J Microbiol Immunol Infect.
2007;40:209-215

Original Article

Clinical experience of 17 cases of imported malaria at a Taiwan university hospital, 1999-2005

Hsing-Chun Chung[1], Jann-Tay Wang[1], Hsin-Yun Sun[1], Jiun-Ling Wang[1], Yi-Chun Lo[1], Wang-Huei Sheng[1], Szu-Min Hsieh[1], Chi-Tai Fang[1,2], Po-Ren Hsueh[1,3], Yee-Chun Chen[1], Shan-Chwen Chang[1]

[1]Division of Infectious Diseases, Department of Internal Medicine, and Departments of [2]Medical Research and [3]Laboratory Medicine, National Taiwan University Hospital, Taipei, Taiwan

Received: April 6, 2006 Revised: July 30, 2006 Accepted: August 1, 2006

Background and Purpose: Malaria had been eradicated in Taiwan since 1965, but there are currently 30 to 50 imported cases annually. The management of imported malaria continues to be challenging due to evolving drug resistance of *Plasmodium* parasites.

Methods: We retrospectively analyzed the clinical presentations, treatment, and outcomes of all 16 adult patients (17 episodes) with imported malaria diagnosed during 1999-2005. The clinical and laboratory features were obtained from the medical records.

Results: Malaria was acquired in sub-Saharan Africa in 6 cases and Southeast Asia in 11 cases. The initial presentations were nonspecific, including fever (17/17 cases), headache (11/17), nausea, vomiting or diarrhea (10/17), cough (3/17), thrombocytopenia (15/17), mild hyperbilirubinemia (13/17), leukopenia (6/17) and anemia (4/17). Careful travel history led to the correct diagnosis in 16 of 17 cases. All 17 cases survived without any recrudescence. Four cases presented with hyperparasitaemia (>5%). Two patients were admitted to an intensive care unit for complicated malaria, and both were cured by artesunate plus mefloquine. Some suboptimal practices, such as non-standard therapeutic regimen and lack of daily parasitemia counting were noted.

Conclusions: A differential diagnosis of malaria should be made in all patients who have fever after travel to any endemic area. To further improve the management of imported malaria, timely consultation of an experienced infectious disease specialist is necessary.

Key words: Artesunate; Combination drug therapy; Malaria; *Plasmodium falciparum*; *Plasmodium vivax*

Introduction

Malaria is an important infectious disease worldwide. According to recent data from the World Health Organization (WHO), there are more than one million deaths and up to 500 million clinical malaria cases each year, mainly in Africa and Southeast Asia [1]. Although malaria has been eradicated in Taiwan since 1965 [2], there are approximately 30 to 50 imported cases annually [3]. The management of imported malaria continues to be challenging due to evolving drug resistance of *Plasmodium* parasites. Chloroquine has not been effective for the treatment of *Plasmodium falciparum* malaria since the early 1990s. The efficacy of sulfadoxine-pyrimethamine (SP) also rapidly declined in the mid-1990s [4]. Quinine has become the first-line therapy for imported malaria in Taiwan since 1992. To minimize recrudescence, a consolidation course of mefloquine has been recommended after completion of the quinine therapy [5]. However, multiresistant *P. falciparum* strains non-susceptible to chloroquine, SP, mefloquine and quinine, have emerged in the Thai-Cambodian border area and elsewhere [6,7]. As a result, imported malaria cases in Taiwan have become more and more difficult to treat in the 21st century. In the meantime, newer and less toxic regimens, such as artemisinin-based combination regimen (ACT), emerged as an alternative to quinine therapy.

Corresponding author: Dr. Shan-Chwen Chang, Division of Infectious Diseases, Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, No.7, Chung-Shan South Road, Taipei 100, Taiwan. E-mail: changsc@ntu.edu.tw

To evaluate the current situation and identify problems in the management of imported malaria in Taiwan, we retrospectively analyzed the clinical presentations, treatment, and outcomes of 16 consecutive patients with 17 episodes of malaria treated at the National Taiwan University Hospital (NTUH) from 1999 through 2005.

