CONSENSUS RECOMMENDATION ON THE TREATMENT OF MALARIA IN SOUTHEAST ASIA

S Looareesuwan[1], P Olliaro[2], NJ White[3], T Chongsuphajaisiddhi[1], A Sabcharoen[1], K Thimasarn[4], F Nosten[3], P Singhasivanon[1], S Supavej[1], S Khusmith[1], S Wylings[2], T Kanyok[2], D Walsh[5], PA Leggat[6], EB Doberstyn[7]

[1]Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; [2]WHO/TDR, World Health Organization, Geneva, Switzerland; [3]Welcome-Mahidol Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; [4]Malaria Division, Ministry of Public Health, Nonthaburi, Thailand; [5]Arm Force Research in Medical Sciences, Bangkok, Thailand; [6]James Cook University of North Queensland, Townsville, Australia; [7]WHO Representative to Thailand

INTRODUCTION

Southeast Asia harbors the most drug resistant malaria parasites in the world. Antimalarial treatment recommendations in recent years have had to undergo a series of changes to accommodate worsening resistance (Looareesuwan *et al,* 1992). The situation is particularly critical on the eastern and western borders of Thailand where *Plasmodium falciparum* has developed resistance to chloroquine, sulphadoxine-pyrimethamine, and now in recent years, mefloquine (Nosten *et al,* 1991). A closed meeting of regional and international experts was held on 27 August 1997 to review recent information on treatment responses, and provide evidence-based recommendations for treatment.

EPIDEMIOLOGY

There is considerable variation in antimalarial drug sensitivity in the Southeast Asia region, even over short geographical distances. Thus treatment recommendations must be based on precise, up-to-date local knowledge. In some areas within the region *Plasmodium falciparum,* surprisingly, still retains sensitivity to chloroquine, and in others sulpha-doxine-pyrimethamine sensitivity is retained by chloroquine resistant parasites. Both these drugs are inexpensive and relatively well tolerated. They should be used if there is unequivocal evidence of sensitivity. Unfortunately, in many parts of the region, resistance to both these compounds is prevalent, and quinine, mefloquine, or the artemisinin derivatives are used. In Papua New Guinea, where low grade chloroquine-resistant *P. falciparum* infections exists, amodiaquine has largely replaced chloroquine.

TREATMENT OF MULTIDRUG-RESISTANT FALCIPARUM MALARIA

In areas with mefloquine resistant parasites, the combination of an artemisinin derivative and mefloquine is the current treatment of choice (Looareesuwan *et al,* 1992a,b, 1993a,b, 1994a,b; Karbwang *et al,* 1992; Luxemburger *et al,* 1994; Price *et al,* 1997). Oral artesunate and artemether give equivalent results (Bunnag *et al,* 1991, 1996; Price *et al,* 1995; Karbwang *et al,* 1995) and should be given for at least 3 days (Looareesuwan *et al,* 1996) in a dose of 4 mg/kg/day. Despite their short half lives these drugs can be administered in a single daily dose (Bunnag *et al,* 1991; Nosten *et al,* 1974). The dose of mefloquine should be 25 mg/kg of base (ter Kuile *et al,* 1992), and should be split : the first dose should be 15 mg/kg, and the second 10 mg/kg after a delay of 8 to 24 hours. Mefloquine may be given on the second day of treatment in combination with the artemisinin derivatives or after completion of the artemisinin treatment (Looareesuwan *et al,* 1993b, 1996). This reduces the risk of vomiting (Fenol *et al,* 1995), which is more likely in an acutely ill patient. There is increasing evidence to support deployment of the combination of an artemisinin derivative with mefloquine de-novo, but no firm recommendations can yet be made. The combination ensures rapid treatment responses (Lumxemburger *et al,* 1995), is very well. It also reduces gametocyte carriage and therefore lowers transmission potential (Price *et al,* 1996). However, in the absence of mefloquine resistance, some authorities still prefer to use mefloquine alone (using doses of 15 mg of base/kg in semi-immune patients, and 25 mg/kg in non-immunes). Others prefer to use a single administration of a combination of an artemisinin derivative

