 3 days (MAS3) was conducted in 1995-97 in 108 Karen women with acute uncomplicated falciparum malaria in the second or third trimesters of pregnancy. The MAS3 regimen was more effective than the Q7 regimen: day 63 cure rates were 98.2% (95% CI 94.7-100) (n = 65) for MAS3 and 67.0% (95% CI 43x3-90x8) (n = 41) for Q7, P = 0x001. The MAS3 regimen was also associated with less gametocyte carriage; the average person-gametocyte-weeks for MAS3 was 2.3 (95% CI 0-11) and for Q7 was 46x9 (95% CI 26-78) per 1000 person-weeks, respectively (P < 0.001). MAS3 was significantly better tolerated. These evident advantages must be balanced against a possible increased risk of stillbirth with the use of mefloquine in pregnancy. Further randomized studies assessing the safety and efficacy of other artemisinin-containing combination regimens in pregnancy are needed urgently.

9850401
McGready R, Cho T, Cho JJ, Simpson JA, Luxemburger C, Dubowitz L, Looareesuwan S, White NJ, Nosten F
Artemisinin derivatives in the treatment of falciparum malaria in pregnancy.
Trans R Soc Trop Med Hyg. 1998 Jul-Aug;92(4):430-3.
An artemisinin derivative (artesunate or artemether) was used for the treatment of multidrug-resistant Plasmodium falciparum malaria in 83 Karen pregnant women in Thailand; 55 women were treated for recrudescent infection following quinine or mefloquine, 12 for uncomplicated hyperparasitaemic episodes, and 16 had not declared their pregnancy when treated. The women were followed weekly until delivery. Artesunate and artemether were well tolerated and there was no drug-related adverse effect. Recrudescence within 42 d occurred in 16% of the treated episodes. Overall 73 pregnancies (88%) resulted in live births, 3 (4%) in abortions and 2 (3%) in still births, and 5 women were lost to follow-up before delivery. There was no congenital abnormality in any of the newborn children, and the 46 children followed for more than one year all developed normally.

11712093
McGready R, Cho T, Keo NK, Thwai KL, Villegas L, Looareesuwan S, White NJ, Nosten F

Artemisinin antimalarials in pregnancy: a prospective treatment study of 539 episodes of multidrug-resistant Plasmodium falciparum.
Clin Infect Dis. 2001 Dec 15;33(12):2009-16. Epub 2001 Nov 9.
The emergence and spread of multidrug-resistant Plasmodium falciparum compromises the treatment of malaria, especially during pregnancy, where the choice of antimalarials is already limited. Artesunate (n=528) or artemether (n=11) was used to treat 539 episodes of acute P. falciparum malaria in 461 pregnant women, including 44 first-trimester episodes. Most patients (310 [57.5%]) received re-treatments after earlier treatment with quinine or mefloquine. By use of survival analysis, the cumulative artemisinin failure rate for primary infections was 6.6% (95% confidence interval, 1.0-12.3), compared with the re-treatment failure rate of 21.7% (95% confidence interval, 15.4-28.0; P=.004). The artemisinins were well tolerated with no evidence of adverse effects. Birth outcomes did not differ significantly to community rates for abortion, stillbirth, congenital abnormality, and mean gestation at delivery. These results are reassuring, but further information about the safety of these valuable antimalarials in pregnancy is needed.

11816439
McGready R, Cho T, Samuel, Villegas L, Brockman A, van Vugt M, Looareesuwan S, White NJ, Nosten F
Randomized comparison of quinine-clindamycin versus artesunate in the treatment of falciparum malaria in pregnancy.
Trans R Soc Trop Med Hyg. 2001 Nov-Dec;95(6):651-6.
In areas where multidrug-resistant Plasmodium falciparum (MDR-Pf) is prevalent, only quinine is known to be safe and effective in pregnant women. On the western border of Thailand, 7 days of supervised quinine (30 mg/kg daily) cures two-thirds of P. falciparum-infected women in the 2nd and 3rd trimesters of pregnancy. Artesunate is effective against MDR-Pf and the limited data on its use in pregnancy suggest it is safe. An open randomized comparison of supervised quinine (10 mg salt/kg every 8 h) in combination with clindamycin (5 mg/kg every 8 h) for 7 days (QC7) versus artesunate 2 mg/kg per day for 7 days (A7) was conducted in 1997-2000 in 129 Karen women with acute uncomplicated falciparum malaria in the 2nd or 3rd trimesters of pregnancy. There was no difference in the day-42 cure rates between the QC7 (n = 65) and A7 (n = 64) regimens with an efficacy of 100% in both, confirmed by parasite genotyping. The A7 regimen was also associated with less gametocyte carriage; the average person-gametocyte-weeks for A7 was 3 (95% CI 0-19) and for QC7 was 39 (95% CI 21-66) per 1000 person-weeks, respectively (P < 0.01). There was no difference in gastrointestinal symptoms between the groups but there was significantly more tinnitus in the QC7 group compared to the A7 group (44.9% vs 8.9%; RR 5.1; 95% CI 1.9-13.5; P < 0.001). The favourable results with quinine-clindamycin mean that there is a useful back-up treatment for women with falciparum malaria who experience quinine and artesunate failures in pregnancy. Adherence to the 7-day regimen and cost (US$18.50 per treatment) are likely to be the main obstacles to this regimen.

15307434
McGready R, Keo NK, Villegas L, White NJ, Looareesuwan S, Nosten F
Artesunate-atovaquone-proguanil rescue treatment of multidrug-resistant Plasmodium falciparum malaria in pregnancy: a preliminary report.
Trans R Soc Trop Med Hyg. 2003 Sep-Oct;97(5):592-4.
Pregnant women are particularly vulnerable to malaria infections. Multidrug resistance in Plasmodium falciparum seriously compromises treatment in some endemic areas. Between April 1999 and October 2001, we treated and prospectively followed 27 Karen pregnant women with multiple recrudescent P. falciparum infections who were resistant to all other antimalarials with a triple combination of artesunate-atovaquone-proguanil. The treatment was well tolerated and we found no evidence of toxicity for the mothers and the fetus. All but 1 woman were cured (cure rate 96%, 95% CI 89-100). The triple combination of artesunate (4 mg/kg/d), atovaquone (20 mg/kg/d), and proguanil (8 mg/kg/d) may provide a much needed, albeit expensive, 3-d rescue treatment for pregnant women exposed to multidrug- resistant P. falciparum malaria.

10715685
McGready R, Nosten F
The Thai-Burmese border: drug studies of Plasmodium falciparum in pregnancy.
Ann Trop Med Parasitol. 1999 Dec;93 Suppl 1:S19-23.
Plasmodium falciparum malaria is increasing world-wide, as is resistance to the available antimalarials. On the Thai-Burmese border this problem is most acute in pregnant women, as options for their treatment are even more restricted because of the unknown effects of antimalarials on the foetus. Presented here are the results of descriptive, clinical, drug studies on quinine, mefloquine and artemisinin derivatives for P. falciparum in pregnant women. Mefloquine and quinine have high failure rates for primary and recrudescent infections. Artemisinin-based treatments in pregnant women have proved safe, tolerable and efficacious. However, randomized drug studies with these drugs and other new antimalarials are required to define the true safety and efficacy of these drugs in pregnant women.

12955371
McGready R, Stepniewska K, Edstein MD, Cho T, Gilveray G, Looareesuwan S, White NJ, Nosten F
The pharmacokinetics of atovaquone and proguanil in pregnant women with acute falciparum malaria.
Eur J Clin Pharmacol. 2003 Oct;59(7):545-52. Epub 2003 Aug 30.
OBJECTIVE: To determine the pharmacokinetic properties of atovaquone, proguanil, and the triazine metabolite cycloguanil in women with recrudescent multi-drug resistant falciparum malaria during the second and third trimesters of pregnancy treated by artesunate-atovaquone-proguanil. METHODS: Serial plasma concentrations of atovaquone, proguanil and cycloguanil were measured in 24 women at baseline and after the final dose of the 3-day treatment with atovaquone (20 mg/kg/day) plus proguanil (8 mg/kg/day) plus artesunate (4 mg/kg/day) daily. RESULTS: The triple combination was well tolerated and highly effective. The outcomes of pregnancy were all normal. Population mean (+/- SEM) oral clearance (Cl/F) estimates were 313+/-33 ml/h/kg and 1109+/-43 ml/h/kg, total apparent volume of distribution (Vd/F) 13.0+/-1.3 l/kg and 22.9+/-1.4 l/kg, and terminal elimination half-life; 29.1 h and 14.3 h, for atovaquone and proguanil, respectively. Using conventional and population pharmacokinetic analyses, Cl/F and Vd/F estimates for both drugs were approximately twice, and plasma concentrations less than half those reported previously in healthy subjects and patients with acute malaria. CONCLUSION: Artesunate-atovaquone-proguanil is a promising treatment for multi-drug resistant falciparum malaria during pregnancy, but the dose of atovaquone-proguanil may need to be increased.

10796551
McIntosh HM, Olliaro P
Artemisinin derivatives for treating severe malaria.
Cochrane Database Syst Rev. 2000;(2):CD000527.
BACKGROUND: Artemisinin derivatives may have advantages over quinoline drugs for treating severe malaria since they are fast acting and effective against quinine resistant malaria parasites. OBJECTIVES: The objective of this review was to assess the effects of artemisinin drugs for severe and complicated falciparum malaria in adults and children. SEARCH STRATEGY: We searched the Cochrane Infectious Diseases Group trials register, Cochrane Controlled Trials Register, Medline, Embase, Science Citation Index, Lilacs, African Index Medicus, conference abstracts and reference lists of articles. We contacted organisations, researchers in the field and drug companies. SELECTION CRITERIA: Randomised and pseudo-randomised trials comparing artemisinin drugs (rectal, intramuscular or intravenous) with standard treatment, or comparisons between artemisinin derivatives in adults or children with severe or complicated falciparum malaria. DATA COLLECTION AND ANALYSIS: Eligibility, trial quality assessment and data extraction were done independently by two reviewers. Study authors were contacted for additional information. MAIN RESULTS: Twenty three trials are included, allocation concealment was adequate in nine. Sixteen trials compared artemisinin drugs with quinine in 2653 patients. Artemisinin drugs were associated with better survival (mortality odds ratio 0.61, 95% confidence interval 0.46 to 0.82, random effects model). In trials where concealment of allocation was adequate (2261 patients), this was barely statistically significant (odds ratio 0.72, 95% CI 0.54 to 0.96, random effects model). In 1939 patients with cerebral malaria, mortality was also lower with artemisinin drugs overall (odds ratio 0.63, 95% CI 0.44 to 0.88, random effects model). The difference was not significant however when only trials reporting adequate concealment of allocation were analysed (odds ratio 0.78, 95% CI 0.55 to 1.10, random effects model) based on 1607 patients. No difference in neurological sequelae was shown. Compared with quinine, artemisinin drugs showed faster parasite clearance from the blood and similar adverse effects. REVIEWER'S CONCLUSIONS: The evidence suggests that artemisinin drugs are no worse than quinine in preventing death in severe or complicated malaria. No artemisinin derivative appears to be better than the others.

10796519
McIntosh HM, Olliaro P
Artemisinin derivatives for treating uncomplicated malaria.
Cochrane Database Syst Rev. 2000;(2):CD000256.
BACKGROUND: Artemisinin derivatives are a relatively new group of drugs with antimalarial properties. As resistance to other antimalarial drugs continues to increase, artemisinin drugs may be useful alternatives. OBJECTIVES: The objective of this review was to assess the effects of artemisinin drugs for treating uncomplicated falciparum malaria. SEARCH STRATEGY: We searched the Cochrane Infectious Diseases Group trials register, the Cochrane Controlled Trials Register, Medline, Embase, Science Citation Index, Lilacs, African Index Medicus; conference abstracts and reference lists of relevant articles. We contacted organisations, researchers in the field and drug companies. SELECTION CRITERIA: Randomised and quasi-randomised trials of artemisinin derivatives, alone or in combination with other antimalarials, compared with standard antimalarial treatments, in adults or children with uncomplicated falciparum malaria. Only trials where treatment was given by mouth or suppository were included. Comparisons between different artemisinin derivatives and treatment regimens were also included. DATA COLLECTION AND ANALYSIS:

Eligibility and trial quality were assessed and data were extracted independently by the two reviewers. MAIN RESULTS: Forty-one trials involving over 5000 patients were included. Variation in study design and quality made synthesis of the data problematic. Allocation concealment was adequate in only two trials. Most data were from areas of multidrug resistant falciparum malaria in South East Asia. Compared with standard antimalarial treatments, artemisinin drugs showed fast parasite clearance and high cure rates at follow-up, provided the duration of treatment with artemisinin drugs was adequate. Combination with mefloquine improved sustained parasite clearance and was effective in multidrug resistant areas. When doses were adequate, the combination shortened the duration of treatment. We found no evidence that artemisinin drugs are more harmful than standard treatment drugs over a typical trial period of 28 days. REVIEWER'S CONCLUSIONS: The evidence suggests that artemisinin drugs are effective and safe for treating uncomplicated malaria. There is no evidence from randomised trials that one artemisinin derivative is better than the others. In areas where there is mefloquine resistance, combination therapy with an artemisinin derivative appears to improve sustained parasite clearance compared with either drug alone.

10212902
McIntosh HM, Olliaro P
Treatment of severe malaria with artemisinin derivatives. A systematic review of randomised controlled trials.
Med Trop (Mars). 1998;58(3 Suppl):61-2.
This systematic review of randomised or pseudorandomised trials aimed at summarising the effectiveness and safety of artemisinin drugs for treating severe falciparum malaria in adults and children. Survival was better with artemisinin drugs in 1.265 patients compared with 1.183 treated with quinine (OR: 0.68; 95% CI: 0.55-0.84). However, the difference is barely significant when only studies with adequate concealment of allocation at enrolment are included in the analysis (OR: 0.77; 95% CI: 0.61-0.98). In 1784 patients with cerebral malaria, mortality was also lower with artemisinin drugs overall (OR: 0.70; 95% CI: 0.55-0.90), but not significantly better than quinine in studies reporting adequate concealment of allocation. No difference in neurological sequelae has been demonstrated. Artemisinin drugs clear parasites from the blood faster than quinine. Adverse effects are similarly common with artemisinin drugs and quinine, although reporting varies between trials. There is no evidence from this review that any one artemisinin derivative is better than the others, but comparative studies are few, small and heterogeneous.

10212900
McIntosh HM, Olliaro P
Treatment of uncomplicated malaria with artemisinin derivatives. A systematic review of randomised controlled trials.
Med Trop (Mars). 1998;58(3 Suppl):57-8.
This systematic review of randomised or pseudorandomised trials was aimed at summarising the effectiveness and safety of artemisinin drugs for treating uncomplicated falciparum malaria. Ninety-three potentially eligible studies were identified and 38 met the inclusion criteria. Most data are from Southeast Asian areas of mefloquine-resistant falciparum malaria, Thailand in particular. Artemisinin drugs achieve high cure rates at follow-up in all endemic areas represented by the studies included provided that the duration of treatment is adequate. Combination with mefloquine improves sustained parasite clearance and is effective in multidrug resistant areas. Provided the dose of both drugs is adequate, the combination can shorten the duration of treatment. There is no evidence from randomised trials that any artemisinin derivative is better than the others. Data from just over 4,300 patients are included for analysis in this review. Despite the large amount of clinical research that has been done, variation in study design, quality and comparisons make synthesis of the data problematic. It is extremely difficult to draw clear conclusions from the existing database.

16506047
Mehlotra RK, Ziats MN, Bockarie MJ, Zimmerman PA
Prevalence of CYP2B6 alleles in malaria-endemic populations of West Africa and Papua New Guinea.
Eur J Clin Pharmacol. 2006 Feb 28;.
OBJECTIVE: Cytochrome P450 2B6 (CYP2B6) is involved in the metabolism of artemisinin drugs, a novel series of antimalarials. Our aim was to analyze the prevalence of the most commonly observed CYP2B6 alleles in malaria-endemic populations of West Africa (WA) and Papua New Guinea (PNG). METHODS: Using a post-PCR ligation detection reaction-fluorescent microsphere assay, frequencies of CYP2B6*1A, *2, *3, *4, *5, *6, *7, and *9 were determined in WA (n=166) and PNG (n=174). To compare with the results of previous studies, we also determined the allele frequencies in 291 North Americans of various ethnic groups. RESULTS: Significant differences were observed between WA and PNG for the frequencies of alleles CYP2B6*1A (45% vs 33%, P = 0.003), *2 (4% vs. 0%, P

11590286
Mehta KS, Halankar AR, Makwana PD, Torane PP, Satija PS, Shah VB

Severe acute renal failure in malaria.
J Postgrad Med. 2001 Jan-Mar;47(1):24-6.
BACKGROUND: We have noticed a recent rise in the incidence and severity of acute renal failure (ARF) in malaria. AIM: To study the incidence, severity and outcome of ARF in malaria. SETTING and DESIGN: It is a retrospective analysis of data of one year from a tertiary medical centre in a metropolitan city. MATERIALS AND METHODS: Patients with ARF and smear positive malaria were evaluated. STATISTICAL ANALYSIS: Results were expressed as mean, range and standard deviation. RESULTS: Out of 402 detected smear positive malaria, 24 had ARF. Eighteen were of the age group 21-40 years. Plasmodium falciparum (PF) was detected in 16, Plasmodium vivax in three, and mixed infection in five. Non-oliguric ARF was seen in 14. Eighteen showed severe ARF (Serum creatinine >5 mg%). Twenty-two patients needed dialysis. Prolonged ARF lasting for 2-6 weeks was seen in eight. Seventeen patients recovered completely, while seven showed fatal combination of disseminated intravascular coagulation (DIC), acute respiratory distress syndrome (ARDS), severe ARF and PF malaria. No response was seen to chloroquine and artesunate given alone and twenty patients required quinine. CONCLUSION: ARF necessitating dialysis was seen in 92% of patients with ARF in malaria. PF infection, severe ARF, DIC and ARDS were poor prognostic factors. Resistance was noted to both chloroquine and artesunate.

16103582
Menard D, Djalle D, Manirakiza A, Yapou F, Siadoua V, Sana S, Matsika-Claquin MD, Nestor M, Talarmin A
Drug-resistant malaria in Bangui, Central African Republic: an in vitro assessment.
Am J Trop Med Hyg. 2005 Aug;73(2):239-43.
We used an in vitro isotopic drug sensitivity assay to assess the sensitivity of Plasmodium falciparum isolates collected in Bangui, Central African Republic between March and July 2004. We tested antimalarials that are currently in use in this country (chloroquine, amodiaquine, quinine, and pyrimethamine), antimalarials that will become available in this region in the future (artemisinin and halofantrine), and prophylactic antimalarials (mefloquine, doxycycline, and atovaquone). The proportions of resistant isolates were 37% for chloroquine, 15.9% for amodiaquine, 0% for quinine, 0% for dihydroartemisinin, 1.6% for mefloquine, 3.8% for halofantrine, 4.0% for atovaquone, and 38.3% for pyrimethamine. No multi-resistant isolates (showing resistance to more than three drugs) were found. A positive correlation was found between the 50% inhibitory concentrations values for the following drugs: chloroquine and amodiaquine; quinine and halofantrine; chloroquine and dihydroartemisinin; chloroquine and halofantrine; amodiaquine and dihydroartemisinin; dihydroartemisinin and mefloquine; chloroquine and quinine; and quinine and dihydroartemisinin. These findings suggest that the Ministry of Health should recommend a interim policy with the amodiaquine plus sulfadoxine-pyrimethamine combination as the first-line antimalarial drug in Bangui until better alternative treatments such as artemisinin-based combination therapies become available at low prices in the Central African Republic.

15940847
Menard D, Madji N, Manirakiza A, Djalle D, Koula MR, Talarmin A
Efficacy of chloroquine, amodiaquine, sulfadoxine-pyrimethamine, chloroquine-sulfadoxine-pyrimethamine combination, and amodiaquine-sulfadoxine-pyrimethamine combination in Central African children with noncomplicated malaria.
Am J Trop Med Hyg. 2005 May;72(5):581-5.
This paper reports a two-phase study in Bangui, Central African Republic (CAR): first, we assessed the clinical efficacy to chloroquine (CQ), sulfadoxine-pyrimethamine (SP), and amodiaquine (AQ), then we tested the efficacy of two combinations: CQ + SP and AQ + SP. We used the standard 14-day WHO 2001 protocol to compare therapeutic responses in children under 5 years of age with acute uncomplicated Plasmodium falciparum malaria in Bangui between February 2002 and March 2004. The overall treatment failure rates with CQ, AQ, SP, CQ + SP, and AQ + SP were 40.9%, 20.0%, 22.8%, 7.2%, and 0%. These findings suggest that the Ministry of Health should recommend an interim policy with AQ + SP combination as the first-line antimalarial drug in Bangui until best alternative treatments like artemisinin-based combination therapies (ACTs) become available at low prices in the CAR.

16172492
Menard D, Matsika-Claquin MD, Djalle D, Yapou F, Manirakiza A, Dolmazon V, Sarda J, Talarmin A
Association of failures of seven-day courses of artesunate in a non-immune population in Bangui, Central African Republic with decreased sensitivity of Plasmodium falciparum.
Am J Trop Med Hyg. 2005 Sep;73(3):616-21.
We assessed the efficacy and safety of a seven-day course of artesunate for the treatment of uncomplicated Plasmodium falciparum malaria in 55 non-immune patients living in Bangui, Central African Republic. The parasitologic cure rates were 100%, 95%, and 85% on days 14, 28, and 42, respectively. There were no significant differences in parasitemia density, 50% inhibitory concentration of dihydroartemisinin, and

frequency of mutant P. falciparum multidrug resistance 1 codon 86 between patients who were cured and those who displayed recrudescence. However, the 90% inhibitory concentration for dihydroartemisinin and the number of genotypes isolated were both higher in the recrudescent patients (five- and two-fold, respectively). We found an association between recrudescence and decreased sensitivity. This suggests that the use of artemisinin compounds alone will select resistant strains. We conclude that artesunate should not be used in monotherapy even in seven-day courses, but only in combination with other anti-malarials to prevent the emergence of resistant P. falciparum.

10212891
Meshnick SR
Artemisinin antimalarials: mechanisms of action and resistance.
Med Trop (Mars). 1998;58(3 Suppl):13-7.
Artemisinin derivatives are an important new class of antimalarial agents. These compounds contain endoperoxide bridges which are essential for antimalarial activity. Artemisinin is believed to act via a two-step mechanism. Artemisinin is first activated by intraparasitic heme-iron which catalyzes the cleavage of this endoperoxide. A resulting free radical intermediate may then kill the parasite by alkylating and poisoning one or more essential malarial protein(s). No clinically relevant artemisinin-resistant human malaria has yet been reported. However, an artemisinin-resistant strain of murine malaria has been developed and may offer clues to the kinds of resistance that may someday develop in human malarias.

12435450
Meshnick SR
Artemisinin: mechanisms of action, resistance and toxicity.
Int J Parasitol. 2002 Dec 4;32(13):1655-60.
Artemisinin and its derivatives are widely used throughout the world. The mechanism of action of these compounds appears to involve the heme-mediated decomposition of the endoperoxide bridge to produce carbon-centred free radicals. The involvement of heme explains why the drugs are selectively toxic to malaria parasites. The resulting carbon-centred free radicals are alkylate heme and proteins, one of which is the translationally controlled tumour protein. Clinically relevant artemisinin resistance has not been demonstrated, but it is likely to occur since artemisinin resistance has been obtained in laboratory models. At high doses, artemisinin can be neurotoxic but toxicity has not been found in clinical studies. The mechanism of neurotoxicity may be similar to the mechanism of action.

8801435
Meshnick SR, Taylor TE, Kamchonwongpaisan S
Artemisinin and the antimalarial endoperoxides: from herbal remedy to targeted chemotherapy.
Microbiol Rev. 1996 Jun;60(2):301-15.
Artemisinin and its derivatives are endoperoxide-containing compounds which represent a promising new class of antimalarial drugs. In the presence of intraparasitic iron, these drugs are converted into free radicals and other electrophilic intermediates which then alkylate specific malaria target proteins. Combinations of available derivatives and other antimalarial agents show promise both as first-line agents and in the treatment of severe disease.

9132599
Miller LG, Panosian CB
Ataxia and slurred speech after artesunate treatment for falciparum malaria.
N Engl J Med. 1997 May 1;336(18):1328.

15999841
Millet P
[The future outlook of antimalarials]
Rev Prat. 2005 Apr 30;55(8):875-9.
Spreading of resistance to chloroquine in the early 1960's had a dramatic impact on malaria treatment worldwide. The development of new antimalarial drugs, at first driven by political interests, is now centred on the need to limit disease extension due to a strong sensibilisation by NGO and the medias. Difficulties in using antimalarial drugs are mostly the result of geographic variabilities of drug resistance of Plasmodium falciparum to existing drugs, implying a decision "a la carte" for malaria treatment in each endemic country. To fight against resistance situations, the NGO Medecins sans frontieres and the World Health Organization have launched the concept of multiple antimalarial drug therapies based on artemisinin derivatives. Such strategy has been initiated in order to limit extension of drug resistance to existing antimalarial treatments,

waiting for a new innovative drug able to provide a "universal" treatment worldwide which does not exist at present.

10656043
Mishra SK, Mohanty S
Ptyalism as a side effect in the treatment of falciparum malaria with artemisinin.
Ann Trop Med Parasitol. 1999 Jun;93(4):413-4.

11068361
Mizuno Y, Ohtomo H, Kimura M, Takeuchi T
[Studies on current trend of imported malaria in Japan--pediatric cases in recent 20 years]
Kansenshogaku Zasshi. 2000 Sep;74(9):694-8.
Imported malaria has been increasing according to the recent globalization of Japan. There are about 120 clinical cases of malaria which include a few pediatric cases (approximately 1%) every year. Generally, pediatric cases often have an atypical onset and course compared to adult cases, and also develop serious and fatal effects in a short time. In this study, we examined imported malaria cases in subjects under 15 years old from 1980 to 1999 conducted by Research group on clinical evaluation against orphan drugs in the treatment of imported tropical diseases and parasitic diseases. During the 20 years we found 44 clinical cases in children. Of these 70% were foreign cases. Among the species of parasites, there were 21 cases of Vivax malaria and 17 cases of Falciparum malaria and a few cases of Malariae and Ovale malaria were also found, which is rare even in adults. Concerning the drugs chosen in Japan for chemotherapy to treat malaria, chloroquine and primaquine seemed to be employed most frequently before 1990, however mefloquine or artesunate seemed to be more common after 1990. Also, most pediatric cases were former residents or refugees from tropical countries, however some cases were in Japanese children who had recently visited those areas with their families. There have been no fatalities in pediatric cases of malaria, however tropical diseases, including malaria, must be rule out, when examining pyretic children, considering the number of travelers going abroad has been increasing.

15941413
Mockenhaupt FP, Ehrhardt S, Dzisi SY, Teun Bousema J, Wassilew N, Schreiber J, Anemana SD, Cramer JP, Otchwemah RN, Sauerwein RW, Eggelte TA, Bienzle U
A randomized, placebo-controlled, double-blind trial on sulfadoxine-pyrimethamine alone or combined with artesunate or amodiaquine in uncomplicated malaria.
Trop Med Int Health. 2005 Jun;10(6):512-20.
The therapeutic efficacy of sulfadoxine-pyrimethamine (SP) alone, SP plus amodiaquine (AQ), and SP plus artesunate (AS) was assessed in a randomized, placebo-controlled, and double-blind trial among 438 children with uncomplicated Plasmodium falciparum malaria in northern Ghana. Clinical and parasitological responses were monitored for 28 days following treatment; 86%, 98% and 97% of SP-, SP + AQ-, and SP + AS-treated patients achieved adequate clinical and parasitological response (ACPR) within 2 weeks, respectively. Parasite clearance was better with SP + AS than with SP or SP + AQ treatment but re-infections were more common. Polymerase chain reaction (PCR)-corrected rates of ACPR at day 28 were 72.2% for SP, 94.1% for SP + AQ ($P < 0.0001$), and 94.5% for SP + AS ($P < 0.0001$). Gametocyte prevalence and density 1 week after treatment were highest in children treated with SP, and lowest in patients receiving SP + AS. No severe adverse events attributable to study medication were observed. In northern Ghana, more than one of four children suffered SP treatment failure within 4 weeks. Both SP + AQ and SP + AS are efficacious alternative therapeutic options in this region. Although SP + AS and SP + AQ treatments have virtually identical cure rates, rapid parasite clearance and pronounced gametocidal effects are the advantages of the former, whereas cost and a lower rate of late re-infections are those of the latter.

16417707
Mohamed AO, Eltaib EH, Ahmed OA, Elamin SB, Malik EM
The efficacies of artesunate-sulfadoxine-pyrimethamine and artemether-lumefantrine in the treatment of uncomplicated, Plasmodium falciparum malaria, in an area of low transmission in central Sudan.
Ann Trop Med Parasitol. 2006 Jan;100(1):5-10.
In an efficacy trial of artemisinin-based combination treatments (ACT) in central Sudan, cases of uncomplicated, Plasmodium falciparum malaria were given artesunate-sulfadoxine-pyrimethamine (ASP) or artemether-lumefantrine (AL) as first-line treatment. On enrolment, the 71 patients given ASP were similar to the 72 given AL, apart from having generally lower parasitaemias (geometric mean counts of 4893 nu. 10,215 asexual parasites/microl) and having a lower mean age (15 nu. 23 years). Each patient was treated on days 0, 1 and 2, and all 137 who completed follow-up without further, unscheduled treatment were found aparasitaemic and afebrile from day 2 until the last follow-up, on day 28. No moderate or severe adverse

side-effects, clinical failures or parasitological failures were observed among these 137 patients. ACT therefore appear both efficacious and safe for the treatment of uncomplicated malaria in central Sudan.

15107507
Mohanty AK, Rath BK, Mohanty R, Samal AK, Mishra K
Randomized control trial of quinine and artesunate in complicated malaria.
Indian J Pediatr. 2004 Apr;71(4):291-5.
OBJECTIVE: To study the comparative efficacy of the quinine and artesunate in complicated malaria in children. METHODS: All cases admitted to the Pediatrics ward of our hospital with clinical features of complicated malaria (WHO criteria) having asexual forms of P. falciparum in the peripheral smear, were included in the study. Relevant investigations were carried out for confirmation of diagnosis and to assess the prognosis. The patients were sub-grouped into 6 categories as per clinical presentations and each subgroup received alternatively either quinine or artesunate by systematic random sample method. Every odd number received quinine (Group-1) and every even number received artesunate (Group-2). 40 cases in each group were considered for the study and the data obtained were compiled and analyzed by suitable statistical tests. RESULTS: 80 children with complicated malaria enrolled in the present study, of which 48 were boys and 32 were girls. The mean age was 7.93+3.56 years. The most common presentations were fever, splenomegaly and altered sensorium. The CRT, FCT and PCT were significantly less in the artesunate group (50.4 +/- 31.49 hrs; 43.55 +/- 20.12 hrs, and 41.67 +/- 16.78 hrs respectively) as compared to the quinine group (70.15 +/- 17.56 hrs, 62.23 +/- 16.99 hrs, and 52.24 +/- 12.69 hrs respectively) (p

9231210
Mohanty S, Mishra SK, Satpathy SK, Dash S, Patnaik J
alpha, beta-Arteether for the treatment of complicated falciparum malaria.
Trans R Soc Trop Med Hyg. 1997 May-Jun;91(3):328-30.
alpha, beta-Arteether is an ethyl ether derivative of artemisinin which is an efficient schizontocidal drug in mild falciparum malaria. The present study reports the efficacy of the drug in severe falciparum malaria. Fifty patients with severe falciparum malaria were given intramuscular arteether, 150 mg, once daily on 3 consecutive days. The median fever clearance time was 72 h (range 12-120 h) and the median parasite clearance time was 2 d (range 1-4 d). Rapid recovery from coma was observed in cerebral malaria patients (after a median of 18 h, range 6-72 h). The recovery from other complications was also faster and complete. Two patients died; both had cerebral malaria and haemolytic jaundice, one had respiratory distress needing ventilatory support and the other had severe anaemia. Recrudescence within 28 d was observed in 7 patients. Drug toxicity or significant side effects were not noticed in any patient.

9629623
Mordmuller B, Graninger W, Kremsner PG
[Malaria therapy in the era of chloroquine resistance]
Wien Klin Wochenschr. 1998 May 8;110(9):321-5.
Despite few efforts to develop new antimalarial compounds by the major pharmaceutical companies, some promising new therapeutics have been developed and tested clinically by small groups and companies throughout the world. Really new substances are scarce but combinations of known medicarnents have been shown to be a rational and effective approach to overcome problems with single compounds. Additionally, combination regimens are more easily authorized and accepted for treatment than completely new substances. Some examples in this respect are combinations of either atovaquone, doxycycline or clindamycin with a 'classical' antimalarial. Artemisinin, benflumetol and pyronaridine were originally developed in China and disperse currently to the rest of the world. First independent and international clinical trials gave promising results and one should bear in mind those substances for future applications. Especially artemisinin and its derivatives are of great interest because they represent, besides quinine, the only other therapeutic option for the treatment of multidrug-resistant severe malaria.

16282381
Morel CM, Lauer JA, Evans DB
Cost effectiveness analysis of strategies to combat malaria in developing countries.
BMJ. 2005 Dec 3;331(7528):1299. Epub 2005 Nov 10.
OBJECTIVE: To determine the cost effectiveness of selected malaria control interventions in the context of reaching the millennium development goals for malaria. DESIGN: Generalised cost effectiveness analysis. DATA SOURCES: Efficacy data came from the literature and authors' calculations supported by expert opinion. Quantities for resource inputs came from the literature and from expert opinion; prices came from the WHO-CHOICE database. METHODS: Costs were assessed in year 2000 international dollars, and effects were assessed as disability adjusted life years averted by a 10 year implementation programme. Analysis was restricted to sub-Saharan regions where the most deadly form of malaria, Plasmodium falciparum, is most prevalent. The impact on population health for various interventions, and their

combinations, was evaluated at selected coverage levels by using a state-transition model. Sensitivity analysis was done for age weights and discounting. RESULTS: High coverage with artemisinin based combination treatments was found to be the most cost effective strategy for control of malaria in most countries in sub-Saharan Africa. CONCLUSIONS: A much larger infusion of resources than those currently available is needed to make headway in the fight to roll back malaria. On cost effectiveness grounds, in most areas in sub-Saharan Africa greater coverage with highly effective combination treatments should be the cornerstone of malaria control. However, treatment alone can achieve less than half the total benefit obtainable through a combination of interventions-scaling up the use of impregnated mosquito nets or indoor spraying with insecticides is also critical. Intermittent presumptive treatment of pregnant women can bring a small but important additional health gain at relatively low cost.

8926885
Morillon M, Baudon D, Dai B
[Malaria in Vietnam in 1996: brief synthesis of epidemiological data]
Med Trop (Mars). 1996;56(2):197-200.
Vietnam is in a tropical region where malaria is considered as a public health problem. Plasmodium falciparum is responsible for 72% of cases of malaria and Plasmodium vivax for 28%. Analysis of available data shows that the situation is complex. The overall incidence of malaria is low, i.e. approximately 8.5: 1000 in 1995 but the disease is unevenly distributed over the country which has a variety of terrain and climates. Hilly and mountainous areas are the most affected especially in the center of the country where the annual incidence can exceed 10%. In most provinces, the majority of people are not immunized and malaria is unstable. Emergence of chemoresistant parasites is a major problem. Resistance rates of Plasmodium falciparum ranges from 40.78% to 61.67% for chloroquine and from 25.80% to 47.40% for sulfamides. Locally produced artemisinin derivatives are being more and more widely used in order to cope with this problem local. Given the great epidemiological variability of malaria in Vietnam, careful analysis needed before attempting any type of group and individual prophylaxis.

15278440
Moritz E, Seidensticker S, Gottwald A, Maier W, Hoerauf A, Njuguna JT, Kaiser A
The efficacy of inhibitors involved in spermidine metabolism in Plasmodium falciparum, Anopheles stephensi and Trypanosoma evansi.
Parasitol Res. 2004 Sep;94(1):37-48. Epub 2004 Jul 29.
In the present study, we have tested the effect of different polyamine inhibitors of the spermidine metabolizing enzymes deoxyhypusine synthase and homospermidine synthase in different chloroquine resistant Plasmodium falciparum strains, in the mosquito Anopheles stephensi (Diptera: Culicidae) and in a Trypanosoma evansi clone I from strain STIB 806 K China. Recent experiments have shown that agmatine is a growth inhibitor of the malaria parasite P. falciparum (Kaiser et al. 2001) in vitro. A comparison of agmatine efficacy with the new antimalarials artemisinin, triclosan and conventional chloroquine showed similar or even better results on the basis of growth inhibition and the reduction of developmental forms. However, no effect of triclosan or agmatine was observed at the ribonucleic acid level. In a second set of experiments, we tested the effect of 1,7-diaminoheptane and agmatine on oocyst formation in A. stephensi after infection with Plasmodium yoelii. Agmatine had an antisporozoite effect since 1,000 microM led to a 59.5% inhibition of oocysts. A much weaker inhibitor of oocyst formation was 1,7-diaminoheptane. The most effective in in vitro inhibition of T. evansi was dicyclohexylamine, an inhibitor of spermidine biosynthesis with an IC(50) value of 47.44 microM and the deoxyhypusine inhibitor 1,7-diaminoheptane with an IC(50) value of 47.80 microM. However, both drugs were ineffective in in vivo experiments in a Trypanosoma mouse model. Two different spermidine analogues, 1,8-diaminooctane and 1,3-diaminopropane with IC(50) values of 171 microM and 181.37 microM, respectively, were moderate inhibitors in vitro and ineffective in vivo.

12617695
Mturi N, Musumba CO, Wamola BM, Ogutu BR, Newton CR
Cerebral malaria: optimising management.
CNS Drugs. 2003;17(3):153-65.
Cerebral malaria is one of the most common nontraumatic encephalopathies in the world. Children living in sub-Saharan Africa bear the brunt of the disease, but cerebral malaria is being seen increasingly in adults throughout the world, including outside malarious areas. There are differences in the clinical presentation and pathophysiology between African children and nonimmune adults from any region. Mortality is high (10-20%). Parenteral antimalarials are the only interventions that have been shown to affect outcome. The cinchona alkaloids (quinine and quinidine) are the mainstay of antimalarial treatment, but the artemisinin derivatives are increasingly being used. Aggressive treatment and prevention of convulsions may be important, particularly in children. Other ancillary treatments that can be used to augment standard antimalarial drugs, such as exchange blood transfusions, osmotic diuretics and pentoxifylline, may improve outcome but have not been subjected to rigorous clinical trials. There is little support for corticosteroids or

deferoxamine (desferrioxamine) in cerebral malaria. Other adjuncts have not been adequately tested. Further research is required on drugs that interfere with the pathophysiological processes to prevent neurological complications and death.

16242017
Mubyazi GM, Gonzalez-Block MA
Research influence on antimalarial drug policy change in Tanzania: case study of replacing chloroquine with sulfadoxine-pyrimethamine as the first-line drug.
Malar J. 2005 Oct 20;4:51.
INTRODUCTION: Research is an essential tool in facing the challenges of scaling up interventions and improving access to services. As in many other countries, the translation of research evidence into drug policy action in Tanzania is often constrained by poor communication between researchers and policy decision-makers, individual perceptions or attitudes towards the drug and hesitation by some policy decision-makers to approve change when they anticipate possible undesirable repercussions should the policy change as proposed. Internationally, literature on the role of researchers on national antimalarial drug policy change is limited. OBJECTIVES: To describe the (a) role of researchers in producing evidence that influenced the Tanzanian government replace chloroquine (CQ) with sulfadoxine-pyrimethamine (SP) as the first-line drug and the challenges faced in convincing policy-makers, general practitioners, pharmaceutical industry and the general public on the need for change (b) challenges ahead before a new drug combination treatment policy is introduced in Tanzania. METHODS: In-depth interviews were held with national-level policy-makers, malaria control programme managers, pharmaceutical officers, general medical practitioners, medical research library and publications officers, university academicians, heads of medical research institutions and district and regional medical officers. Additional data were obtained through a review of malaria drug policy documents and participant observations were also done. RESULTS: In year 2001, the Tanzanian Government officially changed its malaria treatment policy guidelines whereby CQ--the first-line drug for a long time was replaced with SP. This policy decision was supported by research evidence indicating parasite resistance to CQ and clinical CQ treatment failure rates to have reached intolerable levels as compared to SP and amodiaquine (AQ). Research also indicated that since SP was also facing rising resistance trend, the need for a more effective drug was indispensable but for an interim 5-10 year period it was justifiable to recommend SP that was relatively more cost-effective than CQ and AQ. The government launched the policy change considering that studies (ethically approved by the Ministry of Health) on therapeutic efficacy and cost-effectiveness of artemisinin drug combination therapies were underway. Nevertheless, the process of communicating research results and recommendations to policy-making authorities involved critical debates between policy makers and researchers, among the researchers themselves and between the researchers and general practitioners, the speculative media reports on SP side-effects and reservations by the general public concerning the rationale for policy change, when to change, and to which drug of choice. CONCLUSION: Changing national drug policy will remain a sensitive issue that cannot be done overnight. However, to ensure that research findings are recognised and the recommendations emanating from such findings are effectively utilized, a systematic involvement of all the key stakeholders (including policy-makers, drug manufacturers, media, practitioners and the general public) at all stages of research is crucial. It also matters how and when research information is communicated to the stakeholders. Professional organizations such as the East African Network on Malaria Treatment have potential to bring together malaria researchers, policy-makers and other stakeholders in the research-to-drug policy change interface.

11091003
Mueller MS, Karhagomba IB, Hirt HM, Wemakor E
The potential of Artemisia annua L. as a locally produced remedy for malaria in the tropics: agricultural, chemical and clinical aspects.
J Ethnopharmacol. 2000 Dec;73(3):487-93.
The plant Artemisia annua L. (Asteraceae) is listed in the Chinese pharmacopoeia as a remedy for various fevers including malaria, and contains the well-established antimalarial compound artemisinin. In this study, a hybrid form of A. annua was successfully cultivated in Central Africa. The aerial parts of the plant contained 0.63-0.70% artemisinin per dry weight, and approximately 40% of this artemisinin could be extracted by simple tea preparation methods. Five malaria patients who were treated with A. annua tea showed a rapid disappearance of parasitaemia within 2-4 days. An additional trial with 48 malaria patients showed a disappearance of parasitaemia in 44 patients (92%) within 4 days. Both trials showed a marked improvement of symptoms. In our opinion, these results justify further examinations of the antimalarial effect of A. annua preparations.

15109558
Mueller MS, Runyambo N, Wagner I, Borrmann S, Dietz K, Heide L

Randomized controlled trial of a traditional preparation of Artemisia annua L. (Annual Wormwood) in the treatment of malaria.
Trans R Soc Trop Med Hyg. 2004 May;98(5):318-21.
The Chinese medicinal plant Artemisia annua L. (Annual Wormwood) contains the antimalarial compound artemisinin. The locally grown herb may offer an additional tool for the control of malaria, especially in poor countries where modern antimalarial drugs are often unavailable. In an open, randomized, controlled pilot trial, we investigated the efficacy and safety of traditional tea preparations of Artemisia annua in the treatment of uncomplicated malaria. Treatment resulted in a quick resolution of parasitaemia and of clinical symptoms. After 7 d of medication, cure rates were on average 74% for the Artemisia preparations compared with 91% for quinine. However, recrudescence rates were high in the Artemisia groups. Therefore, monotherapy with Artemisia annua L. cannot be recommended as alternative to modern antimalarials, but may deserve further investigation.

15361108
Muheki C, McIntyre D, Barnes KI
Artemisinin-based combination therapy reduces expenditure on malaria treatment in KwaZulu Natal, South Africa.
Trop Med Int Health. 2004 Sep;9(9):959-66.
INTRODUCTION: There is growing international evidence that artemisinin-based combination therapy (ACT) is one of the few effective measures available to 'Roll Back Malaria'. However, concerns about the costs and affordability of ACT are obstacles to its widespread implementation. This paper explores some economic aspects of the implementation of artemether-lumefantrine (AL) to replace sulphadoxine-pyrimethamine (SP) in the KwaZulu Natal (KZN) province, South Africa. METHODS: Recurrent and capital costs for malaria treatment were compared at baseline and post-intervention for nine clinics and a sentinel rural district hospital. Changes in the unit costs of, and total expenditure on, malaria services were calculated and the cost effectiveness of AL relative to SP was assessed. RESULTS: The number of outpatient malaria cases and inpatient admissions both declined by 94% between 2000 and 2002. After accounting for the role of concurrent improvements in vector control, it was conservatively estimated that 36% of the decline in outpatient cases and 46% for inpatient admissions was attributable to changing the first-line drug to AL. Although AL is considerably more expensive than SP, its improved cure rate and reduced malaria transmission resulted in an estimated 201,065 US dollars cost saving in 2002 alone for the subdistrict studied. DISCUSSION: In the context of effective vector control and low efficacy of existing monotherapy, ACT can reduce total expenditure on malaria services. However, the relevance of these findings requires careful consideration in countries with currently effective treatment policies and higher intensity malaria transmission.

11807801
Mukanganyama S, Widersten M, Naik YS, Mannervik B, Hasler JA
Inhibition of glutathione S-transferases by antimalarial drugs possible implications for circumventing anticancer drug resistance.
Int J Cancer. 2002 Feb 10;97(5):700-5.
A strategy to overcome multidrug resistance in cancer cells involves treatment with a combination of the antineoplastic agent and a chemomodulator that inhibits the activity of the resistance-causing protein. The aim of our study was to investigate the effects of antimalarial drugs on human recombinant glutathione S-transferase (GSTs) activity in the context of searching for effective and clinically acceptable inhibitors of these enzymes. Human recombinant GSTs heterologously expressed in Escherichia coli were used for inhibition studies. GST A1-1 activity was inhibited by artemisinin with an IC(50) of 6 microM, whilst GST M1-1 was inhibited by quinidine and its diastereoisomer quinine with IC(50)s of 12 microM and 17 microM, respectively. GST M3-3 was inhibited by tetracycline only with an IC(50) of 47 microM. GST P1-1 was the most susceptible enzyme to inhibition by antimalarials with IC(50) values of 1, 2, 1, 4, and 13 microM for pyrimethamine, artemisinin, quinidine, quinine and tetracycline, respectively. The IC(50) values obtained for artemisinin, quinine, quinidine and tetracycline are below peak plasma concentrations obtained during therapy of malaria with these drugs. It seems likely, therefore, that GSTs may be inhibited in vivo at doses normally used in clinical practice. Using the substrate ethacrynic acid, a diuretic drug also used as a modulator to overcome drug resistance in tumour cells, GST P1-1 activity was inhibited by tetracycline, quinine, pyrimethamine and quinidine with IC(50) values of 18, 27, 45 and 70 microM, respectively. The ubiquitous expression of GSTs in different malignancies suggests that the addition of nontoxic reversing agents such as antimalarials could enhance the efficacy of a variety of alkylating agents.

15569805
Murray CK, Ellis MW, Hospenthal DR
Susceptibility of Leptospira serovars to antimalarial agents.
Am J Trop Med Hyg. 2004 Nov;71(5):685-6.

Leptospirosis has recently been described to cause concomitant infection with malaria. Only doxycycline has proven to have chemoprophylactic and therapeutic efficacy for both malaria and leptospirosis. To assess whether other traditional antimalarial agents have antileptospiral activity, we performed broth microdilution susceptibility testing of 16 Leptospira serovars (6 species/14 serogroups) to various agents. Artemisinin, atovaquone, chloroquine, mefloquine, primaquine, proguanil, pyrimethamine, sulfadoxine, quinine, quinidine, and combinations of atovaquone/proguanil and pyrimethamine/sulfadoxine all had a 90% minimum inhibitory concentration (MIC(90)) > 25 microg/mL (the upper limit of testing). The only agents identified with the potential to treat both infections other than doxycycline (MIC(90) = 1.56 microg/mL) were azithromycin (MIC(90) = 0.002 microg/mL) and clindamycin (MIC(90) = 0.2 microg/mL).

16098946
Mutabingwa TK
Artemisinin-based combination therapies (ACTs): best hope for malaria treatment but inaccessible to the needy!
Acta Trop. 2005 Sep;95(3):305-15.
Artemisinin-based combination therapies (ACTs) are the best anti-malarial drugs available now. Artemisinin enhances efficacy and has the potential of lowering the rate at which resistance emerges and spreads. Under low transmission intensity, ACTs have an additional public health benefit of reducing the overall malaria transmission and studies are urgently needed to investigate modalities of attaining similar benefits under high transmission. Despite being recommended by WHO since 2001, overall deployment of ACT has been slow. Limiting factors are high cost, limited knowledge and public awareness on the concept of combination therapy (CT) and ACT in particular, limited knowledge on safety of ACTs in pregnancy, operational issue such as inappropriate drug use, lack of suitable drug formulations, lack of post-marketing surveillance (PMS) systems, and the imbalance between demand and supply. Through concerted efforts of multilateral organizations, the local scientific community with involvement of policy-makers progress has been on several fonts leading to improved ACT uptake rates in the last 2 years. Of 43 countries that had adopted ACT by February 2005, 18 (42%) adopted the policy in 2004. Preference to co-formulated Coartem has led to a surge in its demand with consequent shortage. Alternative ways for increased production of ACTs are urgently needed otherwise most policies will remain adopted on paper. Despite limitations, opportunities are opening up for effective malaria control. Insecticides, insecticide-treated nets (ITNs) and ACTs are proven efficacious controls available that should be accessed by many. Substantial funding is now available for biomedical malaria research and for policy implementation. While the Global Fund is the financial engine behind the scaling up of ACT uptake, delays in cash flow after grant approval has led to many countries adopting ACT in 2004 but only few (nine) implementing it. Clear policies on granted funds and minimal politics within funding agencies might improve the situation. Increased interest in drug development together with the public and private sector partnership have led to new anti-malarials, some less expensive and therefore affordable by poor malaria endemic countries. Dihydroartemisinin-piperaquine (Artekin) has a cost advantage over other ACTs (USD 1 for an adult treatment) making it a potential best candidate for deployment in Africa. Part of available funds should be invested into capacity building and strengthening (personnel, resources and infrastructure) of institutions in malaria endemic countries. This will create enabling environment and a critical mass of scientists and public health experts to spearhead ACT policy implementation. Active involvement of scientists from malaria endemic countries in recent International Scientific Forums like the Malaria in Pregnancy Working Group and the Consortium on ACT Implementation is the best way forward to emulate.

15850631
Mutabingwa TK, Anthony D, Heller A, Hallett R, Ahmed J, Drakeley C, Greenwood BM, Whitty CJ
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 Apr 23-29;365(9469):1474-80.
BACKGROUND: Many countries in Africa are considering a change to combination treatment for falciparum malaria because of the increase in drug resistance. However, there are few effectiveness data for these combinations. Our aim was to study the effectiveness of three drug combinations that have proven efficacious in east Africa compared with amodiaquine monotherapy. METHODS: We undertook a randomised trial of antimalarial drug combinations for children (aged 4-59 months) with uncomplicated malaria in Muheza, Tanzania, an area with a high prevalence of resistance to sulfadoxine-pyrimethamine and chloroquine. Children were randomly allocated 3 days of amodiaquine (n=270), amodiaquine +sulfadoxine-pyrimethamine (n=507), or amodiaquine+artesunate (n=515), or a 3-day six-dose regimen of artemether-lumefantrine (n=519). Drugs were taken orally, at home, unobserved by medical staff. The primary endpoint was parasitological failure by day 14 assessed blind to treatment allocation. Secondary endpoints included day 28 follow-up and gametocyte carriage. Analysis was by intention to treat. FINDINGS: Of 3158 children screened, 1811 were randomly assigned treatment and 1717 (95%) reached the 14-day

follow-up. The amodiaquine group was stopped early by the data and safety monitoring board. By day 14, the parasitological failure rates were 103 of 248 (42%) for amodiaquine, 97 of 476 (20%) for amodiaquine+sulfadoxine-pyrimethamine, 54 of 491 (11%) for amodiaquine+artesunate, and seven of 502 (1%) for artemether-lumefantrine. By day 28, the parasitological failure rates were 182 of 239 (76%), 282 of 476 (61%), 193 of 472 (40%), and 103 of 485 (21%), respectively. The difference between individual treatment groups and the next best treatment combination was significant (p

14964805
Myint HY, Tipmanee P, Nosten F, Day NP, Pukrittayakamee S, Looareesuwan S, White NJ
A systematic overview of published antimalarial drug trials.
Trans R Soc Trop Med Hyg. 2004 Feb;98(2):73-81.
Systematic database searches identified 435 antimalarial drug treatment trials, involving 82,616 patients, conducted and published between 1966 and December 2002. Of these trials 72% were randomised; 64 (15%) trials involved severe malaria, 47 (11%) studied Plasmodium vivax, 3 Plasmodium malariae or Plasmodium ovale, and the remainder (74%) assessed treatment responses in uncomplicated falciparum malaria. Twelve trials (2.7%) specifically evaluated antimalarial treatments in pregnant women. Overall 49% of trials were conducted in Asia (29% from Thailand alone) and 42% in Africa. Half of all the patients studied had been in trials published in the past 7 years. There has been a recent rise in the proportion of trial enrolling children, and a tripling in the average number of patients recruited per trial (from approximately 100 in the 1970s to 300 currently). Chloroquine was given to over half the patients in antimalarial drug trials (n = 53552) compared with artemisinin derivatives (n = 12463), mefloquine-sulphadoxine-pyrimethamine (n = 9153), mefloquine (n = 5546) and sulphadoxine-pyrimethamine (n = 5909). The quality of safety and efficacy data for recently evaluated drugs contrasts with a relative paucity of data for older 'established' compounds.

9516041
Na-Bangchang K, Karbwang J, Congpoung K, Thanavibul A, Ubalee R
Pharmacokinetic and bioequivalence evaluation of two generic formulations of oral artesunate.
Eur J Clin Pharmacol. 1998 Jan;53(5):375-6.

9031394
Na-Bangchang K, Tipwangso P, Thanavibul A, Tan-ariya P, Suprakob K, Kanda T, Karbwang J
Artemether-pyrimethamine in the treatment of pyrimethamine-resistant falciparum malaria.
Southeast Asian J Trop Med Public Health. 1996 Mar;27(1):19-23.
In vitro susceptibility and clinical response of multidrug resistant Plasmodium falciparum to the combination artemether-pyrimethamine were evaluated in patients with acute uncomplicated falciparum malaria. Sixty patients were randomized to receive 3 oral regimens of the combination artemether-pyrimethamine as follows: Regimen-I: artemether (300 mg) plus pyrimethamine (100 mg) on the first day, then placebo on the two consecutive days; Regimen-II: artemether (300 mg) plus pyrimethamine (100 mg) on the first day, then artemether (150 mg) plus pyrimethamine (50 mg) on the second day, and placebo on the third day; Regimen-III: artemether (300 mg) plus pyrimethamine (100 mg) on the first day, then artemether (150 mg) plus pyrimethamine (50 mg) on the second and third days. All patients had a rapid initial response to treatments with 95% of parasitemia being cleared within the first 24 hours. PCT24hours and PCT48hours were similar among the three drug regimens (11 vs 4, 6 vs 12, and 9 vs 11 patients for a 1-day, 2-day, and 3-day combination regimen, respectively). Fever was cleared within 48 hours in all patients in either group. Transient mild nausea, vomiting and loss of appetite were found in a few patients during the first 2 days of treatment. Seven patients did not complete the 28 day follow-up period (5 vs 2 in a 1-day vs 2-day regimen), the reason for withdrawal was not associated with drug-related adverse effects. Only 53 patients were therefore qualified for the efficacy assessment. There was 15, 13 and 5 patients in a 1-day, 2-day and 3-day combination regimens, respectively, who had reappearance of the parasitemia between days 11 and 21. The cure rates of the 3 treatment groups were statistically significantly different (0, 27.8, and 75% for a 1-day, 2-day and 3-day combination regimen, respectively). Two patients developed P. vivax malaria on days 20 and 24. All of the isolates were highly resistant to pyrimethamine, with MIC of 10(-5) M. There is potential advantage of this combination therapy in reducing the dosage and treatment period of artemisinin derivative, which is therefore likely to improve complaince in clinical practice. The use of a 3-day combination regimen (300 mg artemether plus 100 mg pyrimethamine on the first day, then 150 mg artemether plus 50 mg pyrimethamine on the second and third days) seems to be a good alternative regimen to sulfadoxine/ pyrimethamine in areas where P. falciparum is sensitive to pyrimethamine eg in Africa.

15215143
Nacher M, Silachamroon U, Singhasivanon P, Wilairatana P, Phumratanaprapin W, Fontanet A, Looareesuwan S

Comparison of artesunate and chloroquine activities against Plasmodium vivax gametocytes.
Antimicrob Agents Chemother. 2004 Jul;48(7):2751-2.
The gametocidal activities of chloroquine and artesunate were compared. The relative risk (RR) of having detectable gametocytes appear after treatment initiation was lower in artesunate-treated patients (n = 792) than in chloroquine-treated patients (n = 695) (RR = 0.29; 95% CI = 0.2 to 0.40; P < 0.0001). The duration and magnitude of gametocyte carriage were also lower for artesunate than chloroquine. By reducing the transmission of Plasmodium vivax to the vector, artesunate could therefore reduce the incidence of P. vivax malaria.

11069212
Navaratnam V, Mansor SM, Sit NW, Grace J, Li Q, Olliaro P
Pharmacokinetics of artemisinin-type compounds.
Clin Pharmacokinet. 2000 Oct;39(4):255-70.
Various compounds of the artemisinin family are currently used for the treatment of patients with malaria worldwide. They are characterised by a short half-life and feature the most rapidly acting antimalarial drugs to date. They are increasingly being used, often in combination with other drugs, although our knowledge of their main pharmacological features (including their absorption, distribution, metabolism and excretion) is still incomplete. Such data are particularly important in the case of combinations. Artemisinin derivatives are converted primarily, but to different extents, to the bioactive metabolite artenimol after either parenteral or gastrointestinal administration. The rate of conversion is lowest for artelinic acid (designed to protect the molecule against metabolism) and highest for the water-soluble artesunate. The absolute and relative bioavailability of these compounds has been established in animals, but not in humans, with the exception of artesunate. Oral bioavailability in animals ranges, approximately, between 19 and 35%. A first-pass effect is highly probably for all compounds when administered orally. Artemisinin compounds bind selectively to malaria-infected erythrocytes to yet unidentified targets. They also bind modestly to human plasma proteins, ranging from 43% for artenimol to 81.5% for artelinic acid. Their mode of action is still not completely understood, although different theories have been proposed. The lipid-soluble artemether and artemotil are released slowly when administered intramuscularly because of the 'depot' effect related to the oil formulation. Understanding the pharmacokinetic profile of these 2 drugs helps us to explain the characteristics of the toxicity and neurotoxicity. The water-soluble artesunate is rapidly converted to artenimol at rates that vary with the route of administration, but the processes need to be characterised further, including the relative contribution of pH and enzymes in tissues, blood and liver. This paper intends to summarise contemporary knowledge of the pharmacokinetics of this class of compounds and highlight areas that need further research.

15189457
Ndayiragije A, Niyungeko D, Karenzo J, Niyungeko E, Barutwanayo M, Ciza A, Bosman A, Moyou-Somo R, Nahimana A, Nyarushatsi JP, Barihuta T, Mizero L, Ndaruhutse J, Delacollette C, Ringwald P, Kamana J
[Efficacy of therapeutic combinations with artemisinin derivatives in the treatment of non complicated malaria in Burundi.]
Trop Med Int Health. 2004 Jun;9(6):673-9.
Faced with the problem of resistance to chloroquine and sulfadoxine-pyrimethamine, the Ministry of Public Health of Burundi decided to study the efficacy of two artemisinin-based combinations, the fixed combination of artemether-lumefantrine and the combination of amodiaquine + artesunate. The efficacy of these combinations for the treatment of uncomplicated falciparum malaria was studied in two sites representative of the country, in Kigobe neighbourhood of Bujumbura, the capital city, and in Buhiga, a rural area. The study followed the standardized WHO protocol from October 2001 to November 2002. A total of 295 children under 5 years were included; 153 children were treated with artesunate and amodiaquine (77 at Buhiga and 76 at Kigobe), and 142 children with the combination of artemether-lumefantrine (64 at Buhiga and 78 at Kigobe). Among the 295 children, 290 were followed up to 14 days. In the group of 149 children treated with artesunate and amodiaquine, 142 (95.3%, 95% CI: 91.9-98.7%) presented with adequate clinical and parasitological response, five (3.3%) with late parasitological failure, one (0.7%) with late clinical failure and one (0.7%) with early treatment failure. Among the 141 children treated with artemether-lumefantrine, 140 (99.3%, 95% CI: 97.9-100%) presented with adequate clinical and parasitological response and one (0.7%) with late parasitological failure at Buhiga. Side-effects were comparable in both groups except for the vomiting. Vomiting was more frequent in the artesunate + amodiaquine on D1 and D2. Both treatments decreased the gametocyte carriage but without getting full clearance in all the patients. During a consensus workshop, the Ministry of Public Health agreed on the combination of artesunate and amodiaquine as the first line drug for the treatment of uncomplicated falciparum malaria in Burundi including epidemic outbreak.

