MALARIA TRENDS AND CHALLENGES IN THE GREATER MEKONG SUBREGION

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Abstract. This report provides an overview of the epidemiological patterns of malaria in the Greater Mekong Subregion (GMS) from 1998 to 2007, and highlights critical challenges facing national malaria control programs and partners in effort to build on their successes as they move towards malaria pre-elimination and elimination as a programmatic goal. Epidemiological data provided by malaria programs show a drastic decline in malaria deaths and confirmed malaria positive cases over the last 10 years in the GMS. More than half of confirmed malaria cases and deaths recorded in the GMS occur in Myanmar, however, reporting methods and data management are not comparable between countries despite effort made by WHO to harmonize data collection, analysis and reporting among WHO Member States. Malaria is concentrated in forested/forest-fringe areas of the region mainly along international borders providing strong rationale to develop harmonized cross-border pre-elimination programs in conjunction with national efforts. Across the Mekong Region, the declining efficacy of recommended first-line antimalarials, *eg* artemisinin-based combination therapies (ACTs) against falciparum malaria on the Cambodia-Thailand border, the prevalence of counterfeit and substandard antimalarial drugs, the lack of health services in general and malaria services in particular in remote settings, and the lack of information and services targeting migrants and mobile population present important barriers to reach or maintain malaria pre-elimination programmatic goals. Strengthening networking between research institutions and non-government organizations will increase knowledge-based decision and action.

INTRODUCTION

Despite substantial improvements in the epidemiological situation, malaria remains one of the main public health concerns in the GMS. Within the region as a whole, progress in malaria control has been substantial over the last 10 years, but highly variable between countries with over half the documented burden occurring in Myanmar. Continuous collection and analysis of relevant malaria indicators at each level of the

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health care system, from the village through the national level, is expected to provide the essential information needed to measure success and failure of national malaria programs and identify remaining malaria hot spots. Data analyzed by ministries of health provide important insights into the changing malaria situation, which might guide adjustments of national and sub-regional malaria program activities and the prioritization of the malaria research agenda in the GMS.

MATERIALS AND METHODS

The GMS comprises Cambodia, Lao PDR, Myanmar, Thailand, Vietnam, and Yunnan Province in China. The secondary data used for this study originate from the national malaria control programs in the six countries of the GMS, and were obtained via the World Health Organization's Western Pacific and South-East Asia Regional Offices to whom WHO member States report to annually on their health data. All six national malaria control programs produce annual estimates of the number of confirmed malaria cases, the proportion of confirmed malaria cases that are *Plasmodium falciparum*, and the number of deaths attributed to malaria. The number of confirmed malaria cases is defined as the number of patients with lab-based confirmation of malaria diagnosis, whether by microscopy or rapid diagnostic tests (WHO, 1999, 2000; Graves, 2006). Estimates of malaria cases and deaths in Myanmar were not available for 2007; therefore 2006 data were used.

While country-specific data can help to track trends and compare transmission patterns between countries, provinces, and districts, it does not accurately reflect the overall disease burden of malaria as the data are largely derived from passive case detection in public health facilities only. The routine malaria information collected from the health information system has several further limitations including low coverage, unequal distribution of and varying levels of reporting from public health facilities, differing health care seeking practices among populations, and lack of systematic inclusion of data from other sources such as community malaria workers, private practitioners, traditional healers, shop-keepers, faith-based organizations, and self-treated cases. For example, in Cambodia RDT-positive cases managed by Village Malaria Workers in remote villages are not included yet in the Health Information System. This is an important limitation in the Mekong Region, as in most GMS countries only a fraction of malaria cases are managed in the public sector. For instance, a recent study on the health information system in Vietnam found that national malaria figures greatly underestimate the malaria burden, largely because private health facilities, which in some communities have coverage levels twice that of public health facilities, are not accounted for in official figures (Erhart *et al*, 2007). Similarly, less than 20% of individuals in Cambodia seek their first malaria treatment in the nearest public health facility (Socheat *et al*, 2003b; Incardona *et al*, 2007). Results from a Lao PDR survey demonstrated that approximately 53% of respondents self-medicated for malaria (National Statistics Center, 2001). Despite its known limitations, the routine health information system is recognized by WHO as a useful, if imperfect, instrument to provide country information on major disease trends and for detection of epidemics (WHO, 2000; Guitran *et al*, 2006; Cibulski *et al*, 2007; WHO, 2008a).