(*ie* artesunate 4 mg/kg, artemether 4 mg/kg, or artemisinin 20 mg/kg) together with mefloquine (15mg/kg) (Hien *et al,* 1994). Single dose treatments allow directly observed therapy to be given and thus ensure compliance. Where mefloquine or quinine are used alone (or with a tetracycline), primaquine is often added in a single adult dose of 45 mg for its gametocytocidal activity. The impact of this practice on malaria incidence has not been evaluated. There is no advantage in adding primaquine to artemisinin-containing regimens for its gametocytocidal activity. In some areas artemisinin or its derivatives (artesunate, artemether) are used alone (or sometimes combined with tetracyclines in adults), but combinations with mefloquine are preferred. Ideally these drugs should be used alone only for recrudesent infections following mefloquine treatment.

Quinine containing regimens are a second choice, as at least 7 day's treatment is required with quinine, and compliance is poor. This is because "cinchonism" is common and often sufficiently severe to stop the patient taking their treatment. Thus a large proportion of infections receive inadequate doses of quinine, because patients fail to complete their prescribed course. Quinine should be given in a dose of 10 mg salt/kg of 3 times daily and should be combined with doxycycline (3 mg/kg once daily), or tetracycline (4 mg/kg 4 times daily) in adults (Looareesuwan *et al,* 1992; Karbwang *et al,* 1994a,b). Although the course of quinine may be shortened *eg* to 5 days combined with 7 days tetracycline, this gives inferior treatment responses to the full 7 day courses of both drugs.

CHILDREN AND PREGNANT WOMEN

With the exception of the tetracyclines, there is no reason to withhold any of the above drugs from children. Children are more likely to vomit antimalarial drugs than adults but otherwise tolerate antimalarial treatment well. Chloroquine, sulphadoxine-pyrimethamine, and quinine are considered safe throughout pregnancy (although there is a theoretical risk of kernicterus if sulphadoxine in used near term). There are less data for mefloquine, although most authorities also consider mefloquine to be safe in pregnancy. There is limited experience with the artemisinin derivatives, but there is no suggestion of adverse effect in pregnancy and these drugs should be used in mefloquine-resistant areas in the second and third trimester (Looareesuwan *et al,* 1985). Quinine is still considered the treatment of choice in the first trimester of pregnancy in multidrug resistant areas (Mcgready *et al,* 1998). Primaquine should not be used in pregnancy, or in breast feeding mothers. The other drugs are considered safe during lactation. In general there are still insufficient data on antimalarial drugs in pregnancy. The outcome of pregnancies which are exposed to antimalarial drugs should be documented, where possible, to provide information and more confident assessment of risk. Those antimalarial treatment regimens based on body weight are not changed in young children or in pregnancy.

TREATMENT FAILURES

In high transmission areas it is difficult to identify low grade resistance. In low transmission areas most recrudescences occur within 28 days of treatment, and infections which occur within this time are more likely to be a recrudescence than a newly acquired infection. With the slowly eliminated drugs, such as mefloquine, recrudescent infection may occur long after 28 days (Smithius *et al,* 1993), but as resistance worsens the time to recrudescence shortens. Recrudescences following chloroquine may respond to sulphadoxine-pyrimethamine treatment if the majority of parasites in the area are sensitive to this drug. Failures following sulphadoxine-pyrimethamine can be treated either with mefloquine or quinine. Recrudescences following mefloquine should be treated with 7 days of an artemisinin derivative (plus tetracycline or doxycycline in adults (Looareesuwan *et al,* 1994) or if these are not available, with the quinine-tetracycline combination. Mefloquine should not be readministered, as failure rates are three times higher, and adverse neurological reactions more likely.

NEW DRUGS

Halofantrine is more effective than mefloquine against multidrug resistant falciparum malaria (ter Kuile *et al,* 1993), but the high doses required produce an unacceptable risk of cardiotoxicity (Nosten *et al,* 1993; Nosten, 1995). There have been encouraging results in large clinical trials

with atovaquone-proguanil (Looareesuwan *et al,* 1996), and artemether-benflumetol (van Vugt *et al,* 1998). Both these new compounds are extremely well tolerated but further data on clinical use and resistance potential are required, before firm recommendations can be made.