Methods

All malaria patients treated at NTUH from 1999 through 2005 were included in this study. The diagnosis of malaria and the identification of species were based on microscopic examination of thin blood smears. The results were further confirmed by parasitologists from the Laboratory Research and Development Center, Centers for Disease Control, Department of Health, Executive Yuan, Taiwan. Hyperparasitemia was defined as more than 5% of infected peripheral red blood cells. Severe *falciparum* malaria is defined as the occurrence of any one of the following conditions at presentation or during hospitalization: cerebral malaria, generalized convulsions, metabolic acidosis with respiratory distress, acute renal failure, acute pulmonary edema, adult respiratory distress syndrome, circulatory collapse, or shock [8]. The clinical and laboratory features of each case, from presentations to outcomes, were obtained from the medical records.

Results

Demographic and geographic features

Sixteen adult patients with malaria were treated at NTUH from 1999 through 2005. One patient had two separate episodes of *Plasmodium vivax* infection. The interval between these two episodes was 4 months and the two episodes were acquired in two different countries. He received complete chloroquine plus primaquine therapy in the first *vivax* malaria episode, so reinfection rather than relapse was likely. Thus, there were in total 17 cases of malaria during the past 6 years.

Of these 16 patients, 8 were foreign nationals and 8 were Taiwanese citizens. Most (10/16) of these patients were men, with a male-to-female ratio of 10:6, and a median age of 36 years (range, 20-77 years). *P. falciparum* was identified as the causative species in 8 cases (including 2 cases of mixed infections with *P. falciparum* and *P. vivax*), *P. vivax* in 9 cases, and *Plasmodium malariae* in 2 cases. Malaria was acquired in sub-Saharan Africa in 6 cases (5 *P. falciparum*, 1 *P. malariae*), and Southeast Asia in 11 cases (2 mixed infection, 7 *P. vivax*, 1 *P. falciparum* and 1 *P. malariae*). All *P. vivax* infections were acquired in Southeast Asia. Three *P. falciparum* cases, 3 *P. vivax* cases (including one of mixed infection) and both *P. malariae* cases had previous malaria infection histories. Chloroquine was the chemoprophylactic agent. All 8 Taiwanese patients did not have good compliance with the chemoprophylactic drug therapy when traveling to the endemic areas. Seven patients had past histories of malaria infection; 3 were Taiwanese and 4 were foreign nationals.

Clinical and laboratory presentations

Fever was the initial manifestation in all cases, and 11 cases had headache. Three cases developed hyperpyrexia with a body temperature above 40°C. Seven of the 17 cases had the characteristic fever patterns — several chill-fever episodes within a day (*P. falciparum* infection) or tertian fever (*P. vivax* or *P. malariae* infection). Myalgia or arthralgia was more common in patients infected with *P. vivax* than in those infected with *P. falciparum*. One patient with cerebral malaria (mixed infection) presented with binocular blindness and altered consciousness in the emergency room (ER). Symptoms mimicking gastroenteritis and upper respiratory tract infection occurred in 10 and 3 cases, respectively.

All 17 cases were admitted to this hospital via the ER. The most common initial laboratory abnormalities were thrombocytopenia (platelet count $<100 \times 10^9$/L) and hyperbilirubinemia (serum bilirubin level >1.2 mg/dL) [Table 1]. Thrombocytopenia can be severe, ranging from 14×10^9/L to 83×10^9/L (median, 60×10^9/L) in patients with *falciparum* malaria, and ranging from 4×10^9/L to 92×10^9/L (median, 66×10^9/L) in those with tertian malaria. Initial leukopenia ($<4.0 \times 10^9$/L) was found in both patients infected with *P. malariae*, but was not common in patients infected with *P. falciparum* or *P. vivax*, with 1 (12.5%) and 3 cases (38%), respectively. Only 4 cases had anemia (hemoglobin <11 g/dL) in the ER, but another six cases developed anemia during hospitalization. Hyperbilirubinemia was usually mild, with a median serum bilirubin of 2.3 mg/dL in cases with *falciparum* malaria, and 1.85 mg/dL in cases with tertian malaria. Serum glucose level was not evaluated in all patients, but none had hypoglycemic symptom complaints. There was no bacterial coinfection in any patient. With careful history review, the diagnosis of malaria was made on the day visiting the hospital by an infectious disease