12435698

Nealon C, Dzeing A, Muller-Romer U, Planche T, Sinou V, Kombila M, Kremsner PG, Parzy D, Krishna S
Intramuscular bioavailability and clinical efficacy of artesunate in gabonese children with severe malaria.
Antimicrob Agents Chemother. 2002 Dec;46(12):3933-9.
Artesunate (ARS) is a water-soluble artemisinin derivative that is a potential alternative to quinine for the treatment of severe childhood malaria. We studied the pharmacokinetics and bioavailability of ARS given by the intramuscular (i.m.) route in an open crossover study design. Fourteen children were randomized to receive intravenous (i.v.) ARS in a loading dose (2.4 mg/kg of body weight) followed 12 h later by an i.m. dose (1.2 mg/kg) (group I), and 14 children were randomized to receive i.m. ARS (2.4 mg/kg) followed by an i.v. dose of ARS (1.2 mg/kg) (group II). We carried out a two-compartment analysis of ARS and dihydroartemisinin (DHA; the principal antimalarial metabolite) levels in 21 children (groups I and II combined). Absorption of i.m. ARS was rapid, with the maximum concentration of DHA in serum being achieved in less than 1 h in most children (median time to the maximum concentration of drug in serum, 35.1 min; range, 10.8 to 71.9 min). The absolute bioavailability of DHA was a median of 86.4% (range, 11.4 to 462.1%), the median steady-state volume of distribution was 1.3 liters/kg (range, 0.5 to 7.9 liters/kg), and the median clearance was 0.028 liters/kg/min (range, 0.001 to 1.58 liters/kg/min). There were no major adverse events attributable to ARS. Parasite clearance kinetics were comparable between the two treatment groups. These results support the use of i.m. ARS in children with severe malaria.

12791054
Newman RD, Parise ME, Slutsker L, Nahlen B, Steketee RW
Safety, efficacy and determinants of effectiveness of antimalarial drugs during pregnancy: implications for prevention programmes in Plasmodium falciparum-endemic sub-Saharan Africa.
Trop Med Int Health. 2003 Jun;8(6):488-506.
Plasmodium falciparum malaria in pregnancy poses substantial risk to a pregnant woman and her neonate through anaemia and low birth weight (LBW), respectively, and is responsible for up to 35% of preventable LBW in malaria-endemic areas. Chemoprophylaxis or intermittent preventive treatment (IPT) with an effective antimalarial can ameliorate the adverse effects of malaria during pregnancy. Current guidelines from the WHO recommend that women in highly malarious areas receive IPT with an effective antimalarial. Two central considerations in evaluating drugs for use during pregnancy are safety for the mother and her foetus and effectiveness, which is determined by efficacy, cost, availability, deliverability and acceptability of the drug. These factors may be scored and potential drugs or drug combinations ranked in order of potential effectiveness for use in prevention programmes. The seven most promising regimens are all IPT, primarily because they are more easily delivered and less expensive than chemoprophylaxis. Currently, IPT with sulphadoxine-pyrimethamine (SP) is more likely to have the best overall effectiveness in preventing adverse outcomes associated with malaria in pregnancy. Its low cost, wide availability, easy deliverability and acceptability make it the clear choice in countries where efficacy of the drug remains good. For countries where resistance to SP is rising or already high, amodiaquine (alone or in combination with SP or artesunate) artesunate + SP, chlorproguanil-dapsone (with and without artesunate) and artemether-lumefantrine require urgent evaluation for use in pregnancy.

10990500
Newton CR, Hien TT, White N
Cerebral malaria.
J Neurol Neurosurg Psychiatry. 2000 Oct;69(4):433-41.
Cerebral malaria may be the most common non-traumatic encephalopathy in the world. The pathogenesis is heterogeneous and the neurological complications are often part of a multisystem dysfunction. The clinical presentation and pathophysiology differs between adults and children. Recent studies have elucidated the molecular mechanisms of pathogenesis and raised possible interventions. Antimalarial drugs, however, remain the only intervention that unequivocally affects outcome, although increasing resistance to the established antimalarial drugs is of grave concern. Artemisinin derivatives have made an impact on treatment, but other drugs may be required. With appropriate antimalarial drugs, the prognosis of cerebral malaria often depends on the management of other complications-for example, renal failure and acidosis. Neurological sequelae are increasingly recognised, but further research on the pathogenesis of coma and neurological damage is required to develop other ancillary treatments.

9629838
Newton CR, Warrell DA
Neurological manifestations of falciparum malaria.
Ann Neurol. 1998 Jun;43(6):695-702.
Plasmodium falciparum remains one of the most common causes of central nervous system infection worldwide. Recently, differences between the pathophysiology of cerebral malaria in African children and nonimmune adults have been discovered, new syndromes occurring after malaria infection described, and

mechanisms for the pathogenesis proposed. In addition, new antimalarial agents have been examined worldwide and initial studies on supportive studies conducted. This paper reviews these new advances, putting them into the perspective of the more established knowledge.

11425421
Newton P, Proux S, Green M, Smithuis F, Rozendaal J, Prakongpan S, Chotivanich K, Mayxay M, Looareesuwan S, Farrar J, Nosten F, White NJ
Fake artesunate in southeast Asia.
Lancet. 2001 Jun 16;357(9272):1948-50.
Artesunate is a key antimalarial drug in the treatment of multidrug-resistant Plasmodium falciparum malaria in southeast Asia. We investigated the distribution of counterfeit artesunate tablets by use of the validated, simple, and inexpensive Fast Red TR dye technique. We also aimed to identify distinguishing characteristics of the fake drugs. Of 104 shop-bought "artesunate" samples from Cambodia, Laos, Myanmar (Burma), Thailand, and Vietnam, 38% did not contain artesunate. Characteristics such as cost and physical appearance of the tablets and packaging reliably predicted authenticity. The illicit trade in counterfeit antimalarials is a great threat to the lives of patients with malaria. The dye test will assist national malaria control authorities in urgently needed campaigns to stop this murderous trade.

10722499
Newton P, Suputtamongkol Y, Teja-Isavadharm P, Pukrittayakamee S, Navaratnam V, Bates I, White N
Antimalarial bioavailability and disposition of artesunate in acute falciparum malaria.
Antimicrob Agents Chemother. 2000 Apr;44(4):972-7.
The pharmacokinetic properties of oral and intravenous artesunate (2 mg/kg of body weight) were studied in 19 adult patients with acute uncomplicated Plasmodium falciparum malaria by using a randomized crossover design. A sensitive bioassay was used to measure the antimalarial activity in plasma which results from artesunate and its principal metabolite, dihydroartemisinin. The oral study was repeated with 15 patients during convalescence. The mean absolute oral bioavailability of the antimalarial agent in patients with acute malaria was 61% (95% confidence interval [CI], 52 to 70%). The absorption and elimination of oral artesunate were rapid, with a mean elimination half-life of antimalarial activity of 43 min (95% CI, 33 to 53 min). Following oral administration to patients with acute falciparum malaria, peak antimalarial activity in plasma and the area under the plasma concentration-time curve were approximately double those during convalescence and the apparent volume of distribution and clearance were approximately half those during convalescence (P < or = 0.005). Acute malaria is associated with a significant reduction in the clearance of artesunate-associated antimalarial activity.

10073271
Newton P, White N
Malaria: new developments in treatment and prevention.
Annu Rev Med. 1999;50:179-92.
Malaria still kills some 0.5-2.5 million people per year in the tropics. Resistance to the cheap, most commonly used antimalarials continues to spread alarmingly and could outpace drug development. The artemisinin derivatives have had an important clinical impact both on the treatment of resistant falciparum malaria and on the incidence of disease in low-transmission areas. A few promising new antimalarials are being tested clinically but there is an imperative need for cheap, well-tolerated drugs that can be used in short courses, and for strategies to delay the onset of drug resistance. Bed nets have been shown to reduce the incidence of severe malaria in many areas but an effective vaccine is urgently needed.

12830403
Newton PN, Angus BJ, Chierakul W, Dondorp A, Ruangveerayuth R, Silamut K, Teerapong P, Suputtamongkol Y, Looareesuwan S, White NJ
Randomized comparison of artesunate and quinine in the treatment of severe falciparum malaria.
Clin Infect Dis. 2003 Jul 1;37(1):7-16. Epub 2003 Jun 23.
A randomized, open-label comparison of artesunate and quinine was conducted in 113 adults with clinically severe falciparum malaria in western Thailand. Mortality was 12% with artesunate and 22% with quinine treatment (relative risk, 0.53; 95% confidence interval, 0.23-1.26; P=.22). Multiple logistic regression analysis found admission plasma lactate level, Glasgow Coma Scale score, and total serum bilirubin level to be independent risk factors for death. Coma recovery and times to normalize plasma lactate levels were similar, but the parasite clearance time was much shorter among artesunate-treated patients (P=.019). Fewer patients became hypoglycemic during artesunate therapy (10%) than during quinine therapy (28%) (P=.03). Artesunate is at least as effective as quinine in the treatment of adults with severe malaria. Larger trials are required to determine whether mortality is reduced among patients treated with artesunate.

15793155

Newton PN, Chaulet JF, Brockman A, Chierakul W, Dondorp A, Ruangveerayuth R, Looareesuwan S, Mounier C, White NJ
Pharmacokinetics of oral doxycycline during combination treatment of severe falciparum malaria.
Antimicrob Agents Chemother. 2005 Apr;49(4):1622-5.
The pharmacokinetics of oral doxycycline administered at 200 mg every 24 h were investigated in 17 patients recovering from severe Plasmodium falciparum malaria. The data suggest that the doses of doxycycline currently recommended (circa 3.5 mg/kg of body weight daily) may not be optimal.

11706665
Newton PN, Chierakul W, Ruangveerayuth R, Silamut K, Teerapong P, Krudsood S, Looareesuwan S, White NJ
A comparison of artesunate alone with combined artesunate and quinine in the parenteral treatment of acute falciparum malaria.
Trans R Soc Trop Med Hyg. 2001 Sep-Oct;95(5):519-23.
In some areas clinicians have combined parenteral artesunate and quinine in the belief that the 2 drugs would be additive or synergistic in severe malaria. A randomized comparison of the effectiveness of intravenous (i.v.) artesunate versus i.v. artesunate and i.v. quinine together on parasite clearance was conducted in 1998/99 amongst 69 patients with uncomplicated and severe Plasmodium falciparum malaria in western Thailand. The parasite clearance time did not differ significantly between the 2 treatment groups (P = 0.12), but adverse events were significantly more frequent in the artesunate plus quinine group (P = 0.05). Quinine did not have a significant antipyretic effect and artesunate did not affect the electrocardiographic QTc interval. There is no benefit evident from combining parenteral administration of these 2 antimalarial drugs in the acute phase of treatment.

11435316
Newton PN, Chotivanich K, Chierakul W, Ruangveerayuth R, Teerapong P, Silamut K, Looareesuwan S, White NJ
A comparison of the in vivo kinetics of Plasmodium falciparum ring-infected erythrocyte surface antigen-positive and -negative erythrocytes.
Blood. 2001 Jul 15;98(2):450-7.
Ring-infected erythrocyte surface antigen (RESA)-positive, Plasmodium falciparum-negative red blood cells (RBCs) are cells from which the malaria parasite has been removed by the host without the destruction of the erythrocyte ("pitting"). The survival of RESA-RBCs in vivo was assessed in 14 severe and 6 uncomplicated falciparum malaria patients. The mean RESA-RBC life of 183 hours (95% confidence interval [CI], 136-246) was longer than the median parasite clearance time of 66 hours (range, 30-108 hours) but shorter than the mean red cell life of 1027 hours (95% CI, 840-1213) (P =.0004), with a median ratio of 0.2:1.0 (range, 0.1-0.7). The estimated median percentage of parasites pitted/body transit was 0.003% (range, 0.001%-0.05%). The rate of rise of the RESA-RBC count during the first 24 hours after antimalarial treatment was significantly faster (P =.036) and the subsequent RESA-RBC survival significantly shorter (P =.017) after treatment with an artemisinin derivative than after treatment with quinine. Parasitization of red cells leads to changes in the erythrocyte that shorten their survival even if the parasite is removed subsequently.

11897605
Newton PN, van Vugt M, Teja-Isavadharm P, Siriyanonda D, Rasameesoroj M, Teerapong P, Ruangveerayuth R, Slight T, Nosten F, Suputtamongkol Y, Looareesuwan S, White NJ
Comparison of oral artesunate and dihydroartemisinin antimalarial bioavailabilities in acute falciparum malaria.
Antimicrob Agents Chemother. 2002 Apr;46(4):1125-7.
Plasma antimalarial activity following oral artesunate or dihydroartemisinin (DHA) treatment was measured by a bioassay in 18 patients with uncomplicated falciparum malaria. The mean antimalarial activity in terms of the bioavailability of DHA relative to that of artesunate did not differ significantly from 1, suggesting that DHA can be formulated to be an acceptable oral alternative to artesunate.

12685644
Ngo T, Duraisingh M, Reed M, Hipgrave D, Biggs B, Cowman AF
Analysis of pfcrt, pfmdr1, dhfr, and dhps mutations and drug sensitivities in Plasmodium falciparum isolates from patients in Vietnam before and after treatment with artemisinin.
Am J Trop Med Hyg. 2003 Mar;68(3):350-6.
We have analyzed artemisinin sensitivity in Plasmodium falciparum isolates obtained from patients in South Vietnam and show that artemisinin sensitivity does not differ before and after drug treatment. There was an increase in the level of mefloquine resistance in the isolates after drug treatment that was concomitant with a decrease in chloroquine resistance, suggesting that treatment with artemisinin has selected for increased

mefloquine resistance. Mutations in the pfmdr1 gene, previously shown to be associated with sensitivity to mefloquine, were selected against. All isolates resistant to chloroquine encoded Thr-76 in the pfcrt gene consistent with an essential role in the mechanism of chloroquine resistance. Mutations in pfmdr1 also were linked to chloroquine resistance. High levels of mutation in dhfr and dhps genes, which have previously been associated with Fansidar resistance, also were found, suggesting that this drug would not be useful for malaria control in this part of Vietnam.

14614668
Nguyen MH, Davis TM, Cox-Singh J, Hewitt S, Tran QT, Tran BK, Nguyen TH, Vo NP, Doan HN, Le DC
Treatment of uncomplicated falciparum malaria in southern Vietnam: can chloroquine or sulfadoxine-pyrimethamine be reintroduced in combination with artesunate?
Clin Infect Dis. 2003 Dec 1;37(11):1461-6. Epub 2003 Nov 3.
The effectiveness of chloroquine or sulfadoxine-pyrimethamine administered with artesunate for treating uncomplicated falciparum malaria was assessed in 2 Vietnamese provinces where the sensitivity of parasites in vitro to conventional therapies had increased with the removal of drug pressure. In the province of Dac Lac, where potential malaria exposure begins at birth, 57 subjects (mean age, 9.6 years) were randomized to receive artesunate-chloroquine (group 1) or artesunate-sulfadoxine-pyrimethamine (group 2). In the province of Binh Phuoc, 66 nonimmune workers and their relatives (mean age, 24.2 years) were similarly randomized. By day 28 of follow-up, >96% of Dac Lac patients and

7819809
Nguyen TA
[Malaria in Vietnam. Environment, prevention and treatment]
Bull Soc Pathol Exot. 1993;86(5 Pt 2):494-9.
In Viet-nam, malaria rages in mountainous and wooded areas, as well as in coastal areas. In these geographical zones, the diversified features of environment have different repercussions on the development of Anopheles species. The main vector species have strict oecological requirements: An. dirus, disseminated in the forests, colonizes stagnant and shaded water, such as rain water collected in ground dips and in cavities of trees and rocks; An. minimus selects its breeding-sites in pure and slightly current streamlets, in the hilly areas. On the contrary, An. sundaicus, first-rate coastal vector, adjusts itself to diversified biotopes, which nevertheless all have common features: saltiness of water (optimum 1-7 g NaCl/litre), faint sunning, stagnant or slightly current water, with floating green algae (Ceratophyllum, Najas). P. falciparum prevails in the wooded areas (P. f.: 75%; P. v.: 25%); but in the coastal areas where Anopheles hyrcanus pullulates, P. vivax reaches the same ratios as P. falciparum. In Viet-nam, the prevention and antimalarial fight are centred on three measures: diagnosis, treatment and watching of diseases, antivectorial fight, antimalarial fight combined with first medical care. Owing to the spreading of P. falciparum chemoresistance to chloroquine (27 to 76%) and to Fansidar (22 to 83%), we had to have recourse to new antimalarials: artemisinine and artesunate tested in several regions of the country (tests in vitro and in vivo during 28 days) revealed their high schizonticidal capacity, but the recrudescence reached 30 to 50%.(ABSTRACT TRUNCATED AT 250 WORDS)

15112707
Niagia S
Ghana battles drug-resistant malaria with artesunate.
Lancet. 2004 Apr 24;363(9418):1372.

4029221
Niu XY, Ho LY, Ren ZH, Song ZY
Metabolic fate of Qinghaosu in rats; a new TLC densitometric method for its determination in biological material.
Eur J Drug Metab Pharmacokinet. 1985 Jan-Mar;10(1):55-9.
Since the sixties, the emergence of malarial parasites resistant to the most potent anti-malarials has posed a serious problem to the therapy of malaria. Qinghaosu, a new sesquiterpene isolated from a Chinese medicinal herb Qing-hao (Artemisia annua Linn) is being used for the treatment of malaria in China with good results even in cases resistant to common anti-malarial agents. In this paper, a sensitive method of high specificity using TLC for the determination of Qinghaosu in biological specimens and in the study of the metabolism of the drug in rats is described. Qinghaosu was shown to be completely and rapidly absorbed after oral administration. However, a very low plasma level was obtained even after a dose of 300 mg/kg. Liver was found to be the chief site of its inactivation. When Qinghaisu was given intramuscularly, significant and more persistent plasma levels were detected. Qinghaosu was shown to pass the blood-brain and blood-

placenta barriers after i.v. injection. Very little unchanged Qinghaosu was found in the urine and feces in 48 hours regardless of administration route (i.v., i.m. or p.o.).

15047999
Njuguna P, Newton C
Management of severe falciparum malaria.
J Postgrad Med. 2004 Jan-Mar;50(1):45-50.
Plasmodium falciparum is the most common cause of severe and life-threatening malaria. Falciparum malaria causes over one million deaths every year. In Africa, a vast majority of these deaths occur in children under five years of age. The presentation of severe malaria varies with age and geographical distribution. The mortality rate is higher in adults than in children but African children develop neuro-cognitive sequelae following severe malaria more frequently. The management of severe malaria includes prompt administration of appropriate parenteral anti-malarial agents and early recognition and treatment of the complications. In children, the complications include metabolic acidosis (often caused by hypovolaemia), hypoglycaemia, hyperlacticacidaemia, severe anaemia, seizures and raised intracranial pressure. In adults, renal failure and pulmonary oedema are more common causes of death. In contrast, concomitant bacterial infections occur more frequently in children and are associated with mortality in children. Admission to critical or intensive care units may help reduce the mortality, and the frequency and severity of sequelae related to severe malaria.

16046187
Noedl H
Artemisinin resistance: how can we find it?
Trends Parasitol. 2005 Sep;21(9):404-5.

12641401
Noedl H, Faiz MA, Yunus EB, Rahman MR, Hossain MA, Samad R, Miller RS, Pang LW, Wongsrichanalai C
Drug-resistant malaria in Bangladesh: an in vitro assessment.
Am J Trop Med Hyg. 2003 Feb;68(2):140-2.
Forty-four Plasmodium falciparum isolates from Bangladesh and 22 from western Thailand were successfully tested for their drug susceptibility. High degrees of resistance were observed against chloroquine with geometric mean IC50s of 114.25 and 120.5 nM, respectively, for Bangladesh and western Thailand. Most isolates from both sites were sensitive to quinine, and all were sensitive to artesunate. Many isolates were considered in vitro resistant to mefloquine, but the geometric mean IC50 for the Thai isolates (98.79 nM) was 1.6 times (P = 0.002) higher than that of isolates from Bangladesh (60.3 nM). The high prevalence of in vitro mefloquine resistance in Bangladesh suggests that close surveillance is necessary to delay widespread multidrug resistant problems in the area.

15504891
Noedl H, Teja-Isavadharm P, Miller RS
Nonisotopic, semiautomated plasmodium falciparum bioassay for measurement of antimalarial drug levels in serum or plasma.
Antimicrob Agents Chemother. 2004 Nov;48(11):4485-7.
A simple, nonisotopic, semiautomated bioassay for the measurement of antimalarial drug levels in plasma or serum based on the quantitation of histidine-rich protein II in malaria culture is presented. The assay requires only small sample volumes and was found to be highly sensitive and reproducible. The results closely paralleled those obtained with isotopic bioassays (R = 0.988, P < 0.001) and high-performance liquid chromatography-electrochemical detection (R = 0.978, P < 0.001).

11495642
Noedl H, Wernsdorfer WH, Krudsood S, Wilairatana P, Kollaritsch H, Wiedermann G, Looareesuwan S
Antimalarial activity of azithromycin, artemisinin and dihydroartemisinin in fresh isolates of Plasmodium falciparum in Thailand.
Acta Trop. 2001 Sep 1;80(1):39-44.
Antibiotics with antimalarial activity may offer an interesting alternative for the treatment of multidrug-resistant falciparum malaria. Azithromycin, a relatively recent semisynthetic derivative of erythromycin, was tested for its in vitro activity against fresh isolates of Plasmodium falciparum. As the reportedly slow onset of action of azithromycin suggests its combination with fast-acting substances, such as artemisinin-derivatives, dihydroartemisinin (DHA) was tested parallel as a possible combination partner. The effective concentrations found for azithromycin in this study (EC(50) = 29.3 micromol/l, EC(90) = 77.1 micromol/l blood medium

mixture (BMM)) are comparable to those of other antimalarials in the antibiotics class and are considerably higher than those found for mefloquine or quinine. The absence of an activity correlation between azithromycin and chloroquine, quinine and artemisinin emphasises the independence of azithromycin drug response from the sensitivity to these drugs. A weak activity correlation (rho(EC90) = 0.352; p = 0.028), which could point to a potential cross-sensitivity but is probably of little clinical importance, was found with mefloquine above the EC(50) level. Provided that further clinical trials support the combination of these drugs, DHA may offer an interesting combination partner for azithromycin owing to its rapid onset of action and the comparatively low effective concentrations (EC(50) = 1.65 nmol/l, EC(90) = 7.10 nmol/l BMM). This combination may serve as an interesting alternative for tetracycline and doxycycline, which cannot be used in pregnant women and children, and exhibit phototoxicity. Nevertheless, the relatively high cost of this combination, as well as the controversial reports of the clinical efficacy, may limit the usefulness of azithromycin in malaria therapy and require an adjustment of previously used treatment regimens.

11791959
Noedl H, Wernsdorfer WH, Krudsood S, Wilairatana P, Viriyavejakul P, Kollaritsch H, Wiedermann G, Looareesuwan S
In vivo-in vitro model for the assessment of clinically relevant antimalarial cross-resistance.
Am J Trop Med Hyg. 2001 Dec;65(6):696-9.
Cross-resistance may be considered one of the most important factors leading to decreased drug susceptibility of Plasmodium falciparum. The study aimed to determine whether clinically relevant cross-sensitivity of P. falciparum existed between artemisinin and mefloquine. Seventy-six patients with falciparum malaria were admitted and treated with artemisinin derivatives. Treatment response parameters were assessed and in vitro drug sensitivity tests were performed with artemisinin, mefloquine, quinine, and chloroquine. Distinct in vitro cross-sensitivity between artemisinin and mefloquine was observed (p = 0.604; P < 0.001). To assess the relevance of this finding for clinical cross-resistance, we used an analytical model based on the relation of in vivo treatment response parameters (fever, parasite and symptom clearance) to a single reference drug with in vitro drug sensitivity data of several other drugs. Artemisinin (R = 0.554; P = 0.009) and mefloquine (R = 0.615; P = 0.002) in vitro drug sensitivities were equally well reflected in the in vivo treatment response to artemisinin, thereby suggesting the clinical relevance of in vitro cross-sensitivity.

12856311
Noedl H, Wongsrichanalai C, Miller RS, Myint KS, Looareesuwan S, Sukthana Y, Wongchotigul V, Kollaritsch H, Wiedermann G, Wernsdorfer WH
Plasmodium falciparum: effect of anti-malarial drugs on the production and secretion characteristics of histidine-rich protein II.
Exp Parasitol. 2002 Nov-Dec;102(3-4):157-63.
Plasmodium falciparum histidine-rich protein II (HRP2) is one of the best documented malaria proteins. However, little is known about the development of HRP2 concentrations under the influence of anti-malarial drugs. HRP2 levels were determined in cell medium mixture, cellular compartment, and in culture supernatant using a double-site sandwich ELISA specific for HRP2. Characteristic increases in the overall HRP2 levels were found during the later ring and the trophozoite stages. Throughout the later schizont development, rupture, and reinvasion, however, the HRP2 levels remained comparatively stable. When the cultures were exposed to serial dilutions of anti-malarial drugs, a distinct inhibition of HRP2 production was seen with increasing concentrations of drugs, resulting in sigmoid dose-response curves, similar to those obtained from conventional drug sensitivity assays. HRP2 therefore allows for a very accurate estimation of parasite development and its inhibition and may therefore be ideally suited for use in drug sensitivity or bioassays.

8053025
Nosten F
Artemisinin: large community studies.
Trans R Soc Trop Med Hyg. 1994 Jun;88 Suppl 1:S45-6.
Prospective randomized trials with oral artemisinin derivatives have been conducted in over 1000 patients to determine the optimum treatment of multi-drug resistant falciparum malaria on the Thai-Burmese border. These drugs have proved valuable in 3 settings. (i) Primary treatment of uncomplicated malaria in combination with mefloquine, when they accelerate the rate of recovery, eliminate the risk of dangerous early failures, and if given for 3 d or more improve overall cure rates; (ii) treatment of recrudescent infections, which otherwise have a high failure rate; and (iii) oral treatment of patients with high parasitaemias (> or = 4%) but no clinical evidence of severity (a group who would usually receive parenteral quinine). The parenteral formulation of artemether is absorbed if given rectally, and this may offer a practical alternative method of treating severe malaria in rural areas.

15047997

Nosten F, Ashley E
The detection and treatment of Plasmodium falciparum malaria: time for change.
J Postgrad Med. 2004 Jan-Mar;50(1):35-9.
In most countries where malaria is endemic, P. falciparum malaria is on the rise. This is primarily due to the spread of drug-resistant strains. Drug resistance is mediated by spontaneous changes in the parasite genome that allow resistant parasites to escape the action of the drugs. The spread of drug resistance increases the transmission of malaria parasites. The consequences for the populations at risk are profound both in terms of consequences for health and economy. In order to halt the progression of drug resistance, we need to change the way antimalarials are used. As in tuberculosis and HIV/AIDS, we must use a combination of drugs for the treatment of malaria. Taking into account the pharmacokinetic and pharmacodynamic properties of the various anti-malarial agents, artemisinin-based combination therapy (ACT) seems to be the best option. This strategy should be used in conjunction with early diagnosis and appropriate vector control measures to achieve reduction in the emergence and spread of drug resistance.

12076181
Nosten F, Brasseur P
Combination therapy for malaria: the way forward?
Drugs. 2002;62(9):1315-29.
Unless new strategies are deployed to combat malaria, the already enormous health and economic burden related to the disease in tropical countries is bound to worsen. The main obstacle to malaria control is the emergence of drug resistant strains of Plasmodium falciparum. As for HIV/AIDS and tuberculosis, the use of combinations of antimalarial drugs reduces the risk of selecting for resistant mutants of the plasmodial parasites. In large field trials, the combination of an artemisinin derivative and a partner drug with an unrelated mode of action (in this case mefloquine), has shown a remarkable double effect: preventing the emergence and spread of drug resistance, and interrupting the transmission of P. falciparum. This has opened the way for a new approach to the deployment of antimalarial drugs. Coupled with early detection and confirmed diagnosis, this strategy represents the only way forward in the chemotherapy of malaria. Massive economic assistance will be needed to detect and treat adequately the estimated 500 million cases of malaria per year, but without radical action there is no prospect of 'Rolling Back' malaria.

10212897
Nosten F, Hien TT, White NJ
Use of artemisinin derivatives for the control of malaria.
Med Trop (Mars). 1998;58(3 Suppl):45-9.
Since 1994, the combination of mefloquine and artesunate is the standard treatment for uncomplicated Plasmodium falciparum malaria in the population of displaced persons on the Western border of Thailand. As a result, the fall of mefloquine efficacy was stopped and the incidence of falciparum malaria reduced. This is attributed to the effects of the artemisinin derivatives on transmissibility. Similar trends were observed in Vietnam where artemisinin is widely used. Combination therapies that include an artemisinin derivative could have a major role in the control of malaria and the spread of drug resistance.

7930743
Nosten F, Luxemburger C, ter Kuile FO, Woodrow C, Eh JP, Chongsuphajaisiddhi T, White NJ
Treatment of multidrug-resistant Plasmodium falciparum malaria with 3-day artesunate-mefloquine combination.
J Infect Dis. 1994 Oct;170(4):971-7.
Studies of 652 adults and children with acute uncomplicated falciparum malaria were done to determine the optimum treatment of multidrug-resistant Plasmodium falciparum malaria on the Thai-Burmese border. Single-dose artesunate (4 mg/kg) plus mefloquine (25 mg of base/kg) gave more rapid symptomatic and parasitologic responses than high-dose mefloquine alone but did not improve cure rates. Three days of artesunate (total dose, 10 mg/kg) plus mefloquine was 98% effective compared with a 28-day failure rate of 31% with high-dose mefloquine alone (relative risk [RR], 0.06; 95% confidence interval [CI], 0.02-0.2; P < .0001). By day 63, the reinfection adjusted failure rates were 2% and 44%, respectively (P < .0001). Artesunate also prevented high-grade failures. Both drugs were well tolerated. No adverse effects were attributable to artesunate. Vomiting was reduced significantly by giving mefloquine on day 2 of treatment (RR, 0.40; 95% CI, 0.20-0.79; P = .009. Artesunate (10 mg/kg over 3 days) plus mefloquine (25 mg/kg) is currently the most effective treatment for falciparum malaria in this area of increasing mefloquine resistance.

11071185
Nosten F, van Vugt M, Price R, Luxemburger C, Thway KL, Brockman A, McGready R, ter Kuile F, Looareesuwan S, White NJ
Effects of artesunate-mefloquine combination on incidence of Plasmodium falciparum malaria and mefloquine resistance in western Thailand: a prospective study.

Lancet. 2000 Jul 22;356(9226):297-302.
BACKGROUND: Worsening drug resistance in Plasmodium falciparum malaria is a major threat to health in tropical countries. We did a prospective study of malaria incidence and treatment in an area of highly multidrug-resistant P. falciparum malaria. METHODS: We assessed incidence of P. falciparum malaria and the in-vivo responses to mefloquine treatment over 13 years in two large camps for displaced Karen people on the northwest border of Thailand. During this time, the standard mefloquine dose was first increased, and then combined artesunate and mefloquine was introduced as first-line treatment for uncomplicated P. falciparum malaria. FINDINGS: Early detection and treatment controlled P. falciparum malaria initially while mefloquine was effective (cure rate with mefloquine [15 mg/kg] and sulphadoxine-pyrimethamine in 1985, 98% [95% CI 97-100]), but as mefloquine resistance developed, the cure rate fell (71% [67-77] in 1990). A similar pattern was seen for high-dose (25 mg/kg) mefloquine monotherapy from 1990-94. Since the general deployment of the artesunate-mefloquine combination in 1994, the cure rate increased again to almost 100% from 1998 onwards, and there has been a sustained decline in the incidence of P. falciparum malaria in the study area. In-vitro susceptibility of P. falciparum to mefloquine has improved significantly (p=0.003). INTERPRETATION: In this area of low malaria transmission, early diagnosis and treatment with combined artesunate and mefloquine has reduced the incidence of P. falciparum malaria and halted the progression of mefloquine resistance. We recommend that antimalarial drugs should be combined with artemisinin or a derivative to protect them against resistance.

10212903
Nosten F, van Vugt M, White NJ
Intrarectal artemisinin derivatives.
Med Trop (Mars). 1998;58(3 Suppl):63-4.
The artemisinin derivatives are the most potent antimalarials. They are rapidly absorbed orally, parenterally and intra-rectally. The latter mode of administration is particularly interesting in rural tropics. Preliminary studies have shown that artemisinin and its derivatives artesunate and artemether are effective when given intrarectally. More studies are needed to establish the optimum regimen.

16185238
Nsimba B, Jafari-Guemouri S, Malonga DA, Mouata AM, Kiori J, Louya F, Yocka D, Malanda M, Durand R, Le Bras J
Epidemiology of drug-resistant malaria in Republic of Congo: using molecular evidence for monitoring antimalarial drug resistance combined with assessment of antimalarial drug use.
Trop Med Int Health. 2005 Oct;10(10):1030-7.
In Congo, urgent efforts are needed to help with the revision of the national antimalarial drug policy. Despite its high resistance level, chloroquine (CQ) is still extensively used as the first-line treatment for uncomplicated Plasmodium falciparum malaria. The study was conducted in children under 5 years with uncomplicated malaria in Pointe-Noire and Brazzaville, the two largest cities that contain approximately 60% of the population of Congo. We investigated by polymerized chain reaction and sequencing methods the frequency distribution of molecular markers for antimalarial drug resistance, including mutations in P. falciparum chloroquine resistance transporter (pfcrt) gene associated with CQ resistance and mutations in dihydrofolate reductase (dhfr) and dihydropteroate synthetase (dhps) genes conferring resistance to sulphadoxine/pyrimethamine (SP) among pre-treatment P. falciparum isolates, as well as assessing antimalarial drug use in the community. pfcrt (K76T) mutation was present in most isolates (96.4%, n = 138) and high frequency (69.2%, n = 133) of triple-mutant dhfr-S108N, N51I, C59R was observed. The quintuple mutant (dhfr-S108N, N51I, C59R and dhps-A437G or S436A, K540E) considered as molecular marker for SP treatment failure was not found because dhps-K540E mutation was absent in isolates tested; this is a clear evidence for the excellent efficacy of SP that we previously described in the same population. The complete absence of the dhps-K540E mutation is a deterrent component for using this molecular marker as an early warning tool for SP resistance testing in that population. Poor compliance issues related to the antimalarial drug use including inappropriate manufacturing practices reported in this study require intensive attention and should be taken into account when implementing drug policy change. If Congo changes its treatment policy from CQ to SP monotherapy, this will not last long. The strategy of combining SP with other affordable and effective antimalarial drugs such as the artemisinin derivatives to improve efficacy and to delay the development of parasite resistance is essential.

15307433
Obonyo CO, Ochieng F, Taylor WR, Ochola SA, Mugitu K, Olliaro P, ter Kuile F, Oloo AJ
Artesunate plus sulfadoxine-pyrimethamine for uncomplicated malaria in Kenyan children: a randomized, double-blind, placebo-controlled trial.
Trans R Soc Trop Med Hyg. 2003 Sep-Oct;97(5):585-91.
Plasmodium falciparum has developed resistance to almost all routinely used antimalarial drugs. Sulfadoxine-pyrimethamine (SP) has replaced chloroquine as first-line treatment of uncomplicated malaria

infection in Kenya but resistance to SP is already reported. The addition of artemisinin derivatives to SP may delay the development of drug resistance, improve cure rates, and reduce transmission. The efficacy and safety of artesunate plus SP in the treatment of uncomplicated P. falciparum malaria was evaluated in a randomized trial of 600 children at Siaya District Hospital, western Kenya between October 1999 and March 2000. Children aged < 5 years were randomly assigned to receive SP alone (1.25 mg/kg based on pyrimethamine), or in combination with artesunate (4 mg/kg/d) for either 1 or 3 d. Parasitological failure by days 14 and 28 (polymerase chain reaction [PCR]-corrected for new infections) were the primary endpoints. Treatment failure rates by day 14 were 25.5% in the SP alone group, 16.2% (risk difference [delta]-9.3%, 95% CI -17.3 to -1.2%, P= 0.027) in the 1-dose artesunate group, and 9.4% (delta-16.2%, 95% CI -23.6 to -8.7%, P< 0.001) in the 3-dose artesunate group. Corresponding rates by day 28 were 46.0% in the SP alone group, 38.2% (delta-7.8%, 95% CI -17.7 to 2.1%, P= 0.16) in the 1-dose artesunate group, and 26.0% (delta-20.0%, 95% CI -29.4 to -10.6%, P < 0.001) in the 3-dose artesunate group. The artesunate and SP combination was well tolerated. There were no serious drug-related adverse events. Parasite clearance and gametocyte carriage were reduced significantly in both combination groups compared with SP alone. Three days of artesunate were required to reduce significantly the risk of treatment failure by day 28. However, the high background rate of parasitological failure with SP may make this combination unsuitable for widespread use in Kenya.

10825049
Ohrt C, Mirabelli-Primdahl L, Looareesuwan S, Wilairatana P, Walsh D, Kain KC
Determination of failure of treatment of plasmodium falciparum infection by using polymerase chain reaction single-strand conformational polymorphism fingerprinting.
Clin Infect Dis. 1999 Apr;28(4):847-52.
The inability to distinguish failures of treatment of Plasmodium falciparum infection from new infections is an important impediment to the evaluation of antimalarial drugs. On the basis of a pilot study utilizing polymerase chain reaction (PCR) single-strand conformational polymorphism (SSCP) analysis to genotype P. falciparum isolates, we sought to confirm that PCR SSCP analysis could reliably distinguish infections for which treatment failed from unrelated infections with a sample size adequate to estimate the accuracy of this technique. PCR SSCP analysis of the MSP-1, MSP-2, and GLURP genes was performed on 72 paired isolates recovered from 36 individuals for whom treatment failed in Thailand. In every case (100% [95% confidence interval (CI), 90%-100%]), the PCR SSCP pattern of the recrudescent isolates matched that of the primary isolate. We determined whether PCR SSCP analysis could separate unrelated infections by comparing each recrudescent isolate with each of the unrelated primary isolates. Of 1,260 comparisons, 1,258 (99.8% [95% CI, 99.4%-100%]) were unique. The results indicate that PCR SSCP analysis can be used to differentiate infections for which treatment failed from reinfections.

16032560
Olliaro P
Drug resistance hampers our capacity to roll back malaria.
Clin Infect Dis. 2005 Aug 15;41 Suppl 4:S247-57.
Widespread drug resistance in parasites aggravates the burden of malaria. The extent of the problem is due mainly to the limited armamentarium of drugs used thus far to treat malaria and to policies and practices constrained by limited resources. All drugs in use are affected except, thus far, artemisinin derivatives. The scale and impact of resistance has been underestimated, leading to the continued use of failing drugs, which contributes to the rise in resistance and increased morbidity and mortality due to malaria. Pharmacological, epidemiological, and operational aspects factor the development and spread of resistance. Although the problem is complex, much can be done to reverse the course of events: adopt adequate tests to assess resistance, encourage and sustain development of new drugs, protect drugs against resistance through use of combinations, expand access to prompt and effective treatment, and promote evidence-based policies and sensible practices. The current situation favors the development of sensible strategies to restrain resistance.

11703847
Olliaro P, Taylor WR, Rigal J
Controlling malaria: challenges and solutions.
Trop Med Int Health. 2001 Nov;6(11):922-7.
Antimalarial drug resistance is a major public health challenge and the principal reason for the erosion of efficacious treatments. Cost and the limited number of antimalarial drugs in current use impose considerable constraints on malaria control, especially in sub-Saharan Africa. The paper describes a multilateral, multidisciplinary research project on artemisinin-based combination therapy, which offers a new and potentially highly effective way to prevent or retard the development of drug resistance.

11286794

Olliaro PL, Haynes RK, Meunier B, Yuthavong Y
Possible modes of action of the artemisinin-type compounds.
Trends Parasitol. 2001 Mar;17(3):122-6.
Artemisinin-type compounds are used for the treatment of uncomplicated and severe forms of malaria. They reduce parasitaemia more rapidly than any other antimalarial compound known, and are effective against multidrug-resistant parasites. However, uncertainties remain as to how they act on the parasite and cause toxicity. In this review, we summarize current ideas.

14506210
Olliaro PL, Taylor WR
Antimalarial compounds: from bench to bedside.
J Exp Biol. 2003 Nov;206(Pt 21):3753-9.
The emergence and spread of drug-resistant malaria parasites is the major threat to effective malaria control. So far, malaria control has relied heavily on a restricted number of chemically related drugs belonging to either the quinoline or the antifolate groups. Only recently have the artemisinin-type compounds been used widely, predominantly in Southeast Asia. Experience has shown that resistance eventually curtails the life span of antimalarial drugs. If measures are not applied to contain resistance, the investment put into the development of new drugs will be squandered. Current efforts focus, on the one hand, on research into novel compounds with mechanisms of action that are different to the traditionally used drugs, and, on the other hand, on measures to prevent or delay resistance when drugs are introduced. Drug discovery and development are long, risky and expensive ventures. Whilst very few new antimalarial drugs were developed in the last quarter of the 20th century (only four of the nearly 1,400 drugs registered worldwide during 1975-1999), various private and public institutions are at work to discover and develop new compounds. Today, the antimalarial pipeline is relatively healthy. Projects are underway at different stages of drug development, from pre-development to registration. However, there is relatively little novelty, as current development projects still rely upon the traditional quinoline, antifolate and, in particular, artemisinin compounds. New structures are expected from the more upstream discovery efforts but it will take time before they become drugs. Therefore, whilst waiting for the drugs of tomorrow, there is a pressing need for immediately available, effective and affordable drugs that will have long life spans. Drug combinations that have independent modes of action are seen as a way of enhancing efficacy while ensuring mutual protection against resistance. Most research work has focussed on the use of artesunate combined with currently used standard drugs, namely mefloquine, amodiaquine, sulfadoxine/pyrimethamine and chloroquine. There is clear evidence that combinations improve efficacy without increasing toxicity. However, the absolute cure rates that are achieved by combinations vary widely and are dependent on the level of resistance of the standard drug. From these studies, further work is underway to produce fixed dose combinations that will be packaged in blister packs. Malaria control programmes need efficacious drugs that can be used with ease by the populations of endemic countries. This review will summarise current antimalarial drug developments and outline recent clinical research that aims to bring artemisinin-based combinations to those that need them most.

15047998
Olliaro PL, Taylor WR
Developing artemisinin based drug combinations for the treatment of drug resistant falciparum malaria: A review.
J Postgrad Med. 2004 Jan-Mar;50(1):40-4.
The emergence and spread of drug resistant malaria represents a considerable challenge to controlling malaria. To date, malaria control has relied heavily on a comparatively small number of chemically related drugs, belonging to either the quinoline or the antifolate groups. Only recently have the artemisinin derivatives been used but mostly in south east Asia. Experience has shown that resistance eventually curtails the life-span of antimalarial drugs. Controlling resistance is key to ensuring that the investment put into developing new antimalarial drugs is not wasted. Current efforts focus on research into new compounds with novel mechanisms of action, and on measures to prevent or delay resistance when drugs are introduced. Drug discovery and development are long, risky and costly ventures. Antimalarial drug development has traditionally been slow but now various private and public institutions are at work to discover and develop new compounds. Today, the antimalarial development pipeline is looking reasonably healthy. Most development relies on the quinoline, antifolate and artemisinin compounds. There is a pressing need to have effective, easy to use, affordable drugs that will last a long time. Drug combinations that have independent modes of action are seen as a way of enhancing efficacy while ensuring mutual protection against resistance. Most research work has focused on the use of artesunate combined with currently used standard drugs, namely, mefloquine, amodiaquine, sulfadoxine/pyrimethamine, and chloroquine. There is clear evidence that combinations improve efficacy without increasing toxicity. However, the absolute cure rates that are achieved by combinations vary widely and depend on the level of resistance of the standard drug. From these studies, further work is underway to produce fixed dose combinations that will be packaged

in blister packs. This review will summarise current antimalarial drug developments and outline recent clinical research that aims to bring artemisinin based combinations to those that need them most.

15366176
Omari A, Garner P
Malaria in endemic areas.
Clin Evid. 2003 Jun;(9):850-60.

16235412
Omari AA, Gamble C, Garner P
Artemether-lumefantrine (six-dose regimen) for treating uncomplicated falciparum malaria.
Cochrane Database Syst Rev. 2005 Oct 19;(4):CD005564.
BACKGROUND: The World Health Organization recommends artemether-lumefantrine for treating uncomplicated malaria. We sought evidence of superiority of the six-dose regimen over existing treatment regimens as well as its effectiveness in clinical situations. OBJECTIVES: To evaluate the six-dose regimen of artemether-lumefantrine for treating uncomplicated falciparum malaria. SEARCH STRATEGY: We searched the Cochrane Infectious Diseases Group Specialized Register (April 2005), CENTRAL (The Cochrane Library Issue 1, 2005), MEDLINE (1966 to April 2005), EMBASE (1974 to April 2005), LILACS (1982 to April 2005), conference proceedings, and reference lists of articles. We also contacted experts in malaria research and the pharmaceutical company that manufactures artemether-lumefantrine. SELECTION CRITERIA: Randomized controlled trials comparing six doses of artemether-lumefantrine administered orally with standard treatment regimens (single drug or combination), or supervised with unsupervised treatment, for uncomplicated falciparum malaria. DATA COLLECTION AND ANALYSIS: Two authors independently applied inclusion criteria to potentially relevant trials, assessed trial quality, and extracted data, including adverse events. Total failure by day 28 (day 42 for sulfadoxine-pyrimethamine and day 63 for mefloquine) was the primary outcome. MAIN RESULTS: Nine trials (4547 participants) tested the six-dose regimen. Total failure at day 28 for artemether-lumefantrine was lower when compared with amodiaquine (270 participants, 1 trial), amodiaquine plus sulfadoxine-pyrimethamine (507 participants, 1 trial), but not with chloroquine plus sulfadoxine-pyrimethamine (201 participants, 2 trials). In comparisons with artemisinin derivative combinations, artemether-lumefantrine performed better than amodiaquine plus artesunate (668 participants, 2 trials), worse than mefloquine plus artesunate (270 participants, 4 trials), and no differently to dihydroartemisinin-napthoquine-trimethoprim (89 participants, 1 trial). AUTHORS' CONCLUSIONS: The six-dose regimen of artemether-lumefantrine appears more effective than antimalarial regimens not containing artemisinin derivatives.

15040555
Omari AA, Gamble C, Garner P
Artemether-lumefantrine for uncomplicated malaria: a systematic review.
Trop Med Int Health. 2004 Feb;9(2):192-9.
BACKGROUND: The World Health Organization (WHO) is promoting artemether-lumefantrine for treating uncomplicated malaria. The objective of this review is to summarize available evidence of its effects compared with other antimalarial regimens. METHODS: We sought randomized and quasi-randomized studies comparing artemether-lumefantrine with any other antimalarial drug regimen. Databases searched were MEDLINE (to February 2003), EMBASE (to February 2003), and the Cochrane Controlled Trials Register (issue 1, 2003). Conference proceedings and reference article lists were searched and malaria researchers and the drug manufacturer were contacted. Two reviewers independently applied inclusion criteria and extracted data. RESULTS: Six trials (1698 participants) studied the four-dose regimen. Fever and parasite clearance tended to be shorter with artemether-lumefantrine, but parasitological failure on day 28 was more common with artemether-lumefantrine in comparison with mefloquine (one trial, n = 233), halofantrine (one trial, n = 86) and mefloquine-artesunate (one trial, n = 537); but less common with chloroquine (two trials, n = 378). For the six-dose regimen, two studies compared artemether-lumefantrine with mefloquine-artesunate, but there was insufficient data to demonstrate any meaningful comparative effects for day 28 parasitaemia, and no difference in parasite or fever clearance time was detected. There were 11 parasitological failures with artemether-lumefantrine and none with mefloquine-artesunate. CONCLUSION: There is no evidence to demonstrate the four-dose regimen of artemether-lumefantrine results in a higher cure rate than other antimalarial regimens against which it has been tested, apart from chloroquine in areas with high chloroquine resistance. Artemether-lumefantrine has potential advantages over non-artemisinin regimens because of the faster clearance time and gametocyte clearance. There is insufficient evidence about the six-dose regimen to know whether it is less or more effective than current antimalarial drug regimens.

12137676
Omari AA, Preston C, Garner P
Artemether-lumefantrine for treating uncomplicated falciparum malaria.
Cochrane Database Syst Rev. 2002;(3):CD003125.
BACKGROUND: Artemether-lumefantrine is being promoted by the World Health Organization for treating uncomplicated malaria. It is expensive. We sought evidence of its superiority over existing treatment regimens. OBJECTIVES: To compare artemether-lumefantrine with other antimalarial drugs for treating uncomplicated falciparum malaria. SEARCH STRATEGY: We searched the Cochrane Infectious Diseases Group specialized trials register (April 2002), the Cochrane Controlled Trials Register (Issue 2, 2002), MEDLINE (1966 to April 2002), EMBASE (1988 to April 2002), conference proceedings, and reference lists of articles. We contacted experts in malaria research and the pharmaceutical company that manufactures artemether-lumefantrine. SELECTION CRITERIA: Randomized and quasi-randomized trials comparing artemether-lumefantrine administered orally with standard treatment regimens (single drug or combination). DATA COLLECTION AND ANALYSIS: Two reviewers independently applied inclusion criteria to potentially relevant trials, assessed trial quality, and extracted data. Parasitaemia on day 28 (day 42 for sulfadoxine-pyrimethamine and day 63 for mefloquine) was the primary outcome. Adverse event information was collected from the studies. MAIN RESULTS: Eight trials (2117 participants) met the inclusion criteria. In the four studies against single agents, failure rates for artemether-lumefantrine tended to be higher in comparisons against sulfadoxine-pyrimethamine, halofantrine, and mefloquine. This difference was statistically significant for mefloquine. When compared with chloroquine, artemether-lumefantrine was better in two studies, but the failure rate for chloroquine at these sites was over 50%. All single agent studies used four doses of artemether-lumefantrine. In comparisons against combination treatment, three trials tested artemether-lumefantrine against mefloquine-artesunate and showed that artemether-lumefantrine was inferior for day 28 cure (Relative Risk 6.33, 95% confidence interval 3.08 to 13.01). If this comparison is confined to the two trials where participants received six doses, artemether-lumefantrine was associated with higher cure rates, but this was not statistically significant (Relative Risk 4.20, 95% confidence interval 0.55 to 31.93). REVIEWER'S CONCLUSIONS: Artemether-lumefantrine is more effective than chloroquine in chloroquine resistant areas. Artemether-lumefantrine is less effective than mefloquine or mefloquine combined with artesunate. We found no evidence to confirm or refute whether artemether-lumefantrine was better than sulfadoxine-pyrimethamine.

12804451
Omari AA, Preston C, Garner P
Artemether-lumefantrine for treating uncomplicated falciparum malaria.
Cochrane Database Syst Rev. 2003;(2):CD003125.
BACKGROUND: Artemether-lumefantrine is being recommended by the World Health Organization for treating uncomplicated malaria. It is expensive. We sought evidence of its superiority over existing treatment regimens. OBJECTIVES: To compare artemether-lumefantrine with other antimalarial drugs for treating uncomplicated falciparum malaria. SEARCH STRATEGY: We searched the Cochrane Infectious Diseases Group specialized trials register (February 2003), the Cochrane Controlled Trials Register (Issue 1, 2003), MEDLINE (1966 to February 2003), EMBASE (1988 to February 2003), conference proceedings, and reference lists of articles. We contacted experts in malaria research and the pharmaceutical company that manufactures artemether-lumefantrine. SELECTION CRITERIA: Randomized and quasi-randomized trials comparing artemether-lumefantrine administered orally with standard treatment regimens (single drug or combination). DATA COLLECTION AND ANALYSIS: Two reviewers independently applied inclusion criteria to potentially relevant trials, assessed trial quality, and extracted data. Parasitaemia on day 28 (day 42 for sulfadoxine-pyrimethamine and day 63 for mefloquine) was the primary outcome. Adverse event information was collected from the studies. MAIN RESULTS: Six trials (1698 participants) tested a four dose regimen. Failure rates for artemether-lumefantrine tended to be higher (comparisons included sulfadoxine-pyrimethamine, halofantrine, and mefloquine; difference statistically significant for mefloquine). When compared with chloroquine, artemether-lumefantrine was better in two studies, but the failure rate for chloroquine at these sites was over 50%. Two trials (419 participants) tested a six dose regimen against mefloquine plus artesunate. Artemether-lumefantrine was associated with higher failure rates but the studies were small. REVIEWER'S CONCLUSIONS: The four dose regimen of artemether-lumefantrine seems to be less effective than most other current antimalarial regimens. The six dose regimen is largely untested.

15318201
O'Neill PM
Medicinal chemistry: a worthy adversary for malaria.
Nature. 2004 Aug 19;430(7002):838-9.

16144496
O'Neill PM
The therapeutic potential of semi-synthetic artemisinin and synthetic endoperoxide antimalarial agents.
Expert Opin Investig Drugs. 2005 Sep;14(9):1117-28.
Artemisinin derivatives such as artesunate, dihydroartemisinin and artemether are playing an increasing role in the treatment of drug-resistant malaria. They are the most potent antimalarials available, rapidly killing all asexual stages of the parasite Plasmodium falciparum. This review highlights the recent developments in the area of improved second-generation semi-synthetic artemisinin derivatives and fully synthetic antimalarial endoperoxide drugs. In pursuit of synthetic analogues of the artemisinins, one of the major challenges for chemists in this area has been the non-trivial development of techniques for the introduction of the peroxide bridge into candidate drugs. Although chemical research has enabled chemists to incorporate the endoperoxide 'warhead' into synthetic analogues of artemisinin, significant drawbacks with many candidates have included comparatively poor antimalarial activity, non-stereoselective syntheses and chemical approaches that are not readily amenable to scale up. However, very recent progress with synthetic 1,2,4-trioxolanes provides a new benchmark for future medicinal chemistry efforts in this area.

8893847
O'Neill PM, Bishop LP, Storr RC, Hawley SR, Maggs JL, Ward SA, Park BK
Mechanism-based design of parasite-targeted artemisinin derivatives: synthesis and antimalarial activity of benzylamino and alkylamino ether analogues of artemisinin.
J Med Chem. 1996 Oct 25;39(22):4511-4.
Several artemisinin derivatives linked to benzylamino and alkylamino groups were synthesized in order to enhance accumulation within the malaria parasite. The in vitro antimalarial activity was assessed against the chloroquine sensitive HB3 strain and the chloroquine resistant K1 strain of Plasmodium falciparum. In general the incorporation of amino functionality enhances the activity relative to artemisinin. The most potent analogue in the series was compound 6 which was severalfold more active than artemisinin against both strains of P. falciparum used in the study.

15163175
O'Neill PM, Posner GH
A medicinal chemistry perspective on artemisinin and related endoperoxides.
J Med Chem. 2004 Jun 3;47(12):2945-64.

16222725
O'Neill PM, Rawe SL, Borstnik K, Miller A, Ward SA, Bray PG, Davies J, Oh CH, Posner GH
Enantiomeric 1,2,4-trioxanes display equivalent in vitro antimalarial activity versus Plasmodium falciparum malaria parasites: implications for the molecular mechanism of action of the artemisinins.
Chembiochem. 2005 Nov;6(11):2048-54.
The aim of this study was to synthesise pure enantiomers of potent antimalarial 1,2,4-trioxanes, which are related to the natural antimalarial artemisinin, and then to assay each against a panel of Plasmodium falciparum strains. The working hypothesis was that if the artemisinin derivatives interact with a specific protein-target site, then there should be stereoselective differences in their activity. In five different P. falciparum isolates, however, the trioxane enantiomers (+)-7 a, (-)-7 a and (+)-7 b, (-)-7 b, showed the same level of in vitro antiparasitic activity.

2698608
Onori E, Majori G
Recent acquisitions on chemotherapy and chemoprophylaxis of malaria.
Ann Ist Super Sanita. 1989;25(4):659-73.
The most recent acquisitions on chemotherapy and chemoprophylaxis of malaria are reviewed. With regard to chemotherapy, candidate antimalarial compounds have been divided into four groups, according to their stages of development. Mefloquine and the combination of mefloquine with sulfadoxine/pyrimethamine belong to the first group: they have completed clinical trials and have been registered in several countries for routine clinical use. The second group is characterized by chemical compounds which are in an advanced stage of development, including clinical trials. The compounds considered in this group are: a) the 9-phenanthrenemethanols, among which halofantrine is the most promising one; b) the sesquiterpene lactones such as Qinghaosu, artemether, artesunate, artesunic acid and arteether which must be further tested in order to find more effective drug regimens capable of eliminating recrudescences and for the completion of toxicity studies; c) pyronaridine, which appears to be a promising antimalarial, effective also against chloroquine-resistant P. falciparum, but still requiring further investigations on resistance and cross-resistance, as well as its pharmacokinetics, tolerability and bioavailability; d) enpiroline, another promising

compound, which needs to be further studied in Phase II and Phase III investigations with naturally acquired malaria. The third group is composed of seven chemical classes of compounds that are in an advanced pre-clinical development, namely: the 4-aminoquinolines, such as dabechin, piperaquine, hydroxypiperaquine, tripiperaquine, dichlor-quinazine and the Mannich base compounds, the 8-aminoquinolines, the 4-quinolinemethanols, the quinolones, the naphthoquinones, the quinazolines and the dihydrotriazines. Among the many antimalarial compounds of interest, which can be considered at the moment as leads for further studies, only the acridandione derivatives such as floxacrine, the antibiotics, antifungal agents or their metabolites, plant substances such as Yingzhaosu A and quassinoids have been mentioned. Malaria chemoprophylaxis, especially in chloroquine-resistant P. falciparum areas, has become a real problem. The attempts to secure protection under these circumstances with the utilization of amodiaquine, the combination of sulfadoxine/pyrimethamine (Fansidar), sulfalene/pyrimethamine (Metakelfin), of pyrimethamine/dapsone (Maloprim), with or without chloroquine, had to be abandoned or to be used with caution in view of the severe complications following the weekly administration of these drugs. The combination of chloroquine with proguanil or chlorproguanil, which could be recommended on theoretical bases, did not meet the expectations when tested in the field. (ABSTRACT TRUNCATED AT 400 WORDS)

15234659
Onwujekwe O, Uzochukwu B, Shu E, Ibeh C, Okonkwo P
Is combination therapy for malaria based on user-fees worthwhile and equitable to consumers? Assessment of costs and willingness to pay in Southeast Nigeria.
Acta Trop. 2004 Jul;91(2):101-15.
OBJECTIVES: To examine the equity implications of the costs of an episode of malaria, the benefit/cost ratios of using two artemisinin-based combination therapy (CT) from the consumers' view and inequities in willingness to pay (WTP) for CT. METHODS: A cross-sectional survey was conducted in Southeast Nigeria, where there is a moderate to high level of malaria resistance to chloroquine and sulfadoxine-pyrimethamine formulations. WTP was elicited from respondents using the bidding game (BG) and the structured haggling technique (SH). A socio-economic status (SES) index was used to examine the level of inequity in the key variables. In the benefit/cost ratios, the average cost of CT in Nigeria and price of Coartem were, respectively, used as the cost inputs while the mean WTP was the measure of benefit. Multiple regression analyses were used to determine the validity of the WTP estimates. RESULTS: More than 90% of the respondents were willing to pay for CT. The mean WTP in the BG was 301.1 Naira while it was 438.0 Naira in the SH. People in the highest SES quartile (Q4) were more willing to pay for CT than the lowest SES quartile (Q1). In the regression models, the SES quartiles were significantly related to levels of WTP. The benefit/cost ratios were higher in the SH group, and the ratio was only more than 1 using Coartem in only the SH group. The Q1 groups had the least benefit cost-ratios but the trend of SES differentials in benefit/cost ratios were not statistically significant in the BG group but was in the SH group. CONCLUSION: CT based on user-fees may not be worthwhile and equitable because there are economic and equity constraints to its wide-scale use. Benefit/cost ratios depend on the type of questions that were used to elicit WTP. Governments and donors should be willing to commit funds to make CT affordable to the poor consumers for the intervention to be used to significantly reduce the burden of malaria.