This paper aggregates the number of malaria cases and deaths at the regional level to produce estimates on malaria morbidity and mortality for the GMS. The sub-national areas are provinces for Cambodia, Lao PDR, Thailand and Vietnam, and are states and

Table 1

Confirmed *P. falciparum* and *P. vivax* malaria among patients investigated for malaria infections, 2007.

Country	*P. falciparum* cases	*P. vivax* cases	Proportion of falciparum cases
Cambodia	36,955	5,563	86.9%
Lao PDR	18,773	264	98.6%
Vietnam	11,078	3,503	76.0%
Myanmar[a]	114,671	86,008	74.0%
Thailand	16,557	16,621	49.9%
China (Yunnan Province)	1,358	4,727	22.3%

Source: National malaria control programs
[a]2006 data

divisions for Myanmar and prefectures for Yunnan Province. However, comparisons in the number of cases and deaths between countries or sub-national areas do not account for differences in reporting methods and sources of data (such as the various combinations of active and passive case detection used by countries and importance of the private sector to deliver health commodities), or the varied definitions of indicators used between countries. Therefore, any interpretation of the data presented here should take into account these limitations.

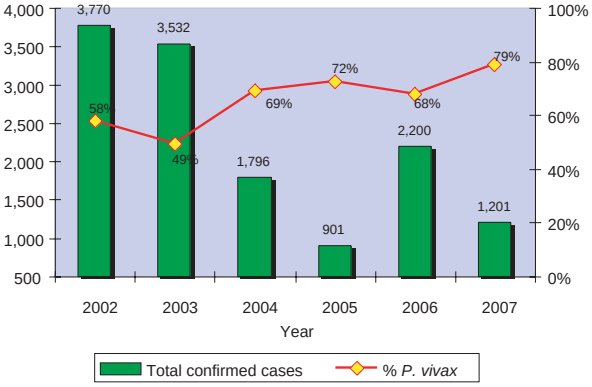
RESULTS

Epidemiological profile of the GMS

The epidemiology of malaria is impacted by the physical environment of the Greater Mekong Subregion. The most prevalent malaria vectors are *Anopheles dirus,* which breeds predominantly in forested areas and preferentially bites humans outdoors, and *An. minimus,* which is widespread in the forest fringe/foothills areas and bites both humans and animals outdoors (WHO, 2005). In the hilly, forested areas of Southeast Asia, malaria transmission is perennial (Trung *et al,* 2004). Most of the population in this region live in rice-growing and plains areas, which are generally free of malaria transmission. The at-risk population typically live in remote, hard-to-reach villages in or close to forested areas in close proximity to the vectors and where accessibility to health services is poorest.

The majority of confirmed malaria cases in the region are *Plasmodium falciparum* (Table 1). Yunnan Province is the only region in the GMS where most reported malaria cases are caused by *P. vivax*. The type of malaria parasite has implications on the severity of illness, risk of death, and the optimal drug therapy; therefore identifying the parasite during diagnosis has important implications for case management (Socheat *et al,* 2003a). However, these national figures mask the highly varied distribution of parasite species that exist within countries. In Thailand, for instance, although half of the confirmed cases nationwide were *P. falciparum* in 2007, this proportion was considerably smaller in the Thai provinces bordering Cambodia, where the number of vivax cases was more than double the number of falciparum cases (Fig 1).

Additionally, the health information system likely underestimates the prevalence



Source: Malaria cluster, BVBD, MOPH Thailand.