Table 1. Initial clinical and laboratory presentations of 17 cases with malaria treated at National Taiwan University Hospital, 1999-2005

Initial presentation	*Plasmodium falciparum* (n = 8)[a] No. (%)	*Plasmodium vivax* (n = 9)[a] No. (%)	*Plasmodium malariae* (n = 2) No. (%)	Overall (n = 17) No. (%)
Clinical				
Fever	8 (100)[a]	9 (100)[a]	2	17 (100)
Hyperpyrexia (>40°C)	1 (12.5)	2 (22)	0	3 (17.6)
Tertian fever	0 (0)	1 (11)	2	3 (17.6)
Multiple febrile episodes within a day	4 (50)[b]	1 (11)[b]	0	4 (23.5)
Headache	7 (87.5)[a]	6 (67)[a]	0	11 (64.7)
Myalgia or arthralgia	2 (22)[b]	4 (44)[b]	0	5 (29.4)
Nausea or vomiting or diarrhea	5 (63)[b]	5 (56)[b]	1	10 (58.8)
Cough or rhinorrhea	2 (22)	1 (11)	0	3 (17.6)
Palpable liver	1 (12.5)	0 (0)	0	1 (5.9)
Laboratory				
Leukopenia (white blood cell $<4.0 \times 10^9$/L)	1 (12.5)	3 (33)	2	6 (35.3)
Anemia (hemoglobin <11 g/dL)	3 (38)	1 (11)	0	4 (23.5)
Thrombocytopenia (platelet $<100 \times 10^9$/L)	7 (87.5)[a]	8 (89)[a]	1	14 (82.4)
Hyperbilirubinemia (total bilirubin >1.2 mg/dL)	7 (88)[a]	6 (67)[a,c]	0 (0)[c]	11 (64.7)

[a]Two patients co-infected with *P. falciparum* and *P. vivax*.

[b]Includes the one who had cerebral malaria with mixed infection.

[c]Includes one patient each in the *P. falciparum* and *P. vivax* groups in whom bilirubin levels were not measured.

specialist in 16 cases. The travel history was neglected in one patient until the characteristic tertian fever occurred during hospitalization. The interval between admission and diagnosis in this patient was 3 days.

Hyperparasitemia developed in 4 of the *P. falciparum*-infected patients, including a patient with cerebral malaria. All patients with hyperparasitaemia fulfilled the WHO criteria of severe malaria. Two cases, including the one with cerebral malaria, suffered from blackwater fever, shock, acute renal failure, acute respiratory distress syndrome, disseminated intravascular coagulation, and hyperbilirubinemia. Both cases were admitted to the intensive care unit, and one patient required short-term ventilator support and hemodialysis. The other two patients presented with hypotension (systolic blood pressure <100 mm Hg) in ER, but had no other complications during the whole course.

Therapy for malaria and drug toxicity

The regimens of antimalarial therapy are summarized in Table 2.

