OVERVIEW

DRUG RESISTANT MALARIA ON THE THAI-MYANMAR AND THAI-CAMBODIAN BORDERS

Chansuda Wongsrichanalai[1], Jeeraphat Sirichaisinthop[2], Jerome J Karwacki[1], Kanungnit Congpuong[3], R Scott Miller,[1] Lorrin Pang and Krongthong Thimasarn[3]

[1]Armed Forces Research Institute of Medical Sciences (AFRIMS), Bangkok 10400, Thailand; [2]Office of Vector Borne Disease Control No. 1, Phra Buddhabaht, Saraburi, Thailand; [3]Malaria Division, Department of Communicable Disease Control, Ministry of Public Health, Nonthaburi, Thailand

Abstract. 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.

INTRODUCTION

Although sporadic cases of multi-drug resistant (MDR) malaria are reported from various endemic areas of the world, MDR malaria is primarily a problem of Southeast Asia and a few other foci. This is based on the definition that multi-drug resistance of *Plasmodium falciparum* malaria is "resistance to more than two operational anti-malarial compounds of different chemical classes" (Wernsdorfer *et al,* 1994). The Southeastern border of Thailand and Cambodia has long been known as the epicenter of drug resistant malaria. From the mid-1980s to mid-1990s, the problem of mefloquine resistance intensified on both the Thai-Cambodian border and the western border of Thailand with Myanmar (Thimasarn *et al,* 1995; Shanks, 1994; Nosten *et al,* 1991). For the past decade, Mae Sot, an area in Tak Province, on the central part of the Thai-Myanmar border, has become a new focus of the MDR malaria problem (Fig 1).

Since the mid-1990s, the number of falciparum malaria cases on the Thai-Cambodian border has significantly dropped. Today in Mae Sot, the malaria situation is relatively well controlled within the Thai territory but there continue to be a large number of cases detected annually, especially among immigrants from Myanmar.

What is the current situation of drug resistant malaria in Thailand? What are the explanations for the epidemiology of drug resistant malaria in these two border areas?

The purposes of this paper are 1) to describe the malaria situation on the Thai-Cambodian border more than one decade ago and the

Correspence**:** Dr Chansuda Wongsrichanalai, US Army Medical Component, Armed Forces Research Institute of Medical Sciences (AFRIMS), 315/6 Rajvithi Road, Bangkok 10400, Thailand.
Tel: (662) 644-5775, 644-4499 ext 2688; Fax: (662) 644-4784
E-mail: ChansudaW@thai.amedd.army.mil
Disclaimer: The views of the authors do not purport to reflect the position of the US Army or US Department of Defense.

contrasting situation on the Thai-Myanmar border at Mae Sot today, 2) to consider the introduction of artesunate-mefloquine combination in 1995 as one of the multiple factors contributing to the seemingly improved MDR phenomenon in Mae Sot and 3) to hypothesize an evolutionary mechanism of resistance to artemisinin compounds on the Thai-Myanmar border.

BACKGROUND

Selection of drug resistant malaria parasites

Two key mechanisms are thought to be involved in the natural selection of drug resistant parasites. One is treatment failure as pointed out by Wernsdorfer (1994). In a malaria endemic area, drug failure may occur by several means and because the patients get relief from major clinical symptoms, it is sometimes unrecognized unless there is a good follow-up system. In such an instance, the sensitive parasites are killed by the drug and the remaining or recrudescing ones tend to be of the resistant type. Propagation of the resistant parasites eventually results in an epidemic if there is no effective early warning system to detect and destroy the parasite reservoir early enough.

The other mechanism is associated with re-infection, especially in relation to drugs with a long terminal elimination phase (White, 1998). Here, treatment of the primary infection is successful but the anti-malarial drug maintains sub-lethal concentrations in the host's blood stream for an extended period. Re-infection during such a period exposes the parasites to drug levels that fail to eliminate them, but rather act as a pressure leading to selection of resistant mutants.

