REVIEW

CHLOROQUINE AS A SECOND LINE TREATMENT FOR MALARIA IN LAO PDR: RISKS AND BENEFITS

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Abstract. Chloroquine (CQ) is a cheap, safety and valuable drug. After CQ-resistant *Plasmodium falciparum* appeared in Southeast Asia, CQ was replaced by artemisinin combination therapy (ACT) as first line treatment of malaria in Lao PDR, and CQ now is used as a second-line treatment for uncomplicated *P. vivax*, *P. ovale* and *P. malariae* infections. There was report of widespread availability of CQ, particularly in the private sector, which may have been distributed as a first-line treatment of uncomplicated malaria, and possibly contributing to the failure of artemether-lumefantrine treatment. In this paper the literature on history, efficacy and drug interaction of CQ, CQ-resistant *P. falciparum* and *P. vivax*, and malaria treatment guidelines of Lao PDR and other endemic countries in the surrounding region were reviewed. Risks and benefits of CQ as second line treatment are discussed and suggestions are recommended.

Keywords: chloroquine, benefit, malaria treatment, risk, Lao PDR

INTRODUCTION

Chloroquine (CQ), a 4-aminoquinoline, was first synthesised in 1934 as a blood asexual schizonticidal and a cheap alternative for malaria prophylaxis and treatment (Cooper and Maqwere, 2008). CQ was first introduced in 1969 to Lao PDR for mass drug administration combined with DDT spraying, supported by the World Health Organization (WHO) (Ministry of Health, Lao PDR, 2010). Thereafter, CQ has been the first-line therapy for all human malaria infections in Lao PDR. Since the first report of CQ resistant *Plasmodium falciparum* in Southeast Asia and South America (Peters, 1971), and subsequent increasing reports of CQ-resistant *P. vivax* from many regions of the world have posed a major problem in malaria control (Biard, 2009). In 2005 CQ was replaced by artemisinin combination therapy (ACT), artemether-lumefantrine (AL), for treatment of uncomplicated *P. falciparum* and in 2011 for uncomplicated *P. vivax* (ACTwatch Group and Phanalasy, 2017).

Unlike others countries, such as Cameroon (Ndam *et al*, 2017), Kenya (Mwai, 2009), Malawi (Kubin *et al*, 2003), Tanzania (Mulliqan *et al*, 2006), Zambia (Mwanza

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et al, 2016) and Hainan, China (Liu *et al*, 1995), where CQ was officially withdrawn from the market, in Lao PDR, CQ is still included in the national treatment guidelines as a second-line treatment for uncomplicated *P. vivax*, *P. ovale* and *P. malariae* infections. It was not unexpected that there was report of widespread availability of CQ, particularly in the private sector (ACTwatch Group and Phanalasy, 2017), which may have been distributed as a first-line treatment of uncomplicated malaria and may have played a role leading to the failure of AL treatment (ACTwatch Group *et al*, 2017b).

Although CQ is still being used as a second line treatment, there remains a number of issues: 1) the curtailment of consumption of CQ and promotion of the use of the recommended first line treatment, 2) kinds of intervention, which will drive consumer awareness and demand for AL as first-line treatment, 3) factors influencing first-line treatment acceptance, 4) need for survey on the efficacy of CQ, as to date there is no adequate evidence of CQ efficacy against *P. vivax* in Lao PDR, and 5) risks and benefits of CQ as a second line treatment for malaria in Lao PDR.

In order to address these pressing issues, literature on the history, efficacy and drug interaction of CQ, CQ-resistant *P. falciparum* and *P. vivax*, and malaria treatment guidelines of Lao PDR and others endemic countries in the region are reviewed.

HISTORY

During World War II, the world supply of quinine was cut off as Japan took over Java. As part of the war effort, scientists attempted to develop new synthetic antimalarials, resulting in 16,000 compounds being synthesised and tested, and resochin (later named chloroquine) was one of the first tested compounds (Andersag *et al*, 1941; Rosenthal, 2001). By 1946, US clinical trials showed that CQ is a powerful antimalarial. CQ proved to be the most effective and widely used drug in malaria endemic countries throughout the world in the 1950s and 1960s, as the main drug of choice in the WHO Global Eradication Programme (Meshnick and Dobson, 2017).