15678806
Orjuela P, Gonzalez I, Osorio L
[Combination therapy as a strategy to prevent antimalarial drug resistance]
Biomedica. 2004 Dec;24(4):423-37.
Resistance of Plasmodium falciparum to antimalarials is considered one of the factors responsible for the impairment of the malaria treatment and control worldwide. Resistance emerges as a result of selection and then disemination of spontaneous mutant parasites with reduced drug susceptibility. Combination therapy is considered as the main strategy to control antimalarial drug resistance. Currently, combination therapies that include artemisinin derivatives are highly recommended. Combination therapy has been used in Colombia for more than 20 years; however, its impact on preventing the dissemination of drug resistance is unknown. This paper reviews the theoretical bases and clinical studies that support the use of combination therapy.

11706664
Orrell C, Taylor WR, Olliaro P
Acute asymptomatic hepatitis in a healthy normal volunteer exposed to 2 oral doses of amodiaquine and artesunate.
Trans R Soc Trop Med Hyg. 2001 Sep-Oct;95(5):517-8.
Combination antimalarial therapy is being explored to delay development of resistance to falciparum malaria. This report describes an unexpected drug-induced hepatitis in a previously healthy young woman exposed to 2 doses of amodiaquine and artesunate. Use of these combinations should be closely monitored.

16034957

Orton L, Garner P
Drugs for treating uncomplicated malaria in pregnant women.
Cochrane Database Syst Rev. 2005 Jul 20;(3):CD004912.
BACKGROUND: Women are more vulnerable to malaria during pregnancy, and malaria infection may have adverse consequences for the fetus. Identifying safe and effective treatments is important. OBJECTIVES: To compare the effects of drug regimens for treating uncomplicated falciparum malaria in pregnant women. SEARCH STRATEGY: We searched the Cochrane Infectious Diseases Group Specialized Register (May 2005), Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 2, 2005), MEDLINE (1966 to May 2005), EMBASE (1974 to May 2005), LILACS (May 2005), reference lists, and conference abstracts. We also contacted researchers in the field, organizations, and pharmaceutical companies. SELECTION CRITERIA: Randomized and quasi-randomized controlled trials of antimalarial drugs for treating uncomplicated malaria in pregnant women. DATA COLLECTION AND ANALYSIS: Both authors assessed trial eligibility and methodological quality, and extracted data. We performed a quantitative analysis only where we could combine the data. We combined dichotomous data using relative risk (RR) with 95% confidence intervals (CI). MAIN RESULTS: Six trials (513 participants) met the inclusion criteria. Two were quasi-randomized, and none described allocation concealment. Data were scarce for the primary outcome, treatment failure. One trial compared artesunate plus mefloquine with quinine and reported fewer treatment failures at day 63 with the combination (RR 0.09, 95% CI 0.02 to 0.38; 106 participants). AUTHORS' CONCLUSIONS: There is insufficient reliable research on malaria treatment options in pregnancy.

16235366
Osei-Akoto A, Orton L, Owusu-Ofori SP
Atovaquone-proguanil for treating uncomplicated malaria.
Cochrane Database Syst Rev. 2005 Oct 19;(4):CD004529.
BACKGROUND: Many conventional treatments for uncomplicated malaria are failing because malaria parasites develop resistance to them. One way to combat this resistance is to treat people with a combination of drugs, such as atovaquone-proguanil. OBJECTIVES: To compare atovaquone-proguanil with other antimalarial drugs (alone or in combination) for treating children and adults with uncomplicated Plasmodium falciparum malaria. SEARCH STRATEGY: We searched the Cochrane Infectious Diseases Group Specialized Register (June 2005), CENTRAL (The Cochrane Library Issue 2, 2005), MEDLINE (1966 to June 2005), EMBASE (1980 to June 2005), LILACS (1982 to June 2005), reference lists, and conference abstracts. We also contacted relevant pharmaceutical manufacturers and researchers. SELECTION CRITERIA: Randomized controlled trials comparing atovaquone-proguanil with other antimalarial drugs for treating children and adults confirmed to have uncomplicated P. falciparum malaria. DATA COLLECTION AND ANALYSIS: Three authors independently assessed trial eligibility and methodological quality, and extracted data for an intention-to-treat analysis (where possible). We used relative risk (RR) and 95% confidence intervals (CI) for dichotomous data. We contacted trial authors for additional information where needed. MAIN RESULTS: Ten trials, with a total of 2345 participants, met the inclusion criteria. The trials were conducted in four geographical regions and were often small, but they included comparisons across eight drugs. Nine trials were funded by a pharmaceutical company, only three carried out an intention-to-treat analysis, and allocation concealment was unclear in seven. Atovaquone-proguanil had fewer treatment failures by day 28 than chloroquine (RR 0.04, 95% CI 0.00 to 0.57; 27 participants, 1 trial), amodiaquine (RR 0.22, 95% CI 0.13 to 0.36; 342 participants, 2 trials), and mefloquine (RR 0.04, 95% CI 0.00 to 0.73; 158 participants, 1 trial). There were insufficient data to draw a conclusion for this outcome from comparisons with sulfadoxine-pyrimethamine (172 participants, 2 trials), halofantrine (205 participants, 1 trial), artesunate plus mefloquine (1063 participants, 1 trial), quinine plus tetracycline (154 participants, 1 trial), and dihydroartemisinin-piperaquine-trimethoprim-primaquine (161 participants, 1 trial). Adverse events were mainly common symptoms of malaria and did not differ in frequency between groups. AUTHORS' CONCLUSIONS: Data are limited but appear to suggest that atovaquone-proguanil is more effective than chloroquine, amodiaquine, and mefloquine. There are insufficient data for comparisons against sulfadoxine-pyrimethamine, halofantrine, artesunate plus mefloquine, quinine plus tetracycline, and dihydroartemisinin-piperaquine-trimethoprim-primaquine in treating malaria. There are not enough data to assess safety, but a number of adverse events were identified with all drugs. Large trials comparing atovaquone-proguanil with other new combination therapies are needed.

11592502
Otoguro K, Kohana A, Manabe C, Ishiyama A, Ui H, Shiomi K, Yamada H, Omura S
Potent antimalarial activities of polyether antibiotic, X-206.
J Antibiot (Tokyo). 2001 Aug;54(8):658-63.
In the course of our screening program to discover antimalarial antibiotics, which are active against drug resistant Plasmodium falciparum in vitro and rodents infected with P. berghei in vivo, from the culture broth of microorganisms, we found a selective and potent active substance produced by an actinomycete strain K99-0413. It was identified as a known polyether antibiotic, X-206. We also compared the in vitro antimalarial

activities and cytotoxicities of 12 known polyethers with X-206. Among them, X-206 showed the most selective and potent inhibitory effect against both drug resistant and sensitive strains of P. falciparum. Comparison of biological activities and ion-affinities of the above antibiotics suggests that monovalent cations play an important biological role for the intracellular growth of P. falciparum in parasitized erythrocytes. Moreover, X-206 showed potent in vivo antimalarial activity on the rodent model, though the therapeutic window was narrow compared with its selective toxicity in vitro. These observations are the first report of antimalarial activity of X-206.

10679261
Padmanaban G, Rangarajan PN
Heme metabolism of Plasmodium is a major antimalarial target.
Biochem Biophys Res Commun. 2000 Feb 24;268(3):665-8.
The malarial parasite manifests unique features of heme metabolism. In the intraerythrocyte stage it utilizes the host hemoglobin to generate amino acids for its own protein synthesis, but polymerizes the acquired heme as a mechanism for detoxification. At the same time the parasite synthesizes heme de novo for metabolic use. The heme biosynthetic pathway of the parasite is similar to that of hepatocytes and erythrocytes. However, while the parasite makes its own delta-aminolevulinate (ALA) synthase that is immunochemically different from that of the host, it imports ALA dehydrase and perhaps the subsequent enzymes of the pathway from the host red cell. Many schizonticidal drugs such as chloroquine and artemisinin act by interfering with the heme metabolism of the parasite and there is scope to design new molecules based on the unique features of this metabolic machinery in the parasite.

15941428
Pagnoni F, Kengeya-Kayondo J, Ridley R, Were W, Nafo-Traore F, Namboze J, Sirima S
Artemisinin-based combination treatment in home-based management of malaria.
Trop Med Int Health. 2005 Jun;10(6):621-2.

2698476
Pan HZ, Lin FB, Zhang ZA
Effect of sodium artesunate on malaria infected human erythrocytes.
Proc Chin Acad Med Sci Peking Union Med Coll. 1989;4(4):181-5.
Oxidative stress in malaria infected human erythrocytes is augmented and the anti-oxidant system is attenuated as compared with normal RBC's. Exacerbation of intra-erythrocytic oxidative stress might provide a means to kill the parasites. Sodium artesunate (SA), an effective Chinese anti-malaria drug, markedly increased the levels of active oxygen species and production of malonyldialdehyde in normal red blood cells and, to a greater extent, in malaria infected red blood cells. SA caused a remarkable decrease of unsaturated fatty acids content in normal red blood cell membrane. These suggest that the anti-oxidative system in red blood cells infected with malaria is jeopardized. Certain active oxygen species generated and accumulated in such red blood cells might in turn kill the parasites. SA augmented intracellular O2-. and H2O2 production, and this may partly account for its antimalaria action.

12927780
Pandey AV, Babbarwal VK, Okoyeh JN, Joshi RM, Puri SK, Singh RL, Chauhan VS
Hemozoin formation in malaria: a two-step process involving histidine-rich proteins and lipids.
Biochem Biophys Res Commun. 2003 Sep 5;308(4):736-43.
Major blood stage antimalarial drugs like chloroquine and artemisinin target the heme detoxification process of the malaria parasite. Hemozoin formation reactions in vitro using the Plasmodium falciparum histidine-rich protein-2 (Pfhrp-2), lipids, and auto-catalysis are slow and could not explain the speed of detoxification needed for parasite survival. Here, we show that malarial hemozoin formation is a coordinated two component process involving both lipids and histidine-rich proteins. Hemozoin formation efficiency in vitro is 1-2% with Pfhrp-2 and 0.25-0.5% with lipids. We added lipids after 9h in a 12h Pfhrp-2 mediated reaction that resulted in sixfold increase in hemozoin formation. However, a lipid mediated reaction in which Pfhrp-2 was added after 9h produced only twofold increase in hemozoin production compared to the reaction with Pfhrp-2 alone. Synthetic peptides corresponding to the Pfhrp-2 heme binding sequences, based on repeats of AHHAAD, neither alone nor in combination with lipids were able to generate hemozoin in vitro. These results indicate that hemozoin formation in malaria parasite involves both the lipids and the scaffolding proteins. Histidine-rich proteins might facilitate hemozoin formation by binding with a large number of heme molecules, and facilitating the dimer formation involving iron-carboxylate bond between two heme molecules, and lipids may then subsequently assist the mechanism of long chain formation, held together by hydrogen bonds or through extensive networking of hydrogen bonds.

10383451
Pandey AV, Tekwani BL, Singh RL, Chauhan VS
Artemisinin, an endoperoxide antimalarial, disrupts the hemoglobin catabolism and heme detoxification systems in malarial parasite.
J Biol Chem. 1999 Jul 2;274(27):19383-8.
Endoperoxide antimalarials based on the ancient Chinese drug Qinghaosu (artemisinin) are currently our major hope in the fight against drug-resistant malaria. Rational drug design based on artemisinin and its analogues is slow as the mechanism of action of these antimalarials is not clear. Here we report that these drugs, at least in part, exert their effect by interfering with the plasmodial hemoglobin catabolic pathway and inhibition of heme polymerization. In an in vitro experiment we observed inhibition of digestive vacuole proteolytic activity of malarial parasite by artemisinin. These observations were further confirmed by ex vivo experiments showing accumulation of hemoglobin in the parasites treated with artemisinin, suggesting inhibition of hemoglobin degradation. We found artemisinin to be a potent inhibitor of heme polymerization activity mediated by Plasmodium yoelii lysates as well as Plasmodium falciparum histidine-rich protein II. Interaction of artemisinin with the purified malarial hemozoin in vitro resulted in the concentration-dependent breakdown of the malaria pigment. Our results presented here may explain the selective and rapid toxicity of these drugs on mature, hemozoin-containing, stages of malarial parasite. Since artemisinin and its analogues appear to have similar molecular targets as chloroquine despite having different structures, they can potentially bypass the quinoline resistance machinery of the malarial parasite, which causes sublethal accumulation of these drugs in resistant strains.

12737317
Pankova-Kholmyansky I, Dagan A, Gold D, Zaslavsky Z, Skutelsky E, Gatt S, Flescher E
Ceramide mediates growth inhibition of the Plasmodium falciparum parasite.
Cell Mol Life Sci. 2003 Mar;60(3):577-87.
In mammalian cells, ceramide mediates death by chemotherapeutic drugs. We analysed, for the first time, the role of ceramide in inhibiting growth of the malaria-causing parasite Plasmodium falciparum. Added exogenously, ceramide significantly decreased the number of parasites, and this effect was abolished by sphingosine-1-phosphate, a biological antagonist of ceramide action. Ceramide can induce death of cancer cells by decreasing glutathione levels, and in our work it induced dose- and time-dependent depletion of glutathione in P. falciparum parasites. N-acetylcysteine, a precursor of glutathione, abrogated the cytotoxic effect of ceramide. Thus, ceramide can mediate growth inhibition of P. falciparum parasites by decreasing glutathione levels. The antimalarial drugs artemisinin and mefloquine induced the death of P. falciparum parasites by sphingomyelinase-generated ceramide and by decreasing parasite glutathione levels. Altogether, ceramide was identified as a signalling molecule capable of inducing growth inhibition of P. falciparum malarial parasites.

15714418
Panosian CB
Economic access to effective drugs for falciparum malaria.
Clin Infect Dis. 2005 Mar 1;40(5):713-7. Epub 2005 Feb 3.
The increasing death toll from drug-resistant falciparum malaria is cause for international concern. In 2002, the US Agency for International Development commissioned the Institute of Medicine (IOM) to recommend global actions to ensure the broadest possible access to new, effective antimalarial treatments. In a report issued in 2004, the IOM Committee on Economics of Antimalarial Drugs recommended a global subsidy of 300 million dollars to 500 million dollars per year to replace increasingly ineffective drugs with coformulated artemisinin combination treatments to be distributed through public and private channels in affected areas. This approach allows the existing market to support the switch to new drugs and keeps treatment costs for consumers at levels similar to the current price of chloroquine. The leverage of an international subsidy of combination therapy can also discourage the distribution of monotherapies (such as solo artemisinins), the use of which might foster increasing resistance to antimalarial drugs in the future.

15388339
Parapini S, Basilico N, Mondani M, Olliaro P, Taramelli D, Monti D
Evidence that haem iron in the malaria parasite is not needed for the antimalarial effects of artemisinin.
FEBS Lett. 2004 Sep 24;575(1-3):91-4.
The role of haem iron (II) and oxidative stress in the activation and antimalarial activity of artemisinin is unclear. Thus, we submitted malaria parasite to modified culture conditions: artemisinin activity increased by 20-30% under an oxygen-rich atmosphere (20% O2 instead of "standard" 1% O2), and by 40-50% in the presence of carboxy-haemoglobin, and 2% carbon monoxide, conditions which inhibit haem iron (II) reactivity. In all cases, parasite growth and chloroquine activity were unaffected. We conclude that in the malaria parasite artemisinin is not activated by haem iron and that free radicals are not needed for its toxicity.

9862239
Park BK, O'Neill PM, Maggs JL, Pirmohamed M
Safety assessment of peroxide antimalarials: clinical and chemical perspectives.
Br J Clin Pharmacol. 1998 Dec;46(6):521-9.

15879383
Parry J
WHO combats counterfeit malaria drugs in Asia.
BMJ. 2005 May 7;330(7499):1044.

14735322
Parshikov IA, Muraleedharan KM, Avery MA, Williamson JS
Transformation of artemisinin by Cunninghamella elegans.
Appl Microbiol Biotechnol. 2004 Jun;64(6):782-6. Epub 2004 Jan 21.
Semi-synthetic derivatives of the anti-malarial drug artemisinin hold great promise in the search for an effective and economical treatment of chloroquine-resistant forms of malaria. Unfortunately, synthetic functionalization of the artemisinin skeleton is often tedious and/or impractical. We seek to utilize 7beta-hydroxyartemisinin, obtained from microbial transformation, as a semi-synthetic precursor for the synthesis of novel 7beta-substituted artemisinin anti-malarial agents. Here we employ liquid cultures of Cunninghamella elegans as a means for the rational and economical bioconversion of artemisinin to 7beta-hydroxyartemisinin in 78.6% yield. In addition, there were three other bioconversion products: 7beta-hydroxy-9alpha-artemisinin (6.0%), 4alpha-hydroxy-1-deoxoartemisinin (5.4%), and 6beta-hydroxyartemisinin (6.5%).

15276165
Pashynska VA, Van den Heuvel H, Claeys M, Kosevich MV
Characterization of noncovalent complexes of antimalarial agents of the artemisinin-type and FE(III)-heme by electrospray mass spectrometry and collisional activation tandem mass spectrometry.
J Am Soc Mass Spectrom. 2004 Aug;15(8):1181-90.
In this study, we demonstrate, using electrospray ionization mass spectrometry (ESI-MS) and collision-induced dissociation tandem mass spectrometry (ESI-MS/CID/MS), that stable noncovalent complexes can be formed between Fe(III)-heme and antimalarial agents, i.e., quinine, artemisinin, and the artemisinin derivatives, dihydroartemisinin, alpha- and beta-artemether, and beta-arteether. Differences in the binding behavior of the examined drugs with Fe(III)-heme and the stability of the drug-heme complexes are demonstrated. The results show that all tested antimalarial agents form a drug-heme complex with a 1:1 stoichiometry but that quinine also results in a second complex with the heme dimer. ESI-MS performed on mixtures of pairs of various antimalarial agents with heme indicate that quinine binds preferentially to Fe(III)-heme, while ESI-MS/CID/MS shows that the quinine-heme complex is nearly two times more stable than the complexes formed between heme and artemisinin or its derivatives. Moreover, it is found that dihydroartemisinin, the active metabolite of the artemisinin-type drugs in vivo, results in a Na(+)-containing heme-drug complex, which is as stable as the heme-quinine complex. The efficiency of drug-heme binding of artemisinin derivatives is generally lower and the decomposition under CID higher compared with quinine, but these parameters are within the same order of magnitude. These results suggest that the efficiency of antimalarial agents of the artemisinin-type to form noncovalent complexes with Fe(III)-heme is comparable with that of the traditional antimalarial agent, quinine. Our study illustrates that electrospray ionization mass spectrometry and collision-induced dissociation tandem mass spectrometry are suitable tools to probe noncovalent interactions between heme and antimalarial agents. The results obtained provide insights into the underlying molecular modes of action of the traditional antimalarial agent quinine and of the antimalarials of the artemisinin-type which are currently used to treat severe or multidrug-resistant malaria.

16495509
Pasvol G
The treatment of complicated and severe malaria.
Br Med Bull. 2006 Feb 22;75-76:29-47. Print 2006.
All cases of falciparum malaria are potentially severe and life threatening, especially when managed inappropriately. A major reason for progression from mild through complicated to severe disease is missed or delayed diagnosis. Once diagnosed, the priority for treatment of complicated and severe disease is the parenteral administration of adequate, safe doses of an appropriate antimalarial, in the setting of the highest possible level of clinical care (i.e. usually an intensive care unit). Supportive management of complications

such as coma, convulsions, metabolic acidosis, hypoglycaemia, fluid and electrolyte disturbances, renal failure, secondary infections, bleeding disorders and anaemia is also important. The most recent advance in antimalarial chemotherapy has been the use of artemisinin derivatives especially intravenous artesunate, which may well revolutionize the management of severe disease. Outside antimalarial therapy, mechanical ventilation and renal replacement have also played an important role in reducing mortality of this life-threatening condition.

12084956
Patel AB, Belsare H
Resistant malaria in a neonate.
Indian Pediatr. 2002 Jun;39(6):585-8.

16124423
Pengsaa K, Sirivichayakul C, Na-Bangchang K, Thaiarporn I, Chaivisuth A, Wongsuwan A, Attanath P, Pojjaroen-Anant C, Wisetsing P, Chanthavanich P, Sabchareon A
Life-saving rectal artesunate for complicated malaria in children.
Southeast Asian J Trop Med Public Health. 2005 May;36(3):597-601.
We report the effectiveness of two regimens of rectal artesunate formulation in treating 13 Thai children with cerebral/complicated falciparum malaria. The drug was given at an initial dose of 40 mg/kg bodyweight, in 3 or 4 divided doses in the first 24 hours, followed by 10 mg/kg bodyweight once daily for three consecutive days. Mefloquine, at a dose of 15 mg/kg bodyweight was given orally at 72 hours after the initial dose of artesunate, followed by 10 mg/kg bodyweight 6 hours later. Three cases with cerebral malaria gained consciousness within 20 hours of artesunate administration. The median time required for reduction of parasitemia by 90% of the initial value (P90) in 13 children was 11.2 hours. No recrudescence was observed in any of the patients during the 28-day follow-up period. Plasma concentrations of artesunate and dihydroartemisinin (active plasma metabolite of artesunate) measured in two patients who received the high initial dose regimen (20 mg/ kg bodyweight) suggested rapid absorption and adequate plasma concentrations of both compounds following the administration of artesunate via the rectal route. Further studies for the optimized regimen of rectal artesunate in the treatment of cerebral/complicated childhood falciparum malaria in areas of multidrug resistance are warranted.

11479001
Pestell K
Dodgy malaria drugs.
Trends Pharmacol Sci. 2001 Aug;22(8):402.

12396319
Peters W, Fleck SL, Robinson BL, Stewart LB, Jefford CW
The chemotherapy of rodent malaria. LX. The importance of formulation in evaluating the blood schizontocidal activity of some endoperoxide antimalarials.
Ann Trop Med Parasitol. 2002 Sep;96(6):559-73.
The activities of artemisinin (QHS) and a number of its semi-synthetic analogues, as well as Fenozan B07 (B07), a synthetic 1,2,4-trioxane, and arteflene (ATF), a synthetic surrogate of yingzhaosu, were compared in mice infected with drug-sensitive Plasmodium berghei or chloroquine-resistant P. yoelii ssp. NS. The studies were stimulated by the observation that B07, in certain aqueous preparations, appears to be equipotent by the subcutaneous (sc) or oral (po) routes in the rodent model but not in a simian model. In the rodent model, B07 was found to undergo rapid alteration (with a half-life of

3307655
Peters W, Li ZL, Robinson BL, Warhurst DC
The chemotherapy of rodent malaria, XL. The action of artemisinin and related sesquiterpenes.
Ann Trop Med Parasitol. 1986 Oct;80(5):483-9.
Artemisinin (Qinghaosu), a poorly soluble sesquiterpene lactone derived from the plant Artemisia annua Linn., and a number of more soluble, semi-synthetic derivatives are rapidly-acting blood schizontocides against Plasmodium berghei and P. yoelii nigeriensis. An oily suspension of artemisinin given s.c. is more effective than aqueous suspensions. The activity is retained against lines resistant to primaquine, cycloguanil, pyrimethamine, sulphonamides, mefloquine and menoctone, but a highly chloroquine-resistant line is much less sensitive. Artemisinin has no causal prophylactic, gametocytocidal or sporontocidal action. Dihydroartemisinin causes the pigment of P. berghei to clump, but in a different fashion from the pigment

changes induced by chloroquine or quinine, reflecting a different mode of action of the sesquiterpenes from that of these other antimalarials.

9307655
Peters W, Robinson BL
The chemotherapy of rodent malaria. LV. Interactions between pyronaridine and artemisinin.
Ann Trop Med Parasitol. 1997 Mar;91(2):141-5.
Two interactions of two potent blood schizontocides, pyronaridine and artemisinin, were assessed in mice infected with chloroquine-resistant Plasmodium yoelii ssp. NS or one of two lines derived from it, namely ART, which is resistant to artemisinin and SPN, which is resistant to pyronaridine. While the drug combination proved to be only additive in its action against P. yoelii ssp. NS, a marked potentiation between the two compounds was observed against the ART and SPN lines. The implications of the findings in terms of the impeding of drug resistance when these compounds are deployed for the treatment of multi-drug-resistant P. falciparum are discussed.

10656034
Peters W, Robinson BL
The chemotherapy of rodent malaria. LVI. Studies on the development of resistance to natural and synthetic endoperoxides.
Ann Trop Med Parasitol. 1999 Jun;93(4):325-9.
Chloroquine-sensitive Plasmodium berghei N and chloroquine-resistant P. yoelii ssp. NS were exposed to selection pressure, in the '2% relapse technique', from artemisinin, artesunate, a bicyclic, synthetic endoperoxide Ro 41-3823 (an analogue of arteflene) or Fenozan B07, a synthetic 1,2,4-trioxane endoperoxide. Whereas resistance against artemisinin did develop to a moderate level in both parasites, only a low level of resistance or none developed to the other compounds, and resistant parasites readily lost resistance once drug-selection pressure was withdrawn. The relevance of these observations and the experience of other investigators are discussed in relation to the possible risk that resistance may be developed in nature once endoperoxides are deployed widely against multidrug-resistant P. falciparum.

10723521
Peters W, Robinson BL
The chemotherapy of rodent malaria. LVIII. Drug combinations to impede the selection of drug resistance, Part. 2: The new generation--artemisinin or artesunate with long-acting blood schizontocides.
Ann Trop Med Parasitol. 2000 Jan;94(1):23-35.
The search for combinations of antimalarial drugs that will impede the selection of drug resistance, especially in Plasmodium falciparum, is currently focused on the use of a member of the artemisinin family, with a short half-life, in association with a relatively long-acting blood schizontocide. Experiments with such 'third-generation' combinations, in mice infected either with chloroquine-sensitive P. berghei or P. chabaudi, or chloroquine-resistant P. yoelii ssp. NS, have produced interesting results. The data collected, using the '2% relapse technique' (2%RT), indicate that a combination of artemisinin with mefloquine can impede to a significant degree, although by no means completely, the selection of resistance to both compounds in P. berghei and in P. yoelii ssp. NS. Similarly, a combination of artesunate with pyronaridine impedes the selection of resistance to these compounds in P. berghei. Parallels are drawn between observations with such combinations in man and in the rodent models which, it is argued, once again demonstrate their value in predicting the protective value of using different types of antimalarials together. Evidence is presented that resistance to single compounds may emerge more rapidly when a high dose is employed in the 2%RT than a lower dose. It is noted also that the rate at which resistance to pyronaridine is selected by a given dose varies with the species of rodent Plasmodium, and the relevance of this to the malarial parasites of human is discussed.

8346987
Peters W, Robinson BL, Rossier JC, Jefford CW
The chemotherapy of rodent malaria. XLVIII. The activities of some synthetic 1,2,4-trioxanes against chloroquine-sensitive and chloroquine-resistant parasites. Part 1: Studies leading to the development of novel cis-fused cyclopenteno derivatives.
Ann Trop Med Parasitol. 1993 Feb;87(1):1-7.
The new Chinese antimalarial blood schizontocide, artemisinin, derived from the plant Artemisia annua, displays a high level of activity against polyresistant Plasmodium falciparum. Several synthetic 1,2,4-trioxanes were examined in a search for compounds that exhibit a similar type of action against drug-resistant parasites. This paper, the first of a series, describes the examination of these trioxanes against drug-sensitive and drug-resistant malaria parasites in a rodent model, using artemisinin and arteether as comparison standards. Cis-fused cyclohexeno-1,2,4-trioxanes (10-17) substituted with various side-chains revealed for the most part variable but weak antimalarial activity. On the other hand, cis-fused cyclopenteno-

1,2,4-trioxanes (18-19) showed greater activity, 19 showing about 1/30th of the activity of arteether against drug-sensitive Plasmodium berghei in vivo, thereby providing a clue to the structure-activity relationship.

8561518
Peters W, Robinson BL, Tovey G, Rossier JC, Jefford CW
The chemotherapy of rodent malaria. L. The activities of some synthetic 1,2,4-trioxanes against chloroquine-sensitive and chloroquine-resistant parasites. Part 3: Observations on 'Fenozan-50F', a difluorinated 3,3'-spirocyclopentane 1,2,4-trioxane.
Ann Trop Med Parasitol. 1993 Apr;87(2):111-23.
A novel difluorinated 3,3'-spirocyclopentane 1,2,4-trioxane ('Fenozan-50F') is a potent blood schizontocide against drug-sensitive and drug-resistant rodent malaria parasites. It also exerts some action against pre-erythrocytic schizogony, is a potent gametocytocide, and exerts a direct sporontocidal effect in infected mosquitoes. In the '4-day test' the ED90s are 6.8 and 6.0 mg/kg/day for four consecutive days by the subcutaneous and oral routes respectively against drug-sensitive Plasmodium berghei N, and 6.3 and 25 mg/kg against chloroquine-resistant P. yoelii NS in vivo. By the oral route against P. berghei N infection in mice, Fenozan-50F is about half as active as arteether but nearly three times as active as sodium artesunate. The activity of Fenozan-50F is retained against a wide spectrum of drug-resistant parasite lines, although those highly resistant to quinine or to artemisinin are less responsive at the ED90 level. At the ultrastructural level the compound, when administered to infected mice, causes marked changes in the membranes and ribosomes of trophozoites and young schizonts and of immature gametocytes, although few changes are apparent in mature gametocytes. Its toxicity appears to be very low when it is administered to mice by either the oral or subcutaneous route. Fenozan-50F is considered to be a good candidate for eventual use as a therapeutic agent for infection with polyresistant malaria in man.

16004705
Peters W, Stewart LB, Robinson BL
The chemotherapy of rodent malaria. LXIII. Drug combinations to impede the selection of drug resistance, part 6: the potential value of chlorproguanil and dapsone in combination, and with the addition of artesunate.
Ann Trop Med Parasitol. 2005 Jul;99(5):457-72.
Resistance is readily produced in rodent malaria using the single-dose, '2%-relapse technique' (2%RT) against the individual compounds chlorproguanil (CPG), chlorcycloguanil (CCG), cycloguanil, dapsone (DDS) and artesunate (ASN). Using the '4-day test', a low level of synergism or a simple additional action between CPG and DDS was observed with multiple dosing of these two compounds in a combination. Resistance to a 1 : 3 combination of CPG-DDS was selected in each of three parasite lines: Plasmodium berghei NK65, P. yoelii ssp. NS and P. chabaudi AS. Of these lines, P. chabaudi AS was found to be the most sensitive to the 1 : 3 combination in the 2%RT (and was also previously found to be the most sensitive when the compounds were used individually). Plasmodium chabaudi AS was also the line found most sensitive to a 7 : 21 : 300 combination of CPG-DDS-ASN (CDA). In mice infected with P. chabaudi AS, compared with the use of the individual components, the CPG-DDS combination only a gave a modest level of protection (as indicated by the increase in the time required to select resistance in the 2%RT) but the triple CDA combination was totally effective over the duration of the experiment. New pharmacokinetic data to be reported elsewhere indicate, however, that the antimalarial action of CPG in mice is exerted by a mechanism that is not associated with the drug's conversion to the antifolate triazine, CCG. The question thus arises as to how, in the present model, the protective action of CDA was effected. The present results nevertheless reinforce the hypothesis that a CDA combination, appropriately proportioned for human use, should be of practical value, in protecting the individual components, when used for the treatment of multidrug-resistant P. falciparum, and possibly other Plasmodium species, in endemic areas. Clinical trials, both with a CPG-DDS combination (Lapdap) and CDA, are currently under way in tropical Africa. Further studies are now required to determine whether DDS, CPG or an as-yet unidentified metabolite of CPG interact with ASN, and whether a simple double combination of ASN with one or other of these would be as protective, against the selection of resistance, as CDA.

10839633
Petras JM, Young GD, Bauman RA, Kyle DE, Gettayacamin M, Webster HK, Corcoran KD, Peggins JO, Vane MA, Brewer TG
Arteether-induced brain injury in Macaca mulatta. I. The precerebellar nuclei: the lateral reticular nuclei, paramedian reticular nuclei, and perihypoglossal nuclei.
Anat Embryol (Berl). 2000 May;201(5):383-97.
Malaria poses a threat across several continents: Eurasia (Asia and parts of Eastern Europe), Africa, Central and South America. Bradley (1991) estimates human exposure at 2,073,000,000 with infection rates at 270,000,000, illnesses at 110,000,000, and deaths at 1,000,000. Significant mortality rates are attributed to infection by the parasite Plasmodium falciparum, with an estimated 90% among African children. A worldwide effort is ongoing to chemically and pharmacologically characterize a class of artemisinin

compounds that might be promising antimalarial drugs. The U.S. Army is studying the efficacy and toxicity of several artemisinin semi-synthetic compounds: arteether, artemether, artelinic acid, and artesunate. The World Health Organization and the U.S. Army selected arteether for drug development and possible use in the emergency therapy of acute, severe malaria. Male Rhesus monkeys (Macaca mulatta) were administered different daily doses of arteether, or the vehicle alone (sesame oil), for a period of either 14 days, or 7 days. Neuropathological lesions were found in 14-day arteether treated monkeys in the precerebellar nuclei of the medulla oblongata, namely: (1) the lateral reticular nuclei (subnuclei magnocellularis, parvicellularis, and subtrigeminalis), (2) the paramedian reticular nuclei (subnuclei accessorius, dorsalis, and ventralis), and the perihypoglossal nuclei (n. intercalatus of Staderini, n. of Roller, n. prepositus hypoglossi). The data demonstrate that the simina meduallry precerebellar nuclei have a high degree of vulnerability when arteether is given for 14 days at dose levels between 8mg/kg per day and 24 mg/kg per day. The neurological consequences of this treatment regimen could profoundly impair posture, gait, and autonomic regulation, while eye movement disorders might also be anticipated.

12358621
Phan GT, de Vries PJ, Tran BQ, Le HQ, Nguyen NV, Nguyen TV, Heisterkamp SH, Kager PA
Artemisinin or chloroquine for blood stage Plasmodium vivax malaria in Vietnam.
Trop Med Int Health. 2002 Oct;7(10):858-64.
Chloroquine-resistant Plasmodium vivax has not yet occurred in Vietnam. The efficacy of artemisinin for P. vivax was not established. We conducted a double-blind randomized study involving 240 inpatients with P. vivax malaria who received artemisinin (40 mg/kg over 3 days) plus placebo chloroquine (Art) or chloroquine (25 mg/kg over 3 days) plus placebo artemisinin (Chl). Patients were followed up with weekly blood smears for 28 days. In each group 113 cases were analysed. All patients recovered rapidly. The median (range) parasite clearance time of regimen Art was 24 h (8-72) and of Chl 24 h (8-64; P = 0.3). Parasites reappeared in two cases in each group on day 14, in eight cases in each group (7%) on day 16 and in 25 (23%) and 18 (16%) cases, respectively, at the end of 4-week follow-up (P = 0.3). The population parasite clearance curve followed a mono-exponential decline. The parasite reduction ratio per 48 h reproduction cycle was 2.3 x 104 for both regimens. We conclude that artemisinin and chloroquine are equally effective in the treatment of P. vivax infections in Vietnam. Reappearance of parasites before day 16 (7%) suggests the emergence of chloroquine resistance. Three days of artemisinin monotherapy does not prevent recrudescence.

12145966
Phan VT
[Artemisinine and artesunate in the treatment of malaria in Vietnam (1984-1999)]
Bull Soc Pathol Exot. 2002 Jun;95(2):86-8.
The long history of the use of Artemisia annua L. to treat malaria (called Quinghao in China and Thanh hao in Vietnam) has led Vietnamese scientists to manufacture locally preparations of artemisinine and artesunate, to test their tolerance for human beings as well as their efficiency in treating P. falciparum and P. vivax infections. Associating these drugs with antibiotics (such as tetracycline or doxycycline) could be an interesting topic for future research. Under the auspices of the National Program against Malaria, specialists will try to prevent the occurrence of drug resistance in Plasmodium and to propose new associations of drugs.

9598450
Philipps J, Radloff PD, Wernsdorfer W, Kremsner PG
Follow-up of the susceptibility of Plasmodium falciparum to antimalarials in Gabon.
Am J Trop Med Hyg. 1998 May;58(5):612-8.
The sensitivity of Plasmodium falciparum to chloroquine, mefloquine, quinine, quinidine, halofantrine, artemisinin, and sulfadoxine/pyrimethamine was investigated in Lambarene, Gabon in 1994. The development of in vitro susceptibility has been traced from 1983 or 1992 to 1994 for chloroquine, mefloquine, halofantrine, and quinine. Standard in vitro microtests according to World Health Organization methodology were performed. Of 33 isolates tested for susceptibility to chloroquine, 31 were resistant, one was borderline, and one isolate was sensitive (mean 50% effective concentration [EC50] = 1.38 micromol/L of blood). With mefloquine, all isolates were fully inhibited below the threshold of resistance (mean EC50 = 0.51 micrmol/L of blood). Of 32 isolates tested with quinine, six had borderline resistance (mean EC50 = 0.54 micromol/L of blood medium mixture). Susceptibility to quinidine was higher with a mean EC50 of 0.15 micromol/L of blood medium mixture. With halofantrine, 26 of 32 isolates matured at 3 nmol/L of blood medium mixture (mean EC50 = 1.64 nmol/L of blood medium mixture), indicating a steep decrease in susceptibility in comparison with 1992. For artemisinin, the mean EC50 was 97.92 nmol/L of blood medium mixture. Sulfadoxine/pyrimethamine showed five of 16 resistant isolates with a mean EC50 of 2.46 nmol/L of blood medium mixture. Whereas chloroquine resistance remained stable with a tendency to decrease, susceptibility to mefloquine and quinine was slightly decreased. A significant increase in the mean EC50 and EC90 in comparison with our previous data from Gabon was found for halofantrine.

8934576
Phillips-Howard PA, Wood D
The safety of antimalarial drugs in pregnancy.
Drug Saf. 1996 Mar;14(3):131-45.
Alternative drugs to chloroquine are required to prevent the deleterious effects of malaria in pregnancy. Fear of potential toxicity has limited antimalarial drug use in pregnancy. Animal toxicity studies have documented teratogenicity when antimalarials are administered at high dosages. Excepting the tetracyclines, there is no evidence to suggest that, at standard dosages, any of the antimalarial drugs are teratogenic. Primaquine is not recommended because of the potential risk of haemolytic effects in the fetus. Rates of spontaneous abortion and birth defects were comparable in pregnant women taking mefloquine, compared with chloroquine-proguanil, or pyrimethamine-sulfadoxine prophylaxis, in the first trimester of pregnancy. Standard doses of quinine do not increase the risk of abortion or preterm delivery. Therapeutic mefloquine does not provoke hypoglycaemia. There is no evidence in the literature to support the hypothetical risk of kernicterus in the newborn, following exposure to antimalarial drugs containing sulphonamides or sulphones prior to delivery. Documentation of the safety of doxycycline, halofantrine, and the artemisinin derivatives in the treatment of malaria in pregnant women is currently limited.

11243450
Phillipson JD
Phytochemistry and medicinal plants.
Phytochemistry. 2001 Feb;56(3):237-43.
A truncated history of the contribution of plants to medicine is given with reference to some of the less well known ancestors of the Harborne family. Six of the top 20 prescriptions dispensed in 1996 were natural products and the clinical use of drugs such as artemisinin, etoposide and taxol has once more focussed attention on plants as sources of novel drug entities. High through-put robotic screens have been developed by industry and it is possible to carry out 50,000 tests per day in the search for compounds which have specificity of action against a key enzyme or a subset of receptors. Bioassay-guided fractionation of plant extracts linked to chromatographic separation techniques leads to the isolation of biologically active molecules whose chemical structures can readily be determined by modern spectroscopic methods. The role of academics in the search for new drugs is discussed by reference to some of our research into natural products with activity on the central nervous system, on pain receptors, the malaria parasite Plasmodium falciparum, the wound healing properties of the sap of species of Croton (Dragon's blood), and a traditional Chinese medicine used to treat eczema. Expertise in phytochemistry has been essential for this research and the strong lead shown by Professor Jeffrey Harborne is gratefully acknowledged.

1881153
Phillipson JD, Wright CW
Can ethnopharmacology contribute to the development of antimalarial agents?
J Ethnopharmacol. 1991 Apr;32(1-3):155-65.
The resistance of Plasmodium falciparum, the cause of tertian malaria, to synthetic antimalarials, together with the resistance of the vector mosquitoes to insecticides, has resulted in a resurgence in the use of quinine and a search for new antimalarial agents. In recent years, artemisinin, isolated from Artemisia annua which is used in Chinese traditional medicine for the treatment of malaria, has proved to be effective in the treatment of cerebral malaria due to chloroquine-resistant strains of P. falciparum. The development of in vitro tests utilising P. falciparum obtained from malaria patients means that it is possible to use bioassay guided fractionation of active extracts in order to isolate active principles. A number of laboratories throughout the world are currently investigating plants used in traditional medicine for their active constituents. Some of their results will be described and in particular two aspects of our investigations with species of Simaroubaceae and Menispermaceae will be discussed. There is every possibility that such approaches which use leads from Ethnopharmacology will result in the development of new antimalarial agents. It is vitally important to those populations relying on traditional medicines for the treatment of malaria that the safety and efficacy of such medicines be established, their active principles determined and that reproducible dosage forms be prepared and made available for use.

12878499
Pickard AL, Wongsrichanalai C, Purfield A, Kamwendo D, Emery K, Zalewski C, Kawamoto F, Miller RS, Meshnick SR
Resistance to antimalarials in Southeast Asia and genetic polymorphisms in pfmdr1.
Antimicrob Agents Chemother. 2003 Aug;47(8):2418-23.
Resistance to antimalarial drugs is a public health problem worldwide. Molecular markers for drug-resistant malaria, such as pfcrt and pfmdr1 polymorphisms, could serve as useful surveillance tools. To evaluate this possibility, sequence polymorphisms in pfcrt (position 76) and pfmdr1 (positions 86, 184, 1034, 1042, and

1246) and in vitro drug sensitivities were measured for 65 Plasmodium falciparum isolates from Thailand, Myanmar, Vietnam, and Bangladesh. The pfcrt Thr76 polymorphism was present in 97% of samples, consistent with observations that chloroquine resistance is well established in this region. Polymorphisms in pfmdr1 clustered into four specific patterns: the wild type (category I), a Tyr86 polymorphism only (category II), a Phe184 polymorphism only (category III), and Phe184 in combination with Cys1034 and/or Asp1042 (category IV). Isolates in categories I and III were more sensitive to chloroquine and more resistant to mefloquine, artesunate, and artemisinin than isolates in categories II and IV (P /=3. The isolates in all 8 samples fell into categories I and III and were significantly more resistant to mefloquine, quinine, artemisinin, and artesunate and more sensitive to chloroquine than the isolates in the 57 samples with

12557835
Pillai DR, Hijar G, Montoya Y, Marouino W, Ruebush TK 2nd, Wongsrichanalai C, Kain KC
Lack of prediction of mefloquine and mefloquine-artesunate treatment outcome by mutations in the Plasmodium falciparum multidrug resistance 1 (pfmdr1) gene for P. falciparum malaria in Peru.
Am J Trop Med Hyg. 2003 Jan;68(1):107-10.
We assessed whether mutations in the Plasmodium falciparum multidrug-resistance gene 1 (pfmdr1) (C1034S, D1042N, and Y1246D) would predict treatment outcome during a 28-day in vivo treatment trial in the Peruvian Amazon. Mefloquine (MQ) was compared with mefloquine-artesunate (MQ-AS) in a randomized, multi-clinic protocol for the first time in the Americas. Of 115 patients enrolled in the in vivo arm, 97 patients were eligible for molecular analysis. All 97 patients remained parasite-free during 28 days of follow-up (MQ, n = 46; MQ-AS, n = 51), indicating 100% clinical efficacy of the MQ and MQ-AS treatment regimens. The reported MQ-sensitive alleles (C1034, D1042, and Y1246) were present in 48.5% (n = 47) of the cases, whereas 49 isolates (50.5%) contained the D1246 mutation reported to confer MQ resistance in vitro. However, neither this mutation nor a double mutation (S1034, D1246; n = 16) was predictive of MQ treatment outcome.

15683042
Pilz JB, Wernsdorfer G, Sirichaisinthop J, Rojanawatsirivet C, Wiedermann G, Wernsdorfer WH
In vitro sensitivity of Plasmodium falciparum to lumefantrine in north-western Thailand.
Wien Klin Wochenschr. 2004;116 Suppl 4:41-6.
Lumefantrine (benflumetol) belongs to the class-2 blood schizontocidal compounds. In combination with artemether it serves as an alternative drug for treating chloroquine-resistant infections with Plasmodium falciparum. In view of activity correlations with mefloquine, it is important to monitor the parasite's intrinsic sensitivity to lumefantrine in areas with multi-drug resistant P. falciparum, the objective of this study. The observations were carried out in 2002 at Mae Sot, northwestern Thailand, near the border to Myanmar. The 41 successfully in-vitro tested parasite isolates yielded a geometric mean cut-off concentration of schizont maturation of 237.54 nM, and EC50, EC90 and EC90 values of 15.13 nM, 86.71 nM and 359.97 nM, respectively. As compared to the findings of 1998 and 1999, the susceptibility to lumefantrine has increased, possibly due to the improved therapeutic response of mefloquine-resistant P. falciparum infections to combined treatment with artesunate + mefloquine. The EC9o and EC99 data of 2002 for lumefantrine in the study area suggest fully curative clinical-parasitological efficacy.

10194084
Pittler MH, Ernst E
Artemether for severe malaria: a meta-analysis of randomized clinical trials.
Clin Infect Dis. 1999 Mar;28(3):597-601.
The treatment of choice for severe malaria is quinine. However, a gradual progression of resistance to quinine has become a concern in parts of the world. Artemisinin-related compounds are a relatively new class of drugs. This meta-analysis assesses the evidence regarding the clinical effectiveness of artemether for severe malaria. Computerized literature searches identified all randomized clinical trials of artemether in comparison with quinine. Standardized data extraction was independently performed by both authors. Results of nine trials, entered in the meta-analysis, demonstrate the absence of a significant difference between artemether and quinine in terms of mortality rate (odds ratio [OR], 0.76; 95% confidence interval [CI], 0.50-1.14). Statistical pooling of data from trials in Southeast Asia showed a trend toward enhanced reduction of mortality (OR, 0.38; 95% CI, 0.14-1.02). These data demonstrate the equality of artemether and quinine for severe malaria and indicate a trend toward greater effectiveness of artemether in regions where there is recognized quinine resistance.

16525102
Piyaphanee W, Krudsood S, Tangpukdee N, Thanachartwet W, Silachamroon U, Phophak N, Duangdee C, Haoharn O, Faithong S, Wilairatana P, Leowattana W, Looareesuwan S
Emergence and clearance of gametocytes in uncomplicated Plasmodium falciparum malaria.
Am J Trop Med Hyg. 2006 Mar;74(3):432-5.

We reviewed the records of 1,175 patients with uncomplicated Plasmodium falciparum malaria to determine the prevalence of gametocytemia. All patients were admitted and received artemisinin combination therapy. Blood films were checked daily until discharge. Circulating gametocytes were observed in 240 (20.2%) of patients and in most cases (222 of 240, 92.5%) gametocytemia was detected during the first 24 hours after admission. Gametocytes were first seen in 174 cases on admission, in 24 cases at 12 hours, and in 24 cases at 24 hours. The longest interval between admission and first appearance of gametocytes was 192 hours. The median gametocyte clearance time was 163 hours (range = 12-806) in the 219 patients in whom gametocytemia resolved. However, 21 patients (9.8%) still had gametocytemia on discharge. Gametocytemia generally is present within the first 24 hours after admission, and emerges in only 1.9% of patients later on during treatment with artemisinin.

14744559
Ploypradith P
Development of artemisinin and its structurally simplified trioxane derivatives as antimalarial drugs.
Acta Trop. 2004 Feb;89(3):329-42.
Artemisinin and simplified trioxane analogs constitute a promising class of antimalarial chemotherapeutic agents. Their development since the early 1970s into clinical trials and clinical use has drawn much attention from medical scientists worldwide although the crude extract containing artemisinin has been used in China for treatment of fever for many centuries. Many research groups have independently and collaboratively conducted various studies on the artemisinin system both in search for the new compounds more antimalarially active than the parent artemisinin and in an attempt to understand its molecular mechanism(s) of action. Ongoing studies have provided a better understanding of the putative intermediates essential for the antimalarial activity and have led to designer trioxanes whose chemical structures have been simplified and modified to increase efficacy while lowering toxicity. Other desirable features beneficial to clinical uses such as bioavailability, drug stability and water solubility have been considered, and portions of the trioxane skeleton have been added or modified to accommodate these parameters accordingly.

12886592
Popov AF, Popova NI, Chirkov VP, Kamara F
[Drug resistant tropical malaria in the Republic of Guinea (West Africa)]
Med Parazitol (Mosk). 2003 Apr-Jun;(2):41-3.

9526568
Posner GH, Cumming JN, Woo SH, Ploypradith P, Xie S, Shapiro TA
Orally active antimalarial 3-substituted trioxanes: new synthetic methodology and biological evaluation.
J Med Chem. 1998 Mar 12;41(6):940-51.
On the basis of a mechanistic understanding of the mode of action of artemisinin-like antimalarials, a series of structurally simple 3-aryl-1,2,4-trioxanes 5 was designed and was prepared in three to five operations from commercial reactants. The 3-aryl group was attached in each case as a nucleophile. In an electronically complementary fashion, 3-(fluoroalkyl)-trioxanes 6 were prepared via attachment of electrophilic fluoroalkyl esters. Both in vitro and in vivo antimalarial evaluations of these new trioxanes showed 12 beta-methoxy-3-aryltrioxanes 5g, 5j, 5k, and 51 to be highly potent, with crystalline fluorobenzyl ether trioxane 5k especially potent even when administered to rodents orally. As shown by rearrangement of hexamethyl Dewar benzene into hexamethylbenzene, iron-induced degradation of some of these 3-aryltrioxanes 5 involves generation of high-valent iron oxo species that might kill malaria parasites.

11738625
Posner GH, Northrop J, Paik IH, Borstnik K, Dolan P, Kensler TW, Xie S, Shapiro TA
New chemical and biological aspects of artemisinin-derived trioxane dimers.
Bioorg Med Chem. 2002 Jan;10(1):227-32.
Joining two 10-deoxoartemisinin trioxane units via a p-diacetylbenzene linker produces new C-10 non-acetal dimers and. 1H NMR spectroscopy allows unambiguous assignment of the stereochemistry at C-10 in these dimers. Successful replacement of both carbonyl oxygen atoms in these diketone dimers by fluorine atoms produces new tetrafluorinated dimers and. Each dimer was evaluated in vitro for antimalarial, antiproliferative, and antitumor activities; ketone dimers and, more than fluorinated dimers and, are promising for chemotherapy of both malaria and cancer.

15196049
Posner GH, O'Neill PM
Knowledge of the proposed chemical mechanism of action and cytochrome p450 metabolism of antimalarial trioxanes like artemisinin allows rational design of new antimalarial peroxides.

Acc Chem Res. 2004 Jun;37(6):397-404.
Evidence is reviewed elucidating the mechanism of iron-induced triggering of antimalarial trioxanes. As prodrugs, trioxanes undergo homolytic, inner-sphere, reductive cleavage by ferrous iron to form sequentially oxy radicals, carbon radicals, high-valent iron-oxo species, epoxides, aldehydes, and dicarbonyl compounds. One or more of these reactive intermediates and neutral alkylating agents likely kill the malaria parasites. Several new, orally active antimalarial peroxides have been designed rationally based on this fundamental mechanistic paradigm. Incorporating metabolism-blocking substituents also provides some new, potent, semi-synthetic artemisinin derivatives.

12620083
Posner GH, Paik IH, Sur S, McRiner AJ, Borstnik K, Xie S, Shapiro TA
Orally active, antimalarial, anticancer, artemisinin-derived trioxane dimers with high stability and efficacy.
J Med Chem. 2003 Mar 13;46(6):1060-5.
In only two steps and in 70% overall yield, naturally occurring trioxane artemisinin (1) was converted on a gram scale into C-10-carba trioxane dimer 3. This new, very stable dimer was then transformed easily in one additional step into four different dimers 4-7. Alcohol and diol dimers 4 and 5 and ketone dimer 7 are 10 times more antimalarially potent in vitro than artemisinin (1), and alcohol and diol dimers 4 and 5 are strongly growth inhibitory but not cytotoxic toward several human cancer cell lines. Water-soluble carboxylic acid derivatives 8aand 9 were easily prepared in one additional step from dimers 4 and 5. Carboxylic acid dimers 8a and 9 are thermally stable even at 60 degrees C for 24 h, are more orally efficacious as antimalarials in rodents than either artelinic acid or sodium artesunate, and are strongly inhibitory but not cytotoxic toward several human cancer cell lines.

9925735
Posner GH, Parker MH, Northrop J, Elias JS, Ploypradith P, Xie S, Shapiro TA
Orally active, hydrolytically stable, semisynthetic, antimalarial trioxanes in the artemisinin family.
J Med Chem. 1999 Jan 28;42(2):300-4.
In only three chemical operations, natural trioxane lactone artemisinin (1) was converted into a series of C-10 carbon-substituted 10-deoxoartemisinin compounds 4-9. The three steps involved lactone reduction, replacement of the anomeric lactol OH by F using diethylaminosulfur trifluoride, and finally boron trifluoride-promoted substitution of F by aryl, heteroaryl, and acetylide nucleophiles. All of these C-10 nonacetal, chemically robust, enantiomerically pure compounds 4-9 have high antimalarial potencies in vitro against Plasmodium falciparum malaria parasites, and furans 5a and 5b and pyrrole 7a are antimalarially potent also in vivo even when administered to rodents orally.

11378030
Posner GP, Meshnick SR
Radical mechanism of action of the artemisinin-type compounds.
Trends Parasitol. 2001 Jun;17(6):266-8.

8873227
Postma NS, Mommers EC, Eling WM, Zuidema J
Oxidative stress in malaria; implications for prevention and therapy.
Pharm World Sci. 1996 Aug;18(4):121-9.
Malaria affects world-wide more than 200 million people, of which 1-2 million die every year. New drugs and treatment strategies are needed to face the rapidly increasing problems of drug resistance. During a malaria infection, both host and parasite are under oxidative stress. Increased production levels of reactive oxygen species (ROS, e.g superoxide anion and the hydroxyl radical) are produced by activated neutrophils in the host and during degradation of haemoglobin in the parasite. The effects of ROS in malaria can be both beneficial and pathological, depending on the amount and place of production. Enhanced ROS production after the administration of pro-oxidants, which is directed against the intra-erythrocytic parasite, inhibits the infection both in vitro and in vivo. However, ROS are also involved in pathological changes in host tissue like damage of the vascular endothelial lining during a malaria infection (cerebral malaria). Pro-oxidants support the host defense against the parasite when working in or near the infected cell but potentially cause vascular damage when working on or near the vascular lining. Examples of pro-oxidants are found among xenobiotics and food components. Important new drugs belonging to the class of pro-oxidants are artemisinin and its derivatives. Anti-oxidants potentially counteract these agents. Treatment with anti-oxidants or chelators of metals to prevent their catalytic function in the generation of ROS may prevent vascular pathology. In addition, the iron chelator desferrioxamine, exhibits an antiparasitic activity, because iron is also essential for the proliferation of the parasite. Cytokines play an important role in ROS-related pathology of malaria, though

their mechanism of action is not completely elucidated. This field might bring up new treatment concepts and drugs. Drugs which prevent host pathology, such as the cerebral complications might be life saving.

11481286
Pradines B, Fusai T, Daries W, Laloge V, Rogier C, Millet P, Panconi E, Kombila M, Parzy D
Ferrocene-chloroquine analogues as antimalarial agents: in vitro activity of ferrochloroquine against 103 Gabonese isolates of Plasmodium falciparum.
J Antimicrob Chemother. 2001 Aug;48(2):179-84.
The in vitro activities of ferrochloroquine, chloroquine, quinine, mefloquine, halofantrine, amodiaquine, primaquine, atovaquone and artesunate were evaluated against Plasmodium falciparum isolates from children with uncomplicated malaria from Libreville (Gabon), using an isotopic, micro, drug susceptibility test. The IC(50) values for ferrochloroquine were in the range 0.43-30.9 nM and the geometric mean IC(50) for the 103 isolates was 10.8 nM (95% CI 8.6-13.5 nM), while the geometric means for chloroquine, quinine, mefloquine, amodiaquine and primaquine were 370 nM, 341 nM, 8.3 nM, 18.1 nM and 7.6 microM, respectively. Ferrochloroquine was active against P. falciparum isolates, 95% of which showed in vitro resistance to chloroquine. Weak positive significant correlations were observed between the responses to ferrochloroquine and that to chloroquine, amodiaquine and quinine, but too low to suggest cross-resistance. There was no significant correlation between the response to ferrochloroquine and those to mefloquine, halofantrine, primaquine, atovaquone or artesunate. Ferrochloroquine may be an important alternative drug for the treatment of chloroquine-resistant malaria.

11787425
Pradines B, Fusai T, Rogier C, Keundjian A, Sinou V, Merckx A, Mosnier J, Daries W, Torrentino M, Parzy D
[Prevention and treatment of malaria: in vitro evaluation of new compounds]
Ann Pharm Fr. 2001 Sep;59(5):319-23.
One of the current options for reducing the morbidity and mortality of malaria are chemoprophylaxis and chemotherapy. For this reason, the increasing prevalence of strains of Plasmodium falciparum resistant to chloroquine and other antimalarial drugs poses a serious problem for control of malaria. There is an urgent need to find and develop novel compounds and to identify novel chemotherapeutic targets. Different approaches to discover new compounds are presented from examples of molecules studied in the Tropical Medicine Institute of the French Army Health Service (IMTSSA) evaluation against isolates of compounds in pharmaceutical development in collaboration with pharmaceuticals (pyronaridine, benflumetol, ferrochloroquine), screening of molecules which are still registered for other pathologies (antibiotics), screening of new synthesized compounds (artemisinin derivatives) and identification of parasitical targets and essential metabolic ways for parasite, and identification of molecules acting on these targets (reversal of resistance to chloroquine, iron chelators).

16535862
Pradines B, Pages JM, Barbe J
Chemosensitizers in drug transport mechanisms involved in protozoan resistance.
Curr Drug Targets Infect Disord. 2005 Dec;5(4):411-31.
The emergence and spread of antiparasitic drug resistance pose a severe and increasing public health threat. Failures in prophylaxis or those in treatment with quinolines, hydroxynaphtoquinones, sesquiterpenic lactones, antifolate drugs, arsenic and antimony containing drugs sulfamides induce reemergence of parasitic-related morbidity and mortality. Resistance is often associated with alteration of drug accumulation into parasites, which results from a reduced uptake of the drug, an increased efflux or, a combination of the two processes. Resistance to quinolines, artemisinin derivatives and arsenicals and expression of an active efflux mechanism are more or less correlated in protozoa like Plasmodium spp., Leishmania spp., and Trypanosoma spp. Various parasite candidate genes have been proposed to be involved in drug resistance, each concerned in membrane transport. Genes encoding membrane glycoproteins, orthologue to the P-glycoproteins identified in MDR human cancer cells, have been described in these resistant pathogens in addition to various membrane proteins involved in drug transport. Several compounds have demonstrated, in the past decade, promising capability to reverse the drug resistance in parasite isolates in vitro, in animal models and for human malaria. These drugs belong to different pharmacological classes such as calcium channel blockers, tricyclic antidepressants, antipsychotic calmodulin antagonists, histamine H1-receptor antagonists, analgesic antipyretic drugs, non-steroidal anti-inflammatory drugs, and to different chemical classes such as synthetic surfactants, alkaloids from plants used in traditional medicine, pyrrolidinoaminoalkanes and derivatives, and anthracene derivatives. Here, are summarized the molecular bases of antiparasitic resistance emphasizing recent developments with compounds acting on trans-membrane proteins involved in drug efflux or uptake.