TREATMENT OF VIVAX MALARIA

Apart from well defined foci of chloroquine resistance in northern Papua New Guinea, Irian Jaya, the Solomon Islands, and Sumatra (Murphy *et al,* 1993), the majority of infections elsewhere remain sensitive to chloroquine. Chloroquine is given in the standard total dose of 25 mg base/kg given over 3 days. Although lower doses are effective, there seems no reason to reduce the standard dose. The sensitivity of *Plasmodium vivax* to a radical curative treatment with primaquine varies considerably in the area. *P. vivax* is relatively resistant to primaquine in Indonesia and in Oceania 22.5 mg of base given daily for 14 days is still associated with a 20% further relapse rate. Further north, *P. vivax* appears more sensitive (Tanariya *et al,* 1995a,b) and many authorities still continue to recommend 15 mg of base/kg daily for 14 days in adults. Recent experience with higher doses of primaquine (adult dose 30 mg base/day) for long periods indicates that this dose is well tolerated provided that primaquine is not given on an empty stomach (Fryaulf *et al,* 1995; Baird *et al,* 1995). Primaquine should not be used in pregnancy or in patients with severe variants of G6PD deficiency. In mild variants of G6PD deficiency 45 mg of base should be given once weekly for six weeks. Chloroquine resistant *P. vivax* infections should be treated with mefloquine (25 mg base/kg). Clinical trials with the new 8-aminoquinolines, WR238605 (etaquine), and CDRI 80/53 (recently approved for use in India) are promising but there insufficient data at present on which to make recommendations.

SEVERE MALARIA

Although there has been a decline in the sensitivity of *Plasmodium falciparum* to quinine in the area over the past 20 years, there are still no unequivocal cases of high grade quinine resistance (Pukittayakamee *et al,* 1994; Looareesuwan *et al,* 1990). Quinine may therefore be relied upon in the treatment of severe malaria. A loading dose of 20 mg of the dihydrochloride salt/kg should be given initially followed by 10 mg/kg eight hourly until oral treatment can be safely administered (White *et al,* 1983). This regimen is safe and effective. The dose should be reduced by one third on the third day of treatment if there is no improvement in order to avoid accumulation of quinine, and possible toxicity.

Although quinine is widely available for purchase over the counter in this area, and therefore self-medication before admission to hospital is common, the initial dose of quinine should not be reduced unless there is clear evidence that the patient has received more than 30 mg/kg over the previous 48 hours (Hien *et al,* 1996). When in doubt, a loading dose should be given. Quinine should be given by slow intravenous infusion and initial infusion rates should not exceed 5 mg base/kg/hour. Intravenous quinine can be infused in saline or dextrose solutions. If this is not possible then intramuscular injection using scrupulous sterile technic (to the anterior thigh, not the buttock) is an acceptable alternative. Hypoglycemia is a serious adverse effect of quinine treatment occurring in approximately 8% of adults, 30% of children, and 50% of pregnant women receiving parenteral quinine for severe malaria (Looareesuwan *et al,* 1985; White *et al,* 1983). At least seven days treatment is required. Oral treatment should be substituted when the patient can take tablets reliably. The artemisinin derivatives artesunate and artemether are at least as good as quinine, and may be better. They also easier to administer and less toxic, although questions still remain over neurotoxicity. In all animals species tested to date, the oil formulated derivatives artemether and arteether have produced an unusual and selective pattern of damage to certain brain stem nuclei (Brewer *et al,* 1994a,b). There has been no evidence neurotoxicity in man. All the artemisinin derivatives have been remarkably well tolerated. Artesunate is given in initial dose of 2.4 mg/kg by intravenous or intramuscular injection, and artemether is given by intramuscular injection in a dose of 3.2 mg/kg initially following 1.6 mg/kg daily. There is evidence from Africa that intramuscular artemether may be absorbed erratically, particularly in severely ill patients (Murphy *et al,* 1997). More information on the pharmacokinetics of these drugs needed particularly in very severe malaria. These compounds are a simple and satis-

factory alternative to quinine. Extensive experience with artemisinin suppositories in Vietnam indicates rectal administration is a satisfactory alternative to parenteral treatment (Hien *et al,* 1991, 1992), and would be of particular benefit in rural areas. Artesunate suppositories have also proved highly effective in trials (Looareesuwan *et al,* 1995), however such suppositories are not widely available.