Thailand experience with drug resistant malaria

Considering development of *P. falciparum* resistance successively to a number of anti-malarial drugs, namely, chloroquine, proguanil, sulfadoxine/pyrimethamine (S/P), quinine and mefloquine (as well as halofantrine), Thailand is arguably the most experienced country in dealing with drug-resistant malaria. The chronology of anti-malarial drug resistance evolution in Thailand has been reviewed by Wernsdorfer *et al* (1994). Briefly, quinine was introduced in 1861 and had been the most widely-used anti-malarial until around World War II, after which chloroquine became popular because of its high efficacy against asexual blood stage parasites, fewer side-effects and the shorter duration of treatment (only 3 days) required. The first observation of *P. falciparum* chloroquine resistance appeared on the Thai-Cambodian border in the late 1950s (Harinasuta *et al*, 1965). In the 1960s, the poor efficacy of chloroquine against falciparum malaria in Thailand became increasingly recognized.

In 1967, sulfadoxine and pyrimethamine (in individual tablets) were found to give a cure rate of 89% (Harinasuta *et al*, 1967). Later studies showed the efficacy of this combination regimen to be around 85-100% (Hall, 1976). In 1971, S/P in the form of fixed dose combination (500 mg sulfadoxine plus 25 mg pyrimethamine per tablet) became available. The Thai Malaria Control Program adopted S/P (to replace chloroquine) as the first line drug for falciparum malaria in 1973. From 1973 to 1975, the quantity of S/P imported into Thailand nearly doubled from 7.7 million to 13 million tablets. The drug was available widely in local pharmacies, and was used for prophylaxis as well as for the treatment of "fever." As could have been predicted, widespread use of the drug without adequate control resulted in the efficacy of S/P being short-lived. By the early 1980s, even an increased dose (*eg* three tablets of S/P, instead of two) gave a cure rate of only 30-40% in the field (Pinichpongse *et al*, 1982).

Several endemic areas in the country had to depend primarily on quinine for falciparum malaria treatment. Clinical trials conducted at the Hospital for Tropical Diseases, Mahidol University indicated a rapid decline of the efficacy of 7-day-course quinine from 94% in 1978-1979 to 76% in 1980-1981 (Harinasuta *et al*, 1991). Tetracycline was added to improve the cure rate and in 1982, the Thai Malaria Control Program began replacing S/P with

quinine-tetracycline combination in many areas especially along the Thai-Cambodian border. The weakness of the regimen was poor compliance in association with the 7-day course. From 1982 to 1984, during which an estimated 9 million tablets of quinine were consumed, quinine *in vitro* sensitivity also significantly dropped (Suebsaeng *et al,* 1986). In order to extend the life span of quinine, its use in conjunction with tetracycline was reserved as a second-line drug for out-patient falciparum malaria cases in Thailand after the introduction of mefloquine. Mefloquine, initially in combination with sulfadoxine and pyrimethamine (as MSP), became the first line drug for out-patient cases of falciparum malaria countrywide in 1985. There was an insidious change-over of regimen to mefloquine alone in 1991 when evidence suggested that there was no superior therapeutic benefit of MSP (Thimasarn *et al,* 1990). Besides, severe side effects due to sulfonamide sensitivity such as Stevens-Johnson syndrome have been documented (WHO, 1990). Mefloquine use, both in the form of MSP or as mefloquine alone, has been restricted to the malaria control program and government hospitals for the treatment of microscopically-confirmed cases of falciparum malaria only. This drug is not legally available over-the-counter and its prophylactic use is discouraged. In spite of these stringent control measures, the efficacy of mefloquine rapidly fell in some areas: in part perhaps due to the impossibilty of one country restricting all access to a drug which was available across neighboring borders.

Loss of mefloquine efficacy

A large-scale field efficacy study of mefloquine on the Thai-Cambodian border during 1983-1985 indicated a 97% cure rate (Pinichpongse *et al,* 1987). Mefloquine treatment failure (RII resistance) was recorded in a non-immune patient as early as 1982, also on the Thai-Cambodian border (Boudreau *et al,* 1982). Soon thereafter several falciparum isolates from that area were documented to have decreased *in vitro* susceptibility to mefloquine (Webster *et al,* 1985). Clinical resistance was also detected in Mae Sot, on the Thai-Myanmar border, in 1987 (Karwacki *et al,* 1989).