12161397

Pradines B, Rolain JM, Ramiandrasoa F, Fusai T, Mosnier J, Rogier C, Daries W, Baret E, Kunesch G, Le Bras J, Parzy D
Iron chelators as antimalarial agents: in vitro activity of dicatecholate against Plasmodium falciparum.
J Antimicrob Chemother. 2002 Aug;50(2):177-87.
The present study was undertaken to explore the antimalarial effect of a series of dicatecholate iron chelators. They may be made more or less lipophilic by increasing or reducing the length of the R substituent on the nitrogen. In vitro activity against the W2 and 3D7 clones of Plasmodium falciparum, toxicity on Vero cells and toxicity on uninfected erythrocytes by measure of the released haemoglobin were assessed for each compound. These findings were compared with the ability of iron(III), iron(II) and ferritin to reverse the inhibitory effect of catecholates. This study shows that increased lipid solubility of catecholate iron chelators does not lead to improved antimalarial activity. However, their activity is well correlated with their interaction with iron and with their toxicity against Vero cells. This study demonstrates a potent antimalarial effect of FR160 (R = C9H19) on five different strains of P. falciparum in vitro. FR160 inhibited parasite growth with an IC50 between 0.8 and 1.5 micro M. The effects of FR160 on mammalian cells were minimal compared with those obtained with malaria parasites. FR160 acted on parasites at considerably higher rates than desferrioxamine, and at all stages of parasite growth. The drug was more effective at the late trophozoite and young schizont stages, although FR160 affected rings and schizonts as well. Ascorbic acid, a free radical scavenger, reduced the activities of FR160 and artesunate. FR160 might induce formation of free radicals, which could explain why FR160 antagonized the effects of artesunate and dihydroartemisinin.

11903989
Pradines B, Tall A, Rogier C, Spiegel A, Mosnier J, Marrama L, Fusai T, Millet P, Panconi E, Trape JF, Parzy D
In vitro activities of ferrochloroquine against 55 Senegalese isolates of Plasmodium falciparum in comparison with those of standard antimalarial drugs.
Trop Med Int Health. 2002 Mar;7(3):265-70.
The in vitro activities of ferrochloroquine, chloroquine, quinine, mefloquine, halofantrine, amodiaquine, artesunate, atovaquone, cycloguanil and pyrimethamine were evaluated against Plasmodium falciparum isolates from Senegal (Dielmo, Ndiop), using an isotopic micro-drug susceptibility test. The IC50 values for ferrochloroquine ranged from 0.55 to 28.2 nM and the geometric mean IC50 for the 55 isolates was 7.9 nM (95% CI, 6.5-9.7 nM). Ferrochloroquine was 35 times more active than chloroquine (35-fold greater against chloroquine-resistant isolates), quinine, mefloquine, amodiaquine, cycloguanil and pyrimethamine. Weak positive correlations were observed between the responses to ferrochloroquine and that to chloroquine, quinine, and amodiaquine, but not compulsorily predictive of cross-resistance. There was no significant correlation between the response to ferrochloroquine and that to mefloquine, halofantrine, artesunate, atovaquone, cycloguanil and pyrimethamine. Ferrochloroquine may be an important alternative drug for the treatment of chloroquine-resistant malaria.

9764335
Price R, Luxemburger C, van Vugt M, Nosten F, Kham A, Simpson J, Looareesuwan S, Chongsuphajaisiddhi T, White NJ
Artesunate and mefloquine in the treatment of uncomplicated multidrug-resistant hyperparasitaemic falciparum malaria.
Trans R Soc Trop Med Hyg. 1998 Mar-Apr;92(2):207-11.
Oral artesunate is the most effective treatment for uncomplicated hyperparasitaemia in falciparum malaria. To assess the contribution of mefloquine to therapeutic efficacy in an area endemic for mefloquine-resistant Plasmodium falciparum, an open randomized comparison of a 5 d course of oral artesunate (total dose 12 mg/kg) with and without a single dose of mefloquine (25 base mg/kg) was conducted in 100 adults and children with uncomplicated hyperparasitaemia (> 4% parasitized red blood cells). Both regimens were well tolerated and gave equally rapid clinical responses (84% of patients were aparasitaemic and 96% were afebrile within 48 h), but the recrudescence rate assessed at day 42 was 6% in those receiving artesunate with mefloquine compared to 36% in those receiving artesunate alone (adjusted hazard ratio 7, 95% confidence interval [95% CI] 2-32; P < 0.01). In addition, the efficacy of a 7 d course of artesunate, with and without the addition of mefloquine, was monitored in 178 patients who were not part of the randomized comparison. The failure rate was again lower in those receiving artesunate and mefloquine--7% (95% CI 2-13) compared with 26% (95% CI 8-44) in patients treated with artesunate alone. An oral regimen of 5 d or more of artesunate, together with mefloquine (25 mg/kg) given on day 2, is an effective treatment for uncomplicated hyperparasitaemic falciparum malaria in this area of high level multidrug resistance.

10403336
Price R, Nosten F, Simpson JA, Luxemburger C, Phaipun L, ter Kuile F, van Vugt M, Chongsuphajaisiddhi T, White NJ
Risk factors for gametocyte carriage in uncomplicated falciparum malaria.

Am J Trop Med Hyg. 1999 Jun;60(6):1019-23.
The factors affecting the development of patent Plasmodium falciparum gametocytemia were assessed in 5,682 patients entered prospectively into a series of antimalarial drug trials conducted in an area of low and seasonal transmission on the western border of Thailand. Of the 4,565 patients with admission thick smear assessments, 110 (2.4%) had gametocytemia. During the follow-up period 170 (3%) of all patients developed patent gametocytemia, which in 89% had developed by day 14 following treatment. In a multiple logistic regression model five factors were found to be independent risk factors at presentation for the development or persistence of gametocytemia during follow up; patent gametocytemia on admission (adjusted odds ratio [AOR] = 7.8, 95% confidence interval [CI] = 3.7-16, P < 0.001), anemia (hematocrit < 0.001), no coincident P. vivax malaria (AOR = 3.5, 95% CI = 1.04-11.5, P < 0.04), presentation with a recrudescent infection (AOR = 2.3, 95% CI = 1.3-4.1, P < 0.004), and a history of illness longer than two days (AOR = 3.3, 95% CI = 1.7-6.6, P < 0.001). Patients whose infections responded slowly to treatment or recrudesced subsequently were also more likely to carry gametocytes than those who responded rapidly or were cured (relative risks = 1.9, 95% CI = 1.3-2.7 and 2.8, 95% CI = 2.0-4.0, respectively; P < 0.001). These data provide further evidence of important epidemiologic interactions between P. falciparum and P. vivax, and drug resistance and transmission potential.

9925529
Price R, Simpson JA, Teja-Isavatharm P, Than MM, Luxemburger C, Heppner DG, Chongsuphajaisiddhi T, Nosten F, White NJ
Pharmacokinetics of mefloquine combined with artesunate in children with acute falciparum malaria.
Antimicrob Agents Chemother. 1999 Feb;43(2):341-6.
Combining artemisinin or a derivative with mefloquine increases cure rates in falciparum malaria patients, reduces transmission, and may slow the development of resistance. The combination of artesunate, given for 3 days, and mefloquine is now the treatment of choice for uncomplicated multidrug-resistant falciparum malaria acquired on the western or eastern borders of Thailand. To optimize mefloquine administration in this combination, a prospective study of mefloquine pharmacokinetics was conducted with 120 children (4 to 15 years old) with acute uncomplicated falciparum malaria, who were divided into four age- and sex-matched groups. The patients all received artesunate (4 mg/kg of body weight/day orally for 3 days and mefloquine as either (i) a single dose (25 mg/kg) on day 2 with food, (ii) a split dose (15 mg/kg on day 2 and 10 mg/kg on day 3) with food, (iii) a single dose (25 mg/kg) on day 0 without food, or (iv) a single dose (25 mg/kg) on day 2 without food. Delaying administration of mefloquine until day 2 was associated with a mean (95% confidence interval) increase in estimated oral bioavailability of 72% (36 to 109%). On day 2 coadministration with food did not increase mefloquine absorption significantly, and there were no significant differences between patients receiving split- and single-dose administration. In combination with artesunate, mefloquine administration should be delayed until the second or third day after presentation.

9886194
Price R, van Vugt M, Nosten F, Luxemburger C, Brockman A, Phaipun L, Chongsuphajaisiddhi T, White N
Artesunate versus artemether for the treatment of recrudescent multidrug-resistant falciparum malaria.
Am J Trop Med Hyg. 1998 Dec;59(6):883-8.
The therapeutic efficacy and toxicity of artesunate (2mg/kg/day for five days, then 1 mg/kg/day for two days: total=12 mg/kg) was compared with that of artemether (4 mg/kg followed by 2 mg/kg/day for two days, then 1 mg/kg/day for four days: total=12 mg/kg) for the treatment of recrudescent multidrug-resistant falciparum malaria in an open randomized trial in 443 patients living on the western border of Thailand. Parasite and fever clearance times were similar in both groups; within 48 hr 94% (95% confidence interval [CI]=91-96%]) of the treated patients were aparasitemic and 93% (95% CI=89-96%) were afebrile. Symptom resolution and resolution of hepatomegaly were slightly slower in the artesunate group; adjusted hazards ratio=1.5 (95% CI=1-2.0, P < 0.01) and 2.2 (95% CI=1.4-8, P=0.04), respectively. There was no significant difference in times to resolution or development of anemia or splenomegaly between treatment groups. By day 28, 3% (95% CI=0.3-5%) of the patients treated with artesunate and 6% of those treated with artemether (95% CI = 2-9%) had recurrent infections (P=0.3). Both regimens were very well tolerated, with no significant adverse effects attributable to either derivative. Overall, these data suggest that the two oral artemisinin derivatives are safe, highly effective, and result in equivalent therapeutic responses in the treatment of drug-resistant falciparum malaria.

10348227
Price R, van Vugt M, Phaipun L, Luxemburger C, Simpson J, McGready R, ter Kuile F, Kham A, Chongsuphajaisiddhi T, White NJ, Nosten F
Adverse effects in patients with acute falciparum malaria treated with artemisinin derivatives.
Am J Trop Med Hyg. 1999 Apr;60(4):547-55.

In prospective studies of acute uncomplicated, multidrug-resistant falciparum malaria on the western border of Thailand, the oral artemisinin derivatives were used alone in the treatment of 836 patients (artesunate 630, artemether 206), were combined with mefloquine (15-25 mg base/kg) in 2,826 patients, and mefloquine alone was used in 1,303 patients. The combined regimens of mefloquine plus an artemisinin derivative were associated with more side effects than those with an artemisinin derivative alone; acute nausea (31% versus 16%), vomiting (24% versus 11%), anorexia (51% versus 34%), and dizziness (47% versus 15%) (P < 0.001). Oral artesunate and artemether alone were very well tolerated. There was no difference in the incidence of possible adverse effects between the two drugs, and no evidence that either derivative caused allergic reactions, neurologic or psychiatric reactions, or cardiovascular or dermatologic toxicity. Blackwater fever occurred in three patients treated with mefloquine plus artesunate regimens. Oral artesunate and artemether are safe and well tolerated antimalarial drugs.

11060779
Price RN
Artemisinin drugs: novel antimalarial agents.
Expert Opin Investig Drugs. 2000 Aug;9(8):1815-27.
Artemisinin and its derivatives, artesunate and artemether, represent a new class of antimicrobial drug with potent activity against Plasmodium falciparum. Although they show excellent efficacy in both severe and uncomplicated malaria, dosage regimens still need to be optimised and pharmacokinetic profiles defined. In the treatment of uncomplicated malaria, the artemisinin drugs should be used in combination with a long acting antimalarial to protect both drugs against the emergence of resistance. In the treatment of severe malaria, parenteral artemether is at least as effective as quinine and is simpler to use. The use of rectal preparations of artesunate and artemisinin at the rural health level will facilitate early initiation of the treatment of falciparum malaria and this may reduce the proportion of patients progressing to severe disease. All of the artemisinin drugs have comparable efficacy; the choice of derivative should be based upon availability, cost and quality of the preparation. Artemisinin, artesunate and artemether are well-tolerated in both adults and children, with no evidence to date of serious clinical toxicity.

10582887
Price RN, Cassar C, Brockman A, Duraisingh M, van Vugt M, White NJ, Nosten F, Krishna S
The pfmdr1 gene is associated with a multidrug-resistant phenotype in Plasmodium falciparum from the western border of Thailand.
Antimicrob Agents Chemother. 1999 Dec;43(12):2943-9.
On the western border of Thailand, Plasmodium falciparum has become resistant to almost all antimalarial agents. The molecular basis of resistance in these parasite populations has not been well characterized. This study assessed genetic polymorphisms in the pfmdr1 gene in 54 parasites collected from the western border of Thailand to determine the relationship of pfmdr1 copy number and codon mutations with parasite sensitivities to mefloquine, chloroquine, halofantrine, quinine, and artesunate assessed in vitro. A point mutation at codon 86 (resulting in a change of Asn to Tyr) was associated with a significantly lower 50% inhibitory concentration (IC(50)) of mefloquine (median, 9 ng/ml versus 52.4 ng/ml; P = 0.003). Overall 35% of the isolates (19 of 54) had an increase in pfmdr1 copy number, and all 19 carried the wild-type allele at codon 86. Increased pfmdr1 copy number was associated with higher IC(50)s of mefloquine (P = 0.04) and artesunate (P = 0.005), independent of polymorphism at codon 86. The relationship between pfmdr1 and resistance to structurally distinct antimalarial agents confirms the presence of a true multidrug-resistant phenotype.

11768332
Price RN, Nosten F
Drug resistant falciparum malaria: clinical consequences and strategies for prevention.
Drug Resist Updat. 2001 Jun;4(3):187-96.
The rising prevalence of multidrug resistant falciparum malaria is occurring at an alarming rate and has serious implications for the health of many of the world's poorest countries. The dangers of not changing treatment practices immediately are huge and irreversible, threatening to both exacerbate the scale and scope of the malaria pandemic, and deprive policymakers of future options against the disease. If a health care disaster is to be avoided then massive and long term funding is urgently required. Funds need to be applied in a cohesive manner, accountable to funding bodies and tailored to the specifics of each endemic region. The key elements of such an approach should be improving early diagnosis and treatment of infection and the deployment of combination regimens containing an artemisinin derivative.These short term measures will need to be accompanied by a longer term strategy to encourage antimalarial drug research and development.

8560531
Price RN, Nosten F, Luxemburger C, Kham A, Brockman A, Chongsuphajaisiddhi T, White NJ

Artesunate versus artemether in combination with mefloquine for the treatment of multidrug-resistant falciparum malaria.
Trans R Soc Trop Med Hyg. 1995 Sep-Oct;89(5):523-7.
To compare the therapeutic efficacy of oral artesunate and artemether in combination with mefloquine for the treatment of multidrug resistant malaria, a trial was conducted in 540 adults and children on the Thai-Myanmar border. Three regimens were compared: artesunate (4 mg/kg/d for 3 d), artemether (4 mg/kg/d for 3 d), both in combination with mefloquine (25 mg/kg), and a single dose of mefloquine (25 mg/kg). The artesunate and artemether regimens gave very similar clinical and parasitological responses, and were both very well tolerated. There was no significant adverse effect attributable to the artemisinin derivatives. Fever and parasite clearance times with mefloquine alone were significantly longer ($P < 0.001$). After adjusting for reinfections the failure rates were 13.9% for the artesunate combination, 12.3% for the artemether combination and 49.2% for mefloquine alone ($P < 0.0001$; relative risk 3.8 [95% confidence interval 2.6-5.4]). Mefloquine should no longer be used alone for the treatment of multidrug resistant falciparum malaria in this area. Three-day combination regimens with artesunate or artemether are well tolerated and more effective.

8642959
Price RN, Nosten F, Luxemburger C, ter Kuile FO, Paiphun L, Chongsuphajaisiddhi T, White NJ
Effects of artemisinin derivatives on malaria transmissibility.
Lancet. 1996 Jun 15;347(9016):1654-8.
BACKGROUND: On the western border of Thailand the efficacy of mefloquine in the treatment of falciparum malaria has declined while gametocyte carriage rates have increased, which suggests increased transmissibility of these resistant infections. We compared the following antimalarial drugs in relation to subsequent Plasmodium falciparum gametocyte carriage: mefloquine, halofantrine, quinine, and the artemisinin derivatives. METHODS: Between 1990 and 1995 we assessed gametocytaemia in a series of prospective studies of antimalarial drug treatment in 5193 adults and children with acute uncomplicated falciparum malaria in an area of malarious hill forest on the western border of Thailand. Weekly parasite counts from thick and thin blood films were done during the 4-week (1990-93) or 9-week (1993-95) follow-up period. Gametocyte positivity rates and person gametocyte week (PGW) rates were calculated to measure gametocyte carriage and transmission potential. FINDINGS: In primary P falciparum infections the gametocyte carriage rate was significantly higher after treatment with mefloquine than after treatment with the artemisinin derivatives (PGW 34.1 [95% CI 25.2-42.9] vs 3.9 [1.9-5.9] per 1000 person weeks; relative risk 8.0 [4.1-15.6]; p

9463672
Price RN, Nosten F, Luxemburger C, van Vugt M, Phaipun L, Chongsuphajaisiddhi T, White NJ
Artesunate/mefloquine treatment of multi-drug resistant falciparum malaria.
Trans R Soc Trop Med Hyg. 1997 Sep-Oct;91(5):574-7.
On the western border of Thailand, in an area endemic for multi-drug resistant Plasmodium falciparum malaria, therapeutic responses were assessed in 1967 patients with uncomplicated falciparum malaria treated with 3 d of artesunate (total dose 12 mg/kg) plus mefloquine (total dose 25 mg/kg). The regimen was well tolerated and resulted in a rapid clinical response; within 48 h, 96% of patients were aparasitaemic and 94% were afebrile. After correcting for reinfections, the cure rate by day 42 was 89% (95% confidence interval [95% CI] 87-91%). Three independent factors were found to predict recrudescence: age < 14 years (adjusted hazards ratio [AHR] = 1.6, 95% CI 1.1-2.3), initial parasitaemia greater than > 40,000/microL (AHR = 1.6, 95%, CI 1.2-2.2), and pure P. falciparum infections (AHR = 1.8, 95% CI 1.3-2.7). These 3 factors combined accounted for 62% of all treatment failures. Patients who received mefloquine on admission with a high admission parasitaemia (> 40,000/microL) had a three-fold (95% CI 1.3-7) risk of subsequent recrudescence compared with those who received their mefloquine on the second or third day ($P = 0.01$). There has been no decline in the efficacy of the 3 d artesunate plus mefloquine regimen since it was introduced in 1992. This regimen is safe, well tolerated, and highly effective in the treatment of multi-drug resistant falciparum malaria.

15288742
Price RN, Uhlemann AC, Brockman A, McGready R, Ashley E, Phaipun L, Patel R, Laing K, Looareesuwan S, White NJ, Nosten F, Krishna S
Mefloquine resistance in Plasmodium falciparum and increased pfmdr1 gene copy number.
Lancet. 2004 Jul 31-Aug 6;364(9432):438-47.
BACKGROUND: The borders of Thailand harbour the world's most multidrug resistant Plasmodium falciparum parasites. In 1984 mefloquine was introduced as treatment for uncomplicated falciparum malaria, but substantial resistance developed within 6 years. A combination of artesunate with mefloquine now cures more than 95% of acute infections. For both treatment regimens, the underlying mechanisms of resistance are not known. METHODS: The relation between polymorphisms in the P falciparum multidrug resistant gene 1 (pfmdr1) and the in-vitro and in-vivo responses to mefloquine were assessed in 618 samples from

patients with falciparum malaria studied prospectively over 12 years. pfmdr1 copy number was assessed by a robust real-time PCR assay. Single nucleotide polymorphisms of pfmdr1, P falciparum chloroquine resistance transporter gene (pfcrt) and P falciparum Ca2+ ATPase gene (pfATP6) were assessed by PCR-restriction fragment length polymorphism. FINDINGS: Increased copy number of pfmdr1 was the most important determinant of in-vitro and in-vivo resistance to mefloquine, and also to reduced artesunate sensitivity in vitro. In a Cox regression model with control for known confounders, increased pfmdr1 copy number was associated with an attributable hazard ratio (AHR) for treatment failure of 6.3 (95% CI 2.9-13.8, p

16417708
Raeisi A, Ringwald P, Safa O, Shahbazi A, Ranjbar M, Keshavarz H, Nateghpour M, Faraji L
Monitoring of the therapeutic efficacy of chloroquine for the treatment of uncomplicated, Plasmodium falciparum malaria in Iran.
Ann Trop Med Parasitol. 2006 Jan;100(1):11-6.
Between 2002 and 2004, the standardized 28-day protocol recently developed by the World Health Organization was used to explore the efficacy of chloroquine, in the treatment of uncomplicated, Plasmodium falciparum malaria, in five sentinel sites in southern Iran. All but 14 of the 158 patients enrolled (128, 28 and two from the provinces of Sistan-Baluchestan, Hormozgan and Kerman, respectively) were successfully followed-up. The overall frequency of treatment failure by day 28 was 78.5%, with 17.4% of the patients being classed as early treatment failures, 34.7% as late clinical failures, and 26.4% as late parasitological failures. There appeared to be no significant change in the frequency of treatment failure between the 2002-2003 and 2003-2004 transmission seasons, nor any significant between-site variation in the efficacy of chloroquine. Given these observations, the replacement of chloroquine, as the first-line drug for the treatment of uncomplicated, P. falciparum malaria in Iran, was inevitable. Artesunate-sulfadoxine-pyrimethamine is now the recommended first-line treatment, with artemether-lumefantrine used for second-line treatment. The efficacies of these combination therapies are currently being evaluated and monitored.

16463750
Rajab JA, Waithaka PM, Orinda DA, Scott CS
Analysis of cost and effectiveness of pre-transfusion screening of donor blood and anti-malarial prophylaxis for recipients.
East Afr Med J. 2005 Nov;82(11):565-71.
OBJECTIVES: To determine the prevalence of malaria in donor units in a low and a high endemic region in Kenya and evaluate the cost effectiveness of recipient anti-malarial prophylaxis and pre-transfusion screening (using an automated method) as options to prevent post transfusion malaria. DESIGN: A descriptive cross-sectional study. SETTING: Two regional blood banks, Nairobi and its environs (National Blood Transfusion Services, Nairobi) a low malaria endemic region and western region (National Blood Transfusion Services, Kisumu) high malaria endemic region. SUBJECTS: All the donated units were included in the study for analysis, during the duration of study, from the two study sites. MAIN OUTCOME MEASURES: Prevalence of malaria in donor units in low endemic area (Nairobi) and high endemic area (Kisumu). Cost per case prevented for the two options, Option I Prophylactic administration of anti-malarial (sulfadoxine pyrimethamine SP) drugs to recipients, and Option II pre-transfusion screening using an automated technique. RESULTS: A malaria prevalence of 0.67% was found in Nairobi and its environments (low endemic) and 8.63% for Kisumu and its environments (high endemic area). The cost analysis showed a cost per case prevented of Ksh.105 (US$1.4) adult, Ksh.52.5 (US$0. 69) and paediatric for the option of recipient prophylaxis using an SP based drug. The cost escalated to Ksh.592 (US$7.79) adult Ksh.444 (US$5.84) paediatric if the prophylaxis was upgraded to the recommended artemisinin derivative (ACT-artemisinin based combination) and for the option of pre-transfusion screening using an automated technique the cost was Ksh.2.08 (US$0.03). CONCLUSION: The prevalence of malaria in donors showed the expected regional variation in the low and high endemic areas and was comparable to data obtained elsewhere. If malaria positive donor units were to be excluded from the national blood supply, an estimated 5% (compared to 1.3% for human Immunodeficiency virus, 3.6% for hepatitis B virus and 1.3% for hepatitis C virus) would be wasted. The cost per case prevented of transfusion-associated malaria is considerably higher for recipient antimalarial prophylaxis than pre-transfusion screening using an automated technique. The cost escalates by five to seven times if the newer artemesinin based combination antimalarial drugs are adopted.

12363062
Ramharter M, Noedl H, Thimasarn K, Wiedermann G, Wernsdorfer G, Wernsdorfer WH
In vitro activity of tafenoquine alone and in combination with artemisinin against Plasmodium falciparum.
Am J Trop Med Hyg. 2002 Jul;67(1):39-43.
Emergence and spread of drug-resistant falciparum malaria has created an urgent demand for alternative therapeutic agents. This study was conducted to assess the in vitro blood schizontocidal activity of

tafenoquine, the most advanced candidate drug of the 8-aminoquinolines, and of its 1:1 combination with artemisinin in fresh isolates of Plasmodium falciparum in an area with multi-drug resistance, measuring the inhibition of schizont maturation. In 43 successfully tested parasite isolates, the mean effective concentrations (ECs) of tafenoquine were 209 nmol/L for the EC50, and 1,414 nmol/L for the EC90. Tafenoquine showed no significant activity relationships with mefloquine, artemisinin, and chloroquine. With quinine, a highly significant activity relationship was observed at the EC50, but not at the EC90. The EC50, and EC90 of the tafenoquine-artemisinin combination were 15.9 nmol/L and 84.3 nmol/L. The combination was synergistic. Tafenoquine appears to be a promising candidate for treating multidrug-resistant falciparum malaria, especially in combination with artemisinin derivatives.

15909266
Ramharter M, Oyakhirome S, Klouwenberg PK, Adegnika AA, Agnandji ST, Missinou MA, Matsiegui PB, Mordmuller B, Borrmann S, Kun JF, Lell B, Krishna S, Graninger W, Issifou S, Kremsner PG
Artesunate-clindamycin versus quinine-clindamycin in the treatment of Plasmodium falciparum malaria: a randomized controlled trial.
Clin Infect Dis. 2005 Jun 15;40(12):1777-84. Epub 2005 May 3.
BACKGROUND: Artemisinin-based drug combinations are the mainstay in the fight against drug-resistant malaria in Africa. Currently available antimalarial drug combinations that include artemisinins are pharmacokinetically unmatched and are therefore potentially increasing the risk of selection of resistant mutants in areas in which the rate of transmission of malaria is high. We tested the potential value of artemisinin-based combination therapy with a short elimination half-life for the treatment of uncomplicated Plasmodium falciparum malaria in sub-Saharan Africa. METHODS: We conducted an open-label, randomized, controlled clinical trial to evaluate the efficacy and tolerability of oral artesunate-clindamycin therapy given twice daily for 3 days (artesunate, 2 mg/kg, and clindamycin, 7 mg/kg, per dose), compared with a standard quinine-clindamycin regimen given twice daily for 3 days (quinine, 15 mg/kg, and clindamycin, 7 mg/kg, per dose), for the treatment of uncomplicated falciparum malaria in 100 Gabonese children aged 3-12 years. The primary end point of the study was the polymerase chain reaction-corrected cure rate for the per-protocol population. RESULTS: The activity of artesunate-clindamycin was comparable to that of quinine-clindamycin in the per-protocol analysis of cure rates at day 28 of follow-up (87% versus 94%). No serious adverse events were reported, and tolerability was good and was similar in both groups. Times to clearance of fever and clearance of parasites were significantly shorter in the artesunate-clindamycin group. CONCLUSIONS: Artesunate-clindamycin and other matching artemisinin-based combinations with a short plasma half-life merit further attention for use in regions in which the rate of transmission of malaria is high.

11339883
Randrianarivelojosia M, Raharimalala LA, Randrianasolo L, Ratsimbasoa A, Rason MA, Ariey F, Jambou R
Madagascan isolates of Plasmodium falciparum showing low sensitivity to artemether in vitro.
Ann Trop Med Parasitol. 2001 Apr;95(3):237-43.
In Madagascar, although chloroquine (CQ) remains the first-line treatment of choice for malaria, the gradual spread of resistance to this antimalarial drug is of increasing concern. As part of a larger investigation of the effectiveness of the second- and third-line drugs used to treat malaria, the in-vitro susceptibilities of Plasmodium falciparum collected in Madagascar to CQ, mefloquine (MQ) and artemether (ART) were therefore investigated. Median inhibitory concentrations (IC(50)) were determined for isolates collected from residents of two villages in the foothills of the central highlands. The IC(50) for ART ranged from 0.23-17.50 nM [N = 51; geometric mean = 4.02 nM; 95% confidence interval (CI) = 2.99-5.05 nM], four isolates exhibiting IC(50) (> 12 nM) indicative of resistance to this drug. The artemether IC(50) were found to be correlated with those of CQ (N = 46; Spearman's r = 0.51; P = 0.0002), which varied widely (0.4-254.3 nM; mean = 23.4 nM; CI = 7.1-39.7 nM; N = 46). Five (11%) of the 46 isolates exposed to CQ in vitro were considered resistant to this drug (i.e. to have IC(50) > 100 nM), with IC(50) ranging from 109-245.3 nM (mean = 171.6 nM; CI = 110.4-232.8 nM). However, all the CQ-resistant isolates were considered sensitive to ART and vice versa. All the isolates tested also appeared sensitive to MQ (IC(50) = 2.21-43.1 nM; mean = 10.5 nM; CI = 7.95-13.07 nM; N = 46), the IC(50) for MQ being correlated with those for CQ (N = 46; Spearman's r =0.46; P = 0.001). There was no significant correlation between ART and MQ activities. Although the sample was fairly small, the present results indicate that P. falciparum in Madagascar is generally becoming less sensitive to CQ and ART. The observation of a correlation between the IC(50) for these two drugs perhaps indicates that artemisinin derivatives would be better used in combination with antimalarial drugs other than 4-aminoquinolines.

14993622
Rath K, Taxis K, Walz G, Gleiter CH, Li SM, Heide L

Pharmacokinetic study of artemisinin after oral intake of a traditional preparation of Artemisia annua L. (annual wormwood).
Am J Trop Med Hyg. 2004 Feb;70(2):128-32.
Artemisia annua L. (annual wormwood) contains the antimalarial artemisinin. Aqueous preparations of the dried herb are included in the pharmacopoeia of the People's Republic of China for treatment of fever and malaria. Fourteen healthy male volunteers received one liter of tea prepared from nine grams of Artemisia annua leaves. Blood samples were taken and artemisinin was detected by reversed phase high-performance liquid chromatography. The mean +/- SD maximum plasma concentration of artemisinin was 240 +/- 75 ng/mL and the mean +/- SD area under the plasma concentration-time curve was 336 +/- 71 ng/mL x hr. Artemisinin was absorbed faster from herbal tea preparations than from oral solid dosage forms, but bioavailability was similar. One liter of an aqueous preparation of nine grams of Artemisia annua contained 94.5 milligrams of artemisinin (approximately 19% of the usually recommended daily dose). Artemisinin plasma concentrations after intake of this herbal tea are sufficient for clinical effects, but insufficient to recommend such preparations as equivalent substitutes for modern artemisinin drugs in malaria therapy.

16022576
Rathore D, McCutchan TF, Sullivan M, Kumar S
Antimalarial drugs: current status and new developments.
Expert Opin Investig Drugs. 2005 Jul;14(7):871-83.
Malaria continues to be a major threat in the developing world, with > 1 million clinical episodes and 3000 deaths every day. In the last century, malaria claimed between 150 and 300 million lives, accounting for 2 - 5% of all deaths. Currently approximately 40% of the world population resides in areas of active malaria transmission. The disease symptoms are most severe in young children and pregnant women. A total of 90% of the disease-associated mortality occurs in Subsaharan Africa, despite the fact that malaria is indigenous to most tropical regions. A licensed vaccine for malaria has not become a reality and antimalarial drugs are the only available method of treatment. Although chloroquine, the first synthetically developed antimalarial, proved to be an almost magical cure for > 30 years, the emergence and spread of chloroquine-resistant parasites has made it virtually ineffective in most parts of the world. Currently, artemisinin, a plant-derived antimalarial, is the only available drug that is globally effective against the parasite. Although several new drugs have been introduced in the past 30 years, widespread or isolated cases of resistance indicate that their window of effectiveness will be limited. Thus, there is an urgent need to develop new therapeutics and regimens for malaria control. This article presents an overview of the currently available antimalarial chemotherapy options and the efforts being undertaken to develop new drugs based on both the recent technological advances and modifications to the old remedies, and on combination therapies.

10706290
Reed MB, Saliba KJ, Caruana SR, Kirk K, Cowman AF
Pgh1 modulates sensitivity and resistance to multiple antimalarials in Plasmodium falciparum.
Nature. 2000 Feb 24;403(6772):906-9.
Throughout the latter half of this century, the development and spread of resistance to most front-line antimalarial compounds used in the prevention and treatment of the most severe form of human malaria has given cause for grave clinical concern. Polymorphisms in pfmdr1, the gene encoding the P-glycoprotein homologue 1 (Pgh1) protein of Plasmodium falciparum, have been linked to chloroquine resistance; Pgh1 has also been implicated in resistance to mefloquine and halofantrine. However, conclusive evidence of a direct causal association between pfmdr1 and resistance to these antimalarials has remained elusive, and a single genetic cross has suggested that Pgh1 is not involved in resistance to chloroquine and mefloquine. Here we provide direct proof that mutations in Pgh1 can confer resistance to mefloquine, quinine and halofantrine. The same mutations influence parasite resistance towards chloroquine in a strain-specific manner and the level of sensitivity to the structurally unrelated compound, artemisinin. This has important implications for the development and efficacy of future antimalarial agents.

11685892
Reithinger R
Bogus antimalarials: a forgotten tale.
Trends Parasitol. 2001 Aug;17(8):359.

16423307
Reyburn H, Ruanda J, Mwerinde O, Drakeley C
The contribution of microscopy to targeting antimalarial treatment in a low transmission area of Tanzania.
Malar J. 2006 Jan 20;5:4.

BACKGROUND: There is a need for improved targeting of antimalarial treatment if artemisinin combination therapy is to be successfully introduced in Africa. This study aimed to explore why malaria slides are requested and how their results guide treatment decisions in an area of low transmission of P. falciparum. METHODS: Outpatients attending a district hospital in a highland area of Tanzania were studied over a 3-week period. Clinical and social data were collected from patients who had been prescribed an antimalarial or sent for a malaria slide. Hospital slides were re-read later by research methods. RESULTS: Of 1,273 consultations 132(10%) were treated presumptively for malaria and 214(17%) were sent for a malaria slide; only 13(6%) of these were reported positive for P. falciparum but 96(48%) of the 201 slide-negative cases were treated for malaria anyway. In a logistic regression model, adults (OR 3.86, P < 0.01), a history of fever (OR1.72, P = 0.03) and a longer travel time to the clinic (OR 1.77 per hour travelled, P < 0.01) independently predicted the request for a malaria slide. Only a history of a cough predicted (negatively) the prescription of an antimalarial with a negative slide result (OR 0.44, P < 0.01). The sensitivity and specificity of hospital slide results were 50% and 96% respectively. CONCLUSION: Progress in targeting of antimalarials in low malaria transmission settings is likely to depend on consistent use of malaria microscopy and on the willingness of health workers to be guided by negative slide results. Further studies are needed to identify how this can be achieved.

10212898
Ribeiro IR, Olliaro P
Safety of artemisinin and its derivatives. A review of published and unpublished clinical trials.
Med Trop (Mars). 1998;58(3 Suppl):50-3.
The preliminary results of a clinical safety review that partly used the Cochrane methodology are presented. Despite methodological limitations including incomplete databases, this review collated evidence corroborating the benign safety profile of the artemisinin type of compounds. No difference was apparent amongst the various derivatives. At the time the workshop was held, 188 studies had been identified of which 108 (enrolling 9,241 patients) fulfilled criteria for analyses. These included both uncomplicated and severe malaria patients enrolled in either controlled and non-controlled studies as well as healthy volunteers. Safety was assessed by analysing adverse events, as well as clinical laboratory (haematology assessed in 4,062, blood chemistry in 3,893 patients), electrocardiographic (2638 patients) and neurological assessments as reported in the papers. No serious adverse event or severe significant toxicity was reported. Overall, the most commonly reported adverse experiences were gastro-intestinal. Occasional neutropenia (1.3%), reticulocytopenia (0.6%), elevated liver enzymes (0.9%) were reported. Transient bradycardia and prolonged QT interval were reported in circa 1.1% of patients monitored. A neurological assessment was performed primarily in the severe malaria patients. No difference was apparent with respect to quinine. In addition, four cases of neuropsychiatric adverse events were reported in patients receiving concomitant mefloquine.

12379946
Rieckmann K, Cheng Q
Pyrimethamine-sulfadoxine resistance in Plasmodium falciparum must be delayed in Africa.
Trends Parasitol. 2002 Jul;18(7):293-4; author reply 294.

16155128
Robert A, Benoit-Vical F, Claparols C, Meunier B
The antimalarial drug artemisinin alkylates heme in infected mice.
Proc Natl Acad Sci U S A. 2005 Sep 20;102(38):13676-80. Epub 2005 Sep 9.
Heme alkylation by the antimalarial drug artemisinin is reported in vivo, within infected mice that have been treated at pharmacologically relevant doses. Adducts resulting from the alkylation of heme by the drug were characterized in the spleen of treated mice, and their glucuroconjugated derivatives were present in the urine. Because these heme-artemisinin adducts were not observed in noninfected mice, this report confirms that the alkylating activity of this antimalarial drug is related to the presence of the parasite in infected animals. The identification of heme-artemisinin adducts in mice should be considered as the signature of the alkylation capacity of artemisinin in vivo.

15115123
Rojanawatsirivej C, Vijaykadga S, Amklad I, Wilairatna P, Looareesuwan S
Monitoring the therapeutic efficacy of antimalarials against uncomplicated falciparum malaria in Thailand.
Southeast Asian J Trop Med Public Health. 2003 Sep;34(3):536-41.
Increasing antimalarial drug-resistance is an important problem in Thailand. The results of monitoring the antimalarial efficacy are used in decision-making about using antimalarials to treat uncomplicated falciparum malaria in Thailand. In 2002, 552 patients with uncomplicated malaria were treated according to the Thai

National Drug Policy, with mefloquine 25 mg/kg plus artesunate 12 mg/kg and primaquine 30 mg in divided doses for 2 days in high-mefloquine-resistant areas; mefloquine 15 mg/kg plus primaquine 30 mg in non- or low-mefloquine-resistant areas; mefloquine 15 mg/kg plus artesunate 12 mg/kg and primaquine 30 mg in divided doses for 2 days or Coartem (6-dose regimen for adult contains 480 mg artemether and 2880 mg lumefantrine) plus primaquine 30 mg given over 3 days in moderate-mefloquine-resistant areas. The study shows that mefloquine, artesunate plus mefloquine, and artemether plus lumefantrine are effective in the treatment of uncomplicated malaria in most areas of Thailand except for Ranong and Kanchanaburi, where the first-line treatment regimen should be revised.

15689066
Rojanawatsirivet C, Congpuong K, Vijaykadga S, Thongphua S, Thongsri K, Bangchang KN, Wilairatana P, Wernsdorfer WH
Declining mefloquine sensitivity of Plasmodium falciparum along the Thai-Myanmar border.
Southeast Asian J Trop Med Public Health. 2004 Sep;35(3):560-5.
Mefloquine sensitivity of Plasmodium falciparum along the Thai-Myanmar border, both in vitro and in vivo, following different first-line treatments for uncomplicated falciparum malaria patients in these areas during the period 1997--2003 were studied. Standard in vitro micro tests and in vivo efficacy according to World Health Organization methodologies were performed. P. falciparum isolates along the Thai-Myanmar border with in vitro sensitivity to mefloquine have had up to a ten-fold decrease in sensitivity compared to a baseline done in 1986, conducted one year after the drug was first introduced to Thailand. The reduction in the mefloquine sensitivity of P. falciparum isolates in Tak Province developed rapidly, with the highest IC50 of 1,254 nM in 1997. The IC50 declined to 1,067 and 737 nM in 1999 and 2001, respectively, but there was no statistically significant difference in the sensitivity. The sensitivity of P. falciparum isolates from Mae Hong Son, Kanchanaburi, and Ranong, where the first line treatment was mefloquine 15 mg/kg single dose, continued to decline, where in 2001 the IC50 were 1,087, 941, and 1,116 nM, respectively, in these provinces. The difference in sensitivities of P. falciparum isolates in Mae Hong Son and Ranong in 2001, compared to 1997, was statistically significant (p

10560606
Rosenblatt JE
Antiparasitic agents.
Mayo Clin Proc. 1999 Nov;74(11):1161-75.
Several important developments have occurred in recent years in the chemotherapy for and prophylaxis of parasitic infections. Although mefloquine is clearly the most effective agent for prevention of chloroquine-resistant falciparum malaria, its use has been compromised by side effects, both real and imagined. Well-designed studies have shown that side effects occur no more frequently with low-dose mefloquine than with chloroquine. Use of mefloquine in pregnant women has not been associated with birth defects, but the incidence of stillbirths may be increased. Malarone is a new agent that combines atovaquone and proguanil, and it may be as effective as mefloquine; however, it is not yet available in the United States. Several newer agents have appeared in response to the development of multidrug resistant Plasmodium falciparum, especially in Southeast Asia. Halofantrine is available for the treatment of mild to moderate malaria due to P. falciparum and for P. vivax infections. Because of severe toxic effects, use of halofantrine should be restricted to only those unusual and rare situations in which other agents cannot be used. Artemisinin (an extract of the Chinese herbal remedy qinghaosu) and two derivatives, artesunate and artemether, are active against multidrug resistant P. falciparum and are widely used in Asia in oral, parenteral, and rectal forms. The antibacterial azithromycin in combination with atovaquone or quinine has now been reported to treat babesiosis effectively in experimental animals and in a few patients. Azithromycin in combination with paromomycin has also shown promise in the treatment of cryptosporidiosis (and toxoplasmosis when combined with pyrimethamine) in patients with the acquired immunodeficiency syndrome (AIDS). Albendazole is currently the only systemic agent available for treatment of microsporidiosis, an infection primarily of patients with AIDS. In addition, albendazole and ivermectin have emerged as effective broad-spectrum antihelminthics, with albendazole becoming the drug of choice for hydatid disease (echinococcosis), neurocysticercosis, and most intestinal nematode infections (except strongyloidiasis and trichuriasis). Liposomal amphotericin B is the first drug approved by the Food and Drug Administration for the treatment of visceral leishmaniasis.

16359408
Rower S, Bienzle U, Weise A, Lambertz U, Forst T, Otchwemah RN, Pfutzner A, Mockenhaupt FP
Short communication: high prevalence of the cytochrome P450 2C8*2 mutation in Northern Ghana.
Trop Med Int Health. 2005 Dec;10(12):1271-3.
Recently, Ghana has changed the first-line treatment of uncomplicated malaria from chloroquine to amodiaquine (AQ) plus artesunate. AQ may cause adverse events such as agranulocytosis and hepatoxicity. The pro-drug AQ is transformed by cytochrome P450 CYP2C8 to the active metabolite N-

desethylaminodiaquine. Several polymorphic variants of CYP2C8 are known, some with reduced activity. In 200 randomly selected children from Northern Ghana, we determined the allele frequencies of the CYP2C8 variants CYP2C8*1 (wild type), CYP2C8*2, CYP2C8*3, and CYP2C8*4. We did not detect CYP2C8*3 and CYP2C8*4, but CYP2C8*2 showed an allele frequency of 0.1675. AQ metabolism in patients with CYP2C8*2 may be impaired, and with an increase of AQ based treatment the risk of severe adverse events may mount.

11265991
Rozendaal J
Fake antimalaria drugs in Cambodia.
Lancet. 2001 Mar 17;357(9259):890.

15683069
Ruebush TK 2nd, Neyra D, Cabezas C
Modifying national malaria treatment policies in Peru.
J Public Health Policy. 2004;25(3-4):328-45.
Between 1998 and 2001, the Peruvian Ministry of Health made sweeping changes in its malaria treatment policies in response to a resurgence of disease and the spread and intensification of antimalarial drug resistance. On the Pacific Coast, the first-line treatment for uncomplicated Plasmodium falciparum malaria was changed to combination therapy with sulfadoxine-pyrimethamine plus artesunate; in the Amazon region, mefloquine-artesunate combination therapy was introduced. With these changes in treatment policy, Peru became the first country in the Americas to use combination therapy with an artemisinin drug as its first-line treatment for falciparum malaria and the first country in the world to use two different drug combination therapy regimens based on an artemisinin drug in different regions of the country. This paper describes the process involved in assessing the geographic distribution and intensity of antimalarial drug resistance throughout the country and the use of that information to guide decisions related to national malaria treatment policy.

15482401
Rwagacondo CE, Karema C, Mugisha V, Erhart A, Dujardin JC, Van Overmeir C, Ringwald P, D'Alessandro U
Is amodiaquine failing in Rwanda? Efficacy of amodiaquine alone and combined with artesunate in children with uncomplicated malaria.
Trop Med Int Health. 2004 Oct;9(10):1091-8.
We investigated the safety and efficacy of amodiaquine alone (AQ) and combined with artesunate (AQ + AS) in 308 Rwandan children 6-59 months old with uncomplicated Plasmodium falciparum malaria attending three sentinel sites. The two treatment regimes were well tolerated and no serious adverse events were recorded. After excluding new infections, children treated with AQ + AS had fewer clinical failures at day 28 after treatment than those treated with AQ alone: OR = 0.20 [95% CI: 0.06-0.57 (P = 0.001)]. Total (parasitological and clinical) failure was also significantly less frequent in the AQ + AS group: OR = 0.34 [95% CI: 0.17-0.67 (P = 0.001)]. When adjusting for study site, the hazard ratio for treatment failure was 0.37 [95% CI: 0.20-0.68 (P = 0.001)]. Combining AQ with AS increases the efficacy of the treatment but the apparent increase of AQ resistance observed in just a 1-year period is worrying and casts doubts on the suitability of implementing AQ + AS as first-line treatment in Rwanda. Alternative treatments should be identified and tested.

12887037
Rwagacondo CE, Niyitegeka F, Sarushi J, Karema C, Mugisha V, Dujardin JC, Van Overmeir C, van den Ende J, D'Alessandro U
Efficacy of amodiaquine alone and combined with sulfadoxine-pyrimethamine and of sulfadoxine pyrimethamine combined with artesunate.
Am J Trop Med Hyg. 2003 Jun;68(6):743-7.
The safety and the efficacy of amodiaquine (AQ) alone, AQ plus sulfadoxine-pyrimethamine (SP) (AQ plus SP), and artesunate (ART) plus SP (ART plus SP), three possible alternatives to chloroquine (CQ), were investigated in 379 Rwandan children 6-59 months old with uncomplicated Plasmodium falciparum malaria who visited one urban/peri-urban health center and two rural health centers. The three treatment regimens were well tolerated and no serious adverse effects were observed. Children treated with AQ plus SP had less clinical failures than those treated with ART plus SP (odds ratio [OR] = 0.25, 95% confidence interval [CI] = 0.06-0.81, P = 0.01) or AQ alone (OR = 0.33, 95% CI = 0.07-1.10, P = 0.08). Even after new infections were excluded, AQ plus SP was still significantly more efficacious than ART plus SP (P = 0.05). At day 14, the mean packed cell volume was significantly higher in the AQ plus SP group compared with the ART plus SP group (P = 0.02) and with the AQ alone group (P = 0.01). In Rwanda, AQ plus SP has been chosen to

replace CQ as a first-line treatment. However, this is considered an interim measure and new combinations, possibly co-formulated, should be identified and tested.

9452284
Sabchareon A, Attanath P, Chanthavanich P, Phanuaksook P, Prarinyanupharb V, Poonpanich Y, Mookmanee D, Teja-Isavadharm P, Heppner DG, Brewer TG, Chongsuphajaisiddhi T
Comparative clinical trial of artesunate suppositories and oral artesunate in combination with mefloquine in the treatment of children with acute falciparum malaria.
Am J Trop Med Hyg. 1998 Jan;58(1):11-6.
A randomized pilot study to compare the safety and efficacy of artesunate suppositories (15 mg/kg/day for three days) versus oral artesunate (6 mg/kg/day for three days), both in combination with mefloquine (25 mg/kg), was conducted in 52 Thai children with uncomplicated multidrug-resistant falciparum malaria. Forty-five patients (87%) had a full 28-day follow-up in the hospital to assess efficacy and exclude reinfection. Mean [range] times to fever clearance of the two groups were similar (42 hr [15-104] versus 42 hr [6-119]). Artesunate suppositories resulted in significantly longer times to achieve 50% and 90% reductions of the initial parasite counts (17 and 26 hr versus 9 and 15 hr; $P < 0.05$ and $P < 0.001$). Time [range] to parasite clearance was longer in the artesunate suppositories group (42 hr [14-93] versus 35 hr [16-69]), but the difference was not significant. The cure rates by days 28 were not significantly different, 92% for artesunate suppository-treated patients and 100% for oral artesunate-treated patients. Both drug regimens are safe and effective. Further studies are needed to characterize the pharmacokinetic properties and the optimum regimen of artesunate suppositories for the treatment of severe malaria.

11888669
Sadava D, Phillips T, Lin C, Kane SE
Transferrin overcomes drug resistance to artemisinin in human small-cell lung carcinoma cells.
Cancer Lett. 2002 May 28;179(2):151-6.
Multiple drug resistance is a significant problem in small-cell lung cancer (SCLC). Artemisinin (ART) is a natural product used to treat drug-resistant malaria. The drug is effective because the Fe2+ present in infected erythrocytes acts non-enzymatically to convert ART to toxic products. We tested the effects of ART on drug-sensitive (H69) and multi-drug-resistant (H69VP) SCLC cells, pretreated with transferrin (TF) to increase the intracellular Fe2+ level. Antibody staining followed by flow cytometry analysis showed twice the level of TF receptors on the H69VP as compared to the H69 cells. Low doses of ART were cytotoxic to SCLC cells. The cytotoxicity of ART for H69VP cells (IC50=24 nM) was ten-fold lower than for H69 cells (IC50=2.3 nM), indicating that ART is part of the drug resistance phenotype. Pretreatment of H69 cells with 220-880 nM TF did not alter the IC50 for ART. However, in the ART-resistant H69VP cells, pretreatment with TF lowered the ART IC50 to near drug-sensitive levels (IC50=5.4 nM after 4 h pretreatment with 880 nM TF). Desferrioxamine (5 microM) inhibited the effect of TF on the IC50 for ART in drug-resistant cells but did not have an effect on ART cytotoxicity in drug-sensitive cells. DNA fragmentation as measured by ELISA occurred within ART-treated cells, with kinetics indicating apoptosis rather than necrosis. This was confirmed by TUNEL staining. These data indicate the potential use of ART and TF in drug-resistant SCLC.

11487367
Sahr F, Willoughby VR, Gbakima AA, Bockarie MJ
Apparent drug failure following artesunate treatment of Plasmodium falciparum malaria in Freetown, Sierra Leone: four case reports.
Ann Trop Med Parasitol. 2001 Jul;95(5):445-9.
Four cases of Plasmodium falciparum malaria who presented in Sierra Leone in November-December 2000 apparently failed to respond to treatment with artesunate. Three (75%) of the cases fulfilled the World Health Organization's criteria for late treatment failure. Although artesunate ranks only sixth as the first-line drug used by clinicians for the treatment of uncomplicated malaria in Sierra Leone, it is widely sold over the counter in pharmacies in the country. The indiscriminate and injudicious use of artesunate among the Sierra Leonean population is likely to increase the level and frequency of resistance among the local strains of P. falciparum. It is recommended that artesunate be reserved for patients who fail to respond to treatment with another of the antimalarial drugs available. Even then, the artesunate should preferably be used in combination with other, longer-acting antimalarial drugs, to slow the development of further resistance.

10212908
Salako L
Artemisinin and its derivatives: the regulatory and policy implications for African countries.
Med Trop (Mars). 1998;58(3 Suppl):82-4.
In many African countries, the first step for introducing a new drug is its selection on the Essential Drug List (WHO) according to the need, the efficacy, the safety, and the affordability of the product. Requirements for registration of artemisinin and its derivatives are either simple notification or authorization, or full registration.

Procedures may vary from country to country, depending upon the level of development of their national regulatory system. The availability of mechanisms to regulate the distribution and the use of these new antimalarials are also depending upon the availability of manpower to implement them. The only artemisinin derivative which has been evaluated clinically in Africa and registered in some African countries, for the treatment of severe and complicated malaria, is intramuscular (i.m.) artemether. The major advantage of artemether is that it is given i.m., thus can be used at peripheral facilities where treatment with intravenous infusions of quinine would not be possible. Post registration surveillance, while being a component of the drug policy of some African countries, has not yet been adequately managed.

9273568
Salcedo JM, Camargo LM, Braga Mde F, de Maria PS, Macedo Vde O
[The evaluation of the efficacy of artesunate combined with tetracycline in the therapy of falciparum malaria]
Rev Soc Bras Med Trop. 1997 May-Jun;30(3):215-22.
A controlled clinical therapeutic study in hospitalized patients compared artesunate with quinine and mefloquine in patients with uncomplicated falciparum malaria. Forty two patients entered the trial and the follow up was for 28 days with thick blood film taken every 12 hours until became negative. Laboratory examinations included haematological and biochemical tests before and after treatment. Patients had a mean parasitaemia of 42.568 per microliter. Twenty six patients completed 28 days of follow up but 16 did not fulfil this protocol. One in each of the therapeutic groups showed delayed R I resistance. A further patient in the quinine group showed R III resistance. The cure rate was 88.8% for artesunate. 85.7% for mefloquine and 81.8% for quinine; no significant difference was found, the same occurring with the clearance of fever. The artesunate group had a quicker parasitaemia clearance time (37.3 +/- 11.5 hours) when compared with quinine (65.2 +/- 17.4) showing a significant difference (p = 0.0016). Parasite clearance with mefloquine, was intermediate (58.9 +/- 16.6 ours) between the artesunate and quinine. No important side effects were observed with any of the therapeutic regimens and no deaths registered.

10472581
Same-Ekobo A, Lohoue J, Essono E, Ravinet L, Ducret JP
[Rapid resolution of Plasmodium ovale malarial attacks using artesunate (Arsumax)]
Med Trop (Mars). 1999;59(1):43-5.
This randomized, non-comparative clinical trial without placebo was carried out to assess the efficacy and tolerance of artesunate for treatment of acute Plasmodium ovale malarial attacks. Thirty Cameroonese patients were included. All presented acute Plasmodium ovale malarial attacks with parasitemia in excess of 500 asexual forms per mm3. Four days after treatment with artesunate, all 30 patients were asymptomatic with no parasitemia. Reduction rates were 93.9 p. 100 for asexual forms and 75.4 p. 100 for gametocytes. Parasite clearance was achieved within 38.8 hours and fever disappeared within 36.6 hours. Tolerance was excellent in 29 patients. The remaining patient briefly complained of mild vertigo. A transient decrease in reticulocyte levels was observed in one patient initially presenting anemia. Artesunate appears to achieve rapid and complete resolution of acute Plasmodium ovale malarial attacks. Since artesunate eliminates both asexual forms and gametocytes, it also acts on transmission by limiting the duration of survival of asexual forms.

15013738
Sanchez BA, Mota MM, Sultan AA, Carvalho LH
Plasmodium berghei parasite transformed with green fluorescent protein for screening blood schizontocidal agents.
Int J Parasitol. 2004 Mar 29;34(4):485-90.
High priority has been given to new assays that facilitate and accelerate the development of novel antimalarial compounds. Unlike evaluation of drugs in vitro, in which new approaches have been used to expedite identification of parasites, the conventional in vivo murine assay requires determination of parasitemia by light microscopy, an incompatible technique to test large numbers of drugs. We have investigated the possibility of using an autonomously fluorescent Plasmodium berghei strain, stably transformed with the green fluorescent protein, to rapidly quantify parasite growth by flow cytometry. The major improvement of this method is that P. berghei line transformed with green fluorescent protein parasites can be quickly and specifically detected in a drop of parasite-infected blood without any manipulation of the sample. Our results showed a clear correlation between the numbers of fluorescent cells detected by flow cytometry and conventional parasitemia, including a correspondence in the peaks of parasitemia. The validation of P. berghei line transformed with green fluorescent protein for chemotherapy studies was performed by evaluating its response to conventional antimalarial drugs such as chloroquine, quinine and sodium artesunate. The results of drug-susceptibility assays as determined by flow cytometry were comparable with those obtained by microscopic examination of Giemsa-stained slides. This PbGFP parasite should prove to be a rapid, simple and sensitive tool for the examination of the large number of compounds and conditions involved in the initial stages of drug development.

16515515
Schellenberg D, Abdulla S, Roper C
Current Issues for Anti-Malarial Drugs to Control P. falciparum Malaria.
Curr Mol Med. 2006 Feb;6(2):253-60.
Successful malaria control depends heavily on efficacious anti-malarial drugs for the treatment of malaria. Artesunate-containing Combination Treatments (ACT) are increasingly recommended as first line malaria treatment in endemic countries, but implementation of this recommendation is limited by the small number of available and affordable co-formulated anti-malarial drugs. In recent years Intermittent Preventive Treatment has been recommended for malaria control in pregnancy and has been shown to be of potential public health importance in the prevention of malaria and anaemia in children. The use of drugs for malaria treatment or prevention is associated with the development of resistance and recent advances in molecular biology facilitate the evaluation of the impact on drug resistance of new drug-based strategies. This review concentrates on the challenges surrounding the use of ACT, the current understanding of IPT in infants and the use of molecular approaches to enhance our understanding of the effects of interventions on the spread of drug resistance.

16465859
Schlitzer M
[Selective enzyme inhibitor instead of an "iron-triggered cluster bomb"]
Pharm Unserer Zeit. 2006;35(1):8-9.

16500657
Schneider P, Bousema T, Omar S, Gouagna L, Sawa P, Schallig H, Sauerwein R
(Sub)microscopic Plasmodium falciparum gametocytaemia in Kenyan children after treatment with sulphadoxine-pyrimethamine monotherapy or in combination with artesunate.
Int J Parasitol. 2006 Jan 24;.
The effects of drugs on Plasmodium falciparum transmission stages may reduce the spread of parasites in the population and contribute to malaria control. Detailed quantitative studies on (sub)microscopic gametocytaemia have become feasible with the availability of real-time Pfs25 quantitative Nucleic Acid Sequence-based Amplification (QT-NASBA), which can be used to detect gametocyte densities above 20 gametocytes per millilitre from in vitro cultures. Gametocyte dynamics were investigated in children with uncomplicated P. falciparum malaria after treatment with sulphadoxine-pyrimethamine (SP) or a combination of SP and artesunate (SP+AS), in a 28-days drug efficacy study. This study demonstrated that gametocyte prevalence in 873 samples from symptomatic Kenyan children was 2.8 times higher by QT-NASBA compared with microscopy. Microscopy-positive cases showed a significant correlation with QT-NASBA for gametocyte density. At enrolment, gametocyte prevalence was 86% by QT-NASBA compared with 22% by microscopy. Gametocytes were detected in 97% of children in at least one blood sample and in 38% of children in all samples obtained during the 28-days follow-up. Both the risk of gametocyte carriage and gametocyte density were considerably higher after treatment with SP compared with SP+AS. Gametocyte prevalence and density decreased with time in the SP+AS group, but not in the SP-treated children. Our data suggest that the potential of malaria transmission remains high even after treatment with artemisinin combination therapy, although prevalence and density of gametocytes is lower after SP+AS.

11822638
Schuster BG
Demonstrating the validity of natural products as anti-infective drugs.
J Altern Complement Med. 2001;7 Suppl 1:S73-82.
This presentation reviews the synthetic or classical development pathway of drug development and contrasts it with developing natural products as drugs. Also presented is an example of a traditional medicine that has been developed from a natural product and has become a "new/old" antiparasitic drug used in the treatment of malaria. The classic paradigm of synthetic drug development breaks down into drug discovery, drug design, preclinical studies, and clinical studies. This paradigm, constructed to weed out failures, results in a drug-development process that is high risk, time consuming, and expensive. The process requires screening an average of 10,000 active compounds to find a single compound that successfully makes its way through validation to drug approval and the marketplace. Following this paradigm, researchers progress from identifying a chemical lead to testing the compound in humans. The World Health Organization (WHO) Guidelines for the Assessment of Herbal Medicines are based on the classical guidelines and follow the classical approach to validating quality, safety, and efficacy--with one major difference. The starting point is to look at the natural product in humans. By taking into account the traditional experience with the product, the validation standard for safety and efficacy of natural products allows for the prolonged and apparently

uneventful use of a substance to offer testimony of its safety. The reliance, then, is on experience--or what Western regulatory agencies would call "anecdotal information." Since most phytomedicines are a combination of several active ingredients, the WHO guidelines cover two kinds of combination products: Combinations that are already used in traditional medicine are considered "old" combination products. "New" combination products are well-known substances that are now being used in combination. Artemisia annua, a pervasive weed, has been referred to in Chinese medicine for thousands of years as a treatment for fever. In 1971, an extraction of artemisia yielded activity against Plasmodium berghei, a mouse model for malaria. The isolated compound, artemisinin, is an example of a traditional medicine that started out in humans, but which then provided a lead structure for a standard drug-development paradigm. Today, artemisinin derivatives are being used widely in combination therapy, especially in areas of the world where there is multidrug-resistant malaria.