PROPHYLAXIS

In most of Southeast Asia antimalarial prophylaxis is not required as the risk of infection is low, particularly in urban areas. Personal protection, insect repellents, sleeping in side insecticide impregnated mosquito nets, and use of screens in houses should be emphasised. Chloroquine plus proguanil is effective in few areas, but mefloquine is effective in most of region. In areas with mefloquine resistant parasites, daily doxycycline is required. Antimalarial prophylaxis should start one or preferably two weeks before travel to assess adverse effects and should continue for 4 weeks after return from the transmission area. Standby treatment is alternative approach where risk is low or unpredictable, but there is insufficient information on the available drugs to make recommendations. Antimalarial prophylaxis should be given to pregnant women living in endemic areas provided a safe effective drug is available.

REFERENCES

Looareesuwan S, Charoenpan P, Ho M, *et al.* Fatal malaria after an inadequate response to quinine treatment. *J Infect Dis* 1990; 161: 577-80.

Looareesuwan S, Harinasuta T, Chongsuphajaisiddhi T. Drug resistant malaria with special reference to Thailand. *Southeast Asian J Trop Med Public Health* 1992; 23: 621-34.

Looareesuwan S, Kyle DE, Viravan C, *et al.* Treatment of patients with recrudescent falciparum malaria with a sequential combination of artesunate and mefloquine. *Am J Trop Med Hyg* 1992; 47: 794-9.

Looareesuwan S. Overview of clinical studies on artemisinin derivatives in Thailand. *Trans R Soc Trop Med Hyg* 1994; 88 (Suppl 1): 9-11.

Looareesuwan S, Phillips RE, White NJ, *et al.* Quinine and severe falciparum malaria in late pregnancy. *Lancet* 1985; 2: 4-8.

Looareesuwan S, Viravan C, Webster HK, Kyle DE, Hutchinson DB, Canfield CJ. Clinical studies of atovaquone, alone or in combination with other antimalarial drugs, for treatment of acute uncomplicated malaria in Thailand. *Am J Trop Med Hyg* 1996; 54: 62-6.

Looareesuwan S, Viravan C, Vanijanonta S, *et al.* A randomised trial of mefloquine, artesunate, and artesunate followed by mefloquine in acute uncomplicated falciparum malaria. *Lancet* 1992; 339: 821-4.

Looareesuwan S, Viravan C, Vanijanonta S, *et al.* Treatment of acute uncomplicated falciparum malaria with a short course of artesunate followed by mefloquine. *Southeast Asian J Trop Med Public Health* 1993; 24: 230-4.

Looareesuwan S, Vanijanonta S, Viravan C, Wilairatana P, Charoenlarp P, Andril M. Randomised trial of mefloquine alone and artesunate followed by mefloquine for the treatment of acute uncomplicated falciparum malaria. *Ann Trop Med Parasitol* 1994; 88: 131-6.

Looareesuwan S. Overview of clinical studies on artemisinin derivatives in Thailand. *Trans R Soc Trop Med Hyg* 1994; 88 (Suppl 1): 9-11.

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; 54: 210-3.

Looareesuwan S, Wilairatana P, Vanijanonta S, Kyle D, Webster K. Efficacy of quinine-tetracycline for acute uncomplicated falciparum malaria in Thailand. *Lancet* 1992; 339: 369.

Looareesuwan S, Viravan C, Vanijanonta S, *et al.* Randomised trial of mefloquine-doxycycline, and artesunate-doxycycline for treatment of acute uncomplicated falciparum malaria. *Am J Trop Med Hyg* 1994; 50: 784-9.