In 1988, immediately after the opening of check-points on the border with Cambodia near Bo Rai district, Trad Province, occupational migration of gem miners to western Cambodia near the town of Pailin began. By 1989, the cure rates with MSP fell abruptly to 53% and 55% in Bo Rai and Mae Sot, respectively (Malaria Division statistics). That was the same year mefloquine was licensed by US FDA under the trade name "Lariam." *In vivo* monitoring by the Thai Malaria Control Program showed that between 1990 and 1992, MSP cure rates were only 33% on the Thai-Cambodian border and 36% on the Thai-Myanmar border (Ketrangsee *et al,* 1992; Thimasarn *et al,* 1995). Although these studies were based on field evaluation (patients were not observed in hospitals and re-infection could not be ruled out), the several cases of RII and RIII resistance confirmed the severity of mefloquine resistance. *In vitro* assays of isolates collected from Bo Rai demonstrated progressive decline of mefloquine susceptibility from 1985 to 1989, thus supporting the clinical findings (Wongsrichanalai *et al,* 1992). In 1992, entering Cambodia via Bo Rai was prohibited following the enactment of United Nations resolutions and border closure. Malaria incidence in Southeastern Thailand dropped significantly (65,550 cases in 1990, 35,000 in 1992 and 15,000 in 1993; Malaria Division, 1991,1993). Mefloquine resistance continued to progress in Mae Sot. To our knowledge, Mae Sot isolates collected in 1994 possess the highest naturally-selected mefloquine resistance levels ever reported (Wongsrichanalai *et al,* 1999).

The Bo Rai outbreak: a historical perspective

A description of the malaria situation in Check (and Mae Sot) during the fall of mefloquine efficacy (1988-1992) will help to better understand how multiple factors contributed to the development of MDR malaria.

Population dynamics

Beginning in October 1988, a large number of men went to Pailin year-round for gem mining and logging in western Cambodia, where

malaria transmission was intense. In 1989, it was estimated that some 3,000 gem miners crossed the border daily through Bo Rai. The migration was so sudden and there was a lack of preparedness of the control program, therefore no protective measures were implemented. Fifty percent of the first-trip returnees became malaria positive, usually after 2-3 weeks' stay (Malaria Division statistics). Over 50% of the Thai gem miners originated from non-malaria-endemic areas. Gem miners also came from neighboring countries such as Myanmar, Bangladesh and India. The addition of non-immunes to an area of intense transmission resulted in a massive epidemic. This, plus high drug pressure, promoted rapid replacement of the sensitive parasites by resistant strains. To worsen the situation, those fortune seekers had to walk a long distance from Bo Rai along a defined path believed to have been cleared of land mines, thus presenting themselves for mass exposure to infective mosquitos. The gateway District of Bo Rai served as the only accessible commodity and pharmaceutical center. It was necessary for the gem miners to return to Bo Rai every few weeks or whenever they became sick. Often, they re-entered Thailand with severe malaria. Those who survived went back to seek further fortune soon after receiving treatment.

The spread of MDR strains from Bo Rai to Mae Sot resulted in simultaneous deterioration of mefloquine clinical efficacy in both areas (Fontanet and Walker, 1993; Nosten *et al,* l991; Thimasarn *et al,* 1995). Direct bus services were available daily for transportation of migrating gem miners and gem traders, and thus the associated purveyance of resistant malaria parasites, between these two border towns over 600 km apart. A survey conducted by the Malaria Division in 1989 revealed that 31% of the malaria patients in Bo Rai originally came from Mae Sot (Thimasarn *et al,* 1991).

At the same time in Mae Sot, civil unrest in Myanmar drove tens of thousands refugees into camps on the border. There was frequent movement of both the refugees and para-military groups freely across the borders. As a number of these focal reservoirs were inaccessible to any control efforts, the newly introduced MDR-malaria was firmly established in the immediate area of the Thai-Myanmar border.