Severe malaria

There were 4 cases of severe malaria. Two cases received artesunate plus mefloquine; one quinine plus mefloquine plus doxycycline, and one received chloroquine plus mefloquine (Table 2). One patient with cerebral malaria was treated with artesunate plus mefloquine for *falciparum* malaria and artesunate plus primaquine for *vivax* malaria. This patient suffered from artesunate-related reticulocytopenia and mefloquine-related frequent ventricular premature contractions. This patient also had severe anemia (hemoglobin of 3.5 g/dL), which developed after 4 days of primaquine, but her glucose-6-phosphate dehydrogenase (G6PD) level was normal (19.41 U/g). These complications resolved spontaneously without regimen adjustment. The other patient treated with artesunate initially received quinine therapy, and then artesunate plus mefloquine. This patient developed tinnitus, blurred vision, and non-cardiogenic shock after one day of quinine therapy. There was no abnormality in electrocardiography and the above complaints disappeared after quinine was discontinued. However, this patient received transient ventilator support and hemodialysis. The patient who received quinine plus mefloquine plus doxycycline therapy also had tinnitus after one day of quinine therapy, and no regimen adjustment was done. The patient returning from Nigeria, an endemic area with chloroquine-resistant malaria, received chloroquine plus mefloquine therapy. Although relative hypotension occurred after treatment in this patient, the regimen was not changed.

The duration from starting anti-*falciparum* malaria treatment to defervescence was 4, 6, 12, and 17 days,

Table 2. Antimalarial regimens in the 17 cases

Falciparum malaria	Number
Southeast Asia	
Artesunate plus mefloquine[a]	2[c]
Quinine plus doxycycline[a]	1
Sub-Saharan area	
Artesunate plus mefloquine[a]	1[d]
Chloroquine plus mefloquine	1[e]
Quinine plus doxycycline plus mefloquine	1[f]
Quinine plus mefloquine	2
Vivax malaria[b]	
Chloroquine plus primaquine[a]	7
Quinine plus doxycycyline and artesunate plus mefloquine	2[g]
Malariae malaria	
Chloroquine[a] plus primaquine	1[h]
Quinine and mefloquine	1[i]

[a]World Health Organization (2006) recommended regimens for different *Plasmodium* species [13].
[b]All *vivax* malaria were acquired in Southeast Asia.
[c]One patient had severe malaria and needed intensive care unit admission.
[d]The patient had severe malaria and quinine-related side effects. She received an alternative artemisinin-based combination regimen.
[e]The patient had transient hypotension; no regimen adjustment.
[f]The patient had quinine-related tinnitus; no regimen adjustment.
[g]One patient had quinine-related tinnitus.
[h]Acquired in Southeast Asia.
[i]Acquired in sub-Saharan area.

respectively; and to clearance of parasitemia was 3, 4, 5, and 7 days, respectively. The two cases with intensive care unit support had a prolonged duration from starting antimalarials to defervescence, 12 and 17 days, respectively. All 4 patients survived and no recrudescence was noted.

Uncomplicated malaria

In the *falciparum* malaria group, 2 patients received quinine plus mefloquine, 1 patient received quinine plus doxycycline, and 1 patient who had mixed infection with *P. vivax* received artesunate plus mefloquine therapy (Table 2). One other patient received chloroquine plus primaquine for *vivax* malaria. No drug-related toxicity was observed.

The duration from starting anti-*falciparum* malaria treatment to defervescence was 0, 2, 3, and 4 days, respectively. The duration to clearance of the parasitemia was unknown for 1 patient because blood smear was not monitored daily. This patient had defervescence on the fourth day after artesunate plus mefloquine therapy and another blood smear resulted in a negative finding on the twelfth day after antimalarials. The duration to clearance of parasitemia was 2, 3, and 3 days, respectively. Under the above treatment, all patients survived and no recrudescence was noted.

Nine cases were infected with *P. vivax*, and 2 were co-infected with *P. falciparum*. Seven cases received standard chloroquine plus primaquine therapy for *P. vivax* infection. Two patients with *P. vivax* infection received a combination regimen with artesunate plus mefloquine and quinine plus doxycycline. One patient in the combination therapy group had transient prolonged corrected QT interval (QTc) in the electrocardiography after quinine therapy, but no regimen adjustment was performed. Chloroquine plus primaquine was used in 1 *P. malariae*-infected patient and quinine plus mefloquine was used in the other one (Table 2).