Looareesuwan S, Viravan C, Webster HK, Kyle DE, Hutchinson DB, Canfield CJ. Clinical studies of atovaquone, alone or in combination with other antimalarial drugs, for treatment of acute uncomplicated malaria in Thailand. *Am J Trop Med Hyg* 1996; 54: 62-6.

Looareesuwan S, Charoenpan P, Ho M, *et al.* Fatal malaria after an inadequate response to quinine treatment. *J Infect Dis* 1990; 161: 577-80.

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; 89: 469-75.

Luxemburger C, ter Kuile F, Nosten F, *et al.* Single day mefloquine-artesunate combination in the treatment of multi-drug resistant falciparum malaria. *Trans R Soc Trop Med Hyg* 1994; 88: 213-7.

Luxemburger C, Nosten F, Shotar, Raimond D, Chongsuphajaisiddhi T, White NJ. Oral artesunate in the treatment of uncomplicated hyperparasitemic falciparum malaria. *Am J Trop Med Hyg* 1995; 53: 522-5.(Abstract)

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; 22: 380-5.

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; 90: 415-7.

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; 22: 539-3.

Baird JK, Fryauff DJ, Basri H, *et al.* Primaquine for prophylaxis against malaria among nonimmune transmigrants in Irian Jaya, Indonesia. *Am J Trop Med Hyg* 1995; 52: 479- 84.

Brewer TG, Peggins JO, Grate SJ, *et al.* Neurotoxicity in animals due to arteether and artemether. *Trans R Soc Trop Med Hyg* 1994a; 88 (Suppl 1): 33-6.

Brewer TG, Grate SJ, Peggins JO, *et al.* Fatal neurotoxicity of arteether and artemether. *Am J Trop Med Hyg* 1994; 51: 251-9.

Fryauff DJ, Baird JK, Basri H, *et al.* Randomised placebo-controlled trial of primaquine for prophylaxis of falciparum and vivax malaria. *Lancet* 1995; 346: 1190-3.

Nosten F, Luxemburger C, ter Kuile FO, *et al.* Treatment of multidrug-resistant Plasmodium falciparum malaria with 3-day artesunate-mefloquine combination. *J Infect Dis* 1994; 170: 971-7.

Nosten F, ter Kuile F, Chongsuphajaisiddhi T, *et al.* Mefloquine-resistant falciparum malaria on the Thai-Burmese border. *Lancet* 1991; 337: 1140-43.

Nosten F, ter Kuile FO, Luxemburger C, *et al.* Cardiac effects of antimalarial reatment with halofantrine. *Lancet* 1993; 341: 1054-6.

Nosten F. Halofantrine in the treatment of malaria. *Drug Safety* 1995; 13: 271-2.

Price RN, Nosten F, Luxemburger C, *et al.* Artesunate/ Mefloquine treatment of multi-drug resistant falciparum malaria. *Trans R Soc Trop Med Hyg* 1997; 91: 574-7.

Price RN, Nosten F, Luxemburger C, *et al.* Artesunate versus artemether in combination with mefloquine for the treatment of multidrug resistant falciparum malaria. *Trans R Soc Trop Med Hyg* 1995; 89: 523-7.

Price RN, Nosten F, Luxemburger C, *et al.* Effects of artemisinin derivatives on malaria transmissibility. *Lancet* 1996; 347: 1654-8.

Hien TT, Day NPJ, Phu NH, *et al.* A controlled trial of artemether or quinine in Vietnamese adults with severe falciparum malaria. *N Engl J Med* 1996; 335: 76-83.

Hien TT, Arnold K, Hung NT, *et al.* Single dose artemisinin-mefloquine treatment for acute uncomplicated falciparum malaria. *Trans R Soc Trop Med Hyg* 1994; 88: 688- 91.

Hien TT, Tam DTH, Cuc NTK, Arnold K. Comparative effectiveness of artemisinin suppositories and oral quinine in children with acute falciparum malaria. *Trans R Soc Trop Med Hyg* 1991; 85: 210-1.