16222013
Schwarz NG, Oyakhirome S, Potschke M, Glaser B, Klouwenberg PK, Altun H, Adegnika AA, Issifou S, Kun JF, Kremsner PG, Grobusch MP
5-day nonobserved artesunate monotherapy for treating uncomplicated Falciparum malaria in young Gabonese children.
Am J Trop Med Hyg. 2005 Oct;73(4):705-9.
Despite different recommendations from WHO and national authorities, artesunate monotherapy is increasingly used for treating African children with malaria. A 5-day course of oral artesunate (first day: 4 mg/kg body weight, observed intake; and 2 mg/kg body weight on the following days with nonobserved drug intake) yielded a PCR-corrected Day 28 cure rate of 90% (45 of 50 patients; CI 78-97%) in Gabonese children aged between 2 and 18 months. Artesunate was well tolerated, and no severe adverse events were reported.

12479546
Seguro AC, Campos SB
Diuretic effect of sodium artesunate in patients with malaria.
Am J Trop Med Hyg. 2002 Nov;67(5):473-4.
Previously, we described a direct inhibitory effect of sodium artesunate on sodium chloride transport in the thick ascending limb of Henle's loop, indicating that artesunate acts as a diuretic agent. Here we present 2 cases of falciparum malaria treated with 4 intravenous 60-mg doses of sodium artesunate. Neither diuretics nor vasoactive drugs were administered. A rise in diuresis (6 L/24 hours) was accompanied by an increase in natriuresis, and both declined at the end of the treatment. This diuretic effect has not been reported previously in patients and may modify the course of renal failure and respiratory distress syndrome, both of which complicate severe malaria.

15702504
Senior K
Shortfall in front-line antimalarial drug likely in 2005.
Lancet Infect Dis. 2005 Feb;5(2):75.

9463675
Senok AC, Nelson EA, Li K, Oppenheimer SJ
Thalassaemia trait, red blood cell age and oxidant stress: effects on Plasmodium falciparum growth and sensitivity to artemisinin.
Trans R Soc Trop Med Hyg. 1997 Sep-Oct;91(5):585-9.
Knowledge of innate mechanisms of protection against malaria could be used to bolster the existing limited treatments. Oxidant stress may play a role in the protective mechanism and the effect of red blood cell (RBC) age has recently been recognized. This study investigated the role of oxidant stress in the protection against malaria in thalassaemic trait RBC (alpha and beta) using an experimental approach which controlled for cell age. 'Young', 'intermediate' and 'old' RBC obtained by Percoll fractionation and whole blood were used to set up malaria cultures. Antioxidants (vitamin E and dithiothreitol) and pro-oxidants (riboflavin, menadione and artemisinin) were added to modulate oxidant stress effect. Antioxidants improved parasite growth. The degree of improvement was significantly greater with increasing RBC age ($P < 0.0001$), and relatively greater in thalassaemic RBC ($P < 0.0001$). Pro-oxidants had a parasiticidal effect. With the exception of the 'old' RBC fraction, the median inhibitory concentration (IC50) for riboflavin and menadione was significantly higher in normal RBC. In contrast, the IC50 for artemisinin was significantly higher in 'old' thalassaemic RBC but was similar in the 'young' and 'intermediate' fractions and whole blood. These findings suggest that oxidant stress plays a role in mediating the protection against malaria in thalassaemic RBC. Vitamin E and other antioxidant supplementation could feasibly exacerbate clinical malaria. Conversely, pro-oxidant agents

could act as useful adjuvants to therapy. It is important to confirm the reduced sensitivity to artemisinin in 'old' thalassaemic trait RBC, as such an effect may promote selective pressure for the emergence of resistant parasite strains with widespread use of artemisinin.

16356712
Sharma P, Mohan L, Srivastava CN
Phytoextract-induced developmental deformities in malaria vector.
Bioresour Technol. 2005 Dec 12;.
Larvicidal potential of petroleum ether (Pee), carbon tetrachloride (Cte) and methanol extract (Mee) of Artemisia annua, Chenopodium album and Sonchus oleraceus was observed against malaria vector, Anopheles stephensi Liston. The Pee of A. annua with LC(50) 16.85ppm after 24h and 11.45ppm after 48h of treatment was found most effective, followed by Cte of A. annua and Ch. album, Pee of Ch. album and Mee of A. annua. However, no significant larvicidal activity was observed in Mee of Ch. album and all the three extracts of S. oleraceous. The Pee of A. annua was further investigated for its effect on the metamorphosis and the development of the malaria vector. It influenced the early life cycle of An. stephensi by reducing the percentage of hatching, larval, pupal and adult emergence and also lengthening the larval and pupal periods. The growth index was also reduced significantly. As the extract has remarkable effect on the metamorphosis and high larvicidal potential, it could, therefore, be used as an effective biocontrol agent against the highly nuisant malaria vector.

11395957
Sharma P, Pillai CR, Devi Sharma J
In vitro schizontocidal activity of standard antimalarial drugs on chloroquine-sensitive and chloroquine-resistant isolates of Plasmodium falciparum.
Indian J Exp Biol. 2000 Nov;38(11):1129-33.
The expanding foci of multiple drug resistant malaria and emergence of different strains requires the reassessment of antimalarial activity with various drugs. In vitro response of a chloroquine sensitive and a chloroquine resistant isolate of P. falciparum to a group of 6 quinine derived and 3 artemisinin derived standard drugs has been screened, to evaluate schizontocidal activity of the drugs. In a conventional test system the IC50s were derived from the log dose response curves and evaluated by a rigorous statistical interpretation. Analysis by Tukey's test was significant for the quinine related drugs (Q < or = 0.01) and excludes the statistical significance of artemisinin related drugs in these isolates. The dose-responses of these two isolates vary with quinine derivatives, with some overlap at lower doses for the sensitive isolate than for the resistant one which manifests at higher doses.

10448228
Sharma P, Sharma JD
Plants showing antiplasmodial activity--from crude extracts to isolated compounds.
Indian J Malariol. 1998 Jun;35(2):57-110.
The derivation of important antimalarial compounds started with the discovery of Cinchona bark powder with wine. Subsequently, post World War-I was a period of intensive work in maintaining such ethnobotanical records, in which the use of quinine has remained the drug of choice in malaria. After World War-II new chemical techniques were used to fractionate and isolate, and also for structure determinations, which led to an ever increasing number of potential antiplasmodial compounds. Recently experimental studies in animals and in clinical trials, showed the emergence of CQ-sensitive and CQ-resistant strains of Plasmodium. This paper is an attempt to update a historical list of antimalarial plants and their natural products as studied by pharmacognostic extraction methods of crude drug research of those times. Further an attempt has been undertaken to list the compounds as classified into three major groups, namely alkaloids, terpenes and quassinoids and aromatic and miscellaneous compounds. The most promising is a quassinoid, artemisinin derived from Artemisia annua which has caused a resurgence for the quest of newer antimalarial compounds.

15298018
Shetty P
Global fund switches to artemisinin.
Lancet Infect Dis. 2004 Aug;4(8):477.

10678113
Shi YL, Li GF, Zhao JH, Yang JD, Ding DB
Schizontocidal effects of oral artesunate on Plasmodium berghei in mice and P knowlesi in monkeys.
Zhongguo Yao Li Xue Bao. 1999 Aug;20(8):755-8.

AIM: To study the blood schizontocidal effect of oral artesunate on P berghei in mice and P knowlesi in monkey. METHODS: Effects of artesunate and chloroquine were detected with "4-day test" and "28-day test" on P berghei in mice and "7-day test" on P knowlesi in Macaca mudatta. RESULTS: The suppressive efficacy of oral artesunate was inferior to chloroquine on P berghei K173 strain but the time for 50% and 90% reduction and the time of clearance of parasitemia was 10-15 h shorter than that of chloroquine. Its curative effect on RC/K173 line was markedly superior to that of chloroquine. Moreover, artesunate showed no cross-resistance with chloroquine, index of resistance I90 was only 1.4. At 31.6, 10.0, and 3.16 mg.kg-1, artesunate and chloroquine oral administrations cured P knowlesi in all monkeys. Recrudescence did not occur in 105 d. CONCLUSION: The study of effects of oral artesunate in P berghei/mice and P knowlesi/Macaca mulatta model provided a useful index for clinical trial.

8527414
Shukla KL, Gund TM, Meshnick SR
Molecular modeling studies of the artemisinin (qinghaosu)-hemin interaction: docking between the antimalarial agent and its putative receptor.
J Mol Graph. 1995 Aug;13(4):215-22.
Artemisinin (qinghaosu, QHS) is a promising new antimalarial agent that is effective against drug-resistant strains of malaria. The antimalarial activity of this drug appears to be mediated by an interaction of the drug's endoperoxide bridge with intraparasitic hemin. We have carried out a computer-assisted docking of QHS with hemin from various starting configurations and found that, in the most stable docked configuration, the endoperoxide bridge is in close proximity to the hemin iron. In contrast, an inactive analog, deoxyartemisinin (DQHS), docks in a different manner. Further computer analysis of the drug-hemin interaction might aid in the design of new QHS congeners.

9763721
Shwe T, Lwin M, Aung S
Influence of blister packaging on the efficacy of artesunate + mefloquine over artesunate alone in community-based treatment of non-severe falciparum malaria in Myanmar.
Bull World Health Organ. 1998;76 Suppl 1:35-41.
Three studies were carried out to determine the need, acceptability, and efficacy of adding mefloquine to artemisinin derivatives (AD) for the first-line treatment of uncomplicated falciparum malaria. The first was a retrospective study of 255 basic health workers which showed that their recommendation of AD to patients depended on their level of training. None of the paramedics/midwives and only 9% of 129 doctors had prescribed AD, and no one had recommended AD in combination with mefloquine; 72% of patients used courses that were too short for parasitological cure. To promote the addition of mefloquine to AD regimens we conducted intervention workshops with health care providers and subsidized the cost of mefloquine to patients. In the second study, we interviewed 200 patients before and after the intervention to evaluate drug compliance with full doses of AD and use of subsidized mefloquine. After the intervention, we found that only 3.6% had used mefloquine and 62% had taken non-curative doses of AD. In the third study, we provided blister packs of medication in daily doses and compared the intake of AD + placebo (158 patients) with that of AD + mefloquine (222 patients) for 5 days. The compliance with both regimens was 99%. Blood smears for parasites on day 28 showed one positive in the AD + mefloquine group and 7 positive in the AD group. We conclude that provision of blister packs of daily doses is a very effective way to improve compliance with short courses and drug combinations, but the efficacy of the combination in Myanmar in this particular study was only marginally higher than that of AD alone.

15939906
Sibbald B
New malaria combination cheaper and easier to take.
CMAJ. 2005 Jun 7;172(12):1545.

11085351
Sibmooh N, Pipitaporn B, Wilairatana P, Dangdoungjai J, Udomsangpetch R, Looareesuiwan S, Chantharaksri U
Effect of artemisinin on lipid peroxidation and fluidity of the erythrocyte membrane in malaria.
Biol Pharm Bull. 2000 Nov;23(11):1275-80.
The effect of artemisinin on membrane fluidity of erythrocytes was investigated using spin labeling compounds, doxyl stearic acids. The membrane fluidity of erythrocytes from the in vitro culture and malaria patients was determined. In vitro, the erythrocytes in parasite culture showed an increase in membrane fluidity which was associated with the parasite counts and stage of parasites. Artemisinin caused reduction in membrane fluidity and the effect was more pronounced in the erythrocytes infected with schizont stage-

parasites. In vivo, the elevation of plasma TBARs (thiobarbituric acid reactive substances) and reduction of membrane fluidity were evident in Plasmodium falciparum-infected patients, particularly in severe cases. The levels of plasma TBARs were related to the severity of the disease. Treatment with artemisinin alone showed no effect on plasma TBARs, and did not alter the membrane fluidity. Desferrioxamine, however, reduced oxidative damage during the infection without compromising the therapeutic effect of artemisinin. These findings suggested that the infected erythrocytes were prone to the effect of artemisinin. Addition of a chelator such as desferrioxamine is beneficial and can improve the treatment of severe malaria.

11767072
Sibmooh N, Udomsangpetch R, Kujoa A, Chantharaksri U, Mankhetkorn S
Redox reaction of artemisinin with ferrous and ferric ions in aqueous buffer.
Chem Pharm Bull (Tokyo). 2001 Dec;49(12):1541-6.
Artemisinin, a sesquiterpene with endoperoxide bond, possesses potent antimalarial activity against the ring and late stage of chloroqine-resistant Plasmodium falciparum malaria both in vitro and in vivo. The mode of antimalarial activity of artemisinin is iron-dependent. The aim of this study was to investigate the reactions of artemisinin with ferrous and ferric ions in aqueous buffer. Artemisinin generated a cycle of iron oxidation and reduction. It oxidized ferrous and reduced ferric ions with similar rate of reaction (k=10+/-0.5 M(-1) x s(-1) for ferrous and k=8.5+/-2.0 M(-1) x s(-1) for ferric ion). The major active product was dihydroartemisinin which exhibited antimalarial activity at least 3 times more potent than artemisinin. Dihydroartemisinin preferably binds to ferric ion, forming ferric-dihydroartemisinin complex. The re-oxidation of the complex gives artemisinin and ferric ion. This suggests that in aqueous buffer, the reaction of artemisinin with iron may give rise to the active reaction products, one of them being dihydroartemisinin, which is responsible for antimalarial activity.

16091034
Sidhu AB, Valderramos SG, Fidock DA
pfmdr1 mutations contribute to quinine resistance and enhance mefloquine and artemisinin sensitivity in Plasmodium falciparum.
Mol Microbiol. 2005 Aug;57(4):913-26.
The emergence and spread of multidrug resistant Plasmodium falciparum has severely limited the therapeutic options for the treatment of malaria. With ever-increasing failure rates associated with chloroquine or sulphadoxine-pyrimethamine treatment, attention has turned to the few alternatives, which include quinine and mefloquine. Here, we have investigated the role of pfmdr1 3' coding region point mutations in antimalarial drug susceptibility by allelic exchange in the GC03 and 3BA6 parasite lines. Results with pfmdr1-recombinant clones indicate a significant role for the N1042D mutation in contributing to resistance to quinine and its diastereomer quinidine. The triple mutations S1034C/N1042D/D1246Y, highly prevalent in South America, were also found to enhance parasite susceptibility to mefloquine, halofantrine and artemisinin. pfmdr1 3' mutations showed minimal effect on P. falciparum resistance to chloroquine or its metabolite mono-desethylchloroquine in these parasite lines, in contrast to previously published results obtained with 7G8 parasites. This study supports the hypothesis that pfmdr1 3' point mutations can significantly affect parasite susceptibility to a wide range of antimalarials in a strain-specific manner that depends on the parasite genetic background.

12364805
Sidhu AB, Verdier-Pinard D, Fidock DA
Chloroquine resistance in Plasmodium falciparum malaria parasites conferred by pfcrt mutations.
Science. 2002 Oct 4;298(5591):210-3.
Plasmodium falciparum chloroquine resistance is a major cause of worldwide increases in malaria mortality and morbidity. Recent laboratory and clinical studies have associated chloroquine resistance with point mutations in the gene pfcrt. However, direct proof of a causal relationship has remained elusive and most models have posited a multigenic basis of resistance. Here, we provide conclusive evidence that mutant haplotypes of the pfcrt gene product of Asian, African, or South American origin confer chloroquine resistance with characteristic verapamil reversibility and reduced chloroquine accumulation. pfcrt mutations increased susceptibility to artemisinin and quinine and minimally affected amodiaquine activity; hence, these antimalarials warrant further investigation as agents to control chloroquine-resistant falciparum malaria.

9578181
Sidhu JS, Ashton M, Huong NV, Hai TN, Karlsson MO, Sy ND, Jonsson EN, Cong LD
Artemisinin population pharmacokinetics in children and adults with uncomplicated falciparum malaria.
Br J Clin Pharmacol. 1998 Apr;45(4):347-54.
AIMS: To investigate the pharmacokinetics of the antimalarial artemisinin in the field setting using sparsely collected data. METHODS: Artemisinin concentrations were determined by h.p.l.c. in a total of 107 capillary plasma samples collected on the first day and in 33 samples on the last day of a 5-day oral artemisinin

regimen of 10 mg kg(-1) day(-1) in 23 paediatric (aged 2-12 years) and 31 adult (aged 16-45 years) Vietnamese patients with uncomplicated falciparum malaria. The population model was developed using NONMEM, incorporating interoccasion variability and accounting for a systematic change in artemisinin pharmacokinetics with time, modelled as a change in oral bioavailability. RESULTS: Clinical efficacy, in terms of parasite clearance and fever subsidence times, was comparable between children and adults. A one-compartment model with separate pharmacokinetic estimates for children and adults was found best to describe the disposition of artemisinin after oral administration. The population estimates for artemisinin clearance and distribution volume, respectively, were 432 1 h(-1) and 16001 for adults and 14.41 h(-1) kg(-1) and 37.91 kg(-1) for children, with an intersubject variability (collectively for both age groups) of 45% and 104%, respectively. The oral bioavailability was estimated to decrease from Day 1 to Day 5 by a factor of 6.9, a value found to be similar for children and adults. CONCLUSIONS: Artemisinin pharmacokinetic data was successfully derived in both paediatric and adult patients using 2-3 capillary blood samples taken in conjunction with parasitaemia monitoring. This study's findings advocated the dosing of artemisinin to children according to bodyweight and to adults according to a standard dose.

11949208
Silachamroon U, Krudsood S, Phophak N, Looareesuwan S
Management of malaria in Thailand.
Korean J Parasitol. 2002 Mar;40(1):1-7.
The purpose of treatment for uncomplicated malaria is to produce a radical cure using the combination of: artesunate (4 mg/kg/day) plus mefloquine (8 mg/kg day) for 3 days: a fixed dose of artemether and lumefantrine (20/120 mg tablet) named Coartem (4 tablets twice a day for three days for adults weighing more than 35 kg): quinine 10 mg/kg 8-hourly plus tetracycline 250 mg 6-hourly for 7 days (or doxycycline 200 mg as an alternative to tetracycline once a day for 7 days) in patients aged 8 years and over: Malarone (in adult 4 tablets daily for 3 days). In treating severe malaria, early diagnosis and treatment with a potent antimalarial drug is recommended to save the patient's life. The antimalarial drugs of choice are: intravenous quinine or a parenteral form of an artemisinin derivative (artesunate i.v./i.m. for 2.4 mg/kg followed by 1.2 mg/kg injection at 12 and 24 hr and then daily for 5 dayss; artemether i.m. 3.2 mg/kg injection followed by 1.6 mg/kg at 12 and 24 hrs and then daily for 5 days; artemether i.m. (Artemotil) with the same dose of artemether or artesunate suppository (5 mg/kg) given rectally 12 hourly for 3 days. Oral artemisinin derivatives (artesunate, artemether, and dihydroartemisinin with 4 mg/kg/day) could replace parenteral forms when patients can tolerate oral medication. Oral mefloquine (25 mg/kg divided into two doses 8 hrs apart) should be given at the end of the artemisinin treatment course to reduce recrudescence.

16124422
Silachamroon U, Krudsood S, Thanachartwet W, Tangpukdee N, Leowattana W, Chalermrut K, Srivilairit S, Wilaiaratana P, Thimasarn K, Looareesuwan S
An open, randomized trial of three-day treatment with artesunate combined with a standard dose of mefloquine divided over either two or three days, for acute, uncomplicated falciparum malaria.
Southeast Asian J Trop Med Public Health. 2005 May;36(3):591-6.
The combination of artesunate and mefloquine is currently one of the most effective treatments for multidrug-resistant Plasmodium falciparum malaria. Simultaneous, rather than sequential treatment with the two drugs, would allow better patient compliance. We therefore evaluated three-day treatment with artesunate combined with either 2 or 3 days of mefloquine co-administered once a day with artesunate. The study was an open, randomized trial for acute, uncomplicated falciparum malaria and was conducted at the Bangkok Hospital for Tropical Diseases. One hundred and twenty adult patients were randomized to two treatment groups. Group 1 patients received 4 mg/kg/day of artesunate for 3 days and 3 daily doses of 8.0 mg/kg/day mefloquine given with artesunate. Group 2 patients received the same dose of artesunate and the same total dose of mefloquine (25 mg/kg). However, the mefloquine was given as 15 mg/kg on the first day and 10 mg/kg/ on the second day, again with artesunate. The baseline demographic and clinical characteristics of the patients in the two groups were similar. The cure rates for the 3-day and 2-day mefloquine regimens were 100% and 99%, respectively. There were no significant differences in either median fever clearance times (group 1=32 hours; group 2=33 hours) or mean parasite clearance times (group 1=42.3 hours; group 2=43.3 hours). Both regimens were well tolerated and there were no significant differences in the incidence of adverse effects. Nausea or vomiting occurred in 3.8% of patients in both groups and transient dizziness occurred in 4% of group 1 and 9% of group 2 patients. These results suggest that a 3-day regimen of mefloquine administered with artesunate is effective and well tolerated. This practical regimen could improve patient compliance.

12932090
Silachamroon U, Krudsood S, Treeprasertsuk S, Wilairatana P, Chalearmrult K, Mint HY, Maneekan P, White NJ, Gourdeuk VR, Brittenham GM, Looareesuwan S

Clinical trial of oral artesunate with or without high-dose primaquine for the treatment of vivax malaria in Thailand.
Am J Trop Med Hyg. 2003 Jul;69(1):14-8.
We studied prospectively 801 Thai patients admitted to the Bangkok Hospital for Tropical Diseases with acute, symptomatic Plasmodium vivax malaria to determine the optimum duration of treatment with oral artesunate and the safety, tolerability, and effectiveness of a high dose of primaquine in prevention of relapse. Patients were randomly assigned to one of four treatment groups: 1) a five-day course of artesunate (Group A5); 2) a seven-day course of artesunate (Group A7); 3) a five-day course of artesunate plus a 14-day course of high-dose primaquine (0.6 mg/kg, maximum dose = 30 mg) (Group A5 + P); and 4) a seven-day course of artesunate plus a 14-day course of high-dose primaquine (Group A7 + P). During 28 days of observation, P. vivax reappeared in the blood of 50% of those who received artesunate alone (Groups A5 and A7), compared with none of those who received primaquine (Groups A5 + P and A7 + P; $P < 0.0001$). Adverse effects were confined to the 13 patients with a deficiency for glucose-6-phosphate dehydrogenase; high-dose primaquine (0.6 mg/kg of base a day) had to be stopped in four (31%) patients because of a significant decrease in the hematocrit. The combination of five days of artesunate and 14 days of primaquine is a highly effective and generally well-tolerated treatment regimen for vivax malaria in Thailand.

11485095
Silachamroon U, Phumratanaprapin W, Krudsood S, Treeprasertsuk S, Budsaratid V, Pornpininworakij K, Wilairatan P, Looareesuwan S
Frequency of early rising parasitemia in falciparum malaria treated with artemisinin derivatives.
Southeast Asian J Trop Med Public Health. 2001 Mar;32(1):50-6.
To define the frequency of the early rising of parasitemia in falciparum malaria patients treated with artemisinin derivatives, a retrospective chart review of 497 patients admitted to the Hospital for Tropical Diseases, Bangkok in 1996 was carried out. Early rising parasitemia, defined as an increase in the parasite count over the baseline pretreatment level during the first 24 hours of treatment, was found in 59/229 episodes (25.8%) of uncomplicated, and 111/268 episodes (41.3%) of complicated falciparum malaria. All uncomplicated cases were successfully treated without developing any complications. There were 2 deaths and 13 changes of drug regimen in the complicated group. Only one of these unfavorable responses was due to parasite response. Early rising parasitemia was very common in falciparum malaria treated with artemisinin derivatives, despite their ability to clear the parasitemia, and did not indicate failure of the drug used.

15783238
Simooya O
The WHO 'Roll Back Malaria Project': planning for adverse event monitoring in Africa.
Drug Saf. 2005;28(4):277-86.
Artemisinin combination therapies (ACTs) have been recommended for the treatment of malaria in countries where there is widespread resistance to commonly used antimalarial drugs. Several sub-Saharan African countries are, therefore, in the process of introducing ACTs in their malaria drug policies. However, there is limited information about the safety of ACTs outside South East Asia, where their use has been well documented. As with all other new medicinal compounds, the monitoring of a drug's safety or 'pharmacovigilance' is important, especially in areas where co-morbid conditions, such as HIV/AIDS, malnutrition and tuberculosis, are common. Because in most malaria endemic countries, particularly Africa, there are no pharmacovigilance programmes in place, it has been suggested that the introduction of ACTs offers an opportunity for these countries to put drug safety monitoring systems in place. Backed by the WHO Roll Back Malaria department and other international cooperating partners, five African countries, which are in the process of introducing ACTs (Burundi, Democratic Republic of the Congo, Mozambique, Zambia and Zanzibar), have drawn up action plans to introduce pharmacovigilance in their health sector. It is planned that once the safety monitoring of antimalarials has been established, these activities can then be extended to cover medicinal compounds used in other public health programmes, such as HIV/AIDS, tuberculosis and the immunisation programmes. This article looks at the rationale for pharmacovigilance, the process of setting up monitoring centres and the challenges of implementing the project in the region.

10579474
Simpson JA, Price R, ter Kuile F, Teja-Isavatharm P, Nosten F, Chongsuphajaisiddhi T, Looareesuwan S, Aarons L, White NJ
Population pharmacokinetics of mefloquine in patients with acute falciparum malaria.
Clin Pharmacol Ther. 1999 Nov;66(5):472-84.
OBJECTIVE: To construct a population pharmacokinetic model for mefloquine in the treatment of falciparum malaria. BACKGROUND: Mefloquine is the treatment of choice for multidrug-resistant falciparum malaria. The factors that influence the pharmacokinetic properties of mefloquine in acute malaria are not well characterized. METHODS: The pharmacokinetic properties of mefloquine were evaluated in 257 patients

with acute falciparum malaria by use of nonlinear mixed-effects modeling. Two different oral dose regimens were used: (1) a split dose of 15 mg base/kg initially followed by 10 mg/kg 24 hours later (n = 159) and (2) a single dose of 25 mg/kg (n = 98). Mefloquine was combined with artesunate in 105 (41%) patients (74 received a split dose and 31 received a single dose). RESULTS: Splitting the mefloquine dose increased the area under the concentration-time curve [AUC(0-infinity)] by 50% (95% confidence interval [CI], 36% to 65%) for monotherapy and by 20% (95% CI, 3% to 40%) for combined therapy. The apparent volume of distribution (V/F) was significantly lower in patients receiving split doses of mefloquine monotherapy (mean, 8.14 L/kg; 95% CI, 7.49 to 8.86 L/kg) compared with a single dose (mean, 20.37 L/kg; 95% CI, 16.26 to 25.51 L/kg). Patients who received mefloquine monotherapy and cleared parasitemia in less than 48 hours had a significantly higher AUC(0-infinity) independent of any confounders, compared with patients with slower parasite clearance (geometric mean [95% CI], 50,373 ng/mL x day [46,121 to 55,017 ng/mL x day] versus 45,583 ng/mL x day [42,306 to 49,125 ng/mL x day]). CONCLUSIONS: The pharmacokinetic properties of mefloquine in malaria were relatively unaffected by demographic variables (other than body weight) or disease severity. If it is assumed that apparent clearance and volume of distribution are unaffected by dose regimen, then splitting the 25 mg/kg mefloquine dose improves oral bioavailability and the therapeutic response in the treatment of acute falciparum malaria.

16015341
Singer E
International partnership launches malaria model in Zambia.
Nat Med. 2005 Jul;11(7):695.

10778576
Singh SK, Mandal AK, Pal S, Sinha SK, Singh KK, Chaturvedi R, Singh SK, Agrawal JK
Artesunate therapy in falciparum malaria--alone or in combination.
J Assoc Physicians India. 1999 May;47(5):559-60.

14979392
Singhal T
Management of severe malaria.
Indian J Pediatr. 2004 Jan;71(1):81-8.
Prompt diagnosis and early institution of therapy is an important determinant of outcome in severe falciparum malaria. Thick smears are the gold standard for diagnosis; in situations where reliable microscopy is not available, tests based on HRP-2 antigen/parasite LDH are useful. As there is widespread resistance to chloroquine in P falciparum in India, the choice for specific antimalarial therapy is between quinine and artermisinin derivatives. Randomized controlled trials have not revealed any significant benefit of the artemisinin derivatives over quinine in quinine sensitive areas. Also, if quinine is administered in the recommended way, the side effects are no greater than artemisinins. However, as the artemisinin derivatives are easier to administer, their use in severe malaria in India is increasing. It is vital that we use these drugs in a rational and judicious manner to prevent development of drug resistance. Supportive care, early diagnosis and management of complications are as essential as antimalarial therapy. The role of exchange blood transfusion in the management of severe malaria is still controversial. It may be considered in the presence of high parasites counts (>10%) with multiorgan dysfunction if adequate quantities of safe blood are available.

15228257
Sirima SB, Tiono AB, Konate A, Diarra A, Castelli F, Pinoges L, Mugittu K, Taylor WR, Olliaros PL
Efficacy of artesunate plus chloroquine for the treatment of uncomplicated malaria in children in Burkina Faso: a double-blind, randomized, controlled trial.
Trans R Soc Trop Med Hyg. 2003 May-Jun;97(3):345-9.
Chloroquine (CQ)-resistant Plasmodium falciparum is compromising malaria control in Africa. Combining artesunate (AS) with standard antimalarial drugs increases cure rates and may delay drug resistance. We compared the safety and efficacy of CQ alone and CQ combined with AS (CQ-AS) for treating uncomplicated P. falciparum malaria in Burkina Faso between August 1999 and August 2000. Chloroquine (25 mg/kg over 3 d) combined with AS or placebo (4 mg/kg/d for 3 d) was administered to 300 children aged 6 to 59 months in a randomized, double-blind study. Follow-up extended over 28 d. No adverse drug reactions were recorded. By day 14, parasites were cleared in 120/147 (81.6%) CQ AS-treated children compared with 53/143 (37.1%) CQ-treated children (odds ratio [OR] = 7.55, 95% CI 4.27-13.43, P < 0.001). Corresponding rates for day 28 were 71/145 (49.0%) vs. 27/142 (19.0%) (OR= 4.09, 95% CI 2.33-7.21, P < 0.001). Children who received CQ-AS had significantly faster parasite and fever clearance. Despite the beneficial effects of adding

AS, the high failure rate at day 28 of CQ-AS precludes its use as the first-line regimen for treating CQ-resistant P. falciparum in Burkina Faso.

11023091
Sirivichayakul C, Chanthavanich P, Chokejindachai W, Pengsaa K, Kabkaew K, Saelim R
Pleural effusion in childhood falciparum malaria.
Southeast Asian J Trop Med Public Health. 2000 Mar;31(1):187-9.
Pulmonary complication is a rare manifestation of childhood malaria and isolated pleural effusion without pulmonary edema has never been reported in children. We report here an 11-year-old boy who suffered from cerebral malaria and massive right pleural effusion. The patient was treated with intravenous artesunate, albumin, and other supportive treatments. He recovered completely after eight days. The clinical and laboratory courses suggested that the plasma leakage played a role in the pathogenesis of pleural effusion.

15717281
Sisowath C, Stromberg J, Martensson A, Msellem M, Obondo C, Bjorkman A, Gil JP
In vivo selection of Plasmodium falciparum pfmdr1 86N coding alleles by artemether-lumefantrine (Coartem).
J Infect Dis. 2005 Mar 15;191(6):1014-7. Epub 2005 Feb 8.
Artemisinin derivative-based combination therapy is expected to suppress the development of Plasmodium falciparum drug resistance in Africa. We have performed an artemether-lumefantrine (Coartem; Novartis) follow-up clinical trial in Zanzibar, in which pfcrt K76T and pfmdr1 N86Y frequencies were determined before drug administration and in all recurrent parasites during a follow-up period of 42 days. A significant increase in pfmdr1 86N was observed after exposure to the drug. This points to 86N as a potential marker of lumefantrine resistance in vivo, while suggesting that Coartem is not robust enough to avoid selection of resistance-associated mutations in some malarial settings.

8818732
Skinner TS, Manning LS, Johnston WA, Davis TM
In vitro stage-specific sensitivity of Plasmodium falciparum to quinine and artemisinin drugs.
Int J Parasitol. 1996 May;26(5):519-25.
The inhibitory effects of quinine, chloroquine and 4 qinghaosu drugs, artemisinin, artemether, artesunate and dihydroartemisinin, on 4 culture-adapted isolates and 2 standard clones of Plasmodium falciparum were determined in vitro. All isolates were sensitive to the widely used antimalarial drugs quinine (EC50 range 3 x 10(-8)-1 x 10(-7) mol/L) and chloroquine (EC50 range 1 x 10(-9)-7 x 10(-9) mol/L), irrespective of the geographical origin or treatment history of the patients from which they were taken. In general, the qinghaosu drugs were more potent than the conventional antimalarials, having EC50 values of 3 x 10(-11)-3 x 10(-8) mol/L. Stage-specific data indicated that quinine has a primary mode of action on mature parasite forms, achieving 80-100% growth inhibition within 2-4 h of drug exposure. The stage-specific activity of the 3 qinghaosu drugs artemisinin, artemether and dihydroartemisinin differed from that of quinine, and each derivative displayed a unique stage-specific profile. Artemisinin was rapidly effective against both rings and schizonts, achieving 100% growth inhibition within 6-8 h. The inhibitory effects of artemether were less rapid, requiring 10 h to achieve 70-80% ring stage growth inhibition. Dihydroartemisinin was highly effective against all parasite stages in most cases achieving 100% growth inhibition within 2-4 h of exposure. The results confirm that the qinghaosu drugs are potent antimalarials, and suggest different stage-specific profiles compared to conventional antimalarial drugs.

16103584
Slater M, Kiggundu M, Dokomajilar C, Kamya MR, Bakyaita N, Talisuna A, Rosenthal PJ, Dorsey G
Distinguishing recrudescences from new infections in antimalarial clinical trials: major impact of interpretation of genotyping results on estimates of drug efficacy.
Am J Trop Med Hyg. 2005 Aug;73(2):256-62.
The use of molecular genotyping to distinguish recrudescence from new infections has become common in antimalarial clinical trials. However, methods used to interpret genotyping results have not been standardized. We analyzed data from 3,000 patients enrolled in clinical trials at seven sites in Uganda. Late treatment failure requiring genotyping occurred in 51% of the patients. Among samples successfully genotyped, 21% were definitive new infections (no recrudescent strains present on day of failure), 35% were definitive recrudescences (only recrudescent strains present), and 44% were mixed (new and recrudescent strains present). The probability of having a mixed genotyping result increased as transmission intensity increased. At the highest transmission site, the estimated risk of treatment failure increased from 34% to 84% for chloroquine plus sulfadoxine-pyrimethamine, from 18% to 45% for amodiaquine plus sulfadoxine-pyrimethamine, and from 12% to 57% for amodiaquine plus artesunate, depending on whether mixed genotyping results were classified as new infections or recrudescences, respectively. The method used to classify treatment outcomes can have a major impact on estimates of drug efficacy, especially in areas of high transmission intensity.

15548314
Smithuis F, Shahmanesh M, Kyaw MK, Savran O, Lwin S, White NJ
Comparison of chloroquine, sulfadoxine/pyrimethamine, mefloquine and mefloquine-artesunate for the treatment of falciparum malaria in Kachin State, North Myanmar.
Trop Med Int Health. 2004 Nov;9(11):1184-90.
Multi-drug resistant falciparum malaria is widespread in Asia. In Thailand, Cambodia and Vietnam the national protocols have changed largely to artesunate combined treatment regimens but elsewhere in East and South Asia chloroquine (CQ) and sulfadoxine-pyrimethamine (SP) are still widely recommended by national malaria control programmes. In Kachin State, northern Myanmar, an area of low seasonal malaria transmission, the efficacy of CQ (25 mg base/kg) and SP (1.25/25 mg/kg), the nationally recommended treatments at the time, were compared with mefloquine alone (M; 15 mg base/kg) and mefloquine combined with artesunate (MA; 15:4 mg/kg). An open randomized controlled trial enrolled 316 patients with uncomplicated Plasmodium falciparum malaria, stratified prospectively into three age-groups. Early treatment failures (ETF) occurred in 41% (32/78) of CQ treated patients and in 24% of patients treated with SP (18/75). In young children the ETF rates were 87% after CQ and 35% after SP. Four children (two CQ, two SP) developed symptoms of cerebral malaria within 3 days after treatment. By day 42, failure rates (uncorrected for reinfections) had increased to 79% for CQ and 81% for SP. ETF rates were 2.5% after treatment with M and 3.9% after treatment with MA (P > 0.2). Overall uncorrected treatment failure rates at day 42 following M and MA were 23% and 21%, respectively. Chloroquine and SP are completely ineffective for the treatment of falciparum malaria in northern Myanmar. Mefloquine treatment is much more effective, but three day combination regimens with artesunate will be needed for optimum efficacy and protection against resistance.

15024929
Smithuis F, van der Broek I, Katterman N, Kyaw MK, Brockman A, Lwin S, White NJ
Optimising operational use of artesunate-mefloquine: a randomised comparison of four treatment regimens.
Trans R Soc Trop Med Hyg. 2004 Mar;98(3):182-92.
A randomised trial was conducted in adults and children (> 1 year old) with acute falciparum malaria in Western Myanmar to compare the operational effectiveness of 4 different artesunate-mefloquine combinations. All regimens were well tolerated. During 42 days follow-up polymerase chain reaction genotyping-confirmed recrudescence occurred in 11 of 187 (5.9%) patients who received observed single low-dose mefloquine (15 mg/kg) and artesunate (4 mg/kg), 7 of 192 (3.6%) patients following observed single high-dose mefloquine (25 mg/kg) and artesunate (4 mg/kg), 7 of 180 (3.9%) patients following observed artesunate 4 mg/kg on day 0 plus self-administered mefloquine 15 mg/kg on day 1 and 10 mg/kg on day 2 with artesunate 4 mg/kg/day on day 1 and 2, and none of 177 patients who received this 3 d regimen under direct observation (P = 0.01). Compared with 3 d treatment regimens, single dose treatments were followed by significantly more P vivax infections during the 42 d follow-up (P = 0.009). Post treatment anaemia (haemoglobin < 10 g/dL) was reduced by the 3 d regimens. Gametocyte appearance was low with all 4 regimens. Single dose observed mefloquine-artesunate regimens were very effective, but the 3 d artesunate-mefloquine regimen is the best treatment for acute falciparum malaria in Western Myanmar. Active measures to ensure absorption and improve adherence will be necessary to realise this advantage operationally.

12901938
Snow RW, Eckert E, Teklehaimanot A
Estimating the needs for artesunate-based combination therapy for malaria case-management in Africa.
Trends Parasitol. 2003 Aug;19(8):363-9.
Because of inadequacies in national health information systems, the volumes of drugs required to support an effective policy transition toward artesunate-based combination therapy (ACT) are unknown for most African countries. A series of national surveys and population projections have been used to estimate the age-structured fever burden among 41 malaria endemic countries in Africa. Under present fever-management guidelines, commodity costs and internationally agreed coverage targets, the financial resources to meet the needs of ACT in most African countries are huge. Between US$1.6 billion and US$3.4 billion per annum must be found to give Africa the chance to consider a drug policy based on ACT. Substantial reductions in these costs would be achieved through more effective targeting of resources--only 20% of drugs would be required to manage fevers among the most at-risk pediatric patient populations. Better diagnostics would also be an important consideration for a new ACT policy in Africa.

16262741
Sowunmi A, Fehintola FA, Adedeji AA, Gbotosho GO, Tambo E, Fateye BA, Happi TC, Oduola AM
Open randomized study of artesunate-amodiaquine vs. chloroquine-pyrimethamine-sulfadoxine for the treatment of uncomplicated Plasmodium falciparum malaria in Nigerian children.

Trop Med Int Health. 2005 Nov;10(11):1161-70.
BACKGROUND: Artemisinin-based combination antimalarials are currently considered effective alternatives for the treatment of malaria in Africa, but there are few studies of such combinations in Nigerian children. We assessed the safety, treatment efficacy and effects on gametocyte carriage of the combination of artesunate plus amodiaquine and chloroquine plus pyrimethamine-sulfadoxine in children. METHODS: We evaluated 153 children who were aged 12 years or younger who had uncomplicated Plasmodium falciparum malaria. Patients were randomly assigned a combination of artesunate (4 mg/kg of body weight daily for 3 days) plus amodiaquine (30 mg/kg over 3 days), or chloroquine (25 mg/kg over 3 days) plus pyrimethamine-sulfadoxine (25 mg/kg of the sulfadoxine component at presentation). The primary endpoints were the proportions of children with adequate clinical and parasitological response, late parasitological failure, late clinical failure and early treatment failure. The parasitological cure rates on days 14-28 were also used as the primary endpoints. RESULTS: Both regimens were well tolerated; no child was withdrawn because of drug intolerance. All children treated with artesunate plus amodiaquine had adequate clinical and parasitological response (ACPR), while all but five children treated with chloroquine plus pyrimethamine-sulfadoxine had similar response. Fever clearance times were similar in the two treatment groups. However, the proportion of patients whose parasitaemia cleared by day 2 was significantly higher (100 vs. 50%, P = 0.00001) and parasite clearance was significantly faster (1.7 +/- 0.4 vs. 2.5 +/- 0.8 days, P = 0.0001) in children treated with artesunate plus amodiaquine. The cure rates on days 21 (100%vs. 94%, P = 0.03) and 28 (100%vs. 90%, P = 0.003) were also significantly higher in children treated with artesunate plus amodiaquine than in those treated with chloroquine plus pyrimethamine-sulfadoxine. Overall, a significantly higher proportion of children treated with chloroquine plus pyrimethamine-sulfadoxine carried gametocytes at least once during follow-up compared with those treated with artesunate plus amodiaquine [5 of 50 (10%) vs. 1 of 103 (0.97%), P = 0.01]. CONCLUSION: The combination of artesunate plus amodiaquine is therapeutically superior to a combination of chloroquine plus pyrimethamine-sulfadoxine, and significantly reduced gametocyte carriage following treatment.

15595609
Sriram D, Rao VS, Chandrasekhara KV, Yogeeswari P
Progress in the research of artemisinin and its analogues as antimalarials: an update.
Nat Prod Res. 2004 Dec;18(6):503-27.
Malaria is the number one infectious disease in the world today. Worldwide, over two million people die each year from malaria. This shocking reality is largely due to the emergence of drug resistant strains of Plasmodium falciparum. Artemisinin, a sesquiterpene lactone endoperoxide isolated from Artemesia annua has been shown to be a fast acting, safe and effective drug against multidrug-resistant and sensitive strains of P. falciparum. This article reports a survey of the literature dealing with artemisinin related antimalarial issues that have appeared from 1980s to the beginning of 2003. A broad range of medical and pharmaceutical disciplines is covered, including a brief introduction about discovery, phytochemical aspects, antimalarial mechanism of action, pharmacokinetics, and major drawbacks and various structural modifications made to overcome them.

15567011
Staedke SG, Mpimbaza A, Kamya MR, Nzarubara BK, Dorsey G, Rosenthal PJ
Combination treatments for uncomplicated falciparum malaria in Kampala, Uganda: randomised clinical trial.
Lancet. 2004 Nov 27-Dec 3;364(9449):1950-7.
BACKGROUND: Plasmodium falciparum resistance has rendered chloroquine monotherapy ineffective in much of Africa, but data on alternative regimens are limited. We compared chloroquine+sulfadoxine-pyrimethamine, amodiaquine+sulfadoxine-pyrimethamine, and amodiaquine+artesunate for treatment of uncomplicated malaria in Kampala, Uganda. METHODS: Of 1017 consecutive patients aged 6 months to 10 years with uncomplicated malaria who were screened, 418 were randomised to receive: chloroquine (25 mg/kg over 3 days) and sulfadoxine-pyrimethamine (25 mg/kg sulfadoxine, 1.25 mg/kg pyrimethamine, single dose); amodiaquine (25 mg/kg over 3 days) and sulfadoxine-pyrimethamine; or amodiaquine and artesunate (4 mg/kg daily for 3 days). Primary efficacy outcomes were 28-day clinical failure risks, adjusted and unadjusted by genotyping to distinguish new infection and recrudescence. The primary safety endpoint was incidence of serious adverse events during follow-up. Analysis was intention to treat and per protocol. FINDINGS: 18 patients were excluded before enrollment. Of those enrolled, 384 of 400 (96%) were assigned an efficacy outcome and 396 (99%) were assessed for safety. Risk of 28-day clinical treatment failure was significantly higher with chloroquine+sulfadoxine-pyrimethamine (44/125 [35%]) than with amodiaquine+sulfadoxine-pyrimethamine (12/129 [9%]; risk difference 26% [95% CI 16-36]; p

11129130
Stephenson I, Wiselka M
Drug treatment of tropical parasitic infections: recent achievements and developments.
Drugs. 2000 Nov;60(5):985-95.

Drug development offers potential solutions to a number of tropical health diseases, although the expense of pharmaceutical research and lack of return on investment has limited the production of new agents. The greatest successes have been through the development of single dose therapy and mass treatment control programmes for a number of diseases. We review some of the current treatment regimens for malaria, intestinal helminth infection, onchocerciasis, filariasis and schistosomiasis, and their use in clinical practice. Geographical spread and emergence of drug resistant parasites have hindered the control of malaria, the most important global parasitic infection. Artemisinin compounds have proved effective antimalarial agents producing rapid reduction of parasite load and can be used in combination treatment regimens to combat multidrug resistance. Intestinal helminth infections are widespread, giving rise to nutritional deficiencies and impaired childhood cognitive development. Pregnant women in developing countries are at increased risk of morbidity. Treatment with a single dose benzimidazole such as albendazole or mebendazole has beneficial effects on morbidity and rates of transmission. Diethylcarbamazine has been used in the treatment of onchocerciasis and human filariasis. A complicated escalating dose regimen over several weeks is associated with systemic and allergic reactions and may require corticosteroid cover. Simplified regimens for mass population treatment with ivermectin have proved useful and been used in combination with single dose albendazole and diethylcarbamazine. The African Programme for Onchocerciasis Control in West and Central Africa has been one of the most successful mass control programmes virtually eliminating new infections by a combination of chemotherapy, education and vector control. Schistosomiasis is of increasing importance as a result of the creation of new snail habitats by agricultural and economic development. Praziquantel has become the most widely available and effective chemotherapy for schistosomiasis. There have been a number of reports of persistent schistosome egg shedding after treatment posing concerns about the emergence of drug resistance. Eflornithine has been successfully used in patients with human trypanosomiasis failing melarsoprol therapy however expense and availability have limited its potential. Mass control treatment programmes have targeted schoolchildren, adolescents and pregnant women. The integration of schistosomiasis, onchocerciasis, filariasis and helminth control programmes has been considered as a cost-effective method of delivering treatment. It is likely that future control will be based on this optimisation and integration of existing regimens, rather than the development of new agents.

15667710
Stewart LB, Peters W, Robinson BL
The chemotherapy of rodent malaria. LXII. Drug combinations to impede the selection of drug resistance, part 5: rates of development of resistance to some inhibitors of folate metabolism and to artesunate.
Ann Trop Med Parasitol. 2004 Dec;98(8):763-83.
In recent years infection with chloroquine-resistant Plasmodium falciparum has been combatted with two long-acting antimalarials, pyrimethamine and sulfadoxine, in the combination known as Fansidar that exerts a strong, synergistic action on the asexual stages of the parasite. This second-line regimen, however, is failing increasingly because of the selection of resistant clones in endemic areas, and effective, safe, alternative drugs or drug combinations that are also affordable are urgently needed. Antimalarial drugs with shorter half-lives than those of pyrimethamine or sulfadoxine are likely to be slower to select resistant parasites. In the experiments reported here, the baseline in-vivo responses of rodent malarial parasites to chlorproguanil and proguanil and their active metabolites, chlorcycloguanil and cycloguanil, as well as those to dapsone and artesunate, were explored. In general, the most sensitive parasite to all of these compounds was P. chabaudi. When the drugs were used, individually, to select resistance via the '2%-relapse technique', relatively stable resistance to each was obtained in P. chabaudi as well as in P. berghei and P. yoelii ssp. NS, the last of these being also highly resistant to chloroquine. Of most concern was the rapidity and high level of resistance developed by P. chabaudi to artesunate. The experiments also validated the use of chlorcycloguanil or cycloguanil as surrogates for chlorproguanil or proguanil. Further studies to investigate the possible value of administering chlorproguanil-dapsone, with or without artesunate, are under way and will be reported separately.

15361110
Stivanello E, Cavailler P, Cassano F, Omar SA, Kariuki D, Mwangi J, Piola P, Guthmann JP
Efficacy of chloroquine, sulphadoxine-pyrimethamine and amodiaquine for treatment of uncomplicated Plasmodium falciparum malaria in Kajo Keji county, Sudan.
Trop Med Int Health. 2004 Sep;9(9):975-80.
To provide advice on the rational use of antimalarial drugs, Medecins Sans Frontieres conducted a randomized, an open label efficacy study in Kajo Keji, an area of high transmission of malaria in southern Sudan. The efficacy of chloroquine (CQ), sulphadoxine-pyrimethamine (SP) and amodiaquine (AQ) were measured in a 28-day in vivo study, with results corrected by PCR genotyping. Of 2010 children screened, 115 children aged 6-59 months with uncomplicated Plasmodium falciparum malaria were randomized into each group to receive a supervised course of treatment. Of these, 114, 103 and 111 were analysed in the CQ, SP and AQ groups, respectively. The overall parasitological failure rates at day 28 were 93.9% [95% confidence interval (CI) 87.3-97.3] for CQ, 69.9% (95% CI 60.0-78.3) for SP, and 25.2% (95% CI 17.7-34.5)

for AQ. These results provide important missing data on antimalarial drug efficacy in southern Sudan. They indicate that none of the drugs could be used in monotherapy and suggest that even in combination with artemisinin, cure rates might not be efficacious enough. We recommend a combination of artemether and lumefantrine as first-line treatment for uncomplicated P. falciparum malaria cases in Kajo Keji county.

15548313
Stohrer JM, Dittrich S, Thongpaseuth V, Vanisaveth V, Phetsouvanh R, Phompida S, Monti F, Christophel EM, Lindegardh N, Annerberg A, Jelinek T
Therapeutic efficacy of artemether-lumefantrine and artesunate-mefloquine for treatment of uncomplicated Plasmodium falciparum malaria in Luang Namtha Province, Lao People's Democratic Republic.
Trop Med Int Health. 2004 Nov;9(11):1175-83.
The efficacy of the six-dose regimen of artemether-lumefantrine was compared with the combination of artesunate and mefloquine in a randomised, comparative trial in Luang Namtha Province, Northern Laos. Of 1033 screened patients, 201 were positive for Plasmodium falciparum; 108 patients of all age groups (2-66 years) with acute, uncomplicated P. falciparum malaria were enrolled in the study, 100 of whom were followed-up for 42 days. Fifty-three patients received artemether-lumefantrine and 55 received artesunante-mefloquine. Both drug combinations induced rapid clearance of parasites and malaria symptoms; there was no significant difference in the initial therapeutic response parameters. Both regimes were well tolerated. After 42 days, cure rates were 93.6% (95% CI = 82.5-98.7%; 44 of 47 patients) for artemether-lumefantrine and 100% (95% CI = 93.3-100.0%; 53 of 53 patients) for artesunate-mefloquine. The results show the excellent efficacy and tolerability of both artemether-lumefantrine and artesunate-mefloquine in Northern Laos.

10705302
Stoiser B, Looareesuwan S, Thalhammer F, Daxbock F, Chullawichit S, El-Menyawi I, Graninger W, Burgmann H
Serum concentrations of granulocyte-colony stimulating factor in complicated Plasmodium falciparum malaria.
Eur Cytokine Netw. 2000 Mar;11(1):75-80.
Involvement of neutrophils in the control of blood parasites in malaria has been reported. Both, mononuclear phagocytes and neutrophils are known to be stimulated by cytokines such as TNF-alpha in order to augment the defence potency against the parasites. Previously, it has been shown that serum-G-CSF concentrations are increased in patients with bacterial sepsis. In vitro studies have shown that P. falciparum - infected erythrocytes induce the release of G-CSF by several cells such as endothelial cells and monocytes, however, nothing is known about G-CSF serum concentrations during the clinical course of severe P. falciparum malaria. Thus, it was the aim of the present study to investigate the time course for G-CSF serum concentrations in patients with complicated P. falciparum malaria, and to correlate these values with other mediators of inflammation and hematopoesis. Twenty-six patients suffering from complicated P. falciparum malaria were included in the study, and 20, age and sex matched, healthy volunteers were used as the negative control group. Serum samples for determination of G-CSF were taken on day 0, 7 and 14, and measured by ELISA. We found significantly increased serum concentrations of G-CSF in patients with complicated P. falciparum malaria on day 0, values decreasing to within the normal range by day 7. A significant correlation was found between G-CSF (d0) and procalcitonin, the parasite count, erythropoietin and macrophage inflammatory protein, however no correlation could be shown for the neutrophil count. In conclusion, on the day of hospital admission, elevated serum concentrations of G-CSF were detected in patients with complicated P. falciparum malaria, which might indicate a role of G-CSF in the acute defence mechanism against the parasites.

16440076
Sun HY, Fang CT, Wang JT, Kuo PH, Chen YC, Chang SC
Successful treatment of imported cerebral malaria with artesunate-mefloquine combination therapy.
J Formos Med Assoc. 2006 Jan;105(1):86-9.
Treatment of cerebral malaria with intravenous quinine is frequently associated with life-threatening cardiotoxicity. We report a case of imported cerebral malaria successfully treated with artesunate-mefloquine combination therapy. The 27-year-old woman presented with fever, sudden onset of binocular blindness and altered consciousness 10 days after a short stay in Indonesia. Hyperparasitemia with Plasmodium falciparum and P. vivax in more than 5% of red blood cells was demonstrated on peripheral blood smear. She was admitted to the intensive care unit due to shock, jaundice and acute renal failure. Because of a shortage of intravenous quinine, intravenous artesunate was given as an alternative. Her condition stabilized on the 3rd day of therapy, with resolution of fever and disappearance of parasitemia. Consolidation therapy with oral mefloquine and primaquine was then given to prevent recrudescence and relapse. The only adverse event associated with artesunate was transient reticulocytopenia, which resolved after discontinuation of therapy. Her vision completely recovered, along with renal and liver function.

12812357
Suputtamongkol Y, Chindarat S, Silpasakorn S, Chaikachonpatd S, Lim K, Chanthapakajee K, Kaewkaukul N, Thamlikitkul V
The efficacy of combined mefloquine-artesunate versus mefloquine-primaquine on subsequent development of Plasmodium falciparum gametocytemia.
Am J Trop Med Hyg. 2003 May;68(5):620-3.
An open randomized controlled study of mefloquine-artesunate and mefloquine-primaquine for the treatment of uncomplicated Plasmodium falciparum malaria was carried out in Kanchanaburi in the Saiyok District in western Thailand. Weekly parasite counts from thick and thin blood films were done for six weeks. The gametocyte carriage rate was calculated and compared between the two treatment groups. Gametocytes on presentation, recrudescent infection, and reinfection were the significant factors associated with subsequent development of gametocytemia. It is the increased propensity of recrudescent infections to produce gametocytes that drives drug resistance. The results of this study confirmed that the complete eradication of a sexual forms of P. falciparum by effective antimalarial treatment, but not by combination treatment with primaquine, is the most effective means to prevent subsequent gametocytemia.

11736876
Suputtamongkol Y, Newton PN, Angus B, Teja-Isavadharm P, Keeratithakul D, Rasameesoraj M, Pukrittayakamee S, White NJ
A comparison of oral artesunate and artemether antimalarial bioactivities in acute falciparum malaria.
Br J Clin Pharmacol. 2001 Dec;52(6):655-61.
AIMS: Artesunate and artemether are the two most widely used artemisinin derivatives in the treatment of uncomplicated Plasmodium falciparum malaria, but there is little information on their comparative pharmacokinetics. The aim of this study was to examine the relative oral antimalarial bioavailability and pharmacokinetics of the two derivatives. METHODS: The pharmacokinetic properties of oral artesunate and artemether (4 mg kg(-1)) were compared in a randomized cross-over study of 14 adult patients in western Thailand with acute uncomplicated Plasmodium falciparum malaria. Antimalarial activity was compared using a previously validated, sensitive bioassay. RESULTS: Despite a 29% lower molar dose, oral artesunate administration resulted in significantly larger mean area under the plasma antimalarial activity time curve and median maximum plasma antimalarial activity than after oral artemether (P

12224577
Sutherland CJ, Alloueche A, McRobert L, Ord R, Leggat J, Snounou G, Pinder M, Targett GA
Genetic complexity of Plasmodium falciparum gametocytes isolated from the peripheral blood of treated Gambian children.
Am J Trop Med Hyg. 2002 Jun;66(6):700-5.
The genetic complexity of Plasmodium falciparum gametocytes isolated from Gambian children participating in a controlled trial of anti-malarial therapy was investigated. RNA and DNA were prepared from gametocyte-positive blood, which was also used in transmission experiments with Anopheles gambiae mosquitoes. Amplification by a reverse transcriptase-polymerase chain reaction (RT-PCR) of transcripts from the genes for the ring-infected erythrocyte surface antigen and the 16-kD antigen, which exhibit asexual and sexual stage-specific expression, was used to identify 30 post-treatment gametocyte isolates in which trophozoites persisted below the threshold of detection by microscopy. These included isolates from children who received sulfadoxine/pyrimethamine plus artesunate. Twenty-nine gametocyte-positive isolates that were free of subpatent trophozoites were examined further by PCR amplification of polymorphic genomic loci. We estimate that an average minimum of 2.3 genotypes occurred in these gametocyte-only isolates, and many of these were shown to be infective to mosquitoes. Thus, meiotic recombination between different genotypes is predicted to be a common event in this study area.

12932091
Sutherland CJ, Drakeley CJ, Obisike U, Coleman R, Jawara M, Targett GA, Milligan P, Pinder M, Walraven G
The addition of artesunate to chloroquine for treatment of Plasmodium falciparum malaria in Gambian children delays, but does not prevent treatment failure.
Am J Trop Med Hyg. 2003 Jul;69(1):19-25.
In a randomized controlled trial, chloroquine monotherapy was compared with the combination of artesunate and chloroquine for treating uncomplicated Plasmodium falciparum malaria in 536 Gambian children. Chloroquine-treated children exhibited a 28-day clinical failure rate of 15% (95% confidence interval [CI] = 9.2-22%) compared with 11% (7.8-15%) among children receiving the combination (P = 0.08, by Wilcoxon test). Seventy-three percent of chloroquine-treated children exhibited parasitemia during follow-up compared with 49% of children receiving the combination (relative risk = 1.5, 95% CI = 1.3-1.7; chi2 = 21.18, P < 0.001). A significant reduction in clinical and parasitologic treatment failure in the combination group

occurred in the first two weeks following treatment, but this was eroded over weeks three and four of follow-up. The impact of combination therapy on the transmission of chloroquine-resistant parasites is discussed. Chloroquine plus artesunate is not sufficiently efficacious to justify its introduction as a replacement for chloroquine monotherapy in The Gambia.

12185558
Svensson US, Alin H, Karlsson MO, Bergqvist Y, Ashton M
Population pharmacokinetic and pharmacodynamic modelling of artemisinin and mefloquine enantiomers in patients with falciparum malaria.
Eur J Clin Pharmacol. 2002 Aug;58(5):339-51. Epub 2002 Jul 13.
OBJECTIVES: The aims of this study were to investigate whether artemisinin influences the pharmacokinetics of mefloquine enantiomers or vice versa and to model the antiparasitic effect of these drugs alone and in combination in Plasmodium falciparum malaria patients. METHODS: Forty-two male and female patients were randomised to treatment with either oral artemisinin 500 mg daily for 3 days followed by oral mefloquine 750 mg on day 4, oral artemisinin 500 mg daily for 3 days plus oral mefloquine 750 mg on day 1 or a single 750-mg oral dose of mefloquine. The data was modelled using NONMEM. RESULTS: All patients were successfully treated regardless of treatment. The fastest parasite clearance rates were observed in patients receiving artemisinin together with mefloquine on the first day of treatment. A pharmacodynamic model based on the life cycle of P. falciparum successfully described the efficacy of artemisinin, mefloquine and the combination. The time artemisinin concentration stays above a minimum inhibitory concentration was estimated to 2.97 h (relative standard error 4.7 h). The two mefloquine enantiomers exhibited different pharmacokinetics, with an oral clearance of 3.51 (7.9) l/h and 0.602 (6.9) l/h for RS-mefloquine and SR-mefloquine, respectively. In patients receiving only artemisinin the first 3 days, artemisinin oral clearance was 6.9-fold higher the last day of treatment compared with the first day. There was no difference in the pharmacokinetics of mefloquine enantiomers when mefloquine was given alone, in combination with artemisinin or after a 3-day regimen of artemisinin. There was a tendency towards, although non-significant, higher artemisinin concentrations when artemisinin was given together with mefloquine compared with when given alone. CONCLUSIONS: No significant pharmacokinetic interactions were observed after co-administration of artemisinin and mefloquine. The P. falciparum malaria pharmacodynamic model successfully described the antimalarial effect of artemisinin, mefloquine and a combination of the two drugs.