In Lao PDR, with support from WHO, CQ was first introduced in 1969 for mass drug administration combined with DDT spraying, but the official registration of CQ with the Food and Drug Department, Ministry of Health of Lao PDR was in 1992 (Food and Drug Department, Ministry of Health of Lao PDR, unpublished data). Between 1992 and 2008, there were 21 registered brands of CQ with different dosages from manufacturers in China, Cyprus, France, India, Lao PDR, Thailand, and Vietnam (Food and Drug Department, Ministry of Health of Lao PDR, unpublished data). This indicated that, after the emergence and spread of *P. falciparum* resistant to CQ, there was an increase in *P. vivax* resistant strains to CQ in many parts of the world (Baird, 2004; Teka *et al*, 2008; Chehuan *et al*, 2013). However, CQ remains popular and effective in Lao PDR. As the national treatment policy for malaria has been changed to artemisinin combination therapy (ACT) since 2005 (Ministry of Health of Lao PDR, 2010), most of the registered CQ brands have become invalid after its 3-year registration effective period. To date, just only one brand of pre-packaged CQ tablet manufactured locally by CBF pharmaceutical remains on sale until 2019 (Food and Drug Department, Ministry of Health, Lao PDR, unpublished data). Surprisingly, a 2015 survey of outlets conducted in five

southern provinces of Lao PDR found that CQ availability in the private sector accounts for 62.2% of the total anti-malarial market share, both injection and tablet forms of CQ, but their registration licenses had long been invalid (ACTwatch Group and Phanalasy, 2017). Thus, the argument continues as how to curtail the availability (and consumption) of CQ from the private sector and to promote the use of the recommended first line treatment?

The widespread and popularity of non-first line anti-malarial drugs has also been reported in Benin, but there the public health facilities for malaria case management services are free-of-charge for children under 5 years of age and for pregnant women (ACTwatch Group *et al*, 2017a), while in Lao PDR malaria treatment in the public sector is free-of-charge for all age groups. Moreover, in Lao PDR a public-private mix (PPM) program was launched in 2008 to support private pharmacies and health facilities to aid in the management of malaria, and those PPM participators received AL and Rapid diagnostic tests (RDTs) and were permitted to charge USD0.12 and USD0.25 for a treatment dose of AL and RDTs, respectively, which is cheaper than the median price of a treatment dose of CQ (CMPE, 2012). Thus, the situation in Lao PDR is more complicate than in Benin in that the availability of non-first line treatment drugs may not only due to their lower price compared to ACT. Very little is known regarding malaria treatment-seeking behavior among Laotians, as only two studies were conducted in 1999 and 2006 at Khammouane Province, the first study providing a baseline knowledge of respondents regarding prevention of malaria (Uza *et al*, 2002), and the second study showed that >60% of respondents still had incorrect knowledge about malaria transmission, similar to the former study (Khamlome *et al*, 2007). Although, after distribution of insecticide-treated bed nets (ITNs) in several malaria endemic villages of Bolikhamxay, Khammouanne and Vientiane Provinces in 1999, malaria health education activities for the villages, such as group discussion, video programs and posters, were carried out once in each village near a city and in rural area (Uza *et al*, 2002). However, further research on malaria treatment-seeking behavior, knowledge on malaria including transmission and prevention, of residents who live in malaria endemic provinces are required, with special emphasis on the importance of treatment with the recommended first line treatment and on knowledge of the correct and appropriate use of CQ. In addition, further research should be undertaken to identify factors, which influence provider-dispensing behavior and consumer preferences. Information thus obtained from these research studies would lead to innovative strategies to curtail the consumption and availability of CQ in the private sector and to develop a more effective health information program with a comprehensive scientific explanation of malaria transmission, including its entomology and epidemiology in simple language and in the way that risk population could readily understand.

EFFICACY AND DRUG INTERACTION OF CQ

The pharmacology, toxicology and anti-malarial potency of CQ have been published since 1946 (Loeb *et al*, 1946). Thus, CQ has been widely used for malaria treatment and prophylaxis in malaria endemic countries worldwide due to its safety profile, availability and low cost (Rosenthal, 2003; Congpuon *et al*, 2011).