Drug pressure: During 1985-1995, the standard treatment for falciparum malaria all over Thailand was a single 750 mg dose of mefloquine (as MSP or mefloquine alone). In Bo Rai, mefloquine efficacy dropped sharply around 1988-1989. Drug treatment failure was probably the primary mechanism. The hidden cases (of treatment failure) accumulated and the large influx of non-immune gem miners led to an outbreak followed by high consumption of mefloquine and then the re-infection mechanism. Gem miners usually went back to Cambodia as soon as they were physically able to do so after obtaining medical treatment and other supplies. They carried in their blood streams sub-therapeutic levels of mefloquine, which remained for several weeks after the standard single-dose therapy because of its characteristic long terminal elimination phase (White, 1998). There was exceptionally high mefloquine pressure in the Thai-Cambodian border areas at that time, which also included an unknown amount of mefloquine distributed outside of the Thai Malaria Control Program such as in Khmer refugee camps along that same border area. Mefloquine pressure also existed on the Thai-Myanmar border because mefloquine was not only used at malaria clinics but was also the primary anti-malarial for falciparum malaria in Karen refugee camps near Mae Sot (Nosten *et al,* 1991).

Lack of transmission control: The actual epidemic center of the Bo Rai outbreak was in the high-transmission areas of western Cambodia. The abundant neglected gem pits served as mosquito breeding sites. This, plus inaccessibility of any vector control efforts, enhanced vector capacity and transmission of the resistant parasites.

RECENT AND CURRENT SITUATIONS AT MAE SOT

Introduction of artesunate

Small-scale use of artesunate for dose-ranging trials in Thailand began in 1993. On

1 October 1995, the Thai Malaria Control Program instituted an artesunate-mefloquine combination as the standard therapy for out-patients detected at malaria clinics in selected areas in the country designated as "high-level MDR zones," mainly around Mae Sot on the border of Thailand with Myanmar and around the Southeastern border of Thailand with Cambodia. The co-administration of artesunate with mefloquine (300 mg artesunate plus 1,250 mg mefloquine in split dose on the first day, and 300 mg artesunate plus 30 mg primaquine on the second day) became the first-line drug regimen with microscopically-proven falciparum infection.

According to the national malaria statistics, Tak Province, where Mae Sot is located, has carried the largest burden of malaria diagnosis and treatment for foreigners, the majority of whom are from Myanmar, for 8 consecutive years (1992-1999) with an average of approximately 40,000 malaria cases/year. Tak also has the highest number of malaria cases among Thais for 6 of those 8 years accounting for 25,000 cases/year on average. *P. falciparum* cases in Tak account for about 70% of the country total. In spite of the relatively large number of malaria cases in Mae Sot, the malaria situation has been stable and under control within the Thai territory for the past 5 years. This led to the belief by some that the artesunate-mefloquine combination regimen was a key to the halting of mefloquine resistance and thus to the improved malaria situation on the Thai-Myanmar border.

Population movement characteristics

The problem of MDR malaria in both Mae Sot and Bo Rai is associated with population movement. The nature of the movement on the Thai-Myanmar border today is different in several ways from what happened earlier in the same area or on the Thai-Cambodian border.

Currently migrants from Myanmar coming to Mae Sot are predominantly semi-immunes (as opposed to the mostly non-immune gem miners going to Cambodia). Migration occurs most heavily once a year at the beginning of the rainy season (May-June), during which period economic migrants from Myanmar enter Thailand mainly for agricultural employment. A smaller peak of incoming workforce is usually noted towards the end of the year in conjunction with the harvesting season. A large number of these immigrants seek permanent residence in Thailand. In contrast to the situation in Bo Rai a decade ago, movement is largely one-way towards Thailand and occurs through a number of entry points, legal as well as illegal, along the border.

Many of these immigrants (up to 60% of some groups) arrive in Thailand with infections of mefloquine-resistant malaria, indicating that there are still pockets of active transmission of MDR-malaria in the region of the Tak border (AFRIMS Surveillance data, 1999; VBDC, 1999). Some may be exposed during their cross-border journey. Once they arrive in Thailand and receive malaria treatment, they then remain in non- or low-to-moderate transmission areas for at least several months. Migration in the opposite direction of Thai loggers and traders to Myanmar is negligible in quantity compared to the number of incoming Myanmar nationals.