The duration from starting antimalarials to defervescence ranged from 1 to 4 days and the time to clearance of parasitemia ranged from 2 to 7 days. The blood smear of the patient who had 2 episodes of *vivax* malaria was not monitored again after malaria was diagnosed. This patient had defervescence after 1 and 3 days of antimalarials in these episodes.

Discussion

Responding to evolving drug resistance, the WHO revised the antimalarial therapy recommendation in 2006. ACT currently is the first-line therapy for severe malaria. Two cases of severe malaria were treated

with ACT as the first-line therapy at NTUH. Both patients, including the one who had cerebral malaria [9], recovered smoothly. Because of three previously reported cases of intravenous quinine-related life-threatening cardiotoxicity, intravenous quinine was no longer used at NTUH after 1998 [10].

In Taiwan, oral chloroquine (chloroquine phosphate 2500 mg given over 3 days) plus primaquine (15 mg/day for 14 days) was given as the initial therapy for *falciparum* malaria from 1958 until the early 1990s [11]. Quinine (10 mg/kg three times daily for 3-7 days) was used as the first-line therapy for *falciparum* malaria since the early 1990s [11]. To ensure complete cure without recrudescence, a second drug (SP during 1992-1994, and mefloquine after 1994) which is effective against *P. falciparum* was given as consolidation therapy after the completion of quinine or artesunate therapy [10]. Tetracycline (250 mg every 6 h for 3-7 days) or doxycycline (100 mg every 12 h for 7 days) was added in cases acquired in Southeast Asia [12]. Mefloquine is still effective in Africa [13], and might have resistance in Southeast Asia [6,7]. Quinine plus mefloquine was given to patients who came from sub-Saharan Africa and quinine plus doxycycline was given to those who came from Southeast Asia in this study. Currently, artesunate (4 mg/kg/day for 3 days) plus mefloquine (1500 mg over 24 h for a body weight >60 kg, 1250 mg for a body weight <60 kg) is listed as the first-line therapy for *falciparum* malaria in Taiwan. Quinine plus doxycycline is the alternative anti-*falciparum* agent if artesunate is not available or contraindicated [14].

The toxicity of quinine is associated with cinchonism, which can be mild, with tinnitus and blurred vision, to severe, with vomiting, diarrhea, and vertigo. Quinine commonly causes hyperinsulinemic hypoglycemia. The adverse effects of quinine that physicians are mostly concerned of are the increase in QTc interval and QRS widening [15]. Two of 6 patients (33%) treated with quinine and 1 patient who had severe malaria had cinchonism complications. The toxicity of artemisinin derivatives is significantly less than quinine and the drug adherence is better, although there were occasional reports of reticulocytopenia, mild gastrointestinal disturbance, dizziness, and tinnitus after therapy with artemisinin derivatives [15]. In addition to a lower risk of severe adverse effects, artemisinin derivatives also appear to have a better efficacy against *Plasmodium* than quinine [16,17]. Dondorp et al showed an absolute mortality reduction of 34.7% in the artesunate group compared to the quinine group [17]. In 2006, WHO recommended artesunate as the first-line therapy for *falciparum* malaria and quinine as the alternative agent [13]. Unfortunately, artesunate is not licensed in Taiwan, and the major concern is that artesunate is not produced following good manufacturing practice [17].

In addition to drug therapy, several issues were highlighted in this study. First, the nonspecific initial presentations increase the difficulty of a diagnosis of malaria. Second, there was a lack of experience of junior physicians in malaria management. In this study, most patients had nonspecific initial presentations, the majority with fever, headache, thrombocytopenia, and hyperbilirubinemia. Some patients had additional diarrhea, myalgia or arthralgia, and cough, which may confound the diagnosis. Absence of anemia, hepatomegaly or splenomegaly was common. If the travel history is not carefully taken, the diagnosis and treatment of imported malaria can be delayed [8,10,18]. In five patients, although the travel history suggested malaria infections, malaria was still not impressed by junior emergency physicians. The interval from symptoms onset to visiting our emergency department was 1 to 10 days. Fever of unknown origin, rickettsia disease, Q fever or intra-abdominal infection were suspected. Four cases were diagnosed and treated immediately after an infectious disease specialist consultation.