As recommended by WHO, the therapy dose of CQ for children and adults, including pregnant women, is 25 mg/kg divided over 3 days (WHO, 1995). Following the findings of global prevalence of *P. falciparum* resistance to CQ, national policies for malaria treatment in most of the malaria endemic countries have changed from CQ to ACT (Breman *et al*, 2004). Nonetheless, CQ with or without primaquine (PQ) combination remains the first line treatment for *P. vivax* in most areas where *P. vivax* is endemic (Congpuon *et al*, 2011; Abreha *et al*, 2017). A number of reports revealed that CQ increases the effectiveness and reduces the toxicity of PQ (Naing *et al*, 2010; Pukrittayakamee *et al*, 2014; Fasinu *et al*, 2016). In Lao PDR PQ was introduced in 2015 and is distributed only in district and province hospitals, while CQ is widely distributed in the private pharmacies as described above. CQ is needed to be given with PQ for treatment of *P. vivax*, *P. ovale* and *P. malariae*, according to the national malaria treatment guideline of Lao PDR (CMPE, unpublished data). However, concerns over hemolytic adverse effects in G6PD-deficient patients and the limited availability of G6PD testing, have resulted in limiting PQ distribution only to district and province hospitals where G6PD testing is provided (CMPE, unpublished data). There is little doubt that CQ is prescribed as monotherapy or combined with antibiotics and other drugs in private pharmacies, but there is no evidence of the efficacy of CQ and sensitivity of *P. vivax* to CQ in Lao PDR. In the future, studies need to note that the definition of CQ efficacy will be more complicated as CQ will be given with PQ, and studies should not be conducted using CQ monotherapy due to ethical reasons (CMPE, unpublished data).

CQ now is ineffective for *P. falciparum* treatment in Lao PDR (Pillai *et al*, 2001), but the awareness of this among health professionals and the general population has not been evaluated. Thus, the widely availability of CQ in the private pharmacies may due to people still believe that CQ is effective (Mubyazi *et al*, 2005). Oftentimes, the bitter taste of drugs is believed to be an indicator of efficacy, and CQ is more bitter (hence more effective) than AL (Tarimo *et al*, 2001; Rutebemberwa *et al*, 2009). Moreover, in Lao PDR where both dengue and malaria are endemic (Nalongsack *et al*, 2009) CQ have been used for dengue fever treatment as it reportedly produces a substantial reduction of pain in dengue patients, while its clinical and side effects in dengue patients remain unclear (Borges *et al*, 2013). In order to provide answers to the question as the kinds of interventions that will drive consumer awareness and demand for AL as the first-line treatment, this will require understanding of how the general population perceives CQ efficacy, of their treatment-seeking behavior for malaria and of their knowledge regarding the available alternative treatment options.

CQ-RESISTANT *P. FALCIPARUM* AND *P. VIVAX*

In the late 1950s chloroquine-resistant (CQR) *P. falciparum* was first identified simultaneously in Southeast Asia and South America, and then expanded to neighboring regions (Payne, 1987). Pfcrt, a transporter located on the parasite food vacuole membrane, is a one of the key determinants of CQR phenotype in *P. falciparum* (Takahashi *et al*, 2012). CQR *P. falciparum* is now widespread worldwide; an *in vitro* study showed case prevalence of CQR *P. falciparum* infection at the Lao

PDR border with China of 90% (Lin *et al*, 1997), but CQ and Sulfadoxine-Pyrimethamine (SP) remained the first and second line treatments for uncomplicated *P. falciparum* infection. However, several studies between 2001 and 2003 showing CQ- and SP treatment failures, including CQ alone, SP alone and CQ-SP combination (Pillai *et al*, 2001; Guthmann *et al*, 2002; Mayxay *et al*, 2003; Schwobel *et al*, 2003) led to a consideration of a possible change in drug policy (Beren *et al*, 2003). In 2004, AL combination therapy was introduced as a pilot intervention in several provinces (Ministry of Health, Lao PDR, 2010), in 2005, the nationally recommended first-line treatment of *Plasmodium falciparum* by AL was officially declared (Mayxay *et al*, 2012).