Malaria control measures

In Mae Sot, malaria transmission is much less than that in Myanmar. In Thailand, full measures of malaria control are routinely implemented and include not only free services of microscopic diagnosis and same-day treatment (if possible) but also constant case surveillance as well as regular vector control. The reduced transmission resulting from malaria control policies is critical to minimizing risk of exposure of parasites to sub-clinical mefloquine levels, residual of the previous treatment. Even so, there are many places in this heavily forested and rather mountainous border area where mosquito control efforts cannot reach. This scenario is totally opposite to the uncontrolled, intensive transmission in the endemic areas around Pailin in western Cambodia during the Bo Rai outbreak.

Thailand's strong infrastructure includes the availability of 544 malaria clinics in endemic

areas nationwide. As a result, the national malaria mortality rate progressively dropped from 18.2/100,000 people in 1964 to 8.0/100,000 in 1981 and to under 2/100,000 from 1992.

Drug consumption

The amount of mefloquine consumed in Thailand has increased (under 200,000 tablets in 1991 to over 600,000 tablets/year from 1997 onward) during the past decade. This means the present use of mefloquine, which is concentrated in the Mae Sot area, is more than that consumed in Bo Rai over a decade ago. It should be noted that, currently in "the high-level MDR zones," high-dose mefloquine (1,250 mg or 25 mg/kg) is used in combination with artesunate, whereas only the regular dose (750 mg or 15 mg/kg) was used during the Bo Rai epidemic. Although mefloquine pressure remains high, the workload for mefloquine is much less for Mae Sot compared to Bo Rai a decade ago for the following reasons: 1) the initial parasite density is generally lower as a result of earlier diagnosis; 2) the majority of the people are semi-immune, thus parasite elimination is augmented by host immunity; and 3) the bulk of the parasites is initially eliminated by artesunate. In regard to artesunate, the consumption per annum increased over ten-fold from 1994 (30,000 tablets) to 1998 (360,000 tablets).

Efficacy of anti-malarial regimens

Artesunate-mefloquine combination is known to provide pharmacodynamic advantages (White, 1998; Kyle *et al*, 1998). The parasite population is greatly reduced after a course of artemisinin compounds. No clinical resistance has so far been reported. Although the artesunate-mefloquine combination is routinely used in Mae Sot, Bo Rai and a few other areas near the Thai-Cambodian border, elsewhere in Thailand (~ 30% of the falciparum cases) mefloquine alone (750 mg single dose) remains the first-line drug for outpatient cases and its field efficacy is still satisfactory (*ie* >80 % cure rate for 28-day follow-up) (Malaria Division statistics).

***In vitro* susceptibilities**

In Mae Sot, artesunate and mefloquine IC50s and IC90s slightly increased from 1991 to 1994 (Wongsrichanalai *et al*, 1999; AFRIMS surveillance data). The overall *in vitro* susceptibility patterns are consistent with artesunate sensitivity. On average, artesunate IC50s of Mae Sot isolates are 1.5-2 times higher than those of isolates collected from Yala, a southern province of Thailand bordering Malaysia where the efficacy of mefloquine alone is still high and artesunate is not used (Wongsrichanalai *et al*, 1999).

An increase in geometric mean mefloquine IC50 was also found between 1991 and 1994. After 1994, there was no improvement of *in vitro* mefloquine resistance. The geometric mean IC50 was 95.5 (95% CI 75.9-120.1) in 1994, 92.3 (95% CI 70.7-120.6) in 1997 and 109.6 nM (95%CI 92.7-129.7) in 1999. Based on *in vitro* assays, mefloquine resistant isolates, are still prevalent in Mae Sot (Wongsrichanalai *et al*, 1999; AFRIMS surveillance data, 1997-1999).

In vitro correlation between artesunate IC50s and mefloquine IC50s in wild isolates was found in several studies (Wongsrichanalai *et al*, 1999; Pradines *et al*, 1998; Bustos *et al*, 1994; Basco and Le Bras, 1993). Mefloquine and artemisinin compounds are structurally dissimilar so cross-reactivity is unlikely and the clinical and epidemiological implications of this finding are still not known. It may only be suggested that there is perhaps some overlap in the mechanism of actions of these two drugs (Meshnick, 1998; Le Bras, 1998). However, if cross-reactivity between these two drug groups is real, an existing high degree of resistance to mefloquine or quinine could enhance development of artesunate resistance.