Five patients received a “non-standard” antimalarial regimen. One Taiwanese patient with severe *falciparum* malaria acquired in Nigeria received chloroquine therapy initially. Since *P. falciparum* is usually resistant to chloroquine in West Africa, this drug is not an appropriate initial choice. The mefloquine resistance in Africa is currently being further reviewed, and use of chloroquine plus mefloquine may risk treatment failure [13]. Two patients received concurrent artesunate and quinine for *P. vivax* acquired in Indonesia. This regimen was an over-treatment. Although there were sporadic case reports of chloroquine-resistant *vivax* malaria [19-23], chloroquine is still generally effective for *vivax* malaria acquired in Indonesia [13]. Use of concurrent artesunate and quinine in this scenario will cause an unjustified increase in the risk of serious arrhythmia [24]. For *P. malariae* infection, single-agent treatment with chloroquine should be enough [13,25,26]. However, one patient who had *P. malariae* infection received chloroquine and additional primaquine therapy, and the other patient received quinine followed by mefloquine therapy. In both patients, the non-standard regimens are associated with an increased risk of adverse drug reactions, such as quinine-related life-threatening arrhythmia, primaquine-related hemolysis.

Another suboptimal practice was the lack of daily parasitemia evaluation in three cases. Because there is no practical susceptibility testing for malaria parasites, parasitemia evaluation is the only method for detection of drug resistance [8]. Without daily parasitemia monitoring, it will be difficult to differentiate serious adverse drug effects, such as quinine-related shock and lung edema and primaquine-related hemolysis, from uncontrolled drug-resistant malaria. Different approaches are required for the management of these two conditions. Therefore, it is imperative to monitor parasitemia until the clearance of the malaria parasite from blood. In addition to parasitemia evaluation, another underused test is measurement of serum levels of G6PD (only 4 of 10 cases with primaquine therapy had their G6PD level tested). In individuals with G6PD deficiency, primaquine therapy can cause serious hemolysis. Ideally, plasma G6PD levels should be monitored before the start of primaquine for patients with *vivax* malaria [15].

In conclusion, the initial nonspecific presentations of imported malaria increased the difficulty of diagnosis of malaria. A differential diagnosis of malaria should be considered for all febrile patients returning from endemic areas. Some suboptimal practices, such as non-standard therapeutic regimen and lack of daily parasitemia evaluation were noted in this study. To further improve the management of imported malaria, timely consultation with an experienced infectious disease specialist is necessary.