10212904
Tabusso G, Gomes M
What are the World Health Organization's strategies for meeting regulatory requirements? A case study of artesunate.
Med Trop (Mars). 1998;58(3 Suppl):65-9.
The basic scope of WHO for developing new drugs or a new indication, is that of responding to a public health need, at an affordable price. This paper describes the approach taken by the organisation for the development of rectal artesunate and the special arrangements and approach which have made this possible for the WHO to meet regulatory requirements. Regulatory submission is planned in Europe and the USA, harmonising the submission, registration and labelling, and this precedent may constitute a worldwide reference for the deployment of the drug. The approach is novel, fast, and unbureaucratic, and can be applied to other drugs meeting a live-saving need.

11757332
Tagboto S, Townson S
Antiparasitic properties of medicinal plants and other naturally occurring products.
Adv Parasitol. 2001;50:199-295.
Parasitic diseases remain a major public health problem affecting hundreds of millions of people, particularly in tropical developing countries. The limited availability and affordability of pharmaceutical medicines means that the majority of the world's population depends on traditional medical remedies, and it is estimated that some 20,000 species of higher plant are used medicinally throughout the world. Many well-known drugs listed in the modern pharmacopoeia have their origins in nature, including, for example, quinine from the bark of the Cinchona tree for the treatment of malaria, which has been followed by the subsequent development of the synthetic derivatives chloroquine, amodiaquine, primaquine and mefloquine. More recently, the wider recognition of the antimalarial activity of artemisinin from the herb Artemisia annua has led current research to focus on the development of a large number of synthetic and semisynthetic compounds, which are more active than artemisinin. There is an increasing awareness of the potential of natural products, which may lead to the development of much-needed new antiparasitic drugs. In this chapter, we have drawn together a comprehensive list of medicinal plants and other natural products that have been shown to have activity against human and, to a lesser extent, animal parasites. In addition, some of the opportunities and difficulties in working with natural products have been reviewed and discussed,

including the problems involved with evaluating complex mixtures of compounds which may occur in extracts, problems associated with differentiating between general cytotoxicity and genuine antiparasitic activity, and the hope that new technologies will rapidly accelerate new drug discovery and development in this field. Nevertheless, the way forward for natural product medicines, including the conservation of recognized natural products and protection of general biodiversity, the discovery and development process, and the promotion and usage of existing remedies, presents some difficult challenges. Following an initiative by the World Health Organization in August 2000, there is now the opportunity to evaluate scientifically many more traditional medicines and other natural products in validated antiparasite and toxicity screens, which will help establish which substances have potential for new pharmaceutical products. The use of 'untested' traditional medicines will no doubt continue, and there is an urgent need to distinguish between the efficacious and safe products and the ineffective and/or unsafe products, particularly since many remedies are being more widely promoted in developing countries.

10604757
Tanaka Y, Kamei K, Otoguro K, Omura S
Heme-dependent radical generation: possible involvement in antimalarial action of non-peroxide microbial metabolites, nanaomycin A and radicicol.
J Antibiot (Tokyo). 1999 Oct;52(10):880-8.
Antimalarial screening was performed for microbial metabolites that simulate artemisinin in their mode of action, a potent antimalarial component of an herbal remedy with a characteristic peroxide structure. Nanaomycin A was identified in this screen as an antimalarial compound, together with radicicol and several other compounds already reported (J. Antibiotics 51: 153 approximately 160, 1998). Nanaomycin A inhibited in vitro growth of the human malaria parasite Plasmodium falciparum with an IC80 value of 33.1 nM. It was as potent as radicicol and about 1/10 as potent as artemisinin. Studies on the mode of action suggested that the antimalarial action of the two non-peroxides, nanaomycin A and radicicol, involved heme-dependent radical generation, as is for the peroxide artemisinin. Namely, the inhibition of in vitro growth of malaria parasite by nanaomycin A or radicicol was reversed by tocopherol, a radical scavenger added to the assay mixture. Secondly, in a reaction system established for radical detection, in which a test radical donor and beta-alanylhistidine as a radical recipient were incubated with and without hemin, the two compounds caused heme-dependent decreases of beta-alanylhistidine, as did artemisinin. Among the 14 microbial metabolites identified during this screening, a correlation was observed between antimalarial activity and heme-dependent radical generating activity.

9544936
Tanaka Y, Shiomi K, Kamei K, Sugoh-Hagino M, Enomoto Y, Fang F, Yamaguchi Y, Masuma R, Zhang CG, Zhang XW, Omura S
Antimalarial activity of radicicol, heptelidic acid and other fungal metabolites.
J Antibiot (Tokyo). 1998 Feb;51(2):153-60.
In the course of our screening program for artemisinin-like antimalarial compounds from microorganisms, seven fungal metabolites such as radicicol and heptelidic acid were identified as active compounds. Some of them exhibited antimalarial activity in vitro against the human malaria parasite Plasmodium falciparum to the extent of approximately 1/10 as potent as artemisinin. Radicicol was moderately active in vivo against Plasmodium berghei in mice.

10792201
Tanariya P, Tippawangkoso P, Karbwang J, Na-Bangchang K, Wernsdorfer WH
In vitro sensitivity of Plasmodium falciparum and clinical response to lumefantrine (benflumetol) and artemether.
Br J Clin Pharmacol. 2000 May;49(5):437-44.
AIMS: To assess the sensitivity of 103 Plasmodium falciparum isolates to a combination of lumefantrine (benflumetol) and artemether (CGP 56697), with the objective of determining a correlation between in vitro drug sensitivity and therapeutic outcome. METHODS: Patients suffered from uncomplicated falciparum malaria and came from areas of Thailand affected by multidrug resistance. CGP 56697 was given in the form of tablets containing 20 mg artemether and 120 mg lumefantrine. The standard dose regimen, 4 doses of 4 tablets over 48 h, was compared with two lower dose regimens (4 x 2 tablets and 3 x 4 tablets). RESULTS: The parasites showed high resistance to chloroquine, fairly advanced resistance to mefloquine and compromised sensitivity to quinine. Sensitivity to artemisinin and lumefantrine prior to treatment was similar in all treatment groups. The 4 x 4 tablet regimen was more effective than the other regimens in coping with infections with relatively low sensitivity to artemisinin and/or lumefantrine. The EC90 for artemisinin is an important determinant of treatment success. Parasite density at the start of treatment was identified as another critical predictor of treatment outcome. CONCLUSIONS: The results indicate that parasite exposure to the drugs may have been inadequate and/or too short in the cases of treatment failure, particularly marked

in the lower dose regimens. This could probably be remedied by expanding the dose regimen in areas affected by multidrug resistance and in the case of relatively high parasitaemia.

12962427
Tang JS, Chen CL, Ko WC, Chuang CC
Imported malaria in southern Taiwan from 1991 to 2002: a single hospital's experience.
Kaohsiung J Med Sci. 2003 Aug;19(8):398-405.
Malaria, a major public health problem worldwide, is a predominant infectious disease in most tropical and subtropical countries. Before 1965, Taiwan was a hyperendemic area, but most cases are now imported. We present our experience of dealing with various malaria infections. Charts of malaria patients visiting university hospitals in southern Taiwan between January 1991 and June 2002 were available for review. All diagnoses were made by positive blood smear and detailed history that included countries visited, paroxysm of symptoms, and medical treatment. Seventeen patients, 6 women and 11 men (mean age, 32.3 +/- 11.8 years), were enrolled. Six were infected with Plasmodium falciparum, eight with Plasmodium vivax, two with a combination of P. falciparum and P. vivax, and one with an unidentified infection. All Taiwanese patients infected with P. falciparum (n = 5) contracted the disease in Africa or Indonesia. All Taiwanese patients infected with P. vivax (n = 4) contracted the disease in Southeast Asia or Oceania. Fever and chills were the leading symptoms of malaria. P. falciparum infection was treated with quinine and doxycycline/tetracycline, with the addition of artesunate for cerebral malaria. P. vivax infection was treated with chloroquine and primaquine. Maintaining a high degree of suspicion in patients with a history of travel to malaria-endemic areas is the major cornerstone of malaria diagnosis. Erroneous diagnosis and improper treatment leads to greater morbidity and even mortality.

16438129
Tangpukdee N, Krudsood S, Thanachartwet W, Chalermrut K, Pengruksa C, Srivilairit S, Silachamroon U, Wilairatana P, Phongtananant S, Kano S, Looareesuwan S
An open randomized clinical trial of Artekin vs artesunate-mefloquine in the treatment of acute uncomplicated falciparum malaria.
Southeast Asian J Trop Med Public Health. 2005 Sep;36(5):1085-91.
Malaria remains a major cause of morbidity and mortality in tropical countries and subtropical regions in the world. Southeast Asia has the most resistant malaria parasites in the world, which has limited treatment options in this region. In response to this situation, short-course artemisinin-based combination therapies (ACTs) have been developed. The combination of dihydroartemisinin (DHA) and piperaquine (PQP) in the form of Artekin has been developed as an alternative to established combinations, such as artesunate-mefloquine, primarily to reduce treatment costs and toxicity. We conducted a study comparing a standard treatment for acute uncomplicated falciparum malaria (artesunate 4 mg/kg/day together with mefloquine 8 mg/kg/day oral route once a day for 3 days) (Group A) and a combination of dihydroartemisinin 40 mg and piperaquine 320 mg in the form of Artekin given once a day for 3 days (Group B) to determine safety, efficacy, and tolerability. One hundred and eighty patients were randomly enrolled at the ratio of 1:2 into groups A:B. All patients had rapid initial clinical and parasitological responses. There were no significant differences in fever clearance time or parasite clearance time between both groups. The 28-day cure rates were high, at 100% and 99%, in groups A and B, respectively. We conclude that Artekin was as effective and well-tolerated as artesunate-mefloquine, and can be used alternatively as the current treatment for multidrug-resistant P. falciparum malaria.

11262208
Targett G, Drakeley C, Jawara M, von Seidlein L, Coleman R, Deen J, Pinder M, Doherty T, Sutherland C, Walraven G, Milligan P
Artesunate reduces but does not prevent posttreatment transmission of Plasmodium falciparum to Anopheles gambiae.
J Infect Dis. 2001 Apr 15;183(8):1254-9. Epub 2001 Mar 16.
Combination therapy that includes artemisinin derivatives cures most falciparum malaria infections. Lowering transmission by reducing gametocyte infectivity would be an additional benefit. To examine the effect of such therapy on transmission, Gambian children with Plasmodium falciparum malaria were treated with standard regimens of chloroquine or pyrimethamine-sulfadoxine alone or in combination with 1 or 3 doses of artesunate. The infectivity to mosquitoes of gametocytes in peripheral blood was determined 4 or 7 days after treatment. Infection of mosquitoes was observed in all treatment groups and was positively associated with gametocyte density. The probability of transmission was lowest in those who received pyrimethamine-sulfadoxine and 3 doses of artesunate, and it was 8-fold higher in the group that received pyrimethamine-sulfadoxine alone. Artesunate reduced posttreatment infectivity dramatically but did not abolish it completely. The study raises questions about any policy to use pyrimethamine-sulfadoxine alone as the first-line treatment for malaria.

2202689
Tawfik AF, Bishop SJ, Ayalp A, el-Feraly FS
Effects of artemisinin, dihydroartemisinin and arteether on immune responses of normal mice.
Int J Immunopharmacol. 1990;12(4):385-9.
Artemisinin (Qinghaosu) is a potent antimalarial sesquiterpene lactone isolated from the Chinese herb Artemisia annua. Arteether, a potent semisynthetic analogue of dihydroartemisinin is being developed by the World Health Organization as the artemisinin derivative of choice for the treatment of malaria. All three agents in doses of 400 and 600 mg/kg body weight were found to exhibit marked suppression of humoral responses, as measured by the hemolytic plaque assay, with arteether being the most potent. These agents did not alter the delayed-type hypersensitivity response to sheep erythrocytes at the same dose levels. In addition, all three agents were found not to possess any anti-inflammatory activity when tested on carrageenan-induced oedema. These results indicated that these agents have a selective immunosuppressive activity. They did not exhibit immunostimulating activity in contrast to what has been reported for sodium artesunate.

15119074
Taylor WR, Rigal J, Olliaro PL
Drug resistant falciparum malaria and the use of artesunate-based combinations: focus on clinical trials sponsored by TDR.
J Vector Borne Dis. 2003 Sep-Dec;40(3-4):65-72.
Antimalarial drug resistance has now become a serious global challenge and is the principal reason for the decline in antimalarial drug efficacy. Malaria endemic countries need inexpensive and efficacious drugs. Preserving the life spans of antimalarial drugs is a key part of the strategy for rolling back malaria. Artemisinin-based combinations offer a new and potentially highly effective way to counter drug resistance. Clinical trials conducted in African children have attested to the good tolerability of oral artesunate when combined with standard antimalarial drugs. The cure rates of the different combinations were generally dependent on the degree of resistance to the companion drug. They were high for amodiaquine-artesunate, variable for sulfadoxine/pyrimethamine-artesunate, and poor for chloroquine-artesunate.

14720085
Taylor WR, White NJ
Antimalarial drug toxicity: a review.
Drug Saf. 2004;27(1):25-61.
Malaria, caused mostly by Plasmodium falciparum and P. vivax, remains one of the most important infectious diseases in the world. Antimalarial drug toxicity is one side of the risk-benefit equation and is viewed differently depending upon whether the clinical indication for drug administration is malaria treatment or prophylaxis. Drug toxicity must be acceptable to patients and cause less harm than the disease itself. Research that leads to drug registration tends to omit two important groups who are particularly vulnerable to malaria--very young children and pregnant women. Prescribing in pregnancy is a particular problem for clinicians because the risk-benefit ratio is often very unclear. The number of antimalarial drugs in use is very small. Despite its decreasing efficacy against P. falciparum, chloroquine continues to be used widely because of its low cost and good tolerability. It remains the drug of first choice for treating P. vivax malaria. Pruritus is a common adverse effect in African patients. As prophylaxis, chloroquine is usually combined with proguanil. This combination has good overall tolerability but mouth ulcers and gastrointestinal upset are more common than with other prophylactic regimens. Sulfadoxine/pyrimethamine is well tolerated as treatment and when used as intermittent preventive treatment in pregnant African women. Sulfadoxine/pyrimethamine is no longer used as prophylaxis because it may cause toxic epidermal necrolysis and Stevens Johnson syndrome. Mefloquine remains a valuable drug for prophylaxis and treatment. Tolerability is acceptable to most patients and travellers despite the impression given by the lay press. Dose-related serious neuropsychiatric toxicity can occur; mefloquine is contraindicated in individuals with a history of epilepsy or psychiatric disease. Quinine is the mainstay for treating severe malaria in many countries. Cardiovascular or CNS toxicity is rare, but hypoglycaemia may be problematic and blood glucose levels should be monitored. Halofantrine is unsuitable for widespread use because of its potential for cardiotoxicity. There is renewed interest in two old drugs, primaquine and amodiaquine. Primaquine is being developed as prophylaxis, and amodiaquine, which was withdrawn from prophylactic use because of neutropenia and hepatitis, is a potentially good partner drug for artesunate against falciparum malaria. Atovaquone/proguanil is a new antimalarial combination with good efficacy and tolerability as prophylaxis and treatment. The most important class of drugs that could have a major impact on malaria control is the artemisinin derivatives. They have remarkable efficacy and an excellent safety record. They have no identifiable dose-related adverse effects in humans and only very rarely produce allergic reactions. Combining an artemisinin derivative with another efficacious antimalarial drug is increasingly being viewed as the optimal therapeutic strategy for malaria.

16135285
Taylor-Robinson D, Jones K, Garner P
Malaria: uncomplicated, caused by Plasmodium falciparum.
Clin Evid. 2005 Jun;(13):988-1009.

14982789
Teja-Isavadharm P, Peggins JO, Brewer TG, White NJ, Webster HK, Kyle DE
Plasmodium falciparum-based bioassay for measurement of artemisinin derivatives in plasma or serum.
Antimicrob Agents Chemother. 2004 Mar;48(3):954-60.
Artemisinin and its derivatives, artesunate and artemether, are rapidly acting antimalarials that are used for the treatment of severe and uncomplicated multidrug-resistant falciparum malaria. To optimize treatment regimens that use this new class of antimalarials, there is a need for readily available and reproducible assays to monitor drug levels closely in patients. A sensitive and reproducible bioassay for the measurement of the concentrations of artemisinin derivatives in plasma and serum is described. By modifying the in vitro drug susceptibility test, it was found that antimalarial activity in plasma or serum containing an unknown concentration of drug could be equated to the known concentrations of dihydroartemisinin (DHA) required to inhibit parasite growth. Dose-response curves for a Plasmodium falciparum clone (clone W2) and DHA were used as a standard for each assay. Assays with plasma or serum spiked with DHA proved to be reproducible (coefficient of variation,

11791963
Teja-Isavadharm P, Watt G, Eamsila C, Jongsakul K, Li Q, Keeratithakul G, Sirisopana N, Luesutthiviboon L, Brewer TG, Kyle DE
Comparative pharmacokinetics and effect kinetics of orally administered artesunate in healthy volunteers and patients with uncomplicated falciparum malaria.
Am J Trop Med Hyg. 2001 Dec;65(6):717-21.
The single-dose pharmacokinetics of 100 mg of orally administered artesunate (AS) were studied in 6 patient volunteers with uncomplicated falciparum malaria and in 6 healthy volunteers. Plasma concentrations of both the parent drug, AS, and its major metabolite, dihydroartemisinin (DHA), were measured simultaneously by high-performance liquid chromatography (HPLC) with electrochemical detection (ECD). The antimalarial activity of each plasma sample measured by an in vitro bioassay (BA) was used to derive activity concentrations. Artesunate was absorbed rapidly and then almost completely hydrolyzed to DHA in patients, whereas hydrolysis was incomplete in healthy volunteers. The mean +/- standard deviation (SD) maximum concentration (Cmax) of AS was 296+/-110 nmol/L, the time to peak blood level (tmax was 0.71+/-0.66 hr, the half-life (t1/2,z) was 0.41+/-0.34 hr, and the bioavailability over 12 hr (area under the curve [AUC](0-12)) was 253+/-185 nmol hr/L. Measured by HPLC, the Cmax and AUC(0-12) values of DHA in patients with malaria were significantly greater than in volunteers (1,948+/-772 and 1,192+/-315 nmol/L; 4,024+/-1,585 and 1,763+/-607 nmol hr/L, respectively; P < or = 0.05). These differences were even greater when measured by BA. The Cmax for patients with malaria was 2,894+/-2,497 and 795+/-455 nmol/L for volunteers, and AUC(0-12) was 5,970+/-3,625 and 1,307+/-391 nmol hr/L, respectively (P < or = 0.05). In contrast, DHA parameter estimates for t1/2,z and tmax were similar between patients and healthy volunteers, with values of 0.80+/-0.30 versus 0.87+/-0.06 hr and 1.50+/-0.55 versus 1.13+/-0.52 hr, respectively (P > 0.5). Both drug metabolism and tissue protein binding could contribute to the differences between the antimalarial activity of artemisinin drugs in healthy volunteers and malaria infected patients.

14714543
Tenenbaum DJ
An affordable antimalarial.
Environ Health Perspect. 2004 Jan;112(1):A25.

16458889
Teoh KH, Polichuk DR, Reed DW, Nowak G, Covello PS
Artemisia annua L. (Asteraceae) trichome-specific cDNAs reveal CYP71AV1, a cytochrome P450 with a key role in the biosynthesis of the antimalarial sesquiterpene lactone artemisinin.
FEBS Lett. 2006 Feb 20;580(5):1411-6. Epub 2006 Jan 30.
Artemisinin, a sesquiterpene lactone endoperoxide derived from the plant Artemisia annua, forms the basis of the most important treatments of malaria in use today. In an effort to elucidate the biosynthesis of artemisinin, an expressed sequence tag approach to identifying the relevant biosynthetic genes was undertaken using isolated glandular trichomes as a source of mRNA. A cDNA clone encoding a cytochrome P450 designated CYP71AV1 was characterized by expression in Saccharomyces cerevisiae and shown to

catalyze the oxidation of the proposed biosynthetic intermediates amorpha-4,11-diene, artemisinic alcohol and artemisinic aldehyde. The identification of the CYP71AV1 gene should allow for the engineering of semi-synthetic production of artemisinin in appropriate plant or microbial hosts.

8846489
ter Kuile FO, Nosten F, Luxemburger C, Kyle D, Teja-Isavatharm P, Phaipun L, Price R, Chongsuphajaisiddhi T, White NJ
Mefloquine treatment of acute falciparum malaria: a prospective study of non-serious adverse effects in 3673 patients.
Bull World Health Organ. 1995;73(5):631-42.
Between 1990 and 1994, a series of prospective studies were conducted to optimize the treatment of multidrug-resistant falciparum malaria on the borders of Thailand. The tolerance of various treatment regimens containing either mefloquine 15 mg/kg (M15) or 25 mg/kg (M25) was evaluated in 3673 patients aged between 6 months and 88 years. Early vomiting (within 1 hour) is an important determinant of treatment outcome in these areas, despite re-administration of the dose. Overall, 7 % of the patients vomited within an hour. Significant risk factors were age < or = 6 years (relative risk (RR), 3.9) or > or 50 years (RR, 2.7), the higher mefloquine dose (M25) (RRm 2.7), vomiting < 24 hours before enrolment (RR, 2.5), axillary temperature > 38.0 degrees C (RR, 1.6), and parasitaemia > 10,000/microliter (RR, 1.3). In children < or = 2 years, 30% vomited with M25, and 13% did not tolerate a repeat dose. Vomiting was reduced 40% by splitting the higher dose (RR, 0.6; 95% CI, 0.4-0.8), and 50% by giving mefloquine on the second day in combination with artesunate (RR, 0.5; CI, 0.3-0.9). Anorexia, nausea, vomiting, dizziness, and sleeping disorders were 1.1-1.4 times more frequent with M25 than M15 in the three days following treatment, but were similar in the single or split-dose M25 groups, despite twofold higher mefloquine concentrations obtained with the latter. There was no evidence that diarrhoea, headache, and abdominal pain were associated with mefloquine use. High-dose mefloquine is well tolerated but should be given as a split dose.

11706663
Thanh NV, Cowman AF, Hipgrave D, Kim TB, Phuc BQ, Cong LD, Biggs BA
Assessment of susceptibility of Plasmodium falciparum to chloroquine, quinine, mefloquine, sulfadoxine-pyrimethamine and artemisinin in southern Viet Nam.
Trans R Soc Trop Med Hyg. 2001 Sep-Oct;95(5):513-7.
Resistance to antimalarial chemotherapy is a major concern for malaria control in Viet Nam. In this study undertaken in 1998, 65 patients with uncomplicated Plasmodium falciparum malaria were monitored for 28 days after completion of a 5-day treatment course with artemisinin. Overall 36.9% (24/65) of patients had recurrent parasitaemia during the surveillance period. P. falciparum isolates were tested for sensitivity in vitro to chloroquine, mefloquine, quinine, sulfadoxine-pyrimethamine and results were compared to those from a similar study in 1995. Increased parasite sensitivity to sulfadoxine-pyrimethamine, chloroquine and quinine was demonstrated, with significantly lower mean EC50 and EC99 values in 1998 compared to 1995. Parasite sensitivity to mefloquine did not differ significantly in the 2 surveys. Isolates were also tested for sensitivity in vitro to artemisinin in the 1998 survey. The mean EC50 was 0.03 mumol/L and the EC99 was 0.94 mumol/L. Parasite sensitivity to artemisinin will need to be monitored in view of its increasing use in Viet Nam.

9561593
Thimasarn K, Sirichaisinthop J, Chanyakhun P, Palananth C, Rooney W
A comparative study of artesunate and artemether in combination with mefloquine on multidrug resistant falciparum malaria in eastern Thailand.
Southeast Asian J Trop Med Public Health. 1997 Sep;28(3):465-71.
Plasmodium falciparum in Thailand is highly resistant to chloroquine, sulfadoxine-pyrimethamine and there is increasing resistance to quinine and mefloquine. The use of qinghaosu derivatives alone or in combination with mefloquine has been shown successfully effective against multidrug resistant P. falciparum in many clinical trials. However their applications with ambulatory treatment should be assessed. 394 uncomplicated falciparum malaria cases studied at Trat and Chanthaburi malaria clinics, eastern Thailand, were allocated at random to receive either one of the seven following regimens: A) artesunate 600 mg over 2 days and mefloquine 1,250 mg in divided doses. B) artemether 640 mg over 2 days and mefloquine 1,250 mg in divided doses. C) artesunate alone 700 mg over 5 days period. D) artemether alone 800 mg over 5 days period. E) quinine plus tetracycline for 7 days. F) mefloquine 1,250 mg in divided doses and G) artesunate 600 mg over 2 days period and mefloquine 750 mg. The follow-up was on Days 1, 2, 7, 14, 21 and 28. Patients tolerated all regimens very well and there was no serious side effects. The adverse effects did not differ among the seven regimens. The cure rates were 98.7, 97.1, 97.9, 96.7, 92.3, 100 and 95.2%, respectively. There was no significant difference of cure rates among various regimens. A total of 16 P. vivax and 1 P. malariae reinfections were reported among the study groups during the second half of the follow-up period, 14 of which were from the groups administered short action drugs (artesunate, artemether or

quinine). The results suggested that either artesunate 600 mg or artemether 640 mg in combination with mefloquine 1,250 mg over a period of two days should be considered as alternative regimens for treating uncomplicated multi-drug resistant falciparum malaria.

16416385
Thriemer K, Wernsdorfer G, Rojanawatsirivet C, Kollaritsch H, Sirichainsinthop J, Wernsdorfer WH
In vitro activity of artemisinin alone and in combination with retinol against Plasmodium falciparum.
Wien Klin Wochenschr. 2005;117 Suppl 4:45-8.
Increasing resistance of Plasmodium falciparum to antimalarial drugs is an important public health problem, demanding novel therapeutic approaches. This study had the objective of assessing the in vitro activity of artemisinin and its combination with retinol in fresh isolates of P. falciparum in an area with a high proportion of multidrug-resistant strains. The tests were based on the inhibition of schizont maturation. In 45 successfully tested isolates, the mean effective concentrations (ECs) of artemisinin were 10.29 nM for the EC-50 and 34.86 nM for the EC-90. The EC50 and EC90 for artemisinin in the artemisinin-retinol mixture were 2.71 nM and 13.37 nM, respectively. The combination showed synergistic activity. Retinol appears to be a promising partner for the antimalarial therapy with artemisinins.

12435700
Tjitra E, Baker J, Suprianto S, Cheng Q, Anstey NM
Therapeutic efficacies of artesunate-sulfadoxine-pyrimethamine and chloroquine-sulfadoxine-pyrimethamine in vivax malaria pilot studies: relationship to Plasmodium vivax dhfr mutations.
Antimicrob Agents Chemother. 2002 Dec;46(12):3947-53.
Artemisinin-derivative combination therapies (ACT) are highly efficacious against multidrug-resistant Plasmodium falciparum malaria. Few efficacy data, however, are available for vivax malaria. With high rates of chloroquine (CQ) resistance in both vivax and falciparum malaria in Papua Province, Indonesia, new combination therapies are required for both species. We recently found artesunate plus sulfadoxine-pyrimethamine (ART-SP) to be highly effective (96%) in the treatment of falciparum malaria in Papua Province. Following a preliminary study of CQ plus sulfadoxine-pyrimethamine (CQ-SP) for the treatment of Plasmodium vivax infection, we used modified World Health Organization criteria to evaluate the efficacy of ART-SP for the treatment of vivax malaria in Papua. Nineteen of 22 patients treated with ART-SP could be evaluated on day 28, with no early treatment failures. Adequate clinical and parasitological responses were found by day 14 in all 20 (100%) of the patients able to be evaluated and by day 28 in 17 patients (89.5%). Fever and parasite clearance times were short, with hematological improvement observed in 70.6% of the patients. Double (at positions 58 and 117) and quadruple (at positions 57, 58, 61, and 117) mutations in the P. vivax dihydrofolate reductase (PvDHFR) were common in Papuan P. vivax isolates (46 and 18%, respectively). Treatment failure with SP-containing regimens was significantly higher with isolates with this PvDHFR quadruple mutation, which included a novel T-->M mutation at residue 61 linked to an S-->T (but not an S-->N) mutation at residue 117. ART-SP ACT resulted in a high cure rate for both major Plasmodium species in Papua, though progression of DHFR mutations in both species due to the continued use of SP monotherapy for clinically diagnosed malaria threatens the future utility of this combination.

11693875
Tjitra E, Suprianto S, Currie BJ, Morris PS, Saunders JR, Anstey NM
Therapy of uncomplicated falciparum malaria: a randomized trial comparing artesunate plus sulfadoxine-pyrimethamine versus sulfadoxine-pyrimethamine alone in Irian Jaya, Indonesia.
Am J Trop Med Hyg. 2001 Oct;65(4):309-17.
Combining artesunate with existing antimalarial drugs may improve cure rates, delay emergence of resistance, and reduce transmission. We performed a randomized comparative trial to quantify the effect of adding artesunate to sulfadoxine-pyrimethamine in the treatment of uncomplicated falciparum malaria in Indonesia. Using a modified 1997 World Health Organization protocol for assessment of therapeutic efficacy of antimalarial drugs, 105 patients (stratified by age/ethnic group) were randomized: 53 received artesunate orally, 4 mg/kg of body weight, a single daily dose for three days, plus sulfadoxine-pyrimethamine orally (1.25 mg of pyrimethamine/kg of body weight), a single dose on day 0, and 52 patients received sulfadoxine-pyrimethamine alone. Six from the combination group were withdrawn from analysis, as were six of the sulfadoxine-pyrimethamine group. Treatment failure rates on day 14 were 0% in the artesunate plus sulfadoxine-pyrimethamine group and 8.7% in the sulfadoxine-pyrimethamine group (P = 0.12). Treatment failure rates on day 28 were 4.4% and 15.2%, respectively (P = 0.16). Relative risk of treatment failure at 28 days was 0.3 (95% confidence interval [CI] = 0.1-1.3). Mean fever clearance time (1.3 versus 1.7 days) and mean parasite clearance time (1.4 versus 2.0 days) were both faster in the artesunate plus sulfadoxine-pyrimethamine group than in the sulfadoxine-pyrimethamine group (P = 0.08 and P < 0.0001, respectively). Only 20 (39.2%) of 51 patients treated with artesunate plus sulfadoxine-pyrimethamine were still parasitemic on day 1 compared with 45 (86.5%) of 52 patients treated with sulfadoxine-pyrimethamine alone (P = 0.000001, relative risk [RR] = 0.4, 95% CI = 0.3-0.6). Gametocyte carriage was lower following artesunate

plus sulfadoxine-pyrimethamine than following sulfadoxine-pyrimethamine (RR = 0.5, 95% CI = 0.2-1.0 on day 7 and RR = 0.5, 95% CI = 0.2-1.1 on day 14). Mild diarrhea, rash, and itching resolved without treatment. Combined artesunate plus sulfadoxine-pyrimethamine resulted in more rapid fever and parasiteclearance, was well tolerated, reduced risk of treatment failure, and lowered gametocyte carriage.

11230422
Tjitra E, Suprianto S, McBroom J, Currie BJ, Anstey NM
Persistent ICT malaria P.f/P.v panmalarial and HRP2 antigen reactivity after treatment of Plasmodium falciparum malaria is associated with gametocytemia and results in false-positive diagnoses of Plasmodium vivax in convalescence.
J Clin Microbiol. 2001 Mar;39(3):1025-31.
A problem with rapid Plasmodium falciparum-specific antigen histidine-rich protein 2 (HRP2) detection tests for malaria is the persistence of antigen in blood after the disappearance of asexual-stage parasitemia and clinical symptoms, resulting in false-positive (FP) test results following treatment. The ICT P.f/P.v immunochromatographic test detects both HRP2 and a panmalarial antigen (PMA) found in both P. falciparum and Plasmodium vivax. To examine posttreatment antigen persistence with this test and whether persistent sexual-stage forms (gametocytes) are a cause of FP tests after treatment, we compared serial antigen test results with microscopy results from patients symptomatic with P. falciparum malaria in Indonesia for 28 days following treatment with chloroquine (CQ; n = 66), sulfadoxine-pyrimethamine (SP; n = 36), and artesunate plus sulfadoxine-pyrimethamine (ART + SP; n = 15). Persistent FP antigenemia following SP treatment occurred in 29% (HRP2) and 42% (PMA) of the patients on day 7 and in 10% (HRP2) and 23% (PMA) on day 14. The high rates of persistent HRP2 and PMA antigenemia following CQ and SP treatment were strongly associated with the presence of gametocytemia, with the proportion with gametocytes on day 7 posttreatment being significantly greater in those with FP results than in those with true-negative PMA and HRP2 results. Gametocyte frequency on day 14 post-SP treatment was also greater in those with FP PMA results. Following SP treatment, PMA persisted longer than HRP2, giving an FP diagnosis of P. vivax in up to 16% of patients on day 14, with all FP P. vivax diagnoses having gametocytemia. In contrast, PMA was rapidly cleared following ART + SP treatment in association with rapid clearance of gametocytemia. Gametocytes appear to be an important cause of persistent posttreatment panmalarial antigenemia in areas of endemicity and may also contribute in part to persistent HRP2 antigenemia following treatment.

16413873
Toovey S
Artesunate versus quinine for severe falciparum malaria.
Lancet. 2006 Jan 14;367(9505):111; author reply 111-2.

15109547
Toovey S, Jamieson A
Audiometric changes associated with the treatment of uncomplicated falciparum malaria with co-artemether.
Trans R Soc Trop Med Hyg. 2004 May;98(5):261-7; discussion 268-9.
Animal studies have demonstrated artemisinin brain stem toxicity with auditory centres being especially affected; there has, to date, been no evidence of such toxicity with oral artemisinins in humans. Subjects working at a construction site in Mozambique had audiometric assessments taken on joining and leaving the project. Subjects with uncomplicated malarias received co-artemether (artemether-lumefantrine) (n = 150) while age-, gender-, weight- and race-matched controls (n = 150) neither suffered malaria nor received antimalarial therapy. Hearing thresholds were measured at predefined frequencies in treated subjects and controls. Subjects receiving co-artemether had a significantly greater heating loss than controls at all frequencies except 250 Hz and 500 Hz (P values ranging from

8544181
Torok DS, Ziffer H, Meshnick SR, Pan XQ, Ager A
Syntheses and antimalarial activities of N-substituted 11-azaartemisinins.
J Med Chem. 1995 Dec 22;38(26):5045-50.
A two-step reaction sequence between artemisinin and methanolic ammonia followed by treatment with Amberlyst 15 yielded 11-azaartemisinin in 65% yield. Substituting a variety of primary alkyl- and heteroaromatic amines for ammonia in the reaction sequence yields N-substituted 11-azaartemisinins in similar or greater yield. When Amberlyst 15 is replaced by a mixture of sulfuric acid/silica gel, both 11-azaartemisinin and the expected metabolite, 10-azadesoxyartemisinin, are formed in 45% and 15% yields, respectively. In vitro and in vivo test data for a number of novel N-substituted 11-azaartemisinins, against drug-resistant strains of Plasmodium falciparum, show they possess antimalarial activities equal to or greater

than that of artemisinin. The most active derivative, N-(2'-acetaldehydo)-11-azaartemisinin, 17, was 26 times more active in vitro and 4 times more active in vivo than artemisinin.

12930555
Trampuz A, Jereb M, Muzlovic I, Prabhu RM
Clinical review: Severe malaria.
Crit Care. 2003 Aug;7(4):315-23. Epub 2003 Apr 14.
Malaria represents a medical emergency because it may rapidly progress to complications and death without prompt and appropriate treatment. Severe malaria is almost exclusively caused by Plasmodium falciparum. The incidence of imported malaria is increasing and the case fatality rate remains high despite progress in intensive care and antimalarial treatment. Clinical deterioration usually appears 3-7 days after onset of fever. Complications involve the nervous, respiratory, renal, and/or hematopoietic systems. Metabolic acidosis and hypoglycemia are common systemic complications. Intravenous quinine and quinidine are the most widely used drugs in the initial treatment of severe falciparum malaria, whereas artemisinin derivatives are currently recommended for quinine-resistant cases. As soon as the patient is clinically stable and able to swallow, oral treatment should be given. The intravascular volume should be maintained at the lowest level sufficient for adequate systemic perfusion to prevent development of acute respiratory distress syndrome. Renal replacement therapy should be initiated early. Exchange blood transfusion has been suggested for the treatment of patients with severe malaria and high parasitemia. For early diagnosis, it is paramount to consider malaria in every febrile patient with a history of travel in an area endemic for malaria.

8649493
Tran TH, Day NP, Nguyen HP, Nguyen TH, Tran TH, Pham PL, Dinh XS, Ly VC, Ha V, Waller D, Peto TE, White NJ
A controlled trial of artemether or quinine in Vietnamese adults with severe falciparum malaria.
N Engl J Med. 1996 Jul 11;335(2):76-83.
BACKGROUND. Artemisinin (qinghaosu) and its derivatives are rapidly effective antimalarial drugs derived from a Chinese plant. Preliminary studies suggest that these drugs may be more effective than quinine in the treatment of severe malaria. We studied artemether in Vietnam, where Plasmodium falciparum has reduced sensitivity to quinine. METHODS. We conducted a randomized, double-blind trial in 560 adults with severe falciparum malaria. Two hundred seventy-six received intramuscular quinine dihydrochloride (20 mg per kilogram of body weight followed by 10 mg per kilogram every eight hours), and 284 received intramuscular artemether (4 mg per kilogram followed by 2 mg per kilogram every eight hours). Both drugs were given for a minimum of 72 hours. RESULTS. There were 36 deaths in the artemether group (13 percent) and 47 in the quinine group (17 percent; P = 0.16; relative risk of death in the patients given artemether, 0.74; 95 percent confidence interval, 0.5 to 1.11). The parasites were cleared more quickly from the blood in the artemether group (mean, 72 vs. 90 hours; P < 0.001); however, in this group fever resolved more slowly (127 vs. 90 hours, P < 0.001), the time to recovery from coma was longer (66 vs. 48 hours, P = 0.003), and the hospitalization was longer (288 vs. 240 hours, P = 0.005). Quinine treatment was associated with a higher risk of hypoglycemia (relative risk, 2.7; 95 percent confidence interval, 1.7 to 4.4; P < 0.001), but there were no other serious side effects in either group. CONCLUSIONS. Artemether is a satisfactory alternative to quinine for the treatment of severe malaria in adults.

14723988
Tran TH, Dolecek C, Pham PM, Nguyen TD, Nguyen TT, Le HT, Dong TH, Tran TT, Stepniewska K, White NJ, Farrar J
Dihydroartemisinin-piperaquine against multidrug-resistant Plasmodium falciparum malaria in Vietnam: randomised clinical trial.
Lancet. 2004 Jan 3;363(9402):18-22.
BACKGROUND: Southeast Asia has the most resistant malaria parasites in the world, which severely limits treatment options. There is general acceptance that to combat resistance, combinations of antimalarial drugs that include an artemisinin derivative should be used, and, if possible, these should be formulated in a single tablet. METHODS: We did a pilot randomised study in a tertiary referral hospital in Vietnam to compare the efficacy of 3-day regimens of dihydroartemisinin-trimethoprim-piperaquine (DHA-TP total dose 4.8/13.6/48 mg/kg, respectively) with the standard antimalarial regimen in Vietnam, artesunate-mefloquine (A3M total dose 12/25 mg/kg, respectively) in non-immune patients with uncomplicated Plasmodium falciparum malaria. 114 patients were randomised, 76 to DHA-TP and 38 to A3M. The subsequent open randomised trial at a Provincial Health Station compared DHA-TP, dihydroartemisinin-piperaquine, and A3M in 400 patients. In both studies all patients received directly observed therapy and were followed up for 56 days. The primary endpoint was reappearance of P falciparum malaria within 56 days of treatment. Analysis was by intention to treat. FINDINGS: The 56-day cure rate in the pilot study, adjusted for reinfections identified by PCR genotyping, was 97.4% (74/76) in the DHA-TP group and 100% (38/38) in the A3M group. In the second study, cure rates were similar in the three groups; DHA-TP 97.4% (153/157), dihydroartemisinin-piperaquine

98.7% (164/166), and A3M 98.7% (76/77). The DHA-TP and dihydroartemisinin-piperaquine regimens were well tolerated; fewer than 3% of patients had side-effects that might have been related to treatment, compared with 16% of A3M patients (p

12971512
Treeprasertsuk S, Krudsood S, Tosukhowong T, Maek-A-Nantawat W, Vannaphan S, Saengnetswang T, Looareesuwan S, Kuhn WF, Brittenham G, Carroll J
N-acetylcysteine in severe falciparum malaria in Thailand.
Southeast Asian J Trop Med Public Health. 2003 Mar;34(1):37-42.
One hundred and eight patients with severe falciparum malaria underwent a placebo controlled trial with the antioxidant, N-acetylcysteine (NAC), as an adjunctive therapy along with standard intravenous artesunate therapy. Three NAC dosage regimens were used: an intravenous loading dose of 140 mg/kg followed by 70 mg/kg every four hours intravenously for up to 18 doses (Group 1); a single intravenous loading dose followed by oral NAC in the same amount as for Group 1 (Group 2); a regimen identical to Group 1 except that oral NAC was administered after the first 24 hours (Group 3). Fifty-four patients received placebo plus artesunate. Two critically ill patients died in Group 1. No patient sustained an adverse reaction to the NAC other than vomiting, and the deaths were attributed to severe disease with multiple organ involvement. The excellent results with NAC, the lack of adverse effects, and the rationale for NAC benefit supports the need for a large, double blind trial of NAC as an adjunctive therapy for severe malaria.

11414435
Treeprasertsuk S, Viriyavejakul P, Silachamroon U, Vannphan S, Wilairatana P, Looareesuwan S
Is there any artemisinin resistance in falciparum malaria?
Southeast Asian J Trop Med Public Health. 2000 Dec;31(4):825-8.
We reported two cases of complicated falciparum malaria who had poor response to artesunate with delayed parasite clearance times. They were splenectomized patients who were treated with high doses of artemisinin derivatives. Our cases showed the importance of the spleen in the clearance of malaria parasites and had different clinical outcome, one fatal and one recovery. The host factors, the parasitemia count, the quality of antimalarial chemotherapy and blood level of the antimalarial drugs must be considered in relation to the causes of the delayed clearance of parasitemia.

1341087
Trevett A, Lalloo D
A new look at an old drug: artemesinin and qinghaosu.
P N G Med J. 1992 Dec;35(4):264-9.
It is said that William Withering's discovery of digitalis arose out of curiosity engendered during a stage-coach journey, by witnessing an old woman collecting foxgloves by the side of the road. Whilst we are not aware of an analogous stroke of genius reported from ancient China, the story of qinghaosu has certain parallels. Just as foxgloves had been used traditionally for centuries to treat 'afflictions of the heart', the plant Artemesia annua has been used as a treatment for fever in China for almost two thousand years. Artemesia annua, also known as 'sweet wormwood', is found in many parts of the world, but it was not until the early 1970s that Chinese scientists recognized its potential for treating malaria and isolated the active principle, artemesinin or qinghaosu. This paper describes the evidence for the efficacy of this drug and some of its derivatives in the treatment of malaria and the potential of these drugs for the standard management of malaria in Papua New Guinea and elsewhere.

11720077
Tripathi AK, Gupta A, Garg SK, Tekwani BL
In vitro beta-hematin formation assays with plasma of mice infected with Plasmodium yoelii and other parasite preparations: comparative inhibition with quinoline and endoperoxide antimalarials.
Life Sci. 2001 Oct 26;69(23):2725-33.
Formation of beta-hematin in vitro could be catalyzed in the presence of various preparations related to the malaria parasite viz., the cell free homogenate of Plasmodium yoelii, lipid extract of the parasite homogenate, purified malarial hemozoin and synthetic beta-hematin. Plasma from mice infected with P. yoelii also catalyzed in vitro beta-hematin formation with highly significant efficiency. The plasma based beta-hematin formation assay was highly sensitive, as the background absorbance was almost negligible due to absence of any preformed hemozoin. The plasma beta-hematin synthesizing activity was recovered in the lipid extract. The quinoline and endoperoxide antimalarials act by inhibiting hemozoin biosynthesis in the malaria parasite. Therefore, the in vitro beta-hematin formation assay is useful for the screening and identification of blood schizontocidal antimalarials acting through interruption of heme detoxification in the parasite. Quinoline and endoperoxide antimalarials showed about three fold greater inhibition of beta-hematin synthesizing activity in the plasma-based assays as compared to that of P. yoelii homogenate-based assays. The specificity of the inhibition was similar in both preparations. The plasma-based assay

therefore provides a better alternative than the parasite homogenate-based assay for in vitro screening and identification of novel inhibitors of hemozoin biosynthesis as potential blood schizontocidal antimalarials.

10999098
Tripathi BK, Agarwal AK, Gupta B
Artemisinin derivatives for falciparum malaria.
J Assoc Physicians India. 1999 Feb;47(2):230-5.

16178350
Tripathi R, Dhawan S, Dutta GP
Blood schizontocidal activity of azithromycin and its combination with alpha/beta arteether against multi-drug resistant Plasmodium yoelii nigeriensis, a novel MDR parasite model for antimalarial screening.
Parasitology. 2005 Sep;131(Pt 3):295-301.
Many different drug-resistant lines of rodent malaria are available as screening models. It is obligatory to screen new compounds for antimalarial activity against a series of resistant lines in order to identify a compound with potential for the treatment of multi-drug resistant (MDR) malaria infections. Instead of using a battery of resistant lines, a single MDR Plasmodium yoelii nigeriensis strain that shows a wide spectrum of drug resistance to high doses of chloroquine, mepacrine, amodiaquine, mefloquine, quinine, quinidine, halofantrine as well as tetracyclines, fluoroquinolines and erythromycin, was used to assess the blood schizontocidal efficacy of a new macrolide azithromycin and other antibiotics. The present study shows that only azithromycin has the potential to control an MDR P. y. nigeriensis infection in Swiss mice, provided the treatment with a dose of 50-100 mg/kg/day by oral route is continued for a period of 7 days. Tetracycline, oxytetracycline, doxycyline, erythromycin, ciprofloxacin and norfloxacin, although active in vitro, failed to protect the mice. Tetracycline, ciprofloxacin and norfloxacin combinations with chloroquine did not control the infection. Additionally, the antimalarial efficacy of azithromycin can be potentiated with the addition of arteether, which is an ethyl ether derivative of artemisinin. A total (100%) curative effect has been obtained with a shorter regimen of 4 days only.

8631376
Tripathi R, Puri SK, Dutta GP
Sodium beta-artelinate--a new potential gametocytocide.
Exp Parasitol. 1996 Apr;82(3):251-4.
The water-soluble artemisinin analogue sodium beta-artelinate, a fast-acting blood schizontocide, was evaluated for gametocytocidal action against simian malaria Plasmodium cynomolgi B, and a single dose of the compound has been found to be an effective gametocytocide by both oral and intravenous routes. The compound was able to sterilize the circulating gametocytes in rhesus monkey, resulting in loss of mosquito infectivity and oocyst development in the Anopheles stephensi. However, no sporontocidal action has been observed with this compound.

15109245
Trotta RF, Brown ML, Terrell JC, Geyer JA
Defective DNA repair as a potential mechanism for the rapid development of drug resistance in Plasmodium falciparum.
Biochemistry. 2004 May 4;43(17):4885-91.
The development and spread of highly drug-resistant parasites pose a central problem in the control of malaria.Understanding mechanisms that regulate genomic stability, such as DNA repair, in drug-resistant parasites and during drug treatment may help determine whether this rapid onset of resistance is due to an increase in the rate at which resistance-causing mutations are generated. This is the first report to demonstrate DNA repair activities from the malaria-causing parasite Plasmodium falciparum that are specific for ultraviolet light-induced DNA damage. The efficiency of DNA repair differs dramatically among P. falciparum strains with varying drug sensitivities. Most notable is the markedly reduced level of repair in the highly drug-resistant W2 isolate, which has been shown to develop resistance to novel drugs at an increased rate when compared to drug-sensitive strains. Additionally, the antimalarial drug chloroquine and other quinoline-like compounds interfered with the DNA synthesis step of the repair process, most likely a result of direct binding to repair substrates. We propose that altered DNA repair, either through defective repair mechanisms or drug-mediated inhibition, may contribute to the accelerated development of drug resistance in the parasite.

11732148
Trung TN, Davis TM, Hewitt S, Thuan LK, Quang HH, Anh CV, Thuy PT, Thoa NT, Tuan NT, Hang NT, Giang LT

Treatment of falciparum malaria in Vietnamese children: the need for combination therapy and optimized dosage regimens.
Ann Trop Paediatr. 2001 Dec;21(4):307-12.
To assess the in vivo sensitivity of Plasmodium falciparum to mefloquine and artesunate in a hyperendemic area of southern Viet Nam, we studied 41 children and 21 adults from a remote commune who had uncomplicated falciparum malaria without previous treatment. Patients were randomly allocated to artesunate (4 mg/kg on day 0 and 2 mg/kg on days 1-4) or mefloquine (10 mg/kg followed by 5 mg/kg at 6 h). Serial assessments were performed over 28 days. Of 31 patients allocated artesunate, nine (29%) redeveloped parasitaemia during follow-up compared with 23% (seven of 30) who received mefloquine. Of the 41 children, 15 (37%) had recrudescence/re-infection compared with only one of 20 adults (5%; $p < 0.001$). Significantly more children than adults failed on mefloquine treatment (37% vs 0%; $p = 0.021$) and one case showed RIII resistance. There was no significant difference in the case of artesunate. In regression analysis, parasitaemia was an independent predictor of recrudescence/re-infection after mefloquine ($p = 0.02$). These data support the use of combination therapy such as artesunate plus mefloquine for falciparum malaria in a hyperendemic area of Viet Nam. Primarily because of their greater parasite densities, children should be given higher doses of mefloquine (e.g. 25 mg/kg).

15691118
Tu Y
The development of the antimalarial drugs with new type of chemical structure--qinghaosu and dihydroqinghaosu.
Southeast Asian J Trop Med Public Health. 2004 Jun;35(2):250-1.

10774682
Ubalee R, Songthammawat D, Na-Bangchang K, Tan-ariya P, Karbwang J
Ex vivo blood schizontocidal activities of artemisinin derivatives against Plasmodium falciparum.
Southeast Asian J Trop Med Public Health. 1999 Jun;30(2):225-31.
Serum samples collected at intervals from eight healthy volunteers after the administration of the six regimens of artemisinin derivatives were investigated for their ex vivo blood schizontocidal activities against K1 strain Plasmodium falciparum. The regimens included single doses of (a) 300 mg oral artemether; (b) 300 mg intramuscular artemether; (c) 100 mg suppository artemether; (d) 300 mg oral artesunate (Guillin formulation); (e) 300 mg oral artesunate (Arenco formulation); (f) 300 mg oral dihydroartemisinin. Sera collected after various regimens of artemisinin derivatives showed distinct degree of ex vivo blood schizontocidal activities. Activity of sera after suppository dosing was remarkably low and variable comparing to the other two formulations (oral, intramuscular). Median values for Amax (the maximum activity normalized with dose) of sera from oral dosing were 2.4- and 118-fold, while AUA (the area under activity-time curve, normalized with dose) were 0.82- and 2,370-fold of that after the intramuscular and suppository dosing, respectively. Sera from artesunate-Arenco dosing exhibited significantly higher Amax and AUA (medians: Amax 12.4 vs 5.13 nmol/l/mg dose; AUA: 21.9 vs 8.8 nmol x h/ml/mg dose), compared to that from artesunate-Guillin dosing. Among the oral formulations of artemisinin derivatives investigated (artemether, artesunate, dihydroartemisinin), sera collected following a single dose of oral dihydroartemisinin exhibited lowest bioactivity (Amax 2.35 nmol/l/mg dose; AUA: 44 nmol x h/ml/mg dose).

8627034
Udomsangpetch R, Pipitaporn B, Krishna S, Angus B, Pukrittayakamee S, Bates I, Suputtamongkol Y, Kyle DE, White NJ
Antimalarial drugs reduce cytoadherence and rosetting Plasmodium falciparum.
J Infect Dis. 1996 Mar;173(3):691-8.
The in vivo and in vitro effects of antimalarials on cytoadherence and rosette formation were studied in 17 patients with severe and 46 with uncomplicated falciparum malaria. Cytoadherence was increased in severe malaria (P50% inhibition of both cytoadherence and rosetting in vivo and in vitro within 2 hr of drug exposure. Exposure to quinine for > or = to 4 h in vivo reduced rosetting by >50%, but not cytoadherence. Quinine did not reduce cytoadherence or rosetting significantly in vitro with exposure times of < or = to 8 h. These results suggest that artemisinin derivatives are more effective than quinine in preventing pathologic processes in parasitized erythrocytes that contribute to microvascular obstruction in severe malaria.

12174787
Utzinger J, Chollet J, Tu Z, Xiao S, Tanner M
Comparative study of the effects of artemether and artesunate on juvenile and adult Schistosoma mansoni in experimentally infected mice.
Trans R Soc Trop Med Hyg. 2002 May-Jun;96(3):318-23.

Artemether and artesunate, derivatives of the antimalarial artemisinin, also exhibit antischistosomal properties. There is a need to assess comparatively the activity of both compounds against different developmental stages of schistosome parasites. Since artemisinin derivatives will be increasingly used to treat malaria, it is important to study the effects of 7-day monotherapy regimens on schistosome infections. We carried out experiments with mice, infected with juvenile or adult Schistosoma mansoni, and treated with artemether or artesunate at various doses and regimens including those currently used for monotherapy of malaria. Three doses of artemether, at concentrations of 150 or 300 mg/kg, administered to mice with juvenile S. mansoni resulted in worm reductions of 88-97%, which were significantly higher than the 67-77% obtained with artesunate ($P < 0.05$). Total concentrations of 600 or 800 mg/kg artemether, administered over 2 or 4 consecutive days to mice with adult S. mansoni, reduced the worm burden significantly by 46-51% ($P < 0.05$). The reduction of the worm burden observed with artesunate was considerably lower, 24-33%, and not significant when compared with untreated control mice. Seven-day monotherapy regimens of artemether or artesunate given at different concentrations to mice with adult S. mansoni showed total worm reductions of 53-61% or 34-49%, respectively. We conclude that artemether and artesunate are efficacious antischistosomal agents, with artemether displaying consistently higher activities. Our findings may contribute to the current strategic discussions on the effect and use of artemisinin derivatives against schistosomes when they are used in malaria chemotherapy in areas of co-endemicity of both parasites.

14996624
Utzinger J, Keiser J
Schistosomiasis and soil-transmitted helminthiasis: common drugs for treatment and control.
Expert Opin Pharmacother. 2004 Feb;5(2):263-85.
Schistosomiasis is a disease caused by parasitic trematode worms (schistosomes) that currently affects 200 million people living in tropical and subtropical environments. It is a chronic disease and the latest estimates for sub-Saharan Africa are that it kills > 200000 people every year. Soil-transmitted helminthiasis (STH) is caused by intestinal nematodes. More than 2 billion people are infected worldwide and the disease burden might approach that of malaria. Recognising the enormous public health significance of schistosomiasis and STH, particularly among the poor, and in view of readily available drugs that are safe, efficacious and inexpensive, the World Health Assembly recently set forth a resolution for a combined approach for morbidity control of both diseases. This review briefly summarises the geographical distribution, life cycle and global burden of schistosomiasis and STH. The current arsenal of drugs available for morbidity control, including discovery, chemistry, pharmacological properties and aspects of therapeutic efficacy and adverse events in clinical human use is then discussed. The emphasis is on praziquantel, oxamniquine and artemisinin derivatives (against schistosomes) and albendazole, mebendazole, levamisole, pyrantel pamoate and other compounds (against intestinal nematodes). The experience gained with combination chemotherapy in schistosomiasis and STH is briefly discussed. Finally, current research needs and the critical importance for development of novel anthelmintic drugs, so that chemotherapy can continue to serve as the backbone of integrated and sustainable control of schistosomiasis and STH, is highlighted.

11772354
Utzinger J, Xiao S, Keiser J, Chen M, Zheng J, Tanner M
Current progress in the development and use of artemether for chemoprophylaxis of major human schistosome parasites.
Curr Med Chem. 2001 Dec;8(15):1841-60.
Human schistosomiasis, a chronic and debilitating parasitic disease of the tropics, is ranked second after malaria in terms of public health importance. At present, there is no vaccine available, and chemotherapy is the cornerstone of schistosomiasis control. Praziquantel is the drug of choice. Oxamniquine has become difficult to obtain and metrifonate has recently been withdrawn from the market. Rapid re-infection following treatment and concern about praziquantel resistance called for the search of novel drugs for prevention and cure of schistosomiasis. Significant progress has been made with artemether, the methyl ether of dihydroartemisinin, already widely used for the treatment of malaria. The present article reviews the literature that led to the development of artemether for chemoprophylaxis in schistosomiasis, and it summarises the experiences so far obtained with its use to control schistosomiasis in different endemic settings. Topics covered include an overview of the global burden of schistosomiasis and approaches for its control; the nature and features of artemisinin and related derivatives, initially discovered as antimalarials, other bioactivities, and their recent discovery of antischistosomal properties; a historic account disclosing the antischistosomal activity of artemether; in vivo assessment of drug susceptibility of different developmental stages of schistosome parasites; artemether-induced pathology evidenced by scanning and transmission electron microscopy; the possible mechanism of action; in vivo studies with combination therapy of artemether and praziquantel; results of randomised controlled clinical trials of oral artemether for the prevention of patent infection and morbidity; and, ultimately the translation of this knowledge into public health action in different endemic settings towards a more integrated approach of schistosomiasis control.

11730781
Utzinger J, Xiao S, N'Goran EK, Bergquist R, Tanner M
The potential of artemether for the control of schistosomiasis.
Int J Parasitol. 2001 Dec;31(14):1549-62.
Schistosomiasis continues to rank--following malaria--at the second position of the world's parasitic diseases in terms of the extent of endemic areas and the number of infected people. There is yet no vaccine available and the current mainstay of control is chemotherapy with praziquantel used as the drug of choice. In view of concern about the development of tolerance and/or resistance to praziquantel, there is a need for research and development of novel drugs for the prevention and cure of schistosomiasis. Interestingly, derivatives of artemisinin, which are already effectively used in the treatment of malaria, also exhibit antischistosomal properties. Significant advances have been made with artemether, the methyl ether derivative of artemisinin. We review the discovery of the antischistosomal activity of artemether by Chinese scientists two decades ago; the detailed laboratory studies of the susceptibility of, and effect on, the different developmental stages of Schistosoma japonicum, Schistosoma mansoni and Schistosoma haematobium to artemether; the possible mechanism of action and the potential long-term toxicity. Finally, we look at the effect of combined treatment with artemether and praziquantel; and clinical findings thus far obtained from randomised controlled trials with oral artemether for the prevention of patent infections and morbidity. The review intends to create a forum for strategic discussion of how these laboratory and clinical findings could be translated into public health actions. We conclude that artemether--as part of integrated current control measures and adapted to specific socio-ecological and epidemiological settings--has considerable potential to significantly reduce the current burden of schistosomiasis in many parts of the world.

9403348
Valecha N, Gupta S, Usha D, Biswas S, Sharma A, Adak T, Asthana OP, Sharma VP
Efficacy of alpha,beta-arteether in acute uncomplicated P. falciparum malaria.
Int J Clin Pharmacol Res. 1997;17(1):11-5.
A phase-III clinical trial was conducted in 50 patients (42M + 8F) with acute uncomplicated falciparum malaria from Delhi during the period of September to November 1995. Their mean age was 27.2 years, and the mean parasitaemia on day 0 was 0.65%. Patients were hospitalized and treated with a new ethyl derivative of artemisinin developed at CDRI called alpha, beta-arteether, at the dosage of 150 mg I/M for three consecutive days. Peripheral smears were examined every day for 4 days and then weekly up to 28 days. The results of the study showed that the mean parasite and fever clearance times were respectively 19.94 +/- 6.87 and 37.81 +/- 21.67 hours. Within 48 h, 70% of the cases became afebrile and the peripheral smear was negative in 100% of the cases. The drug was well tolerated. Three cases (6%) had recrudescence within 28 days. It is concluded that alpha, beta-arteether is a safe, effective and rapidly acting antimalarial.