THE FUTURE

Currently, artesunate-mefloquine combination is required for the control of malaria in Mae Sot (and the Thai-Cambodian border). The dose is maximal for each drug. Extending the

treatment course to more than two days is known to increase its therapeutic efficacy (Kyle *et al*, 1998) but would likely reduce compliance and therefore is not considered to be practical for operational use in out-patients facilities (at malaria clinics). Efficacy of the current regimen will be maintained as long as each of the two drugs is not functionally overloaded, *ie* artesunate maintains its potency to eliminate the large proportion of the parasites leaving only a small proportion for mefloquine to act on. The malaria situation on the Thai-Myanmar border is in a sense a fitness test for this functional balance between the two drugs.

Because of the short half life of artesunate plus the pharmacodynamic advantages of its co-administration with mefloquine, many believe that resistance to artesunate and similar compounds is unlikely to occur any time soon. In the optimistic view, administration of artesunate with mefloquine possibly helps to delay resistance development to both because their different actions mean that independent mutational determinants are required to encode resistance to both drugs simultaneously. Furthermore, evidence from an *in vitro* study also suggested that certain *P. falciparum* strains might carry genetic traits that allow them to initiate resistance to structurally and mechanically unrelated compounds after continual exposure (Rathod *et al*, 1997). Recently, it was also demonstrated by transfection of plasmids into selected *P. falciparum* strains that mutations in Pgh1 (P-glycoprotein homologue 1, which is encoded by *pfmdr1)*, could confer resistance to mefloquine and that artemisinin IC50s were also altered in the same direction as the levels of mefloquine susceptibility (Reed *et al*, 2000). Drugs in the artemisinin group are relatively new to the parasites in Thailand so it is premature to speculate on their life span.

An additional effect of the artemisinin group of drugs specifically on malaria transmission is difficult to assess. Observations in a refugee camp near Mae Sot (Price *et al*, 1996) and during an artemisinin trial in the Gambia (von Seidlein *et al*, 2000) suggested that significant reduction of gametocyte development can occur after the introduction of artesunate. This needs to be validated in areas of diverse endemicity. The routine addition of primaquine, a gametocytocidal drug, although only at a single 30-mg dose, as a part of standard treatment regimen for falciparum malaria in Thailand complicates such an assessment in the general malaria endemic population in this country.

If the number of migrants from Myanmar declines, there will be fewer malaria cases in Mae Sot and control measures will be more successful. However, because of the unpredictable geo-political situation along the Thai-Myanmar border, there may be a sudden influx of people into Thailand any time. If that happens, the current control efforts may fail, the malaria situation will become unstable and a massive outbreak may follow. A further rapid rise in the number of resistant parasites is then likely as long as the resistance genes are still prevalent and the parasites continue to be exposed to high drug pressure.

In achieving the primary goal of malaria control, which is a reduction of mortality, we seem to have inevitably favored the rise of drug resistance. It seems unavoidable that we must live with drug resistant malaria (Schapira *et al*, 1993). Therefore, more attention is needed to minimize the problem and limit its spread. This can be done in a number of ways including the adoption of rational drug use, improving drug formulations, etc (Wernsdorfer, 1994).

CONCLUSION

There was no significant increase in the level of mefloquine resistance after 1995. Although the precise mechanism of action of the artemisinin drug group is still not adequately understood, it is sensible to assume that mefloquine plus artesunate is currently an effective combination and that the addition of artesunate has prolonged the usefulness of mefloquine as an antimalarial in Thailand.

It is likely that the malaria situation in

Mae Sot is in a precarious balance, such that it would not take much to upset that balance. Will artemisinin group resistance develop? Will mefloquine resistance worsen? After five years of artesunate use as the first line anti-malarial against falciparum malaria, highly mefloquine-resistant strains are still common in Mae Sot. Should the existing malaria control efficiency decrease or other human and environmental conditions fulfill the selection process for resistance development, the future situation in Mae Sot could worsen rapidly much like the problem in Bo Rai a decade ago. These parasites continue to gain additional credit for threatening the efficacy of yet another class of antimalarials the way their predecessors made successful selection of resistance for 4-aminoquinolines and antifolates.