References

1. World Health Organization; United Nations Children's Fund; United Nations Development Programme; World Bank. Roll back malaria parternership. Geneva, Switzerland: World Health Organization; 2005. Available from: http://www.unitedagainstmalaria.org/e/malaria/rollback.html
2. Fang CT, Chang HL, Hsieh WC. Malaria eradication on islands. Lancet. 2001;357:560.
3. Centers for Disease Control. Annual report of national notifiable disease surveillance system. Taipei, Taiwan: Centers for Disease Control; 2005. [In Chinese]. Available from: http://www.cdc.gov.tw/index_info.asp?p_data_id_2=250&act=init.
4. World Health Organization. Antimalarial drug combination therapy: report of a WHO technical consultation. WHO/CDS/RBM/2001.35. Geneva, Switzerland: World Health Organization; 2001. Available from: http://whqlibdoc.who.int/hq/2001/WHO_CDS_RBM_2001.35.pdf
5. ter Kuile FO, Nosten F, Luxemburger C, Kyle D, Teja-Isavatharm P, Phaipun L, et al. Mefloquine treatment of acute *falciparum* malaria: a prospective study of non-serious adverse effects in 3673 patients. Bull World Health Organ. 1995;73:631-42.
6. Bjorkman A, Phillips-Howard PA. The epidemiology of drug-resistant malaria. Trans R Soc Trop Med Hyg. 1990;84:177-80.
7. Baird JK. Effectiveness of antimalarial drugs. N Engl J Med. 2005;352:1565-77.
8. Severe *falciparum* malaria. World Health Organization, Communicable Diseases Cluster. Trans R Soc Trop Med Hyg. 2000;94(Suppl. 1):S1-90.
9. 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;105:86-9.
10. Fang CT, Chang SC, Chang HL, Chen YC, Hsueh PR, Hung CC, et al. Imported malaria: successful treatment of 31 patients in the era of chloroquine resistance. J Formos Med Assoc. 1999;98:683-7.
11. Centers for Disease Control. Malaria eradication in Taiwan. 2nd ed. Taipei, Taiwan: Centers for Disease Control; 2005.
12. Watt G, Loesuttivibool L, Shanks GD, Boudreau EF, Brown AE, Pavanand K, et al. Quinine with tetracycline for the treatment of drug-resistant *falciparum* malaria in Thailand. Am J Trop Med Hyg. 1992;47:108-11.
13. World Health Organization. Guideline for the treatment of malaria. WHO/HTM/MAL/2006.1108. Geneva, Switzerland: World Health Organization; 2006. Available from: http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf
14. Centers for Disease Control. The management of malaria in Taiwan. Taipei, Taiwan: Centers for Disease Control; 2005. [In Chinese]. Available from: http://www.cdc.gov.tw/index_info_info.asp?data_id=915#.
15. Taylor WR, White NJ. Antimalarial drug toxicity: a review. Drug Saf. 2004;27:25-61.
16. Woodrow CJ, Haynes RK, Krishna S. Artemisinins. Postgrad Med J. 2005;81:71-8.
17. Dondorp A, Nosten F, Stepniewska K, Day N, White N; South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group. Artesunate versus quinine for treatment of severe *falciparum* malaria: a randomised trial. Lancet. 2005;366:717-25.
18. Kain KC, Harrington MA, Tennyson S, Keystone JS. Imported malaria: prospective analysis of problems in diagnosis and management. Clin Infect Dis. 1998;27:142-9.
19. Kurcer MA, Simsek Z, Zeyrek FY, Atay S, Celik H, Kat I, et al. Efficacy of chloroquine in the treatment of *Plasmodium vivax* malaria in Turkey. Ann Trop Med Parasitol. 2004;98:447-51.
20. Soto J, Toledo J, Gutierrez P, Luzz M, Llinas N, Cedeno N,

et al. *Plasmodium vivax* clinically resistant to chloroquine in Colombia. Am J Trop Med Hyg. 2001;65:90-3.
21. Whitby M. Drug resistant *Plasmodium vivax* malaria. J Antimicrob Chemother. 1997;40:749-52.
22. Baird JK, Leksana B, Masbar S, Fryauff DJ, Sutanihardja MA, Suradi, et al. Diagnosis of resistance to chloroquine by *Plasmodium vivax*: timing of recurrence and whole blood chloroquine levels. Am J Trop Med Hyg. 1997;56: 621-6.
23. Phillips EJ, Keystone JS, Kain KC. Failure of combined chloroquine and high-dose primaquine therapy for *Plasmodium vivax* malaria acquired in Guyana, South America. Clin Infect Dis. 1996;23:1171-3.
24. Laothavorn P, Karbwang J, Na Bangchang K, Bunnag D, Harinasuta T. Effect of mefloquine on electrocardiographic changes in uncomplicated *falciparum* malaria patients. Southeast Asian J Trop Med Public Health. 1992;23:51-4.
25. White NJ. The treatment of malaria. N Engl J Med. 1996;335: 800-6.
26. World Health Organization. The use of antimalaria drugs: report of an informal consultation. WHO/CDS/RBC/2001.33. Geneva, Switzerland: World Health Organization; 2001. Available from: http://www.who.int/malaria/cmc_upload/0/000/014/923//use_of_antimalarials.pdf