In many countries in Africa, after the change of malaria treatment policy to ACT, CQ has been gradually withdrawn from outlets in the public sector (Ndam *et al*, 2017). As a consequence, many countries have reported an increasing trend of CQ-sensitive *P. falciparum* population and decreasing of *P. falciparum* isolates carrying mutant *pfcrt* (Kubin *et al*, 2003; Mwai *et al*, 2009; Mohammed *et al*, 2013; Ndam *et al*, 2017). The recovery of *P. falciparum* CQ susceptibility in Malawi where the change in drug policy was swift and effective, more than 90% in Tanzania, while in Kenya and Cameroon a much slower recovery were observed. On the other hand, a recent study in Uganda reported the presence of 100% parasites carrying *Pfcrt*76T mutation (Kiwuwa *et al*, 2013). This might be associated with incomplete CQ withdrawal due to its availability as home-pack CQ-SP formulation for several years in Uganda (Källander *et al*, 2006; Nanyunja *et al*, 2011). In Ghana a high variation in the prevalence of *Pfcrt*76T is associated with the level of CQ usage (Asare *et al*, 2014). However, the explanation of the recovery of CQ sensitivity in *P. falciparum* is due to an expansion of wild type allele when drug pressure is relieved or back mutation in *pfcrt* still remains unclear (Ndam *et al*, 2017). To date, CQ is still effective against *P. vivax* in many regions of the world (Liu *et al*, 2014; Ould Ahmedou Salem *et al*, 2015), but to save the useful life of CQ, an effective drug policy is required, and, moreover, to safeguard CQ for its possible re-introduction in combination with other novel anti-malarials in areas where there is a return of *P. falciparum* CQ susceptibility.

CONCLUSION

CQ is a cheap, safety and valuable antimalarial, but the risks associated as a second-line treatment for malaria in Lao PDR need to be considered carefully. There is widespread availability of CQ in the private sector outlets, and some of them provide non-registered brands of CQ. An effective drug policy is required to curtail unsupervised consumption of CQ and to save CQ for possible future reintroduction in combination with other antimalarials. Thus, the most urgent need is to obtain scientific data for evidence-based policy-making. Therefore, an adequate evidence of CQ efficacy against *P. vivax* in Lao PDR, surveys on general perception of CQ efficacy, treatment-seeking behavior for malaria and knowledge of available alternative treatments among the population in malaria endemic areas of Lao PDR are required.

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REFERENCES

Abreha T, Hwang J, Thriemer K, *et al*. Comparison of artemether-lumefantrine and chloroquine with and without primaquine for the treatment of *Plasmodium vivax* infection in Ethiopia. A randomized controlled trial. *PLOS Med* 2017; 14: e1002299.

ACTwatch Group, and Phanalasy S. The malaria testing and treatment landscape in the southern Lao People's Democratic Republic (PDR). *Malar J* 2017; 16: 169.

ACTwatch Group, Zinsou C, Cherifath AB. The malaria testing and treatment landscape in Benin. *Malar J* 2017a; 16: 174.

ACTwatch Group, Phok S, Phanalasy S, Thien ST, Likhitsup A. Private sector opportunities and threats to achieving malaria elimination in the Greater Mekong Subregion: results from malaria outlet surveys in Cambodia, the Lao PDR, Myanmar, and Thailand. *Malar J* 2017b; 16: 180.

Andersag H, Breitner S, Jung H. Quinoline compound and process of making the same. *US Patent* 1941; 2: 233,970.

Asare KK, Boampong JN, Afoakwah R, Ameyaw EO, Sehgal R, Quashie NB. Use of prescribed chloroquine is associated with an increased risk of *pfcrt* T76 mutation in some parts of Ghana. *Malar J* 2014; 13: 246.

Baird JK. Resistance to therapies for infection by *Plasmodium vivax*. *Clin Microbiol Rev* 2009; 22: 508-34.

Baird JK. Chloroquine resistance in *Plasmodium vivax*. *Antimicrob Agents Chemother* 2004; 48: 4075-83.

Beren N, Schwoebel B, Jordan S, *et al*. *Plasmodium falciparum*: correlation of in vivo resistance to chloroquine and antifolates with genetic polymorphisms in isolates from the south of Lao PDR. *Trop Med Int Health* 2003; 8: 775-82.

Borges MC, Castro LA, da'Fonseca BAL. Chloroquine use improves dengue-related symptoms. *Mem Inst Oswaldo Cruz* 2013; 108: 596-9.

Breman JG, Alilio MS, Mills A. Conquering the intolerable burden of malaria: what is needed: a summary. *Am J Trop Med Hyg* 2004; 71: 1-15.

Chehuan YF, Costa MRF, Costa JS, *et al*. In vitro chloroquine resistance for *Plasmodium vivax* isolates from the western Brazilian Amazon. *Malar J* 2013; 12: 226.