There are multiple factors that interact and contribute to the relative success so far of malaria control on the Thai-Myanmar border, compared to that on the Thai-Cambodian border a decade ago. The characteristics of population movement and the well-established infrastructure of the Thai Malaria Control Program account for much of the partially balanced outcome. Use of artesunate plus mefloquine for the control of malaria on Thailand's borders is believed to be only one of these factors. This regimen should not be viewed as a means for universal salvage of antimalarial drug efficacy. In fact, it may turn out to be a double-edged sword if used uncontrolled or without parallel efforts to improve diagnosis and vectorcontrol measures locally as well as regionally.

REFERENCES

Basco LK, Le Bras J. *In vitro* activity of artemisinin derivatives against African isolates and clones of *Plasmodium falciparum*. *Am J Trop Med Hyg* 1993; 49: 301-7.

Boudreau EF, Webster HK, Pavanand K, Thosingha L. Type II mefloquine resistance in Thailand. *Lancet* 1982; ii: 1335.

Bustos MDG, Gay F, Diquet B. *In vitro* tests on Philippine isolates of *Plasmodium falciparum falciparum* against standard antimalarials and four qinghaosu derivatives. *Bull WHO* 1994; 72: 729-36.

Fontanet AL, Walker AM. Predictors and treatment failure in multiple drug-resistant falciparum malaria: results from a 42-day follow-up of 224 patients in eastern Thailand. *Am J Trop Med Hyg* 1993; 49: 463-72.

Hall AP. The treatment of malaria. *Br Med J* 1976; 1: 323-8.

Harinasuta T, Suntharasamai P, Viravan C. Chloroquine-resistant falciparum malaria in Thailand. *Lancet* 1965; 2: 657-60.

Harinasuta T, Viravan C, Reid HA. Sulphormethoxine in chloroquine-resistant falciparum malaria in Thailand. *Lancet* 1967; 1: 1117-9.

Harinasuta T, Bunnag D, Chongsuphajaisiddhi T, Laotavorn J. Efficacy of antimalarial drugs against falciparum malaria in Thailand. In: Laotavorn J,Harinasuta T, eds. Drug resistant malaria, Technical Report Series No. 1 of the Expert Committee on Drug Resistant Malaria, Bangkok. 1991: 40-65.

Karwacki JJ, Webster HK, Limsomwong N, Shanks GD. Two cases of mefloquine resistant malaria in Thailand. *Trans R Soc Trop Med Hyg* 1989; 83: 152-3.

Ketrangsee S, Vijaykadga S, Yamokgul P, Jatapadma S, Thimasarn K, Rooney W. Comparative trial on the response of *Plasmodium falciparum* of halofantrine and mefloquine in Trat Province, eastern Thailand. *Southeast Asian J Trop Med Public Health* 1992; 23: 55-8.

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 dosage regimens? *Med Trop Mars* 1998; 58 (suppl): 38-44.

Le Bras J. *In vitro* susceptibility of African *Plasmodium falciparum* isolates to dihydroartemisinin and the risk factors for resistance to qinghaosu. *Med Trop* 1998; 58 (3S): 18-21.

Malaria Division. Annual Report, BE 2533 and BE 2536. Department of Communicable Diseases Control, Ministry of Public Health, Nonthaburi, Thailand. 1991 and 1994.

Meshnick SR. Artemisinin antimalarials: mechanism of action and resistance. *Med Trop Mars* 1998; 58: (suppl) 13-17.

Nosten F, ter Kuile F, Chongsuphajaisiddhi T, *et al*.

Mefloquine-resistant falciparum malaria on the Thai-Burmese border. *Lancet* 1991; 337: 1140-3.

Pinichpongse S, Doberstyn EB, Cullen JR, Yisunsri L, Thongsombun Y, Thimasarn K. An evaluation of five regimens for the outpatient therapy of falciparum malaria in Thailand. *Bull WHO* 1982; 60: 907-12.

Pinichpongse S, Suebsaeng L, Malikul S, Doberstyn EB, Rooney W. The operational introduction of mefloquine, a new anti-malarial drug by the Malaria Program of Thailand. *Commun Dis J Thai* 1987: 13: 411-24.