10354615
van Agtmael MA, Eggelte TA, van Boxtel CJ
Artemisinin drugs in the treatment of malaria: from medicinal herb to registered medication.
Trends Pharmacol Sci. 1999 May;20(5):199-205.
Registration in Europe of several artemisinin drugs for the treatment of malaria can soon be expected. Artemisinin is isolated from the herb Artemisia annua, in use in China more than 2000 years as a herbal tea against fever. Artemisinin drugs are being used extensively in South-East Asia and increasingly in Africa. Active derivatives have been synthesized - artemether, arteether and artesunate - which are used for oral, intramuscular, rectal and intravenous administration. The origin, mechanism of action, efficacy and safety in patients, the pharmacokinetics and the position of this group of compounds among existing antimalarials are discussed in this review.

15730557
van den Broek I, Amsalu R, Balasegaram M, Hepple P, Alemu E, Hussein el B, Al-Faith M, Montgomery J, Checchi F
Efficacy of two artemisinin combination therapies for uncomplicated falciparum malaria in children under 5 years, Malakal, Upper Nile, Sudan.
Malar J. 2005 Feb 24;4(1):14.
BACKGROUND: The treatment for Plasmodium falciparum malaria in Sudan has been in process of change since 2003. Preceding the change, this study aimed to determine which artemisinin-based combination therapies is more effective to treat uncomplicated malaria in Malakal, Upper Nile, Sudan. METHODS: Clinical trial to assess the efficacy of 2 antimalarial therapies to treat P. falciparum infections in children aged 6-59 months, in a period of 42 days after treatment. RESULTS: A total of 269 children were followed up to 42 days. Artesunate plus Sulfadoxine/Pyrimethamine (AS+SP) and Artesunate plus Amodiaquine (AS+AQ) were both found to be efficacious in curing malaria infections by rapid elimination of parasites and clearance of fever, in preventing recrudescence and suppressing gametocytaemia. The combination of AS+SP

appeared slightly more efficacious than AS+AQ, with 4.4% (4/116) versus 15% (17/113) of patients returning with malaria during the 6-week period after treatment (RR = 0.9, 95% CI 0.81-0.96). PCR analysis identified only one recrudescence which, together with one other early treatment failure, gave efficacy rates of 99.0% for AS+AQ (96/97) and 99.1% for AS+SP (112/113). However, PCR results were incomplete and assuming part of the indeterminate samples were recrudescent infections leads to an estimated efficacy ranging 97-98% for AS+SP and 88-95% for AS+AQ. CONCLUSION: These results lead to the recommendation of ACT, and specifically AS+SP, for the treatment of uncomplicated falciparum malaria in this area of Sudan. When implemented, ACT efficacy should be monitored in sentinel sites representing different areas of the country.

16095643
van den Broek IV, Maung UA, Peters A, Liem L, Kamal M, Rahman M, Rahman MR, Bangali AM, Das S, Barends M, Faiz AM
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 Oct;99(10):727-35.
Bangladesh faces growing levels of Plasmodium falciparum resistance to chloroquine (CQ) and sulfadoxine-pyrimethamine (SP). Alternative antimalarial therapies, particularly combination regimens, need to be considered. Therefore, the efficacy of three antimalarial combination therapies was assessed in Chittagong Hill Tracts. A total of 364 P. falciparum patients were recruited and randomly assigned to either CQ + SP, mefloquine + artesunate (MQ + AS) or lumefantrine + artemether (Coartem). Results showed that CQ + SP therapy was less effective than the two artemisinin-based combination therapies. The day 42 PCR-corrected efficacy rate was 62.4% for CQ + SP, 100% for MQ + AS and 97.1% for Coartem. Failures occurred at a shorter interval after CQ + SP treatment than after Coartem. The artemisinin-based therapies effectively prevented development of gametocytes, whereas CQ + SP did not. All three therapies were well tolerated, although reports of mild complaints during treatment appeared higher with MQ + AS. We conclude that CQ + SP is not a viable option for replacing CQ monotherapy as first-line P. falciparum treatment in this area of Bangladesh. A change to artemisinin-based combination therapy is recommended. Both Coartem and MQ + AS appear to be good options, effective in curing P. falciparum malaria and in preventing recrudescences following treatment.

15828489
Van der Meersch H
[Review of the use of artemisinin and its derivatives in the treatment of malaria]
J Pharm Belg. 2005;60(1):23-9.
This article reviews the development of the artemisinins used in the treatment of drug-resistant Plasmodium falciparum malaria. The story starts in China with Artemisia annua L., a plant that was traditionally used as an antipyretic. The activity of Annual wormwood can be explained by the presence of the active substance artemisinin. Soon, artemether, artemotil, artenimol, artesunate and sodium artesunate, derivatives of artemisinin, have been developed. Each has its own physical and pharmaceutical properties, dosage and dosage forms. Other aspects, such as the general guidelines for use, safety during pregnancy and the perspectives of artemisinin compounds, are being discussed.

9037139
Van Geldre E, Vergauwe A, Van den Eeckhout E
State of the art of the production of the antimalarial compound artemisinin in plants.
Plant Mol Biol. 1997 Jan;33(2):199-209.
For more than three centuries we have relied on the extracts of the bark of Cinchona species to treat malaria. Now, it seems we may be changing to the leaves of a Chinese weed, Artemisia annua, and its active compound artemisinin. Artemisinin-derived drugs have been proved particularly effective treatments for severe malaria, even for multidrug-resistant malaria. However, this promising antimalarial compound remains expensive and is hardly available on a global scale. Therefore, many research groups have directed their investigations toward the enhancement of artemisinin production in A. annua cell cultures or whole plants in order to overproduce artemisinin or one of its precursors. This article provides a brief review of the state of art of the different aspects in A. annua research.

12533765
Van Ha N, Dyk Dao L, Rabinovich SA
Use of nested PCR for differential diagnosis of falciparum malaria reinfection and relapse in drug-resistant patients.
Bull Exp Biol Med. 2002 Oct;134(4):379-81.
Microscopic examination does not allow differentiation of drug-resistant P. falciparum infection relapse from reinfection. However, this differential diagnosis is essential for adequate therapy. Three highly polymorphic

P. falciparum genes (msp1, msp2, and glurp) and their alleles reflecting the structural state of these genes were used as genetic markers for differential diagnosis by PCR with internal primers. In 27 patients the characteristics of these alleles were identical before treatment with artersunate and during repeated manifestation of symptoms 14-28 days after the end of therapy, which attested to malaria relapses. In 24 patients the structure of these allele before mefloquine therapy and during repeated manifestation of the symptoms after 2-3 months was different, which attested to reinfection.

15807800
Van Nam N, de Vries PJ, Van Toi L, Nagelkerke N
Malaria control in Vietnam: the Binh Thuan experience.
Trop Med Int Health. 2005 Apr;10(4):357-65.
OBJECTIVE: The National Malaria Control Program (NMCP) in Vietnam is based on application of insecticide-treated bed nets (ITNs), spraying of insecticides and early microscopic diagnosis of malaria and treatment (EDTM) with artemisinin drugs. This study explores the implementation of the NMCP at provincial level and its impact on malaria incidence (mi) and prevalence in Binh Thuan in southern Vietnam. METHODS: Data on implementation of EDTM, distribution of ITNs, annual mi and Plasmodium index (pi) were derived from intervention logbooks and surveillance records kept by the provincial Malaria Station since 1988. The relation between interventions and the change of pi over time was analysed with Generalized Estimating Equations. RESULTS: Control activities focused on the highly endemic zones where ITNs were distributed free of charge to ethnic minority groups, including twice yearly re-impregnation, from 1992 onwards. This almost completely replaced insecticide spraying. Complete ITN coverage of these groups was achieved in 1995, constituting 40% of the entire population. In all malaria endemic communes, primary health care posts were consecutively upgraded or installed, mainly between 1992 and 1995, offering EDTM with artemisinin drugs free of charge. Before 1994, mi peaked to over 50/1000, pi to over 16% in the highly endemic zones. In 1998, these had decreased to below 9/1000 and 4% respectively. The effects of the interventions could not be discerned with statistical significance. CONCLUSION: Malaria incidence and prevalence declined significantly in Vietnam, possibly due to the malaria control efforts, but coinciding with rapid socioeconomic changes.

8096930
van Thiel PP, van Gool T, Hopperus Buma AP, Tendeloo CH, Leentvaar-Kuijpers A, Kager PA
Artemisinin compounds in treatment of malaria.
Lancet. 1993 Apr 17;341(8851):1034-5.

10761725
Van Vugt M, Angus BJ, Price RN, Mann C, Simpson JA, Poletto C, Htoo SE, Looareesuwan S, White NJ, Nosten F
A case-control auditory evaluation of patients treated with artemisinin derivatives for multidrug-resistant Plasmodium falciparum malaria.
Am J Trop Med Hyg. 2000 Jan;62(1):65-9.
The artemisinin derivatives are now used widely in areas with multidrug-resistant Plasmodium falciparum malaria such as Southeast Asia, but concerns remain over their potential for neurotoxicity. Mice, rats, dogs, and monkeys treated with high doses of intramuscular artemether or arteether develop an unusual pattern of focal damage to brain stem nuclei (particularly those involved in auditory processing). To investigate whether a similar toxic effect occurs in patients treated with these compounds, clinical neurologic evaluation, audiometry and early latency auditory evoked responses were measured in a single-blind comparison of 79 patients who had been treated with > or =2 courses of oral artemether or artesunate within the previous 3 years, and 79 age- and sex-matched controls living in a malaria-endemic area on the northwestern border of Thailand. There were no consistent differences in any of these test results between the cases and controls. This study failed to detect any evidence of significant neurotoxicity in patients treated previously with oral artemether or artesunate for acute malaria.

9449273
van Vugt M, Brockman A, Gemperli B, Luxemburger C, Gathmann I, Royce C, Slight T, Looareesuwan S, White NJ, Nosten F
Randomized comparison of artemether-benflumetol and artesunate-mefloquine in treatment of multidrug-resistant falciparum malaria.
Antimicrob Agents Chemother. 1998 Jan;42(1):135-9.
An open, randomized comparison of artemether-benflumetol (CGP 56 697; Novartis) with artesunate-mefloquine was conducted in 617 patients with acute uncomplicated multidrug-resistant falciparum malaria on the western border of Thailand. Both treatments rapidly and reliably cleared fever and parasitemia, and

there was no significant difference in the initial therapeutic response parameters. Parasite genotyping was used to distinguish recrudescences from new infections. The 63-day cure rate for artesunate-mefloquine (94%) was significantly higher than the cure rate for artemether-benflumetol (81%) (P < 0.001). Both regimens were well tolerated. Nausea, vomiting, dizziness, sleep disorders, and other neurological side effects were between two and four times more common in the artesunate-mefloquine group than in the artemether-benflumetol group (P < 0.001). Artemether-benflumetol is effective and very well tolerated in the treatment of multidrug-resistant falciparum malaria. A higher dose than that used in the present study may improve efficacy.

10674679
van Vugt M, Ezzet F, Nosten F, Gathmann I, Wilairatana P, Looareesuwan S, White NJ
No evidence of cardiotoxicity during antimalarial treatment with artemether-lumefantrine.
Am J Trop Med Hyg. 1999 Dec;61(6):964-7.
Artemether-lumefantrine is a new fixed antimalarial combination effective against multidrug-resistant falciparum malaria. A prospective electrocardiographic study was conducted in 150 patients receiving artemetherlumefantrine and 50 treated with artesunate-mefloquine. There was no evidence for clinically significant changes in the electrocardiographic intervals and in particular no relationship between plasma concentrations of lumefantrine and QTc prolongation. Artemether-lumefantrine does not have significant cardiac effects at therapeutic doses.

12471569
van Vugt M, Leonardi E, Phaipun L, Slight T, Thway KL, McGready R, Brockman A, Villegas L, Looareesuwan S, White NJ, Nosten F
Treatment of uncomplicated multidrug-resistant falciparum malaria with artesunate-atovaquone-proguanil.
Clin Infect Dis. 2002 Dec 15;35(12):1498-504. Epub 2002 Dec 3.
In an open-label trial carried out on the northwest border of Thailand, 1596 patients with uncomplicated multidrug-resistant falciparum malaria were randomly assigned to receive atovaquone-proguanil, atovaquone-proguanil-artesunate, or artesunate-mefloquine and were followed up for 42 days. All 3 regimens were highly effective and well tolerated. Fever duration and parasite clearance times were significantly shorter among patients who received artesunate (P< or =.014). Artesunate-atovaquone-proguanil is a highly effective and well-tolerated treatment for multidrug-resistant falciparum malaria.

11132386
van Vugt M, Looareesuwan S, Wilairatana P, McGready R, Villegas L, Gathmann I, Mull R, Brockman A, White NJ, Nosten F
Artemether-lumefantrine for the treatment of multidrug-resistant falciparum malaria.
Trans R Soc Trop Med Hyg. 2000 Sep-Oct;94(5):545-8.
The efficacy and safety of the 6-dose regimen of artemether-lumefantrine were assessed in an open randomized trial in children and adults presenting with acute, uncomplicated Plasmodium falciparum malaria in Thailand between November 1997 and March 1998. 200 patients were enrolled in 2 centres: 150 received artemether-lumefantrine (i.e., a median total dose of 9.6 mg/kg [interquartile range 8.7-10.7] and 57.9 mg/kg of lumefantrine [52.4-64.0]) and 50 the standard combination of artesunate (12 mg/kg over 3 d) and mefloquine (25 mg/kg). All patients had rapid initial clinical and parasitological responses. The 28 d cure rates were high: 97.7% (95% confidence interval [95% CI] 93.5-99.5%) for artemether-lumefantrine and 100% (95% CI 92.5-100%) for artesunate-mefloquine. The 6-dose regimen of artemether-lumefantrine was better tolerated than, and as effective as, artesunate-mefloquine, the current standard treatment in this area of multidrug-resistant P. falciparum malaria.

11289666
Vennerstrom JL, Ager AL Jr, Andersen SL, Grace JM, Wongpanich V, Angerhofer CK, Hu JK, Wesche DL
Assessment of the antimalarial potential of tetraoxane WR 148999.
Am J Trop Med Hyg. 2000 May;62(5):573-8.
The antimalarial peroxide, dispiro-1,2,4,5-tetraoxane WR 148999, was synergistic with chloroquine, quinine, mefloquine, and artemisinin against both D6 and W2 clones of Plasmodium falciparum. In consideration of the contrasting antagonism between artemisinin and chloroquine, these drug combination data imply that WR 148999 and artemisinin may not share a common mechanism of action. For Plasmodium berghei-infected mice given oral, subcutaneous, and intraperitoneal doses of WR 148999 ranging from 2 to 1024 mg/kg in the Thompson test, median survival times were 8.8, 11.8, and 27.5 days, respectively, compared to 8 days for control animals. Using subcutaneous administration, WR 148999 had a considerably longer duration of action than did artemisinin against P. berghei. WR 148999 did not significantly inhibit cytochrome P450 isozymes CYP 2C9, 2C19, 2D6, 2E1, or 3A4 (IC50 >500 microM) but did inhibit CYP 1A2 with an IC50 value of 36 microM, suggesting that WR 148999 may be metabolized by the latter CYP isozyme. These

results combined with previous observations that formulation strategies and incorporation of polar functional groups in a series of WR 148999 analogs both failed to enhance tetraoxane oral antimalarial activity suggest that oral bioavailability of tetraoxane WR 148999 is more likely a function of extensive first-pass metabolism rather than solubility-limited dissolution.

15318224
Vennerstrom JL, Arbe-Barnes S, Brun R, Charman SA, Chiu FC, Chollet J, Dong Y, Dorn A, Hunziker D, Matile H, McIntosh K, Padmanilayam M, Santo Tomas J, Scheurer C, Scorneaux B, Tang Y, Urwyler H, Wittlin S, Charman WN
Identification of an antimalarial synthetic trioxolane drug development candidate.
Nature. 2004 Aug 19;430(7002):900-4.
The discovery of artemisinin more than 30 years ago provided a completely new antimalarial structural prototype; that is, a molecule with a pharmacophoric peroxide bond in a unique 1,2,4-trioxane heterocycle. Available evidence suggests that artemisinin and related peroxidic antimalarial drugs exert their parasiticidal activity subsequent to reductive activation by haem, released as a result of haemoglobin digestion by the malaria-causing parasite. This irreversible redox reaction produces carbon-centred free radicals, leading to alkylation of haem and proteins (enzymes), one of which--the sarcoplasmic-endoplasmic reticulum ATPase PfATP6 (ref. 7)--may be critical to parasite survival. Notably, there is no evidence of drug resistance to any member of the artemisinin family of drugs. The chemotherapy of malaria has benefited greatly from the semi-synthetic artemisinins artemether and artesunate as they rapidly reduce parasite burden, have good therapeutic indices and provide for successful treatment outcomes. However, as a drug class, the artemisinins suffer from chemical (semi-synthetic availability, purity and cost), biopharmaceutical (poor bioavailability and limiting pharmacokinetics) and treatment (non-compliance with long treatment regimens and recrudescence) issues that limit their therapeutic potential. Here we describe how a synthetic peroxide antimalarial drug development candidate was identified in a collaborative drug discovery project.

10893313
Vennerstrom JL, Dong Y, Andersen SL, Ager AL Jr, Fu H, Miller RE, Wesche DL, Kyle DE, Gerena L, Walters SM, Wood JK, Edwards G, Holme AD, McLean WG, Milhous WK
Synthesis and antimalarial activity of sixteen dispiro-1,2,4, 5-tetraoxanes: alkyl-substituted 7,8,15,16-tetraoxadispiro[5.2.5. 2]hexadecanes.
J Med Chem. 2000 Jul 13;43(14):2753-8.
Sixteen alkyl-substituted dispiro-1,2,4,5-tetraoxanes (7,8,15, 16-tetraoxadispiro[5.2.5.2]hexadecanes) were synthesized to explore dispiro-1,2,4,5-tetraoxane SAR and to identify tetraoxanes with better oral antimalarial activity than prototype tetraoxane 1 (WR 148999). The tetraoxanes were prepared either by peroxidation of the corresponding cyclohexanone derivatives in H(2)SO(4)/CH(3)CN or by ozonolysis of the corresponding cyclohexanone methyl oximes. Those tetraoxanes with alkyl substituents at the 1 and 10 positions were formed as single stereoisomers, whereas the five tetraoxanes formed without the stereochemical control provided by alkyl groups at the 1 and 10 positions were isolated as mixtures of diastereomers. Three of the sixteen tetraoxanes were inactive (IC(50)'s > 1000 nM), but five (2, 6, 10, 11, 12) had IC(50)'s between 10 and 30 nM against the chloroquine-sensitive D6 and chloroquine-resistant W2 clones of Plasmodium falciparum compared to corresponding IC(50)'s of 55 and 32 nM for 1 and 8.4 and 7.3 nM for artemisinin. We suggest that tetraoxanes 13, 16, and 17 were inactive and tetraoxanes 4 and 7 were weakly active due to steric effects preventing or hindering peroxide bond access to parasite heme. Tetraoxanes 1, 10, 11, and 14, along with artemisinin and arteether as controls, were administered po b.i.d. (128 mg/kg/day) to P. berghei-infected mice on days 3, 4, and 5 post-infection. At this dose, tetraoxanes 10, 11, and 14 cured between 40% and 60% of the infected animals. In comparison, artemisinin and tetraoxane 1 produced no cures, whereas arteether cured 100% of the infected animals. There was no apparent relationship between tetraoxane structure and in vitro neurotoxicity, nor was there any correlation between antimalarial activity and neurotoxicity for these seventeen tetraoxanes.

16451346
Vijaykadga S, Rojanawatsirivej C, Cholpol S, Phoungmanee D, Nakavej A, Wongsrichanalai C
In vivo sensitivity monitoring of mefloquine monotherapy and artesunate-mefloquine combinations for the treatment of uncomplicated falciparum malaria in Thailand in 2003.
Trop Med Int Health. 2006 Feb;11(2):211-9.
OBJECTIVE: To monitor the efficacy of anti-malarial treatments in Thailand. METHOD: A 28-day in vivo study in nine provinces along international borders in 2003. The first group comprised 164 patients from four provinces: Mae Hong Son, Chiang Mai, Ratchaburi and Ubon Ratchathani. These patients received 15 mg/kg mefloquine as a single dose. The second group, 58 patients from Kanchanaburi, were treated with 15 mg/kg mefloquine plus artesunate (12 mg/kg). The third group, 196 patients from provinces with high-level mefloquine resistance (Tak, Ranong, Chanthaburi and Trat), received 25 mg/kg of mefloquine plus 12 mg/kg artesunate. In all arms, follow-up blood smears were scheduled for days 1, 2, 3, 7, 14, 21 and 28. All patients

tolerated the regimens well. RESULTS: The percentage of adequate clinical and parasitological response to mefloquine monotherapy was 62.0% in Mae Hong Son, 75.0% in Chiang Mai, 94.0% in Ratchaburi and 89.7% in Ubon Ratchathani. In Kanchanaburi, the percentage of adequate clinical and parasitological response to the artesunate-mefloquine combination was 94.2%. In the third group, this response exceeded 90%, except in Trat, where it was only 78.6% (44 patients). CONCLUSION: Mefloquine monotherapy must urgently be replaced in Mae Hong Son and Chiang Mai. The markedly reduced efficacy of the artesunate-mefloquine combination used in Trat raises questions about the future of this therapy on the southeastern border of Thailand with Cambodia. It is very worrying because no practical and affordable alternative is yet available.

1431937
Vishwakarma RA, Mehrotra R, Tripathi R, Dutta GP
Stereoselective synthesis and antimalarial activity of alpha-artelinic acid from artemisinin.
J Nat Prod. 1992 Aug;55(8):1142-4.
alpha-Artelinic acid [8], a potent, stable, and water-soluble antimalarial agent, has been synthesized from artemisinin [1], the sesquiterpene lactone endoperoxide isolated from Artemisia annua. The blood schizontocidal antimalarial activity of alpha-artelinic acid evaluated against Plasmodium knowlesi is also reported.

11716108
von Seidlein L, Drakeley C, Greenwood B, Walraven G, Targett G
Risk factors for gametocyte carriage in Gambian children.
Am J Trop Med Hyg. 2001 Nov;65(5):523-7.
A widespread reduction in Plasmodium falciparum gametocyte prevalence could reduce malaria transmission. After infection with P. falciparum, a variable proportion of people are found to be gametocytemic. We analyzed risk factors associated with gametocytemia at presentation and 7 days later. We enrolled 1,198 children in 2 antimalarial drug trials between September and December 1998. The children were assigned to 1 of 4 treatment groups: chloroquine only; pyrimethamine-sulfadoxine (PSD) only; PSD combined with 1 dose of artesunate; and PSD combined with 3 doses of artesunate. By the time of enrollment, 200 (17%) of 1,198 children were gametocyte carriers. Three independent risk factors were associated with gametocytemia at enrollment. Children with anemia were more likely to carry gametocytes, whereas children with fever (> 37.4 degrees C) or high parasite densities (> 100,000 parasites/microL) were less frequently gametocyte carriers. Children with at least 2 of the risk factors were 4 times more likely to be gametocytemic than children with < 2 risk factors (odds ratio [OR], 4.4; 95% confidence interval [CI], 2.7-7.1). Seven days after the start of treatment, 355 (37%) of 466 assessable children were found to be gametocyte carriers. Children treated with PSD alone had a significantly higher risk of being gametocytemic by Day 7 compared with children in the other 3 treatment groups. In the subgroup of children who had no detectable gametocytes on enrollment, the effect of treatment with PSD + 3 doses of artesunate was most marked. Nineteen (10%) of 198 children treated with PSD + 3 doses of artesunate became gametocytemic, in contrast to 184 (57%) of 321 children treated with PSD alone (OR, 12.7; 95% CI, 7.3-22.1). Early treatment with highly effective antimalarial therapy has the greatest chance of preventing gametocytemia. The choice of a first-line antimalarial drug for uncomplicated malaria should not only take into consideration the ablation asexual parasitemia but also the suppression of gametocytemia.

11251903
von Seidlein L, Jawara M, Coleman R, Doherty T, Walraven G, Targett G
Parasitaemia and gametocytaemia after treatment with chloroquine, pyrimethamine/sulfadoxine, and pyrimethamine/sulfadoxine combined with artesunate in young Gambians with uncomplicated malaria.
Trop Med Int Health. 2001 Feb;6(2):92-8.
As part of a study to assess the infectivity of gametocytes after treatment with four antimalarial regimens, the efficacy of each treatment was also determined. From September to December 1998, 598 children with uncomplicated malaria were treated; 135 received chloroquine (CQ) alone, 276 received pyrimethamine/sulfadoxine (Fansidar, PSD) alone, 113 received PSD with a single dose of artesunate (PSD + 1ART) and 74 received PSD combined with three doses of artesunate (PSD + 3ART). On day 28 19/63 (30.2%; 95% C.I. 19.2% to 43.1%) of children treated with CQ alone, 5/134 (3.7%; 95% C.I. 1.2% to 8.5%) treated with PSD alone, 1/71 (1.4%, 95% C.I. 0.0% to 7.9%) treated with PSD + 1ART and 0/45 (0.0%; 95% C.I. 0.0% to 7.9%) treated with PSD + 3ART were parasitaemic. The proportion of children with gametocytes on day 7 after treatment with CQ alone was 16/89 (18.0%; 95% C.I. 10.6% to 27.6%), 98/174 (56.3%; 95% C.I. 48.6% to 63.8%) after treatment with PSD alone, 8/70 (11.4%; 95% C.I. 5.1% to 21.3%) after treatment with PSD + 1ART and 4/46 (8.7%; 95% C.I., 2.4% to 20.8%) after treatment with PSD + 3ART. CQ thus has a lower efficacy than PSD or either of the PSD and artesunate combinations. Use of PSD alone as an alternative first line treatment results in a very high post-treatment gametocyte prevalence that is likely to

enhance transmission. There would be greater and more sustainable benefits from using PSD and artesunate combinations.

10665554
von Seidlein L, Milligan P, Pinder M, Bojang K, Anyalebechi C, Gosling R, Coleman R, Ude JI, Sadiq A, Duraisingh M, Warhurst D, Alloueche A, Targett G, McAdam K, Greenwood B, Walraven G, Olliaro P, Doherty T
Efficacy of artesunate plus pyrimethamine-sulphadoxine for uncomplicated malaria in Gambian children: a double-blind, randomised, controlled trial.
Lancet. 2000 Jan 29;355(9201):352-7.
BACKGROUND: Resistance to cheap effective antimalarial drugs, especially to pyrimethaminesulphadoxine (Fansidar), is likely to have a striking impact on childhood mortality in sub-Sharan Africa. The use of artesunate (artesunic acid) [corrected] in combination with pyrimethamine-sulphadoxine may delay or prevent resistance. We investigated the efficacy, safety, and tolerability of this combined treatment. METHODS: We did a double-blind, randomised, placebo-controlled trial in The Gambia. 600 children with acute uncomplicated Plasmodium falciparum malaria, aged 6 months to 10 years, at five health centres were randomly assigned pyrimethaminesulphadoxine (25 mg/500 mg) with placebo; pyrimethamine-sulphadoxine plus one dose of artesunate (4mg/kg bodyweight); or pyrimethamine-sulphadoxine plus one dose 4 mg/kg bodyweight artesunate daily for 3 days. Children were visited at home each day after the start of treatment until parasitaemia had cleared. FINDINGS: The combined treatment was well tolerated. No adverse reactions attributable to treatment were recorded. By day 1, only 178 (47%) of 381 children treated with artesunate were still parasitaemic, compared with 157 (81%) of 195 children in the pyrimethamine-sulphadoxine alone group (relative risk 1.7 [95% CI 1.5-2.0], p

14584381
von Seidlein L, Walraven G, Milligan PJ, Alexander N, Manneh F, Deen JL, Coleman R, Jawara M, Lindsay SW, Drakeley C, De Martin S, Olliaro P, Bennett S, Schim van der Loeff M, Okunoye K, Targett GA, McAdam KP, Doherty JF, Greenwood BM, Pinder M
The effect of mass administration of sulfadoxine-pyrimethamine combined with artesunate on malaria incidence: a double-blind, community-randomized, placebo-controlled trial in The Gambia.
Trans R Soc Trop Med Hyg. 2003 Mar-Apr;97(2):217-25.
A double-blind, community-randomized, placebo-controlled trial was conducted in a rural area of The Gambia between June and December 1999 to test whether a reduction in the infectious reservoir can reduce malaria transmission. Overall 14,017 (85%) individuals living in the study area were treated with either placebo or sulfadoxine-pyrimethamine (SP) combined with a single dose of artesunate (AS). Following the mass drug administration (MDA) 1375 children aged 6 months to 10 years were kept under surveillance for clinical malaria in 18 villages throughout the 1999 malaria transmission season. During a 20-week surveillance period 637 episodes of malaria were detected. The mean incidence rate was 2.5/100 child-weeks in the placebo villages, and 2.3/100 child-weeks in villages that received SP + AS. The mean rate ratio, adjusted for individual and village-level covariates, was 0.91 (95% CI 0.68-1.22, P = 0.49). During the first 2 months of surveillance, the malaria incidence was lower in treated villages. After 2 months the incidence was slightly higher in the MDA group but this was not statistically significant. Overall, no benefit of the MDA could be detected. The reason for the absence of an impact on malaria transmission is probably the very high basic reproductive number of malaria, and the persistence of mature gametocytes, which are not affected by AS treatment.

15569779
Vreugdenhil CJ, Scheper FY, Hoogstraatte SR, Smolders M, Gikunda S, Cobelens FG, Kager PA
Comparison of the parasitologic efficacy of amodiaquine and sulfadoxine-pyrimethamine in the treatment of Plasmodium falciparum malaria in the Bungoma District of western Kenya.
Am J Trop Med Hyg. 2004 Nov;71(5):537-41.
The efficacy of amodiaquine (AQ) and sulfadoxine-pyrimethamine (SP) was assessed in 310 symptomatic children from western Kenya with uncomplicated Plasmodium falciparum malaria. A non-blinded, randomized, 14-day study was performed and parasitologic criteria were used. Of 310 patients included, 238 (77%) completed the study: 120 received AQ and 118 received SP. In those treated with AQ, there were sensitive (S) infections in 107 patients (89.2%, 95% confidence interval [CI] = 82.2, 94.1%), RI resistance in 10 (8.3%, 95% CI = 4.1, 14.8%), RII resistance in 1 (0.8%, 95% CI = 0, 4.6%), and RIII resistance in 2 (1.7%, 95% CI = 0.2, 5.9%). In those treated with SP, there were S infections in 74 patients (62.7%, 95% CI = 53.3, 71.4%), RI resistance in 21 (17.8%, 95% CI = 11.4, 25.9%), RII resistance in 11 (9.3%, 95% CI = 4.7, 16.1%), and RIII resistance in 12 (10.2%, 95% CI = 5.4, 17.1%). Resistance rates were consistently higher in the SP-treated patients (P < 0.001). Resistance to SP in this area has reached such levels that it should no longer be the first-line treatment. Alternative treatment, such as SP plus AQ combination treatment or artemisinin combination treatment, is urgently needed.

10066886
Vroman JA, Alvim-Gaston M, Avery MA
Current progress in the chemistry, medicinal chemistry and drug design of artemisinin based antimalarials.
Curr Pharm Des. 1999 Feb;5(2):101-38.
This review covers developments in relation to artemisinin-based antimalarial agents. Topics covered include a brief introduction to the history and treatment of malaria, and more recently, drug resistant malaria; the discovery of the naturally occurring novel peroxidic antimalarial artemisinin; artemisinin biosynthesis, metabolism and biotransformations; the diversity of proposed mechanisms of action; pharmacokinetics; the insight into structure-toxicity relationships; the total syntheses and the progress made in the syntheses of its analogs; and, ultimately the contribution of these efforts towards rational drug design in order to access potent, non-toxic antimalarial drugs based on artemisinin.

10403324
Vugt MV, Wilairatana P, Gemperli B, Gathmann I, Phaipun L, Brockman A, Luxemburger C, White NJ, Nosten F, Looareesuwan S
Efficacy of six doses of artemether-lumefantrine (benflumetol) in multidrug-resistant Plasmodium falciparum malaria.
Am J Trop Med Hyg. 1999 Jun;60(6):936-42.
The new oral fixed combination artemether-lumefantrine (CGP 56697) has proved to be an effective and well-tolerated treatment of multi-drug resistant Plasmodium falciparum malaria, although cure rates using the four-dose regimen have been lower than with the currently recommended alternative of artesunate-mefloquine. Two six-dose schedules (total adult dose = 480 mg of artemether and 2,880 mg of lumefantrine) were therefore compared with the previously used four-dose regimen (320 mg of artemether and 1,920 mg of lumefantrine) in a double-blind trial involving 359 patients with uncomplicated multidrug-resistant falciparum malaria. There were no differences between the three treatment groups in parasite and fever clearance times, and reported adverse effects. The two six-dose regimens gave adjusted 28-day cure rates of 96.9% and 99.12%, respectively, compared with 83.3% for the four-dose regimen ($P < 0.001$). These six-dose regimens of artemether-lumefantrine provide a highly effective and very well-tolerated treatment for multidrug-resistant falciparum malaria.

16102929
Waako PJ, Smith P, Folb PI
In vitro interactions of Aspilia africana (Pers.) C.D. Adams, a traditional antimalarial medicinal plant, with artemisinin against Plasmodium falciparum.
J Ethnopharmacol. 2005 Nov 14;102(2):262-8. Epub 2005 Aug 15.
Traditional antimalarial medicinal preparations are widely used concurrently with antimalarial drugs in malaria endemic areas. The plant Aspilia africana (Pers.) C.D. Adams is commonly used for traditional treatment of malaria symptoms in East and Central Africa. An in vitro study of interactions between an extract from this plant with artemisinin against two strains of Plasmodium falciparum showed an antagonist relationship against both the chloroquine-sensitive D10 and the chloroquine- and sulphonamide-resistant K1 strains of Plasmodium falciparum. The extract reduced accumulation of radiolabelled dihydroartemisinin ((3)H-DHA) by erythrocytes infected with the chloroquine- and sulphonamide-resistant K1 strain of Plasmodium falciparum while it increased its accumulation by erythrocytes infected with the chloroquine-sensitive D10 strain. These results suggest complex interactions between the antimalarial medicinal plant and artemisinin. This study also proposes an in vitro approach to investigating interactions between antimalarial drugs and traditional medicines.

12219164
Walgate R
New malaria drug candidate could cure in a single dose.
Bull World Health Organ. 2002;80(8):685-6. Epub 2002 Aug 27.

10639360
Walker DJ, Pitsch JL, Peng MM, Robinson BL, Peters W, Bhisutthibhan J, Meshnick SR
Mechanisms of artemisinin resistance in the rodent malaria pathogen Plasmodium yoelii.
Antimicrob Agents Chemother. 2000 Feb;44(2):344-7.
Artemisinin and its derivatives are important new antimalarials which are now used widely in Southeast Asia. Clinically relevant artemisinin resistance has not yet been reported but is likely to occur. In order to understand how the malaria parasite might become resistant to this drug, we studied artemisinin resistance in the murine malaria parasite Plasmodium yoelii. The artemisinin-resistant strain (ART), which is

approximately fourfold less sensitive to artemisinin than the sensitive NS strain, accumulated 43% less radiolabeled drug in vitro (P < 0.01). Within the parasite, the drug appeared to react with the same parasite proteins in both strains. The translationally controlled tumor protein, one of the artemisinin target proteins, did not differ between the strains. No DNA sequence difference was found, but the resistant strain was found to express 2.5-fold-more protein than the sensitive strain (P < 0.01). Thus, the phenotype of artemisinin resistance in P. yoelii appears to be multifactorial.

1303339
Wan YD, Zang QZ, Wang JS
[Studies on the antimalarial action of gelatin capsule of Artemisia annua]
Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi. 1992;10(4):290-4.
The pharmacological and clinical effects of gelatin capsule of Artemisia annua (GCAA) were investigated. The results revealed that the LD50 was 162.5 +/- 10.1g (crude drug)/kg and ED50 was 11.9 +/- 2.4g (crude drug) for clearance of parasitemia in mice infected with Plasmodium berghei therapeutic index being 13.6, which was 3.5 times more than that of artemisinin. The cure rate of COEA for Plasmodium berghei and P. vivax infections was 100%, as well as just like that of the extract tablets of Artemisia annua and chloroquine. This formulation was found to be better than chloroquine in fever subsidence and disappearance of malarial symptoms, while the recrudescence rate was still high, the latter could be inhibited by increasing therapeutic course or daily dosing time or by combination with primaquine.

3289785
Wang HF, Shi WZ, Feng TG, Zhang SF, Li PS, Ganjun, Li GQ, Guo XB
[Clinical study on the treatment of malaria with artemether and artesunate]
Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi. 1988;6(1):26-8.

14744564
Wang JY, Cao WC, Shan CQ, Zhang M, Li GF, Ding DB, Shi YL, Wu BA
Naphthoquine phosphate and its combination with artemisinine.
Acta Trop. 2004 Feb;89(3):375-81.
Naphthoquine phosphate and artemisinine are two antimalarials developed in China. Both drugs have proven to be efficacious and well tolerated as monotherapy as well as in combination in patients suffering from malaria. The Co-naphthoquine, a novel antimalarial combination, is an oral fixed combination tablet of the naphthoquine phosphate and artemisinine. Artemisinin is characterised by a rapid onset of schizonticidal action and a short half-life. Parasite clearance is, however, often incomplete when it is employed as a single agent unless high dosages are used over several days, but such a regimen may reduce patient compliance and increase the danger of toxicity. Naphthoquine phosphate, by contrast, has a slower onset of action and a longer half-life, associated with a low recrudescence rate. The two components act synergistically in animal, and clinically provide more rapid relief of symptoms and a higher cure rate than either component alone. The combination tablet was initially developed by the Academy of Military Medical Sciences (AMMS), Beijing, China.

12292302
Warhurst D
Drug treatment and the control of malaria in Africa: a time of hope?
Afr Health. 1997 Jan;19(2):21-3.
Chloroquine-resistant Plasmodium vivax has not yet occurred in Vietnam. The efficacy of artemisinin for P. vivax was not established. We conducted a double-blind randomized study involving 240 inpatients with P. vivax malaria who received artemisinin (40 mg/kg over 3 days) plus placebo chloroquine (Art) or chloroquine (25 mg/kg over 3 days) plus placebo artemisinin (Chl). Patients were followed up with weekly blood smears for 28 days. In each group 113 cases were analysed. All patients recovered rapidly. The median (range) parasite clearance time of regimen Art was 24 h (8-72) and of Chl 24 h (8-64; P = 0.3). Parasites reappeared in two cases in each group on day 14, in eight cases in each group (7%) on day 16 and in 25 (23%) and 18 (16%) cases, respectively, at the end of 4-week follow-up (P = 0.3). The population parasite clearance curve followed a mono-exponential decline. The parasite reduction ratio per 48 h reproduction cycle was 2.3 x 104 for both regimens. We conclude that artemisinin and chloroquine are equally effective in the treatment of P. vivax infections in Vietnam. Reappearance of parasites before day 16 (7%) suggests the emergence of chloroquine resistance. Three days of artemisinin monotherapy does not prevent recrudescence.

11579870
Warhurst DC, Duraisingh MT
Rational use of drugs against Plasmodium falciparum.

Trans R Soc Trop Med Hyg. 2001 Jul-Aug;95(4):345-6.
Recent studies on resistance to blood schizontocides in Plasmodium falciparum give a rational basis for the use of artemisinins combined with arylaminoalcohols for the treatment of uncomplicated chloroquine-resistant malaria in Africa. In areas where such combinations are introduced, there is reason to believe that the continued use of chloroquine in the community will help protect the new drugs from resistance. In view of several laboratory studies, combinations of artemisinins with antifolates or chloroquine pose a risk of antagonistic interaction. This can be avoided by use of the artemisinin and the companion drug sequentially.

9204715
Warrell DA
Herbal remedies for malaria.
Trop Doct. 1997;27 Suppl 1:5-6.

10697870
Warrell DA
Management of severe malaria.
Parassitologia. 1999 Sep;41(1-3):287-94.
The case fatality of WHO-defined 'severe falciparum malaria' remains unacceptably high, at 10-20%. However, a gradual decline in case fatality in adults and children treated in hospitals may reflect use of improved regimens of antimalarial chemotherapy and increased awareness of important complications of the disease. The development of severe, perhaps inevitably-fatal, malaria might be prevented by early appropriate chemotherapy of uncomplicated disease. At the most peripheral levels of the health service, suppository formulations of artemisinin derivatives can be administered even to patients who are vomiting or prostrated. At dispensaries, clinics or hospitals, where intramuscular or intravenous administration of antimalarial drugs is possible, quinine and artemisinin derivatives are the treatments of choice. There is growing evidence of the safety and efficacy of the quinine loading dose and of the use of artemether and artesunate, based on large, randomised, controlled clinical studies. No safe and effective form of prophylactic ancillary treatment has yet emerged. Results of studies of antipyretics, anticonvulsants (phenobarbitone), anticytokine/anti-inflammatory agents (anti-TNF antibodies, pentoxifylline, dexamethasone), iron chelators and hyperimmune sera have been disappointing. Only blood transfusion and treatment of respiratory, circulatory and renal failure are of obvious benefit. New ideas are needed, based on what is known of the pathophysiology of severe disease.

9285035
Warrell DA
The 1996 Runme Shaw Memorial Lecture: malaria--past, present and future.
Ann Acad Med Singapore. 1997 May;26(3):380-7.
Falciparum malaria may have infected Homo sapiens (and perhaps H erectus) in the Asia Pacific region for more than 100,000 years. This estimate is based on the gene frequency of alpha-thalassaemia, the protection it affords against falciparum malaria and assumptions of untreated mortality from the infection. Up until the end of the 19th century, there was a high mortality from malaria in the coastal parts of Malaya, but the malaria control campaign, begun in 1901 at Klang, was described by Sir Ronald Ross as the first successful antimalarial work in the (then) British Empire. This was extended to Singapore in 1911. When the Far Eastern Association of Tropical Medicine held its Fifth Biennial Congress in Singapore in 1923, malaria was still a major killing disease in parts of Malaya and Sarawak. The mechanism of life-threatening malaria involves cytoadherence of parasitised erythrocytes in microvascular beds, a process enhanced by the products of macrophage activation induced by malarial pyrogen. Improvements in the chemotherapy of life-threatening falciparum malaria with chloroquine and quinine have been countered by the emergence of resistant strains. Artemisinin derivatives may become the treatment of choice during the coming decade. Apart from traditional anti-mosquito methods, control of malaria now involves the use of insecticide-impregnated bed nets, new entomological strategies, including genetic manipulation of mosquitoes and selective chemoprophylaxis. Antigenic diversity and antigenic variation of the malaria parasite have so far defeated attempts to produce an effective vaccine.

11792090
Warrell DA
'To search and studdy out the secrett of tropical diseases by way of experiment'.
Clin Med. 2001 Nov-Dec;1(6):485-94.
William Harvey wrote about malaria, snake bite and rabies, three diseases now having their greatest impact in tropical developing countries. Global malarial mortality has not declined for 50 years. The most effective control measure would be a vaccine. Temporary immunity in humans, through hundreds of bites by

irradiated infected mosquitoes, was achieved in the 1970s. A promising current strategy is effector T-cell vaccination directed at infected hepatocytes. RTS,S/(SB)ASO2, an adjuvanted fusion protein, produced transient protection in 70% of vaccines. Prime (DNA vaccine) boost (poxvirus recombinant) is particularly immunogenic. Pyrethroid-treated bed nets reduce childhood mortality and deplete the mosquito population, interrupting transmission. Chlorproguanil-dapsone is more effective than pyrimethamine-sulfadoxine in treating uncomplicated chloroquine-resistant malaria. Artemisinin derivatives are as effective as quinine in severe disease. Snake bite is an underestimated and neglected cause of morbidity and mortality in rural communities in tropical countries. Sutherland's pressure-immobilisation technique is recommended first-aid for victims of neurotoxic elapid snakes. Rabies post-exposure prophylaxis, using new generation cell culture vaccines, is now feasible in developing countries, employing an economical 8-site intradermal regimen. This Harveian Oration, the first in 350 years to be devoted to tropical medicine, emphasises the importance of this speciality in the twenty-first century.

14615418
Wartenberg M, Wolf S, Budde P, Grunheck F, Acker H, Hescheler J, Wartenberg G, Sauer H
The antimalaria agent artemisinin exerts antiangiogenic effects in mouse embryonic stem cell-derived embryoid bodies.
Lab Invest. 2003 Nov;83(11):1647-55.
Artemisinin is widely used as an agent to treat malaria; the possible antiangiogenic effects of this compound are unknown. In the present study, the antiangiogenic effects of artemisinin were investigated in mouse embryonic stem cell-derived embryoid bodies, which are a model system for early postimplantation embryos and which efficiently differentiate capillaries. Artemisinin dose dependently inhibited angiogenesis in embryoid bodies and raised the level of intracellular reactive oxygen species. Furthermore impaired organization of the extracellular matrix component laminin and altered expression patterns of matrix metalloproteinases 1, 2, and 9 were observed during the time course of embryoid body differentiation. Consequently accelerated penetration kinetics of the fluorescent anthracycline doxorubicin occurred within the tissue, indicating increased tissue permeability. Artemisinin down-regulated hypoxia-inducible factor-1alpha and vascular endothelial growth factor (VEGF) expression, which control endothelial cell growth. The antiangiogenic effects and the inhibition of hypoxia-inducible factor-1alpha and VEGF were reversed upon cotreatment with the free radical scavengers mannitol and vitamin E, indicating that artemisinin may act via reactive oxygen species generation. Furthermore, capillary formation was restored upon coadministration of exogenous VEGF. The data of the present study suggest that the antiangiogenic activity of artemisinin and the increase in tissue permeability for cytostatics may be exploited for anticancer treatment.

15741553
Watkins WM, Sibley CH, Hastings IM
The search for effective and sustainable treatments for Plasmodium falciparum malaria in Africa: a model of the selection of resistance by antifolate drugs and their combinations.
Am J Trop Med Hyg. 2005 Feb;72(2):163-73.
The extensive data on the relationship between parasite genotype and susceptibility to antifolate drugs can now be coupled with pharmacokinetic information to allow construction of models of the selection and spread of antifolate-resistant Plasmodium falciparum. In this report, we have modeled the effect on resistance selection processes of combinations of antifolate antimalarial drugs with artesunate and with amodiaquine under a variety of conditions that can be defined by the user. The model is intended to assist policymakers in forecasting the useful therapeutic life (UTL) for a range of potential combination treatments. The model is especially designed for use by African malaria programs so that the interactions of key variables can be explored and appropriate combinations of drugs can be chosen for field testing. The model provides some important general conclusions: 1) for optimal extension of UTL, combination therapy must be deployed before either constituent drug is used as monotherapy; 2) even short periods of monotherapy can severely limit the usefulness of subsequent combination therapy; and 3) that adding a second drug to rescue an antifolate antimalarial that is overtly failing is an inappropriate and ultimately wasteful exercise.

15115124
Wattanakoon Y, Chittamas S, Pornkulprasit V, Kanda T, Thimasarn K, Rojanawatsirivej C, Looareesuwan S, Bunnag D
Six-years monitoring the efficacy of the combination of artesunate and mefloquine for the treatment of uncomplicated falciparum malaria.
Southeast Asian J Trop Med Public Health. 2003 Sep;34(3):542-5.
Plasmodium falciparum in Thailand is multi-drug resistant. In a previous study it was shown that artesunate and mefloquine were effective, as follow up, we monitored the efficacy of this regimen for six years. During 1997-2002, 516 adult male volunteer patients in Chanthaburi Province were enrolled (50 patients in the first year, 400 patients in 1998-2001 and 66 patients in 2002). The symptom complex and parasite count (thick blood film) were monitored on days 0, 1, 2, 7, 14, 21, 28, 35 and 42. The dosages used were artesunate

(ATS) 150 mg and mefloquine (M) 750 mg at hour 0 and ATS 100 mg and M 500 mg at hour 24. Their ages ranged from 30-35 years and their mean body weights were 54-56 kg. The presenting symptoms were fever 100%, headache 97-100%, anorexia 78-90%, and nausea 28-40%. The geometric mean of parasitemia ranged from 7,357-12,750/mm3. Defervescence in one day was found in 42-76% of patients and 85-100% in 2 days. The sensitivity (S) ranged from 87-94% and RI resistance (recrudescence) ranged from 6-13%. Forty patients demonstrated RI type of response, 37 were cured after being retreated with the same dosage and another 3 patients were cured after the third course of treatment. The aggravated adverse effects included vomiting (8-20%), anorexia (1-41%) and diarrhea (0-16%). These side effects were mild and transient. The efficacy of the artesunate and mefloquine combination for the treatment of uncomplicated falciparum malaria was high. The RI type of response was possibly due to re-infection or multiple broods and not to drug resistance. The adverse effects of anorexia, nausea, vomiting and diarrhea were mild and transient for mefloquine. The combination can be used as stand by treatment in areas of multi-drug resistant falciparum malaria.

12449772
Weerasinghe KL, Galappaththy G, Fernando WP, Wickremasinghe DR, Faizal HM, Wickremasinghe AR
A safety and efficacy trial of artesunate, sulphadoxine-pyrimethamine and primaquine in P falciparum malaria.
Ceylon Med J. 2002 Sep;47(3):83-5.
OBJECTIVE: To determine effectiveness and safety of the combination of artesunate, sulphadoxine + pyrimethamine and primaquine in the treatment of P falciparum malaria. DESIGN: A hospital based prospective study. SETTING: Base Hospital, Moneragala. METHODS: In 30 P falciparum infected patients admitted to the hospital, blood was taken for estimation of haemoglobin, white cell counts, and serum levels of aspartate aminotransferase, alanine aminotransferase, bilirubin and creatinine. They were administered artesunate, sulphadoxine + pyrimethamine (S + P) and primaquine on day 0 (artesunate 4 mg/kg, sulphadoxine 25 mg/kg, pyrimethamine 1.25 mg/kg and primaquine 0.75 mg/kg), and only artesunate on days 1 and 2 (artesunate 4 mg/kg each day). Blood was examined for malarial parasites, and patients were assessed on days 1, 2, 7, 14, 21 and 28. Patients assessed the severity of selected symptoms. Biochemical analyses were done on day 0 and repeated on days 7 and 28. RESULTS: Eight patients presented with fever which resolved in 7 patients in 48 hours. Asexual parasites were cleared in 80% of the 30 patients within 24 hours of treatment and in all 30 by day 7. Gametocytaemia cleared in all patients by day 14. There were no adverse effects experienced by the patients. The white cell and differential counts, liver enzymes and creatinine levels were within normal limits on all follow up days. CONCLUSIONS: The combination of artesunate, S + P and primaquine was found to be effective and safe in the treatment of uncomplicated P falciparum malaria.

9952392
Wenisch C, Linnau KF, Looaresuwan S, Rumpold H
Plasma levels of the interleukin-6 cytokine family in persons with severe Plasmodium falciparum malaria.
J Infect Dis. 1999 Mar;179(3):747-50.
Plasma levels of interleukin (IL)-6, soluble IL-6 receptor, soluble gp130, leukemia inhibitory factor (LIF), and ciliary neutrophic factor (CNTF) were analyzed in 32 patients with severe malaria. Ten had renal failure, 8 had cerebral malaria, and 14 had other causes of severity. Before treatment, the IL-6 and soluble IL-6 receptor plasma levels were significantly higher in persons with cerebral malaria or renal failure than in other groups (P

9546416
Wenisch C, Looareesuwan S, Wilairatana P, Parschalk B, Vannapann S, Wanaratana V, Wernsdorfer W, Graninger W
Effect of pentoxifylline on cytokine patterns in the therapy of complicated Plasmodium falciparum malaria.
Am J Trop Med Hyg. 1998 Mar;58(3):343-7.
The effect of pentoxifylline (PTX) was tested for its capacity to modulate cytokine responses during therapy of severe Plasmodium falciparum malaria in a placebo-controlled, randomized study in 45 adult patients in Bangkok, Thailand. The patients received standard antimalarial treatment with artesunate (120 mg intravenously given immediately, then 60 mg every 12 hr for a total dose of 600 mg). The patients received either low-dose PTX (20 mg/kg/day, n = 15), high-dose PTX (40 mg/kg/day, n = 15), or placebo (n = 15) as continuous infusion for the first three days of antimalarial treatment. Tumor necrosis factor (TNF) and interleukin-6 (IL-6) plasma levels were markedly elevated in all patients prior to treatment. After 6 hr of high-dose PTX treatment, TNF and IL-6 levels significantly decreased while an increase in TNF and IL-6 levels was seen after 6 hr of low-dose PTX or placebo treatment ($P < 0.01$). After 12 and 24 hr of high-dose PTX infusion, TNF-receptor plasma concentrations were lower than in low-dose PTX- or placebo-treated patients ($P < 0.01$), whereas no differences between the groups with regard to IL-6 receptor levels were observed.

We conclude that 40 mg/kg/day of PTX reduces plasma levels of TNF, IL-6, and TNF-receptor in patients with severe malaria. Whether this reduction improves clinical outcome remains to be determined.

7559910
Wenisch C, Parschalk B, Burgmann H, Looareesuwan S, Graninger W
Decreased serum levels of TGF-beta in patients with acute Plasmodium falciparum malaria.
J Clin Immunol. 1995 Mar;15(2):69-73.
Apart from cellular immunity and immunopathology, various cytokines have been implicated in malaria-associated immunosuppression. In this study, serum levels of transforming growth factor-beta (TGF-beta) were determined with an enzyme-linked immunosorbent assay in 37 patients with acute Plasmodium falciparum malaria prior to, during, and after therapy and in 17 healthy controls in Bangkok, Thailand. Patients were treated with artesunate and mefloquine. TGF-beta serum levels were found decreased prior to treatment (14 +/- 11 pg/ml versus 63 +/- 15 pg/ml in healthy controls; P < 0.05). The serum concentrations of TGF-beta increased after initiation of treatment and were within normal range on day 21. Serum levels of both tumor necrosis factor-alpha (TNF-alpha) and soluble TNF-receptor 55 kDa were inversely correlated to serum levels of TGF-beta (r = -0.667 and r = -0.592, n = 37; respectively, P < 0.05 for both). No correlation between parasitemia and serum levels of TGF-beta could be found. The results are compatible with a decreased production and release, an enhanced clearance or utilization, or tissue accumulation of TGF-beta in acute P. falciparum malaria.

7535826
Wenisch C, Presterl E, Graninger W, Looareesuwan S
Circulating L-selectin is elevated in patients with Plasmodium falciparum malaria.
J Infect Dis. 1995 Apr;171(4):1078-9.

8627087
Wenisch C, Wenisch H, Wilairatana P, Looareesuwan S, Vannaphan S, Wagner O, Graninger W, Schonthal E, Rumpold H
Big endothelin in patients with complicated Plasmodium falciparum malaria.
J Infect Dis. 1996 May;173(5):1281-4.
Plasma concentrations of big endothelin-1 were determined by ELISA in 18 patients with complicated Plasmodium falciparum malaria in Bangkok. Before therapy, elevated levels were recorded (21 +/- 12 vs. 2.9 +/- 1.1 pmol/L in age- and sex-matched healthy subjects; P < .001). Even 7 days after therapy, elevated concentrations were seen (25 +/- 14 pmol/L). Plasma endothelin levels were correlated with levels of tumor necrosis factor-alpha (r = .632, P < .01), and a negative correlation with platelet counts was seen (r = .783, P < .005). No relation between plasma endothelin concentrations and parasitemia, fever, or other indices of severe infection (hypotension, renal, hepatic or pulmonary impairment, cerebral malaria) existed. During and after complicated malaria, increased levels of plasma endothelin could contribute to malarial pathology or reflect endothelial damage or both.

14624105
Wernsdorfer WH, Noedl H
Molecular markers for drug resistance in malaria: use in treatment, diagnosis and epidemiology.
Curr Opin Infect Dis. 2003 Dec;16(6):553-8.
PURPOSE OF REVIEW: Malaria and the increasing role of drug resistance as an obstacle to its control are global problems. The identification and implications of molecular markers for antimalarial drug resistance - the subject of this review - are key issues in elucidating and eventually controlling resistance. RECENT FINDINGS: Recent achievements include the successful expression of the Plasmodium falciparum chloroquine resistance transporter gene, pfcrt, in yeast, the identification of polymorphisms on the gamma-glutamylcysteine synthetase gene, ggcs, as potential determinants of chloroquine and mefloquine resistance, and the usefulness of a combined Plasmodium falciparum dihydrofolate reductase gene, pfdhfr, 59ARG and Plasmodium falciparum dihydropteroate synthase gene, pfdhps, 540GLU marker in reliably representing resistance to antifolates. Moreover, treatment with sulfadoxine-pyrimethamine in the presence of pfdhfr 108ASP alone delayed parasite clearance and increased gametocytogony without an overt loss of the overall therapeutic efficacy of the drug. SUMMARY: The use of pfdhfr and pfdhps markers in determining antifolate resistance of Plasmodium falciparum has been consolidated. Similar progress has been made with pfcrt markers for chloroquine resistance, auguring well the operational deployment of molecular techniques. Regarding the molecular basis of resistance to arylaminoalcohols, related drugs, and artemisinin and its derivatives, answers remain elusive, but there are promising new leads.

9815509

Wetsteyn JCFM, Kager PA, van Gool T
The Changing Pattern of Imported Malaria in the Academic Medical Centre, Amsterdam.
J Travel Med. 1997 Dec 1;4(4):171-175.
Background: Since 1988, the incidence of malaria imported into the Netherlands has been stable, but the population groups have remarkably changed. Methods: The records of all patients with malaria in the Academic Medical Centre, Amsterdam, between October 1991 and December 1994 were analyzed. Results: Of the 286 patients, 149 (52%) were Dutch citizens and 114 (40%) were originally from malaria endemic areas (92 immigrants, 22 asylum-seekers), whereas between 1979 and 1988 these figures were 85 and 15%. The remaining 23 (8%) patients were 11 children born in the Netherlands to immigrants, 10 foreigners from nonmalarious areas, and 2 for whom the origin is unknown. Plasmodium falciparum was found in 197 (69%) patients, mostly acquired in subSaharan Africa; P. vivax (61 patients, 21%) was mainly acquired in Asia. Two vivax infections proved to be chloroquine-resistant. The compliance with the malaria chemoprophylaxis was poor: only 38% (30/80) of the Dutch citizens and 8% (4/52) of the settled immigrants and children were fully compliant. Severe complicated falciparum malaria developed in 18 (10%) patients, two of whom died. The majority of the falciparum cases were treated with halofantrine or sulfadoxine-pyrimethamine. Artemisinin was used in two. Conclusions: Among the patients with imported malaria, settled immigrants and their (nonimmune) children constitute a growing number. Compliance with chemoprophylaxis is decreasing in Dutch travelers and remains poor in the immigrants. Quinine was increasingly used both as initial treatment for severe falciparum malaria as well as in patients with nonsevere malaria who were nauseated or vomiting.

10365399
White N
Antimalarial drug resistance and combination chemotherapy.
Philos Trans R Soc Lond B Biol Sci. 1999 Apr 29;354(1384):739-49.
Antimarial drug resistance develops when spontaneously occurring parasite mutants with reduced susceptibility are selected, and are then transmitted. Drugs for which a single point mutation confers a marked reduction in susceptibility are particularly vulnerable. Low clearance and a shallow concentration-effect relationship increase the chance of selection. Use of combinations of antimalarials that do not share the same resistance mechanisms will reduce the chance of selection because the chance of a resistant mutant surviving is the product of the per parasite mutation rates for the individual drugs, multiplied by the number of parasites in an infection that are exposed to the drugs. Artemisinin derivatives are particularly effective combination partners because (i) they are very active antimalarials, producing up to 10,000-fold reductions in parasite biomass per asexual cycle; (ii) they reduce malaria transmissibility; and (iii) no resistance to these drugs has been reported yet. There are good arguments for no longer using antimalarial drugs alone in treatment, and instead always using a combination with artemisinin or one of its derivatives.

15085184
White NJ
Antimalarial drug resistance.
J Clin Invest. 2004 Apr;113(8):1084-92.
Malaria, the most prevalent and most pernicious parasitic disease of humans, is estimated to kill between one and two million people, mainly children, each year. Resistance has emerged to all classes of antimalarial drugs except the artemisinins and is responsible for a recent increase in malaria-related mortality, particularly in Africa. The de novo emergence of resistance can be prevented by the use of antimalarial drug combinations. Artemisinin-derivative combinations are particularly effective, since they act rapidly and are well tolerated and highly effective. Widespread use of these drugs could roll back malaria.