Hien TT, Arnold K, Vinh H, *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; 86: 582-3.

Karbwang J, Bangchang KN, Thanavibul A, Bunnag D, Chongsuphajaisiddhi T, Harinasuta T. Comparison of oral artemether and mefloquine in acute uncomplicated falciparum malaria. *Lancet* 1992; 340: 1245-48.

Karbwang J, Na Bangchang K, Thanavibul A, Ditta-in M, Harinasuta T. A comparative clinical trial of two different regimens of artemether plus mefloquine in multidrug resistant malaria. *Trans R Soc Trop Med Hyg* 1995; 89: 290-8.

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 WHO* 1994; 72: 233-8.

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 WHO* 1994; 72: 233-8.

McGready R, Cho T, Cho JJ, *et al.* Artemisinin derivatives in the treatment of falciparum malaria in pregnancy. *Am J Trop Med Hyg* 1998 (in press).

Smithuis FM, van Woensel JB, Nordlander E, Vantha WS, ter Kuile FO. Comparison of two mefloquine regimens for treatment of *Plasmodium falciparum* malaria on the northeastern Thai-Cambodian border. *Antimicrob Agents Chemother* 1993; 37: 1977-81.

ter Kuile FO, Dolan G, Nosten F, *et al.* Halofantrine versus mefloquine in the treatment of multi-drug resistant falciparum malaria. *Lancet* 1993; 341: 1044-9.

ter Kuile F, Nosten F, Thieren M, *et al.* High dose mefloquine in the treatment of multidrug resistant falciparum malaria. *J Infect Dis* 1992; 166: 1393-400.

ter Kuile FO, Nosten F, Luxemburger C, *et al.* Mefloquine treatment of acute falciparum malaria: A prospective study of non-serious adverse effects in 3,673 patients. *Trans R Soc Trop Med Hyg* 1996; 73: 631-42.

van Vugt M, Brockman A, Gemperli B, *et al.* Randomised comparison of artemether-benflumetol and artesunate-mefloquine in the treatment of multidrug resistant falciparum malaria. *Antimicrob Agents Chemother* 1998; 42: 135-9.

Tanariya P, Na Bangchang K, Tin T, Limpaibul L, Brockelman CR, Karbwang J. Clinical response and susceptibility *in vitro* of *Plasmodium vivax* to the standard regimen of chloroquine in Thailand. *Trans R Soc Trop Med Hyg* 1995a; 89: 426-9.

Tanariya P, Na Bangchang K, Tin T, Limpaibul L, Brockelman CR, Karbwang J. Clinical response and susceptibility *in vitro* of *Plasmodium vivax* to the standard regimen of chloroquine in Thailand. *Trans R Soc Trop Med Hyg* 1995b; 89: 426-9.

Pukrittayakamee S, Supanaranond W, Looareesuwan S, Vanijanonta S, White NJ. Quinine in severe falciparum malaria: evidence of declining efficacy in Thailand. *Trans R Soc Trop Med Hyg* 1994; 88: 324-7.

White NJ, Looareesuwan S, Warrell DA, *et al.* Quinine loading dose in cerebral malaria. *Am J Trop Med Hyg* 1983; 32: 1-5.

White NJ, Warrell DA, Chanthavanich P, *et al.* Severe hypoglycemia and hyperinsulinemia in falciparum malaria. *N Engl J Med* 1983; 309: 61-6.

Murphy SA, Mberu E, Muhia DK, *et al.* The disposition of intramuscular artemether in children with cerebral malaria; a preliminary study. *Trans R Soc Trop Med Hyg* 1997; 91: 331-4.

Murphy GS, Basri H, Purnomo, *et al.* Vivax malaria resistant to treatment and prophylaxis with chloroquine. *Lancet* 1993; 341: 96-100.

Hien TT, Tam DTH, Cuc NTK, Arnold K. Comparative effectiveness of artemisinin suppositories and oral quinine in children with acute falciparum malaria. *Trans R Soc Trop Med Hyg* 1991; 85: 210-1.

Hien TT, Arnold K, Vinh H, *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; 86: 582-3.