Pradines B, Rogier C, Fusai T, Tall A, Trape JF, Doury JC. *In vitro* activity of artemether against African isolates (Senegal) of *Plasmodium falciparum* in comparison with standard antimalarial drugs. *Am J Trop Med Hyg* 1998; 58: 354-7.

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

Rathod PK, McErlean T, Lee PC. Variations in frequencies of drug resistance in *Plasmodium falciparum*. *Proc Natl Acad Sci USA* 1997; 94: 9389-93.

Reed MB, Salba KJ, Caruana SR, Kirk K, Cowman AF. Pgh1 modulates sensitivity and resistance to multiple antimalarials in *Plasmodium falciparum*. *Nature* 2000; 403: 906-9.

Schapira A, Beales PF, Halloran ME. Malaria: living with drug resistance. *Parasitol Today* 1993; 9: 168-74.

Shanks GD. The rise and fall of mefloquine as an antimalarial drug in Southeast Asia. *Milit Med* 1994; 159: 275-81.

Suebsaeng L, Wernsdorfer WH, Rooney W. Sensitivity to quinine and mefloquine of *Plasmodium falciparum* in Thailand. *Bull WHO* 1986; 64: 759-65.

Thimasarn K, Pinichpongse S, Malikul S, Rooney W, Tansophalak S. Phase III double-blind comparative study of Fansimef® and Lariam® for the curative treatment of *Plasmodium falciparum* malaria in Thailand. *Southeast Asian J Trop Med Public Health* 1990; 21: 404-11.

Thimasarn K. Chapter 7, Malaria situation at Bo Rai District. In: Laotavorn J,Harinasuta T, eds. Drug resistant malaria, Technical Report Series No. 1 of the Expert Committee on Drug Resistant Malaria, Bangkok. 1991: 124-30.

Thimasarn K, Sirichaisinthop J, Vijaykadga S, *et al*. *In vivo* study of the response of *Plasmodium falciparum* to standard mefloquine/sulfadoxine/pyrimethamine (MSP) treatment among gem miners returning from Cambodia. *Southeast Asian J Trop Med Public Health* 1995; 26: 204-12.

VBDC, Department of Health. Annual Report Vector Borne Diseases Control Project, 1997. Department of Health, Ministry of Health, Yangon. 1999.

Von Seidlein L, Milligan P, Pinder M, *et al*. Efficacy of artesunate plus pyrimethamine-sulphadoxine for uncomplicated malaria in Gambian children: a double-blind, randomised, controlled trial. *Lancet* 2000; 355: 352-7.

Webster HK, Boudreau EF, Pavanand K, Yongvanitchit K, Pang LW. Antimalarial drug susceptibility testing of *Plasmodium falciparum* in Thailand using a microdilution radioisotope method. *Am J Trop Med Hyg* 1985; 34: 228-35.

Wernsdorfer WH. The development and spread of drug-resistant malaria. *Parasitol Today* 1991; 7: 297-303.

Wernsdorfer WH. Epidemiology of drug resistance in malaria. Acta Tropica 1994; 56; 143-56.

Wernsdorfer WH, Chongsuphajaisiddhi T, Salazar NP. A symposium on containment of mefloquine-resistant falciparum malaria in Southeast Asia with special reference to border malaria. *Southeast Asian J Trop Med Public Health* 1994; 25: 11- 8.

White NJ. Drug resistance in malaria. *Br Med Bull* 1998; 54: 703-15.

Wongsrichanalai C, Webster HK, Wimonwattrawatee T, *et al*. Emergence of multi-drug resistant *Plasmodium falciparum* in Thailand: *in vitro* tracking. *Am J Trop Med Hyg* 1992; 47: 112-6.

Wongsrichanalai C, Wimonwattrawatee T, Sookto P, *et al*. *In vitro* sensitivity to artesunate of *P. falciparum* in Thailand. *Bull WHO* 1999; 77: 392-8.

World Health Organization. Monitoring systems. In: Practical chemotherapy of malaria. Report of a WHO Scientific Group, Geneva: *WHO Tech Rep Ser* 1990; 6: 94.