8053020
White NJ
Artemisinin: current status.
Trans R Soc Trop Med Hyg. 1994 Jun;88 Suppl 1:S3-4.
The compounds derived from the Chinese medicinal plant qinghao (Artemisia annua) are the most rapidly acting of all antimalarial drugs. They are effective when given parenterally, orally or by suppository. No serious adverse effect has yet been reported in humans. The artemisinin derivatives already have an established role in the treatment of multi-drug resistant falciparum malaria, but their wider use will depend on the results of current mortality and toxicity studies.

10697872
White NJ
Delaying antimalarial drug resistance with combination chemotherapy.
Parassitologia. 1999 Sep;41(1-3):301-8.

Resistance to antimalarial drugs arises when spontaneously occurring mutants with gene mutations or amplifications which confer reduced drug susceptibility are selected, and are then transmitted. Simultaneous use of two or more antimalarials with different modes of action and which therefore do not share the same resistance mechanisms will reduce the chance of selection, because the chance of a resistant mutant surviving is the product of the parasite mutation rates for the individual drugs, multiplied by the number of parasites in an infection that are exposed to the drugs. The artemisinin derivatives are very active antimalarials, which produce large reductions in parasite biomass per asexual cycle, and reduce malaria transmissibility. To date no resistance to these drugs has been reported. These drugs therefore make particularly effective combination partners. This suggests that antimalarial drugs should not be used alone in treatment, but always in combination, as in the treatment of tuberculosis or HIV, and that the combination should include artemisinin or one of its derivatives.

10212909
White NJ
Qinghaosu in combinations.
Med Trop (Mars). 1998;58(3 Suppl):85-8.
Antimalarial combinations make therapeutic sense. As we have few antimalarial drugs and even fewer in development, and as the malaria parasite shows a remarkable ability to develop resistance, all possible measures should be taken to protect those drugs that we do have available. Although in experimental animals combinations have been shown unequivocally to delay the onset of resistance, this has not yet been proved formally in human malaria. Yet formal proof is extremely difficult to obtain. However, there is sufficient circumstantial evidence to suggest that resistance can be delayed. As there are no counter arguments and the stakes are high, it seems reasonable that an artemisinin derivative should be combined with all slow acting antimalarial drugs. Those drugs with a particularly vulnerable profile, in which a single or double point mutation confers high level resistance, should not be deployed alone and should always be combined with an artemisinin derivative.

8703186
White NJ
The treatment of malaria.
N Engl J Med. 1996 Sep 12;335(11):800-6.
Increasing drug resistance in Plasmodium falciparum and a resurgence of malaria in tropical areas have effected a change in treatment of malaria in the last two decades. Symptoms of malaria are fever, chills, headache, and malaise. The prognosis worsens as the parasite counts, counts of mature parasites, and counts of neutrophils containing pigment increase. Treatment depends on severity, age of patient, degree of background immunity, likely pattern of susceptibility to antimalarial drugs, and the cost and availability of drugs. Chloroquine should be used for P. vivax, P. malariae, and P. ovale. P. vivax has shown high resistance to chloroquine in Oceania, however. Primaquine may be needed to treat P. vivax and P. ovale to rid the body of hypnozoites that survive in the liver. Chloroquine can treat P. falciparum infections acquired in North Africa, Central America north of the Panama Canal, Haiti, or the Middle East but not in most of Africa and some parts of Asia and South America. In areas of low grade resistance to chloroquine, amodiaquine can be used to effectively treat falciparum malaria. A combination of sulfadoxine-pyrimethamine is responsive to falciparum infections with high grade resistance to chloroquine. Mefloquine, halofantrine, or quinine with tetracycline can be used to treat multidrug-resistant P. falciparum. Derivatives of artemisinin obtained from qinghao or sweet wormwood developed as pharmaceuticals in China are the most rapidly acting of all antimalarial drugs. Children tend to tolerate antimalarial drugs well. Children who weigh less than 15 kg should not be given mefloquine. Health workers should not prescribe primaquine to pregnant women or newborns due to the risk of hemolysis. Chloroquine, sulfadoxine-pyrimethamine, quinine, and quinidine can be safely given in therapeutic doses throughout pregnancy. Clinical manifestations of severe malaria are hypoglycemia, convulsions, severe anemia, acute renal failure, jaundice, pulmonary edema, cerebral malaria, shock, and acidosis. Health workers should be prepared to treat these symptoms accordingly.

10371589
White NJ, Nosten F, Looareesuwan S, Watkins WM, Marsh K, Snow RW, Kokwaro G, Ouma J, Hien TT, Molyneux ME, Taylor TE, Newbold CI, Ruebush TK 2nd, Danis M, Greenwood BM, Anderson RM, Olliaro P
Averting a malaria disaster.
Lancet. 1999 Jun 5;353(9168):1965-7.

10212899

White NJ, Olliaro P
Artemisinin and derivatives in the treatment of uncomplicated malaria.
Med Trop (Mars). 1998;58(3 Suppl):54-6.
Artemisinin and its derivatives are the most rapidly acting antimalarials known to-date and are well-tolerated. All derivatives in use today are produced by semi-synthesis from artemisinin: dihydroartemisinin is the product of the first step; more synthetic steps give rise to artesunate, artemether and arteether which are metabolised back to dihydroartemisinin in the body. Although their residence in the body after oral administration is very short (with half-lives of < 2 hours), they can be administered once daily. By acting on ring stages, they clear peripheral parasitaemia more quickly than other antimalarial drugs and prevent the development into mature sequestering blood stages. They are effective against all human malaria parasites, notably multidrug-resistant Plasmodium falciparum. They have anti-transmission properties, too. So far, resistance to this class of compounds has not been reported. However, when used alone, they require long treatment courses (7 days). So, combination with long-half life drugs such as mefloquine appears to be the best approach to mutually protect both drugs against resistance. While reported in experimental animals, there is no evidence neurotoxicity in human beings. Whether such event could occur after continuous or discontinuous use is not clear.

12641911
White NJ, Pongtavornpinyo W
The de novo selection of drug-resistant malaria parasites.
Proc Biol Sci. 2003 Mar 7;270(1514):545-54.
Antimalarial drug resistance emerges de novo predominantly in areas of low malaria transmission. Because of the logarithmic distribution of parasite numbers in human malaria infections, inadequately treated high biomass infections are a major source of de novo antimalarial resistance, whereas use of antimalarial prophylaxis provides a low resistance selection risk. Slowly eliminated antimalarials encourage resistance largely by providing a selective filter for resistant parasites acquired from others, and not by selecting resistance de novo. The de novo emergence of resistance can be prevented by use of antimalarial combinations. Artemisinin derivative combinations are particularly effective. Ensuring adequate treatment of the relatively few heavily infected patients would slow the emergence of resistance.

15298229
Whitty CJ, Allan R, Wiseman V, Ochola S, Nakyanzi-Mugisha MV, Vonhm B, Mwita M, Miaka C, Oloo A, Premji Z, Burgess C, Mutabingwa TK
Averting a malaria disaster in Africa--where does the buck stop?
Bull World Health Organ. 2004 May;82(5):381-4.
The serious threat posed by the spread of drug-resistant malaria in Africa has been widely acknowledged. Chloroquine resistance is now almost universal, and resistance to the successor drug, sulfadoxine-pyrimethamine (SP), is growing rapidly. Combination therapy has been suggested as being an available and potentially lasting solution to this impending crisis. However, the current cost of combination therapy, and especially that of artemisinin combination therapy (ACT), is potentially a serious drawback, even if a significant part of its cost is passed on to the end-user. If the question of cost is not successfully addressed this could lead to adverse results from the deployment of combination therapy as first-line treatment. These adverse effects range from an increase in potentially fatal delays in infected individuals presenting to medical services, to exclusion of the poorest malaria sufferers from receiving treatment altogether. Urgent steps are needed to reduce the cost of combination therapy to the end-user in a sustainable way if it is to be usable, and some possible approaches are discussed.

16163625
Whitty CJ, Staedke SG
Artemisinin-based combination treatment for malaria in Africa: no perfect solutions.
Clin Infect Dis. 2005 Oct 15;41(8):1087-8. Epub 2005 Sep 13.

14613157
Wiesner J, Ortmann R, Jomaa H, Schlitzer M
New antimalarial drugs.
Angew Chem Int Ed Engl. 2003 Nov 10;42(43):5274-93.
Approximately 40% of the world population live in areas with the risk of malaria. Each year, 300-500 million people suffer from acute malaria, and 0.5-2.5 million die from the disease. Although malaria has been widely eradicated in many parts of the world, the global number of cases continues to rise. The most important reason for this alarming situation is the rapid spread of malaria parasites that are resistant to antimalarial drugs, especially chloroquine, which is by far the most frequently used. The development of new antimalarial

drugs has been neglected since the 1970s owing to the end colonialism, changes in the areas of military engagement, and the restricted market potential. Only in recent years, in part supported by public funding programs, has interest in the development of antimalarial drugs been renewed. New data available from the recently sequenced genome of the malaria parasite Plasmodium falciparum and the application of methods of modern drug design promise to bring significant development in the fight against this disease.

16252578
Wijesundere A, Karunanayake P, Athukorala I, Jayasekara K
Imported quinine resistant Plasmodium falciparum malaria in Sri Lanka.
Ceylon Med J. 2005 Sep;50(3):125-6.

12693586
Wilairatana P, Krudsood S, Chalermrut K, Pengruksa C, Srivilairit S, Silachamroon U, Treeprasertsuk S, Looareesuwan S
An open randomized clinical trial of Artecom vs artesunate-mefloquine in the treatment of acute uncomplicated falciparum malaria in Thailand.
Southeast Asian J Trop Med Public Health. 2002 Sep;33(3):519-24.
The efficacy and safety of Artecom were assessed in an open randomized trial in adults presenting with acute, uncomplicated Plasmodium falciparum malaria in Thailand. Three hundred and fifty-two patients were randomly enroled at the ratio of 2:1 into group A:B and received Artecom (group A) and the standard combination of artesunate and mefloquine (group B) respectively. All patients had rapid initial clinical and parasitological responses. There were no significant differences in fever clearance time and parasite clearance time between the two groups. The 28-day cure rates were high as 97% in both groups. Artecom was effective and well-tolerated as artesunate-mefloquine, the current treatment in this area of multidrug-resistant P. falciparum malaria.

10772548
Wilairatana P, Krudsood S, Chokejindachai W, Bussaratid V, Silachamroon U, Viriyavejakul P, Hendriksen C, Scheiwe MW, Looareesuwan S
A clinical trial of combination of artesunate and mefloquine in the treatment of acute uncomplicated falciparum malaria: a short and practical regimen.
Southeast Asian J Trop Med Public Health. 1998 Dec;29(4):696-701.
The difficulties in treating drug-resistant falciparum malaria in Thailand are compounded by the necessity of giving antimalarials over long periods of time. The resultant fall in patient compliance not only lowers cure rates but also predisposes to the further spread of drug-resistance. Sequential treatment with artesunate given over 5 days followed by mefloquine produced 100% cure rates in previous study, but might not be a suitable regimen for field treatment. We conducted a clinical trial of a combination of artesunate and mefloquine given twice daily for 2 days in 150 patients with acute uncomplicated falciparum malaria. The dose of artesunate (200 mg) and mefloquine (312.5 mg) were given simultaneously in a separate package. All patients were admitted to a hospital in Bangkok for 28 days to exclude re-infection and monitor the possible adverse effects. One hundred and thirty patients completed the study with 28 days follow up. Twenty patients (13%) left the hospital prior to completion of follow-up for reasons unrelated to their treatment. Cure rate was 97% (126/130). There were no RII or RIII failures and all four patients with treatment failures were of the RI type. The mean parasite clearance time and fever clearance time were 46.4 and 42.5 hours, respectively. All patients were tolerated the combination drugs well and there were no serious toxic adverse reactions. The results indicate that combination of artesunate and mefloquine given twice daily for 2 days is effective and well tolerated in patients with acute, uncomplicated falciparum malaria and suitable as an alternative treatment for multidrug resistant falciparum malaria.

12234533
Wilairatana P, Krudsood S, Treeprasertsuk S, Chalermrut K, Looareesuwan S
The future outlook of antimalarial drugs and recent work on the treatment of malaria.
Arch Med Res. 2002 Jul-Aug;33(4):416-21.
With the emergence of multidrug-resistant falciparum malaria, new drugs and drugs in combination are urgently needed. New antimalarial drugs investigated at the Hospital for Tropical Diseases of the Faculty of Tropical Medicine at Mahidol University in Bangkok, Thailand in recent years for treatment of uncomplicated and severe falciparum malaria are as follows: atovaquone, and artemisinin derivatives (artesunate, artemether, arteether, and dihydroartemisinin) combined with other antimalarials.Malarone, artemisinin derivatives combined with lumefantrine or doxycycline, and mefloquine combined with tetracycline or doxycycline have been evaluated with improvement of the cure rate in uncomplicated malaria. Artemisinin derivatives intravenously or intrarectally combined with mefloquine may be alternatives to intravenous

quinine for treatment of severe malaria. In Thailand, drug treatment for uncomplicated malaria consists of the combinations or artesunate plus mefloquine or artemether plus lumefantrine or quinine plus tetracycline. In treatment of severe malaria, antimalarial drugs of choice are intravenous quinine or artemisinin derivatives.

11258492
Wilairatana P, Looareesuwan S
Guideline in management of severe malaria.
J Indian Med Assoc. 2000 Oct;98(10):628-31.
Severe malaria remains a major cause of mortality in the world. Malaria can mimic many diseases and there is no absolute diagnostic clinical features. High index of suspicion is clue for clinical diagnosis. Previous travel history to endemic area should be elicited in all, and in particular, febrile patients. Management of severe malaria needs potent antimalarial drug and intensive care. Artemisinin derivatives can be of altemative use to quinine. Dexamethasone and mannitol have no beneficial value in the management of cerebral malaria. In pulmonary oedema patients whose hydration assessments are difficult to monitor, central venous pressure evaluation may be useful. Acute renal failure patients may need dialysis until uraemic syndrome subsides or patients can void urine. Most severe malaria patients have thrombocytopenia; however, platelet concentrate transfusion is indicated only in patients with systemic bleeding. Morbidity and mortality will be reduced in severe malaria patients with early diagnosis and prompt treatment.

10674681
Wilairatana P, Silachamroon U, Krudsood S, Singhasivanon P, Treeprasertsuk S, Bussaratid V, Phumratanaprapin W, Srivilirit S, Looareesuwan S
Efficacy of primaquine regimens for primaquine-resistant Plasmodium vivax malaria in Thailand.
Am J Trop Med Hyg. 1999 Dec;61(6):973-7.
To define the current efficacy of Fansidar (F. Hoffmann-La Roche Ltd., Basel Switzerland) (pyrimethamine and sulfadoxine), primaquine in a high dose, and artesunate for treating acute Plasmodium vivax malaria, we conducted a comparative clinical trial of these 3 drugs in an open-label study. Patients (15-65 years old) were assigned to 1 of 4 treatments regimens in a serial order. Ninety percent of the patients were infected at Thailand-Myanmar border. Patients in group I (n = 23) received Fansidar (3 tablets, 75 mg of pyrimethamine and 1,500 mg of sulfadoxine, a single dose on the first day), group II (n = 23) received Fansidar (3 tablets, 75 mg of pyrimethamine and 1,500 mg of sulfadoxine, a single dose on the first day) and then received primaquine (30 mg a day for 14 days), group III (n = 23) received primaquine (30 mg a day for 14 days), and group IV (n = 23) received artesunate (200 mg once a day for 3 days) and then primaquine (30 mg a day for 14 days). Cure rates on day 28 of follow-up were 40%, 100%, 100%, and 100% in groups I, II, II, and IV, respectively. There were 4 and 5 patients in group I showing post-treatment reappearance of parasitemia at < or = 16 days and between 17 and 28 days, respectively. Patients in the other 3 groups showed negative parasitemias within 7 days after treatment. Artesunate plus primaquine (group IV) cleared parasitemia faster than the other 3 regimens. There is a high proportion of ineffectiveness of Fansidar for treatment of P. vivax malaria and it should be no longer used for treatment of P. vivax malaria acquired at the Thailand-Myanmar border. A high dose of primaquine is safe and effective in the treatment of P. vivax malaria during the 28-day follow-up period.

9625947
Wilairatana P, Viriyavejakul P, Looareesuwan S, Chongsuphajaisiddhi T
Artesunate suppositories: an effective treatment for severe falciparum malaria in rural areas.
Ann Trop Med Parasitol. 1997 Oct;91(7):891-6.
Artesunate is a potent antimalarial agent available in oral, parenteral and rectal formulations. Artesunate suppositories rapidly reduce and quickly clear parasitaemias. The rapidity of effect, availability and convenient dosage regimen make artesunate in suppository form a promising treatment for severe falciparum malaria, particularly in rural areas where parenteral formulations are unavailable.

15485708
Willcox M, Rasoanaivo P, Sharma VP, Bodeker G
Comment on: Randomized controlled trial of a traditional preparation of Artemisia annua L. (Annual Wormwood) in the treatment of malaria.
Trans R Soc Trop Med Hyg. 2004 Dec;98(12):755-6.

16448598
Wilson ME
Parenteral artesunate for treatment of severe malaria.

Curr Infect Dis Rep. 2006 Jan;8(1):33-4.

1486675
Win K, Than M, Thwe Y
Comparison of combinations of parenteral artemisinin derivatives plus oral mefloquine with intravenous quinine plus oral tetracycline for treating cerebral malaria.
Bull World Health Organ. 1992;70(6):777-82.
A total of 141 cases of strictly defined cerebral malaria were studied in a controlled trial of three regimens: (1) intramuscular artemether plus oral mefloquine, (2) intravenous artesunate plus oral mefloquine, and (3) intravenous quinine (with or without an initial loading dose) plus oral tetracycline. The overall mortalities in each group were 14%, 8.3% and 34.3% respectively. The average parasite clearance time was 27.30 +/- 19.62 hours in regimen 1, 41.84 +/- 17.55 hours in regimen 2, and 47.30 +/- 21.95 hours in regimen 3. No recrudescence was observed in regimens 1 and 2, but 12.1% recrudesced in the third.

10774645
Win LL, Shwe T, Lwin M, Aung S, Zaw AK, Mar KK
Acceptance of short course artesunate plus mefloquine drug combination by malaria patients in rural Myanmar.
Southeast Asian J Trop Med Public Health. 1999 Sep;30(3):418-20.
A cross sectional study was carried out in a rural area of Myanmar to identify malaria patients' acceptance of artesunate plus mefloquine drug combination and to determine the cost borne by patients. The majority (88.5%) preferred this new regimen rather than the other ones they had used before; conviction of drug efficacy was the reason given for the preference by most of them. Traveling on foot to rural health centers or a health assistant's residence for getting the drugs was found to be the main route. Average cost incurred by a patient to get the drug was found to be 274.22 Kyats. Among the cost items, drug cost was the highest item that they had used.

11703851
Winstanley P
Chlorproguanil-dapsone (LAPDAP) for uncomplicated falciparum malaria.
Trop Med Int Health. 2001 Nov;6(11):952-4.
The synergistic antifolate combination of chlorproguanil with dapsone (CPG-DDS; LAPDAP) is being developed by a public-private partnership as a low-cost treatment for uncomplicated falciparum malaria. LAPDAP is rapidly eliminated from the body, giving it low selection pressure for drug resistance. Clinical cases with sulphadoxine-pyrimethamine (SP)-resistant infections acquired in Africa have been predicted to be responsive to LAPDAP, and clinical evidence is available to support this. A regulatory dossier is being prepared for simultaneous submission to the UK Medicines Control Agency and African licencing authorities. The team working on LAPDAP has also started to develop the triple combination of chlorproguanil-dapsone-artesunate (CDA) as a low-cost combination therapy for uncomplicated falciparum malaria. Although LAPDAP does not have regulatory approval (and development of CDA is at an early stage), the development team is keen to communicate with public health scientists to try to anticipate the policy and implementation hurdles that lie ahead. This short paper outlines the current stages that LAPDAP and CDA have reached, and sketches the anticipated public health issues.

15989612
Winstanley P
New prospects for the treatment of malaria.
Expert Opin Investig Drugs. 1997 Apr;6(4):447-51.
This update focuses on drugs for both uncomplicated and severe falciparum malaria. Chloroquine, long the mainstay of therapy, is no longer reliable because of widespread resistance, but is still attractive because of its very low cost. The following strategies for the future use of 4-aminoquinolines in uncomplicated malaria are discussed: the use of other existing 4-aminoquinolines such as amodiaquine, drug-induced reversal of chloroquine resistance, and the development of new 4-aminoquinolines with activity against resistant isolates. Pyrim- ethamine-sulfadoxine is now the drug of first-choice in much of Africa, but resistance to this antifolate combination is expected to become clinically apparent within the next five years. Research into the utility of novel antifolate combinations is described. Mefloquine and halofantrine are drugs which are extensively used in Southeast Asia, but are too expensive for general use in most African countries. The possible roles for artemisinine derivatives (alone and in combination with either mefloquine or benflumitol), pyronaridine and atovaquone-proguanil are described. The absolute importance of drug cost as a determinant of its utility in poorer countries is emphasised.

15991958
Winstanley P, Olliaro P
Clinical trials of chemotherapy for falciparum malaria.
Expert Opin Investig Drugs. 1998 Feb;7(2):261-71.
Plasmodium falciparum remains one of the World's most prevalent and devastating pathogens. Mainly for economic reasons, the parasite's ability to develop resistance to drugs has not been matched by the rate at which new compounds are developed. Even so, there are new drugs (or new combinations of old drugs) currently under investigation, or in the process of development (at the moment): Pyronaridine, a well-tolerated, synthetic drug that may have utility for multi-resistant falciparum malaria in many parts of the world; however,problems remain over the formulation of this drug (which is a major determinant of its bioavailability) and its eventual cost. Chlorproguanil-dapsone (lap dap) is being studied as a possible low-cost'successor' to pyrimethamine-sulfadoxine; the utility of chlorproguanil-dapsone as 'salvage' therapy for clinical cases of pyrimethamine-sulfadoxine failure has yet to be tested in clinical trials. Atovaquone-proguanil (malarone) has utility against multi-resistant parasites; however, it is likely to be expensive (but is currently being provided free-of-charge in certain areas of Africa). Artemether-benflumetol (coartemether) combines the advantages of artemether (a rapid reduction in parasite load) with a second drug that reduces the risk of recrudescence; the cost of this combination is unclear. Rectal artesunate is being studied as an intervention to reduce the proportion of children with falciparum malaria who deteriorate to severe disease; the formulation is appropriate for use in rural health centres.

11880047
Winstanley PA, Ward SA, Snow RW
Clinical status and implications of antimalarial drug resistance.
Microbes Infect. 2002 Feb;4(2):157-64.
Africa carries the greatest burden of disease caused by Plasmodium falciparum, and we can expect this burden to rise in the near future, mainly because of drug resistance. Although effective drugs are available (such as artemether-lumefantrine, mefloquine, atovaquone-proguanil and halofantrine) they are uniformly too expensive for routine use. Affordable options include chloroquine plus sulfadoxine-pyrimethamine (SP), amodiaquine (alone or in combination with SP) and chlorproguanil-dapsone. Artemisinin combination therapy may offer considerable advantages over alternative therapies, but its introduction faces considerable logistic difficulty.

16302041
Wiseman V, Onwujekwe O, Matovu F, Mutabingwa TK, Whitty CJ
Differences in willingness to pay for artemisinin-based combinations or monotherapy: experiences from the United Republic of Tanzania.
Bull World Health Organ. 2005 Nov;83(11):845-52. Epub 2005 Nov 10.
OBJECTIVE: The cost of combination treatment is thought to be one of the greatest barriers to their deployment, but this has not been tested directly. Estimates of willingness to pay were compared across four drug combinations used to treat Tanzanian children with uncomplicated malaria. The reasons behind respondents' valuations and the effect of socioeconomic status on willingness to pay were explored. METHODS: One hundred and eighty mothers whose children had been recruited into a recently completed randomized effectiveness trial of amodiaquine + artesunate (AQ+AS), amodiaquine + sulfadoxine-pyrimethamine (AQ+SP), artemether-lumefantrine (coartemether) and amodiaquine monotherapy (AQ) were interviewed about their willingness to pay for these drugs two weeks after treatment. Estimates of willingness to pay were elicited with the bidding game technique. FINDINGS: A significant difference was detected in the mean amounts respondents were willing to pay, with those who received AQ+AS willing to pay the most, followed by co-artemether, AQ+SP and finally AQ. The amounts patients' mothers were willing to pay for the artemisinin-based combinations, however, fell well short of the market costs. Socioeconomic status was not found to have a statistically significant effect on mean willingness to pay scores for any treatment group. CONCLUSION: This study shows that families who live in an area in which drug resistance to monotherapy is very high are willing to pay more for more effective artemisinin-based combination therapies. These amounts, however, are nowhere near the real costs of delivering the new drugs. Only with subsidies will artemisinin-based combination therapies realistically have any impact.

16386306
Wiwanitkit V
Quantum chemical analysis of alternative pathways for iron activation step for artemisinin, a new antimalarial drug.
J Infect. 2005 Dec 27;.
Malaria is a mosquito-borne parasitic infection. It can be said that malaria is a very important tropical mosquito-borne infectious disease. The selection of antimalarial drugs depends on the species and the reported resistance pattern in each setting. Artemisinins are a new group of antimalarial drugs against the

drug-resistant strains of malarial parasites. The mechanism of action of artemisinin compounds consists of two important steps: (a) activation and (b) alkylation. In the activation step by iron, there are two possible pathways for developing C-4 free radical: (a) 1.5 H-shift and (b) C-C cleavage. Here, the author performs a quantum chemical analysis of the activation reaction of artemisinin by the two alternative pathways. According to this study, the required energy for compound formation in C-C cleavage is more than that for C-O cleavage. It can be noted that the C-C cleavage pathway is less preferable, implying that the 1.5 H-shift should be the more common phenomenon.

7951130
Woerdenbag HJ, Pras N, van Uden W, Wallaart TE, Beekman AC, Lugt CB
Progress in the research of artemisinin-related antimalarials: an update.
Pharm World Sci. 1994 Aug 5;16(4):169-80.
Artemisinin, a sesquiterpene lactone endoperoxide isolated from Artemisia annua L., and a number of its semisynthetic derivatives have shown to possess antimalarial properties. They are all effective against Plasmodium parasites that are resistant to the newest and commonly used antimalarial drugs. This article gives a survey of the literature dealing with artemisinin-related antimalarial issues that have appeared from the end of 1989 up to the beginning of 1994. A broad range of medical and pharmaceutical disciplines is covered, including phytochemical aspects like the selection of high-producing plants, analytical procedures, and plant biotechnology. Furthermore, the organic synthesis of artemisinin derivatives is discussed, as well as their mechanism of action and antimalarial activity, metabolism and pharmacokinetics, clinical studies, side-effects and toxicology, and biological activities other than antimalarial activity.

15683041
Woitsch B, Wernsdorfer G, Prajakwong S, Rojanawatsirivet C, Kollaritsch H, Wernsdorfer WH
Comparative study of the in vitro sensitivity of Plasmodium falciparum to artemisinin in two border areas of Thailand.
Wien Klin Wochenschr. 2004;116 Suppl 4:35-40.
Artesunate was introduced in Thailand in 1995 for the treatment of falciparum malaria in areas of multidrug resistance, where it is used in combination with mefloquine. The studies were conducted between May and August 1999, 2000 and 2001 in the provinces Mae Hong Son and Tak (Mae Sot District) in northwestern Thailand, both on the border to Myanmar. The province of Mae Hong Son is still largely unaffected by multidrug resistance and infections with Plasmodium falciparum are treated with mefloquine alone. In the district of Mae Sot, 350 km southwards, more than 60% of the Plasmodium falciparum isolates were found to be resistant to mefloquine. Between 1999 and 2001, a total of 227 fresh isolates of Plasmodium falciparum were successfully tested for their sensitivity to artemisinin using the WHO standard in vitro microtest. The weighted mean EC5o and EC90 values for 1999-2001 were 9.20 nM and 34.37 nM in Mae Hong Son and 11.18nM and 71.63nM in Mae Sot, respectively. The comparison of the sensitivity to artemisinin between Mae Hong Son and Mae Sot showed no significant difference in 1999, but significant differences in 2000 (p

12631411
Wong JW, Yuen KH, Nagappan S, Shahul WS, Ho SS, Gan EK, Toh WT
Therapeutic equivalence of a low dose artemisinin formulation in falciparum malaria patients.
J Pharm Pharmacol. 2003 Feb;55(2):193-8.
We have evaluated the therapeutic equivalence of a beta-cyclodextrin-artemisinin complex at an artemisinin dose of 150 mg, with a commercial reference preparation, Artemisinin 250 at a recommended dose of 250 mg. One hundred uncomplicated falciparum malarial patients were randomly assigned to orally receive either beta-cyclodextrin-artemisinin complex (containing 150 mg artemisinin) twice daily for five days or the active comparator (containing 250 mg artemisinin) twice daily for five days. The patients were hospitalized for seven days and were required to attend follow up assessments on days 14, 21, 28 and 35. All patients in both treatment groups were cured of the infection and achieved therapeutic success. At day seven of treatment, all patient blood was clear of the parasites and the sublingual temperature of all patients was less than 37.5 degrees C. Moreover, the parasite clearance time in both treatment groups was similar, being approximately three days after initiation of treatment. Comparable plasma artemisinin concentrations were observed between patients in both treatment groups at 1.5 and 3.0 h, although slightly higher levels were obtained with patients in the beta-cyclodextrin-artemisinin complex-treated group. The beta-cyclodextrin-artemisinin complex at a dose of 150 mg artemisinin was therapeutically equivalent to 250 mg Artemisinin 250. Additionally, patients receiving beta-cyclodextrin-artemisinin complex showed less variability in their plasma artemisinin concentrations at 1.5 h post-dosing, which suggested a more consistent rate of drug absorption.

11937421
Wongsrichanalai C, Pickard AL, Wernsdorfer WH, Meshnick SR
Epidemiology of drug-resistant malaria.

Lancet Infect Dis. 2002 Apr;2(4):209-18.
Since the first reports of chloroquine-resistant falciparum malaria in southeast Asia and South America almost half a century ago, drug-resistant malaria has posed a major problem in malaria control. By the late 1980s, resistance to sulfadoxine-pyrimethamine and to mefloquine was also prevalent on the Thai-Cambodian and Thai-Myanmar (Thai-Burmese) borders, rendering them established multidrug-resistant (MDR) areas. Chloroquine resistance spread across Africa during the 1980s, and severe resistance is especially found in east Africa. As a result, more than ten African countries have switched their first-line drug to sulfadoxine-pyrimethamine. Of great concern is the fact that the efficacy of this drug in Africa is progressively deteriorating, especially in foci in east Africa, which are classified as emerging MDR areas. Urgent efforts are needed to lengthen the lifespan of sulfadoxine-pyrimethamine and to identify effective, affordable, alternative antimalarial regimens. Molecular markers for antimalarial resistance have been identified, including pfcrt polymorphisms associated with chloroquine resistance and dhfr and dhps polymorphisms associated with sulfadoxine-pyrimethamine resistance. Polymorphisms in pfmdr1 may also be associated with resistance to chloroquine, mefloquine, quinine, and artemisinin. Use of such genetic information for the early detection of resistance foci and future monitoring of drug-resistant malaria is a potentially useful epidemiological tool, in conjunction with the conventional in-vivo and in-vitro drug-sensitivity assessments. This review describes the various features of drug resistance in Plasmodium falciparum, including its determinants, current status in diverse geographical areas, molecular markers, and their implications.

15691128
Wongsrichanalai C, Prajakwong S, Meshnick SR, Shanks GD, Thimasarn K
Mefloquine--its 20 years in the Thai Malaria Control Program.
Southeast Asian J Trop Med Public Health. 2004 Jun;35(2):300-8.
Due to the deteriorating efficacy of sulfadoxine-pyrimethamine (SP or Fansidar), from the mid-1970s the Thai Malaria Control Program was actively involved in testing potential replacement drugs to be used as the primary therapy for falciparum malaria in Thailand. In 1983, a large-scale field trial of mefloquine, a long-acting antimalarial drug known for its efficacy against chloroquine- and SP-resistant Plasmodium falciparum, was initiated on the Thai-Cambodian border. The study enrolled over 60,000 patients and eventually led to the formal establishment of mefloquine as the first line drug for the treatment of uncomplicated falciparum malaria in the country. Mefloquine has played a significant role in the control of malaria in Thailand for the past two decades, initially in combination with SP, then by itself, and currently in selected areas as a partner drug in the combination therapy with artesunate. Thailand is the country with the most experience in the use of this drug in a malaria control program. We present here a review of mefloquine's pharmacology and usage in Thailand.

11485094
Wongsrichanalai C, Sirichaisinthop J, Karwacki JJ, Congpuong K, Miller RS, Pang L, Thimasarn K
Drug resistant malaria on the Thai-Myanmar and Thai-Cambodian borders.
Southeast Asian J Trop Med Public Health. 2001 Mar;32(1):41-9.
We describe the changing epidemiology of drug resistant malaria in Thailand over the past decade. Factors determining the characteristic patterns of the development and spread of resistance to anti-malarial drugs on the Thai-Cambodian border and the Thai-Myanmar border are explored, namely, population dynamics, drug usage and malaria control measures. The introduction of artesunate-mefloquine combination in selected areas along the two borders in 1995 is believed to be one of the multiple factors responsible for stabilizing the multidrug resistance problems in Thailand today. Other control measures and inter-governmental co-operation must continue to be strengthened in order to limit the spread of drug resistance malaria in the Southeast Asian region.

10881909
Wongsrichanalai C, Thimasarn K, Sirichaisinthop J
Antimalarial drug combination policy: a caveat.
Lancet. 2000 Jun 24;355(9222):2245-7.
This paper presents facts on malaria epidemiology and historical perspectives of antimalarial drug use in Thailand. It also suggests that the use of an artesunate-mefloquine combination for treating falciparum malaria may be one of the factors responsible for the success of the country's control strategies. It is noted that in Thailand Plasmodium falciparum has evolved resistance to chloroquine, sulfadoxine-pyrimethamine, and mefloquine in succession. In view of this, administration of oral artesunate plus mefloquine became the standard treatment for microscopically confirmed uncomplicated falciparum malaria in 1995. The regimen requires administration of 300 mg/day of artesunate for 2 days plus 750 mg mefloquine on the first day, followed by 500 mg on the second day. Overall, it is too early to assume that the addition of artesunate has halted the progression of mefloquine resistance in Thailand. In terms of applicability of the regimen worldwide, the complexity of the factors involved makes it impossible to predict the useful lifespan of the

artesunate-mefloquine combination on the Thai-Myanmar border. Further research is needed into the determination and validation of the most suitable antimalarial regimens for each epidemiologically distinct area and each operationally different circumstance.

10361756
Wongsrichanalai C, Wimonwattrawatee T, Sookto P, Laoboonchai A, Heppner DG, Kyle DE, Wernsdorfer WH
In vitro sensitivity of Plasmodium falciparum to artesunate in Thailand.
Bull World Health Organ. 1999;77(5):392-8.
Reported are the in vitro susceptibilities of Plasmodium falciparum to artesunate, mefloquine, quinine and chloroquine of 86 isolates and to dihydroartemisinin of 45 isolates collected from areas of high resistance to mefloquine within Thailand near the borders with Myanmar and Cambodia, and from southern Thailand where P. falciparum is generally still sensitive to mefloquine. All the isolates were highly sensitive to artesunate, but the geometric mean IC50S were higher in isolates from the Thai-Myanmar and Thai-Cambodian borders than in those from southern Thailand. The IC50S for mefloquine and artesunate were strongly correlated (Pearson r = 0.605; n = 86; P < 0.00001). As expected, the in vitro sensitivities to dihydroartemisinin and artesunate were similar and strongly correlated (at IC50, Pearson r = 0.695; n = 45; P < 0.00002). The correlation between the activity of mefloquine and artesunate requires further investigation in order to determine the potential for development of cross-resistance in nature. Our results suggest that combination with mefloquine is not the ideal way of protecting the usefulness of artemisinin and its derivatives. A search for more suitable partner drugs to these compounds and careful regulation of their use are necessary in the interest of ensuring their long therapeutic life span.

15701735
Woodrow CJ, Haynes RK, Krishna S
Artemisinins.
Postgrad Med J. 2005 Feb;81(952):71-8.
Artemisinins were discovered to be highly effective antimalarial drugs shortly after the isolation of the parent artemisinin in 1971 in China. These compounds combine potent, rapid antimalarial activity with a wide therapeutic index and an absence of clinically important resistance. Artemisinin containing regimens meet the urgent need to find effective treatments for multidrug resistant malaria and have recently been advocated for widespread deployment. Comparative trials of artesunate and quinine for severe malaria are in progress to see if the persistently high mortality of this condition can be reduced.

16413871
Woodrow CJ, Planche T, Krishna S
Artesunate versus quinine for severe falciparum malaria.
Lancet. 2006 Jan 14;367(9505):110-1; author reply 111-2.

16023812
Wright CW
Traditional antimalarials and the development of novel antimalarial drugs.
J Ethnopharmacol. 2005 Aug 22;100(1-2):67-71.
Malaria continues to be a major cause of mortality and morbidity especially throughout the developing world. In the last 25 years or so a number of significant advances have been made that have the potential to make a major contribution to the control of this disease. The discovery of artemisinin and its analogues as potent antimalarial agents have been of immense importance and the latter, as well as some other selected developments are outlined in this brief review.

12020162
Wu Y
How might qinghaosu (artemisinin) and related compounds kill the intraerythrocytic malaria parasite? A chemist's view.
Acc Chem Res. 2002 May;35(5):255-9.
The antimalarial mechanism of qinghaosu (artemisinin) has been a problem since the late 1970s. During the past decade, several molecular level theories were postulated. However, their further development has been very difficult. By looking into the QHS cleavage process and all possible reaction paths available to the resulting transient radicals, the present commentary reveals those major hidden problems with the existing theories and tries to identify some essential features of the parasiticidal events that may take place within the intraerythrocytic malaria parasite. A seemingly more reasonable theory is also introduced.

14677058
Xiao SH, Yao JM, Utzinger J, Cai Y, Chollet J, Tanner M
Selection and reversal of Plasmodium berghei resistance in the mouse model following repeated high doses of artemether.
Parasitol Res. 2004 Feb;92(3):215-9. Epub 2003 Dec 16.
Artemether, a derivative of artemisinin, is effectively used for the treatment of malaria without any clinically relevant resistance to date. Artemether has also been developed as an antischistosomal agent, exhibiting highest activity against immature parasites. Here, we employ a rodent model and investigate whether the proposed artemether treatment schedule to prevent schistosome-attributable morbidity might select for Plasmodium berghei resistance. Mice infected with an ANKA strain of P. berghei were treated with artemether at either 47 mg/kg or 300 mg/kg. Once every 7-10 days, parasitized erythrocytes were passed to the next group of mice, receiving the same doses of artemether, for 50 passages. Resistance development was slow but increased considerably over the final ten passages. At the higher dose of artemether, the indices of resistance were 4.8 and 8.8 after 40 and 50 passages, respectively. Importantly, resistance was unstable, since sensitivity reverted to near-normal after five passages without drug pressure. A moderate index of P. berghei resistance and no apparent reversibility was found in comparative experiments employing pyronaridine. In conclusion, the pace of resistance development in P. berghei to repeated high doses of artemether is slow and reversible.

16126619
Xie LH, Johnson TO, Weina PJ, Si Y, Haeberle A, Upadhyay R, Wong E, Li Q
Risk assessment and therapeutic indices of artesunate and artelinate in Plasmodium berghei-infected and uninfected rats.
Int J Toxicol. 2005 Jul-Aug;24(4):251-64.
Artesunate (AS) is being developed as a potential agent for the treatment of severe and complicated malaria. A risk assessment of the therapeutic index and related hematological changes of AS and artelinate (AL) following daily intravenous injection for 3 days was conducted in Plasmodium berghei-infected and uninfected rats. The minimum doses of AS and AL for parasitemia suppression were 2.3 and 2.5 mg/kg, respectively, and the suppressive doses for half parasitemia (SD50) were 7.4 and 8.6 mg/kg, respectively. The maximum tolerated dose (MTD) for AS was 240 mg/kg with a therapeutic index of 32.6. The MTD for AL was 80 mg/kg with a therapeutic index of 9.3. Hematological changes were studied on days 1 and 8 after the final dosing. In both AS- and AL-treated rats, dose-dependent and rapidly reversible hematological changes (significant reductions in RBC, HCT, Hb, and reticulocyte levels) were seen in the peripheral blood. Bone marrow evaluation revealed a statistically significant reduction in the myeloid/erythroid ratio only at the highest dose of AS (240 mg/kg), albeit still within the normal ratio range (1.0-1.5:1.0). Looking at the respective therapeutic indices the authors have concluded that AS is much safer than AL. Both drugs induced hematological changes in rats that parallel the dose-dependent, reversible anemia and reticulocytopenia previously reported in animals and humans. However, no significant bone marrow depression was seen for either agent.

10374314
Xu C, Ding Y, Qi Z
[Efficacy of dihydroartemisinin in treatment of 37 malaria cases]
Zhonghua Nei Ke Za Zhi. 1997 Mar;36(3):187-9.
Dihydroartemisinin is an efficacious derivative of artemisinin which can be taken orally in treatment of malaria with less side reactions. Thirty-seven cases with malaria were treated with this drug in Beijing and in Ruili City, Yunnan Province. Out of them, 25 cases suffered from falciparum malaria with an average parasitemia of 73,218/microliter and 12 from vivax malaria with an average parasitemia of 4,950/microliter. The dosage was 60 mg daily or 2 mg/kg for paediatric patients for 7 successive days with the first dose doubled. All the patients were clinically cured after treatment. Fever subsided 22-72 hours after the beginning of treatment in falciparum malaria patients with an average fever clearance time of 36.24 +/- 15.30 hours and their parasite clearance time was 24-72 hours with an average parasite clearance time of 44.80 +/- 19.09 hours. One of them had recrudescence 19 days after the disappearance of parasites, hence the recrudescence rate of falciparum malaria was 4.8%. Five early cerebral cases in this series were completely cured after the treatment. All the 12 cases with vivax malaria were also clinically cured after treatment, but 1 case had relapse 35 days after treatment. This patient was completely cured with another course of dihydroartemisinin combined with primaquine. All patients tolerated well the oral administration of dihydroartemisinin and no significant side reactions were seen.

9863230
Xu JH, Zhang YP
[Contragestational effects of dihydroartemisinin and artesunate]
Yao Xue Xue Bao. 1996;31(9):657-61.

In experiments carried out in mice, hamsters, guinea pigs and rabbits both dihydroartemisinin and artesunate showed contragestational effect. In mice and rabbits they caused embryo absorption whereas in hamsters and guinea pigs they induced abortion. The contragestational ED50 of dihydroartemisinin given sc on d 7 of pregnancy in mice and d 5 of pregnancy in hamsters were 32.8(27.7-38.9) mg.kg-1 and 6.1(5.6-6.7) mg.kg-1 respectively. The ED50 of this drug given im on d 18 of pregnancy in guinea pigs was 18.3(13.9-24.2) mg.kg-1. Dihydroartemisinin also showed mid-pregnancy terminating effect in hamsters. The contragestational ED50 of artesunate given sc on d 5 of pregnancy in hamsters and the ED50 of sodium artesunate given sc on d 5-8 of pregnancy in hamsters were 12.2(10.3-14.4) mg.kg-1 and 1.0(0.9-1.2) mg.kg-1 daily respectively. Results of light microscopic examination revealed that dihydroartemisinin was selectively toxic to embryo sac. At dose levels sufficient to induce embryo sac necrosis, dihydroartemisinin did not injure the uterus and ovary of the maternal animals. On the ground of the foregoing observations we consider that dihydroartemisinin, artesunate and their analogous drugs should not be used to treat malaria in pregnant women and there is the possibility to exploit intentional abortion agents from artemisinin derivatives.

3073264
Xuan WY, Zhao Y, Li AY, Xie PS, Cai Y
Experimental studies on the antimalarial activity estimation by artesunate and artemether preparations per skin absorption.
J Tradit Chin Med. 1988 Dec;8(4):282-4.

2239338
Xuan WY, Zhao Y, Li AY, Xie PS, Liu X
[Effect of artesunate transdermal preparation on Plasmodium cynomolgi]
Yao Xue Xue Bao. 1990;25(3):220-2.
Artensunate transdermal preparation at 5, 10, or 15 mg/kg, bid, for 3 days applied locally on the shaved skin of the back of monkeys showed reliable therapeutic effects on Plasmodium cynomolgi, but recrudescence of the parasites was not controlled. If some azone was added in the artesunate transdermal preparation at the dosage of 5 mg/kg, bid, for 3 days, the parasitemia of Plasmodium cynomolgi could be cleared and recrudescence prevented, thus, the antimalarial effects was enhanced.

16288569
Yamey G
Treating Plasmodium falciparum Malaria with Artemisinin Derivatives.
PLoS Med. 2005 Nov;2(11):e414. Epub 2005 Nov 29.

14584382
Yang H, Liu D, Yang Y, Fan B, Yang P, Li X, Li C, Dong Y, Yang C
Changes in susceptibility of Plasmodium falciparum to artesunate in vitro in Yunnan Province, China.
Trans R Soc Trop Med Hyg. 2003 Mar-Apr;97(2):226-8.
We investigated changes in the susceptibility of Plasmodium falciparum to artesunate in vitro using Rieckmann's microtest in Yunnan Province, China, during the period 1988 to 1999. Longitudinal surveillance studies in 1988, 1992 and 1999 revealed that the IC50s were 6.2, 7.2 and 20.7 nmol/L, respectively and mean concentrations completely inhibiting schizont formation (CIMC) were 37.8, 46.1 and 74.0 nmol/L, respectively. The IC50 and CIMC in 1999 were 3.3 and 2 times greater than in 1988. In cross-sectional tests from 1991 to 1993, the susceptibility of P. falciparum isolates from areas in the western and the southern parts of Yunnan Province were similar, but lower than in the south-eastern and central parts of the province. The results suggest that P. falciparum is generally susceptible to artemisinin derivatives but indicate a reduction in susceptibility during the study period in areas where the drugs have been used for a long time.

9561592
Yang HL, Liu DQ, Yang YM, Huang KG, Dong Y, Yang PF, Liao MZ, Zhang CY
In vitro sensitivity of Plasmodium falciparum to eight antimalarials in China-Myanmar and China-Lao PDR border areas.
Southeast Asian J Trop Med Public Health. 1997 Sep;28(3):460-4.
In 1991-1995 by using the Rieckmann in vitro micro-method, susceptibilities of Plasmodium falciparum to eight antimalarials in the China-Lao PDR and China-Myanmar border areas were tested. The resistant rates of P. falciparum to chloroquinine were 95.0%-100%; IC50 114-240nmol/l. P. falciparum resistant rates to amodiaquine resistance accounted for 83.5%-100%, IC50 52-72nmol/l. All cases were sensitive to quinine, IC50 470-608nmol/l. P. falciparum isolates from the Lao PDR frontier were highly sensitive to artesunate,

dihydroartemisinin, and arteether. Resistant rates from other areas were 0-11%. P. falciparum from China-Myanmar and Lao PDR border areas were also sensitive to mefloquine, IC50 68-88nmol/l. A longitudinal survey of the sensitivity of P. falciparum in vivo on the China-Lao PDR border showed that the average defervescent time of falciparum malaria was treated by pyronaridine increased from 32.7 +/- 16.0 hours during 1984-85 to 56.2 +/- 27.4 hours in 1995; the recrudescence rate rose up from 15.2% to 37.5%. The results monitored in vitro showed that all cases assessed in 1988 for response to pyronaridine were sensitive, but 36.4% of cases had emerging resistance, IC50 increased from 13nmol/l to 40 nmol/l. The above results suggested that P. falciparum in these areas has expressed resistance to chloroquine and amodiaquine. However, the parasites are still sensitive to artemisinin, pyronaridine, mefloquine, quinine, but with a declining sensitivities.

6765851
Yang QC, Shi WZ, Li R, Gan J
The antimalarial and toxic effect of artesunate on animal models.
J Tradit Chin Med. 1982 Jun;2(2):99-103.

15456562
Yasir M, Mahmood A
Quinine based combination therapy (QCT): first choice!
J Coll Physicians Surg Pak. 2004 Oct;14(10):643.

11605194
Yasuoka C, Yasuoka A, Yamamoto Y, Genka I, Hatabu T, Kohno S, Oka S, Kano S
[A case of falciparum malaria successfully treated with intravenous artesunate]
Kansenshogaku Zasshi. 2001 Sep;75(9):822-5.
The case was a 47-year-old Nigerian male who was thought to have contracted malaria in Nigeria and then manifested fever with chill, arthralgia and diarrhea in Japan. The blood test at International Medical Center of Japan revealed thrombocytopenia and anemia. Ring forms of 0.03% of his RBCs and ICT Malaria P.f/P.v test was also positive for Plasmodium falciparum. We prescribed mefloquine to him, but the number of the paresites in his peripheral blood did not decrease, and, in fact, they came to increase (maximum 6.66%) 20 hours after the drug treatment. As clinical condition of malaria were liable to change seriously, intravenous Artesunate (a qinghaosu derivative) was decided to be given additionally to the patient. Consequently the parasites disappeared in 20 hours from his blood but a low grade fever still continued possibly because of cholecystitis. At the same time of Artesunate treatment, hemoglobinuria started and anemia worsened partly because of his G-6-PD deficiency. All pending problems were improved by the time he left Japan and those parasites were finally found to be susceptible for mefloquine by the in vitro susceptibility test. This is the first reported case of falciparum malaria successfully treated with intravenous Artesunate in Japan.

16033307
Yeka A, Banek K, Bakyaita N, Staedke SG, Kamya MR, Talisuna A, Kironde F, Nsobya SL, Kilian A, Slater M, Reingold A, Rosenthal PJ, Wabwire-Mangen F, Dorsey G
Artemisinin versus nonartemisinin combination therapy for uncomplicated malaria: randomized clinical trials from four sites in Uganda.
PLoS Med. 2005 Jul;2(7):e190. Epub 2005 Jul 26.
BACKGROUND: Drug resistance in Plasmodium falciparum poses a major threat to malaria control. Combination antimalarial therapy including artemisinins has been advocated recently to improve efficacy and limit the spread of resistance, but artemisinins are expensive and relatively untested in highly endemic areas. We compared artemisinin-based and other combination therapies in four districts in Uganda with varying transmission intensity. METHODS AND FINDINGS: We enrolled 2,160 patients aged 6 mo or greater with uncomplicated falciparum malaria. Patients were randomized to receive chloroquine (CQ) + sulfadoxine-pyrimethamine (SP); amodiaquine (AQ) + SP; or AQ + artesunate (AS). Primary endpoints were the 28-d risks of parasitological failure either unadjusted or adjusted by genotyping to distinguish recrudescence from new infections. A total of 2,081 patients completed follow-up, of which 1,749 (84%) were under the age of 5 y. The risk of recrudescence after treatment with CQ + SP was high, ranging from 22% to 46% at the four sites. This risk was significantly lower ($p < 0.01$) after AQ + SP or AQ + AS (7%-18% and 4%-12%, respectively). Compared to AQ + SP, AQ + AS was associated with a lower risk of recrudescence but a higher risk of new infection. The overall risk of repeat therapy due to any recurrent infection (recrudescence or new infection) was similar at two sites and significantly higher for AQ + AS at the two highest transmission sites (risk differences = 15% and 16%, $p < 0.003$). CONCLUSION: AQ + AS was the most efficacious regimen for preventing recrudescence, but this benefit was outweighed by an increased risk of new infection.

Considering all recurrent infections, the efficacy of AQ + SP was at least as efficacious at all sites and superior to AQ + AS at the highest transmission sites. The high endemicity of malaria in Africa may impact on the efficacy of artemisinin-based combination therapy. The registration number for this trial is ISRCTN67520427 (http://www.controlled-trials.com/isrctn/trial/|/0/67520427.html).

15331836
Yeung S, Pongtavornpinyo W, Hastings IM, Mills AJ, White NJ
Antimalarial drug resistance, artemisinin-based combination therapy, and the contribution of modeling to elucidating policy choices.
Am J Trop Med Hyg. 2004 Aug;71(2 Suppl):179-86.
Increasing resistance of Plasmodium falciparum malaria to antimalarial drugs is posing a major threat to the global effort to "Roll Back Malaria". Chloroquine and sulfadoxine-pyrimethamine (SP) are being rendered increasingly ineffective, resulting in increasing morbidity, mortality, and economic and social costs. One strategy advocated for delaying the development of resistance to the remaining armory of effective drugs is the wide-scale deployment of artemisinin-based combination therapy. However, the cost of these combinations are higher than most of the currently used monotherapies and alternative non-artemisinin-based combinations. In addition, uncertainty about the actual impact in real-life settings has made them a controversial choice for first-line treatment. The difficulties in measuring the burden of drug resistance and predicting the impact of strategies aimed at its reduction are outlined, and a mathematical model is introduced that is being designed to address these issues and to clarify policy options.

12448849
Yoshizawa S, Hike K, Kimura K, Matsumoto T, Furuya N, Tateda K, Kano S, Yamaguchi K
[A case of falciparum malaria successfully treated with intravenous artesunate]
Kansenshogaku Zasshi. 2002 Oct;76(10):888-92.
The case was a 28-year-old Japanese female who was considered to be infected with malaria in India. She manifested fever in Tokyo, Japan, and was brought to Toho University Hospital due to continuous high fever and severe thrombocytopenia. Ring forms at 11% of her RBCs and ICT Malaria P.f/P.v test was also positive for Plasmodium falciparum diagnosis. Not only the high parasitemia and delay of the diagnosis (6 days after the onset of fever), but also her DIC status required prompt and proper treatment. The diagnosis of severe malaria was strongly considered, and intravenous Artesunate (a qinghaosu derivative) was decided to be administered to the patient. After the four series of administration, mefloquine was subsequently given to prevent recrudescence. Parasite clearance time and fever clearance time were 24 hours and 108 hours, respectively. Thrombocytopenia was improved shortly after the treatment, but then anemia was once worsened with following gradual improvement. No other significant side effects were observed and no recrudescence occurred up to 8 months after her discharge. In Japan, very few cases treated with intravenous Artesunate were reported and our results showed its safe and excellent effect for a Japanese malaria patient.

2643631
Yuthavong Y, Butthep P, Bunyaratvej A, Fucharoen S
Decreased sensitivity of artesunate and chloroquine of Plasmodium falciparum infecting hemoglobin H and/or hemoglobin constant spring erythrocytes.
J Clin Invest. 1989 Feb;83(2):502-5.
Plasmodium falciparum infecting hemoglobin (Hb) H and/or Hb Constant Spring erythrocytes in vitro was relatively more resistant than that infecting normal erythrocytes to artesunate and chloroquine, while the sensitivity to pyrimethamine was unchanged. The 50% inhibitory concentrations (IC50) for artesunate in HbH (alpha-thal 1/alpha-thal 2), HbH (alpha-thal 1/Hb Constant Spring), and homozygous Hb Constant Spring erythrocytes were 4.5 +/- 2.8, 8.5 +/- 3.2, and 2.6 +/- 1.6 nM compared with 0.82 +/- 0.35 nM in normal erythrocytes (P less than 0.002 for all three cases). The IC50 for chloroquine were 97 +/- 46, 162 +/- 67, and 93 +/- 36 nM, respectively, in the variant erythrocytes, compared with 48 +/- 13 nM in normal erythrocytes (P less than 0.002, 0.002, and 0.02, respectively). The differences in sensitivity to artesunate and chloroquine of the parasite infecting HbH erythrocytes are probably related to their oxidative mode of action and relatively high amounts of antioxidant enzymes in the host erythrocytes. This novel example of dependence on the host of the malarial parasite drug sensitivity may have implications for chemotherapy of malaria in patients with genetically variant erythrocytes.

12185962
Zhang JT
New drugs derived from medicinal plants.
Therapie. 2002 Mar-Apr;57(2):137-50.
In China, increasing emphasis has been laid in recent years on research on natural products. About 140 new drugs have been developed from Chinese medicinal plants. For example, anisodamine possesses good

effects in the treatment of septic shock and morphine addiction; 3-n-butylphthalide isolated from seeds of celery was shown to be a new cerebral anti-ischemic agent; indirubin was identified as an anti-leukemic drug with no inhibition of bone marrow; huperzine is a potent and reversible inhibitor of acetylcholinesterase (AChE) and its selective action is superior to that of donepezil; clausenamide was shown to be a potassium channel blocker, its nootropic effect was 50-100 times more potent than that of piracetam; bicyclol was synthesized from schizandrin C isolated from Fructus schizandrae. It has remarkable hepatoprotective and certain anti-hepatitis virus actions; salvianolic acid B is a very strong antioxidant agent with potential anti-dementia effects; yingzhaosu A and artemisinin are anti-malaria drugs containing a peroxide ring which is very rarely seen in natural substances.

2239323
Zhao KC, Song ZY
[The pharmacokinetics of dihydroqinghasu given orally to rabbits and dogs]
Yao Xue Xue Bao. 1990;25(2):147-9.
Qinghaosu (QHS), also known as artemisinine and arteannuin, is isolated from the Chinese herb Artemisia annua L. It is highly active against both chloroquine-sensitive and chloroquine-resistant strains of P. berghei and has been approved by the Ministry of Health for the treatment of malaria. When QHS is treated with sodium borohydride, dihydroqinghaosu (DH QHS) is resulted with the antimalarial activity enhanced several fold. This paper reports the pharmacokinetics of DHQHS studied with the radioimmunoassay method. When the drug was given orally in tablet form to rabbits at doses of 10, 20 and 30 mg/kg, peak serum levels of 0.03, 0.05 and 0.13 micrograms/ml, respectively, were obtained in 1 to 2 h. The corresponding T1/2 of the drug were found to be 1.19, 1.00 and 1.10 h and the MRTs were 1.73, 1.36 and 1.53 h. No significant difference between dosages used was observed. When dogs were given DHQHS tablets at the dose of 20 mg/kg, a peak serum concentration of 0.13 micrograms/ml wes reached in about 2 h with a T1/2 of 2.10 h and an MRT of 3.04 h. However, when dogs were given QHS tablets at the dose of 70 mg/kg, no drug was detected in the serum. It would appear that the bioavailability of DHQHS tablets is much higher than that of QHS when given orally to the dog.

2618677
Zhao KC, Xuan WY, Zhao Y, Song ZY
[The pharmacokinetics of a transdermal preparation of artesunate in mice and rabbits]
Yao Xue Xue Bao. 1989;24(11):813-6.
Qinghaosu, also known as artemisinin and arteannuin, is a new type of antimalarial drug isolated from Artemisa annua L. Its low solubility in water and oil limited its widespread clinical use. Artesunate (sodium dihydroqinghaosu hydrogen hemisuccinate monoester) is easily soluble in water and is used iv in the treatment of acute cerebral and malignant malaria. However, artesunate was shown to have a very short half-life when given iv in animals as well as in human beings. A transdermal dosage form of artesunic acid had been prepared and was reported to have reliable suppressing and killing effects on plasmobium berghei in mice. This paper reports results of pharmacokinetic studies of this preparation when applied onto a fixed area of the shaved skin of mice and rabbits. Serum concentration of the drug was determined by a method of radioimmunoassay. The drug was found to be easily absorbed from the skin. The serum concentration-time curve is depicted in figures 1. Peak concentration of 1.8 micrograms/ml was reached at about 2 h when a dose of 25 mg/kg was given to rabbits. For mice, peak serum concentrations of 2.05 and 7.11 micrograms/ml were attained in about 0.5 h after doses of 31.3 and 71.4 mg/kg, respectively, while at a dose of 6.7 mg/kg a peak level of 0.82 micrograms/ml (a concentration more than 5000 times the IC50 of artesunate in in vitro tests on plasmodium berghei for antimalarial activity) was attained at about 4 h after application of the drug. The half-lives of the drug were found to be more than 2 h for both mice and rabbits.

3311413
Zhao Y, Hall IH, Oswald CB, Yokoi T, Lee KH
Antimalarial agents. III. Mechanism of action of artesunate against Plasmodium berghei infection.
Chem Pharm Bull (Tokyo). 1987 May;35(5):2052-61.

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Zhao Y, Li AY, Xie PS, Hou HM, Gu WG, Jia MH, Liu X, Lei TK
Experimental studies on the effect of artesunate sustained released tablet on Plasmodium cynomolgi.
J Tradit Chin Med. 1987 Dec;7(4):287-9.