Center for Malariology, Parasitology and Entomology (CMPE). Public-private mix initiative for the diagnosis and treatment of malaria in Lao PDR. Viantaine: CMPE, 2012.

Cooper RG, Maqwere T. Chloroquine: novel uses and manifestations. *Indian J Med Res* 2008; 127: 305-16.

Congpuon K, Satimai W, Sujariyakul A, *et al*. In vivo sensitivity monitoring of chloroquine for the treatment of uncomplicated vivax malaria in four bordered provinces of Thailand during 2009-2010. *J Vector Borne Dis* 2011; 48: 190-6.

Fasinu PS, Tekwani BL, Avula B, *et al*. Pathway-specific inhibition of primaquine metabolism by chloroquine/quinine. *Malar J* 2016; 15: 466.

Guthmann JP, Kasparian S, Nathan N, *et al*. The efficacy of chloroquine for the treatment of acute uncomplicated *Plasmodium falciparum* malaria in the Lao People's Democratic Republic. *Ann Trop Med Parasitol* 2002; 96: 553-7.

Källander K, Tomson G, Nsungwa-Sabiiti J, Sengyonjo Y, Pariyo G, Peterson S. Community referral in home management of malaria in western Uganda: a case series study. *BMC Int Health Hum Rights* 2006; 6: 2.

Khamlome B, Eto A, Mita T, *et al*. The status of malaria before and after distribution of TINs from 1999 to 2006 in two districts of Khammouane province, Lao PDR. *Southeast Asian J Trop Med Public Health* 2007; 35: 343-50.

Kiwuwa MS, Byarugaba J, Wahlgren M, Kironde F. Detection of copy number variation and single nucleotide polymorphisms in genes involved in drug resistance and other phenotypic traits in *P. falciparum* clinical isolates collected from Uganda. *Acta Trop* 2013; 125: 269-75.

Kubin JG, Cortese JF, Njunju EM, *et al*. Reemergence of chloroquine-sensitive *Plasmodium falciparum* malaria after cessation of chloroquine use in Malawi. *J infect Dis* 2003; 187: 1870-5.

Lin YH, Quan LD, Ming YY. In vitro sensitivity of *Plasmodium falciparum* to eight antimalarials in China-Myanmar border and China-Lao border areas. *Southeast Asian J Trop Med Public Health* 1997; 28: 460-4.

Liu DQ, Liu RJ, Ren DX, *et al*. Changes in the resistance of *Plasmodium falciparum* to chloroquine in Hainan, China. *Bull World Health Organ* 1995; 73: 483-6.

Liu H, Yang HL, Tang LH, *et al*. Monitoring *Plasmodium vivax* chloroquine sensitivity along China-Myanmar border of Yunnan Province, China during 2008-2013. *Malar J* 2014; 13: 364.

Loeb F, Clark WM, Coatney GR, *et al*. Activity of a new antimalarial agent, chloroquine (SN7618). *JAMA* 1946; 130: 1069-70.

Mayxay M, Khanthavong M, Chanthongthip O, *et al*. Efficacy of artemether-lumefantrine, the nationally-recommended artemisinin combination for the treatment of uncomplicated *falciparum* malaria, in southern Laos. *Malaria J* 2012; 11: 184.

Mayxay M, Newton PN, Khanthavong M, *et al*. Chloroquine versus sulfadoxine-pyrimethamine for treatment of *Plasmodium falciparum* malaria in Savannakhet province; Lao people's Democratic Republic: an assessment of national antimalarial drug recommendations. *Clin Infect Dis* 2003; 37: 1021-8.

Meshnick SR, Dobson MJ. The history of antimalarial drugs. [Cited 2017 May 23]. Available from: https://www.google.co.th/?gws_rd=ssl#q=the+history+of+antimalarial

Ministry of Health (MOH), Lao PDR. National strategy for malaria control and pre-elimination 2011-2015. National report 2010. Vientaine: MOH, 2010.

Mohammed A, Ndaro A, Kalinga A, *et al*. Trends in chloroquine resistance marker Pfcrt-K76T mutation ten years after chloroquine withdrawal in Tanzania. *Malar J* 2013; 12: 415.

Mubyazi GM, Gonzales-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; 4: 51.

Mulligan JA, Mandike R, Palmer N, *et al*. The costs of changing national policy: lessons from malaria treatment policy guidelines in Tanzania. *Trop Med Int Health* 2006; 11: 452-61.

Mwai L, Ochong E, Abdirahman A, *et al*. Chloroquine resistance before and after its withdrawal in Kenya. *Malar J* 2009; 8: 106.

Mwanza S, Joshi S, Nambozi M, *et al*. The return of chloroquine-susceptible *Plasmodium falciparum* malaria in Zambia. *Malar J* 2016; 15: 584.

Naing C, Aung K, Win DK, Wah MJ. Efficacy and safety of chloroquine for treatment in patients with uncomplicated *Plasmodium vivax* infections in endemic countries. *Trans R Soc Trop Med Hyg* 2010; 104: 695-705.

Nalongsack S, Yoshida Y, Morita S, Sosouphanh K, Sakamoto J. Knowledge, attitude and practice regarding dengue among people in Pakse, Laos. *Nagoya J Med Sci* 2009; 71: 29-37.

Nanyunja M, Orem JN, Kato F, Kaggwa M, Katureebe C, Saweka J. Malaria treatment policy change and implementation: the case of Uganda. *Malar Res Treat* 2011; 2011: 683167.

Ndam NT, Basco LK, Ngane VF, *et al*. Reemergence of chloroquine-sensitive pfcrt K76 *Plasmodium falciparum* genotype in south-

eastern Cameroon. *Malar J* 2017; 16: 130.

Ould Ahmedou Salem MS, Mohamed Lemine YO, Deida JM, *et al*. Efficacy of chloroquine for the treatment of *Plasmodium vivax* in the Saharan zone in Mauritania. *Malar J* 2015; 14: 39.

Payne D. Spread of chloroquine resistance in *Plasmodium falciparum*. *Parasitol Today* 1987; 3: 241-6.

Peters W. Malaria chemoprophylaxis and chemotherapy. *Br Med J* 1971; 2(5753): 95-8.

Pillai DR, Labbé AC, Vanisaveth V, *et al*. *Plasmodium falciparum* in Laos: chloroquine treatment outcome and predictive value of molecular markers. *J Infect Dis* 2001; 183: 789-95.

Pukrittayakamee S, Tarning J, Jittamala P, *et al*. Pharmacokinetics interaction between primaquine and chloroquine. *Antimicrob Agents Chemother* 2014; 58: 3354-9.

Rosenthal PJ. Antimalarial chemotherapy mechanisms of action, resistance, and new directions in drug discovery. *Humana Press* 2001: 396pp.

Rosenthal PJ. Antimalarial drug discovery: old and new approaches. *J Exp Biol* 2003; 206: 3735-44.

Rutebemberwa E, Nsabagasani X, Pariyo G, Tomson G, Peterson S, Kallander K. Use of drug perceived drug efficacy and preferred providers for febrile children: implications for home management of fever. *Malar J* 2009; 8: 131.

Schwobel B, Jordan S, Vanisaveth V, *et al*. Therapeutic efficacy of chloroquine plus sulfadoxine/pyrimethamine compared with monotherapy with either chloroquine or pyrimethamine/sulfadoxine in uncomplicated *Plasmodium falciparum* malaria in Laos. *Trop Med Health* 2003; 8: 19-24.

Takahashi N, Tanabe K, Tsukahara, *et al*. Large scale survey for novel genotypes of *Plasmodium falciparum* chloroquine-resistance gene (pfcrt). *Malar J* 2012; 11: 92.

Tarimo DS, Minjas JN, Bygbjerg IC: Perception of CQ efficacy and alternative treatments for uncomplicated malaria in children in holoendemic area of Tanzania: implication for the change of treatment policy. *Trop Med Int Health* 2001; 6: 992-7.

Teka H, Petros B, Yamuah L, *et al*. Chloroquine-resistant *Plasmodium vivax* malaria in Debre Zeit, Ethiopia. *Malar J* 2008; 7: 220.

Uza M, Phompida S, Toma T, *et al*. Knowledge and behaviour relating to malaria in malaria endemic villages of Khammouane Province, Lao PDR. *Southeast Asian J Trop Med Public Health* 2002; 33: 246-54.

World Health Organization (WHO). WHO model prescribing information: drug used in parasitic diseases. 2nd ed. Geneva: WHO, 1995.