Fig1–Evolution of confirmed malaria cases and species distribution in 2 provinces in Thailand (Chanthaburi and Trat) bordering Cambodia (2002-2007).

of vivax infections because patients probably seek treatment more infrequently as complications and severe disease are rare, treatment may be more readily available in the private sector (Incardona *et al*, 2007), and because of the increased use of falciparum-specific rapid diagnostic tests which do not capture vivax infections.

A common pattern across the Mekong region is the concentration of malaria along international borders. Many of these border areas are characterized by forest and forest fringe areas with high malaria transmission, poor geographical accessibility, high population mobility, and low population density. Large-scale population movement from highly endemic areas to low endemic zones has contributed substantially to the maintenance and spread of *P. falciparum* within and beyond the region. A well-documented example of extensive migration leading to the spread of malaria is the return of 100,000 to 200,000 gem miners from Borai Province in Cambodia to their home provinces in western Thailand following the Ruby Rush of 1988 to 1992, and the subsequent increase in

[a]2006 data for Myanmar

Fig 2–Distribution of the highest malaria incidence rates within each country in the GMS, 2007[a] (Confirmed malaria cases per 1,000 population).

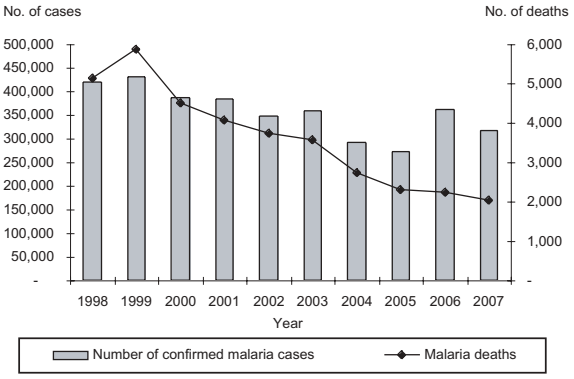
P. falciparum cases (Roony and Thimasarn, 1999). Estimates from clinics in Mae Sot District in Tak Province in western Thailand on the Thai-Myanmar border indicated that 80% of malaria infections were acquired in eastern Thailand on the Thai-Cambodian border.

Fig 2 highlights the four sub-national areas with the highest incidence of confirmed malaria cases within each country. Given the differences in national reporting methods and health system performance, the incidence rates should not be compared

between countries. Nonetheless, the distribution of each country's highest malaria incidence rates demonstrates a high proportion of malaria cases concentrated in border areas across the GMS. The transmission of malaria across borders complicates surveillance and follow-up for national malaria control programs. Therefore, the distribution of malaria in the GMS along international borders underscores the importance of addressing malaria control from a regional standpoint.

The malaria situation from 1998 to 2007

National estimates demonstrate a considerable improvement in malaria morbidity and mortality in the Mekong region over the past decade from 1998 to 2007, including a 60% reduction in the annual number of deaths attributed to malaria, and a 25% reduction in the number of confirmed malaria cases, from 418,859 cases in 1998 to 316,078 cases in 2007 (Fig 3).



Source: National malaria control programs

Fig 3–Malaria cases and deaths in the Greater Mekong Subregion.

Multiple factors have contributed to the region's achievements in alleviating the burden of malaria. Governments and partners made national malaria control a priority by increasing investments in malaria control interventions, strengthening political will, integrating malaria control programs into national health systems adapted to country-specific needs, and intensifying cross-border collaboration in malaria control (Socheat *et al,* 2003a; Van Bortel *et al,* 2008). Environmental changes such as deforestation, economic development (including urbanization), demographic stabilization, greater political stability, and the improved coverage of general health services have also likely contributed to the reduction of malaria morbidity and mortality in the GMS.

The malaria situation across the region is highly variable. For example, in 2007, the incidence of malaria ranged from 0.13 confirmed malaria cases per 1,000 population in Yunnan Province to 3.55 confirmed malaria cases per 1,000 population in Myanmar. The malaria mortality rate for 2007 was lowest in both Vietnam and Yunnan Province, at 0.02 deaths per 100,000 population, and highest in Myanmar, at 2.91 deaths per 100,000.

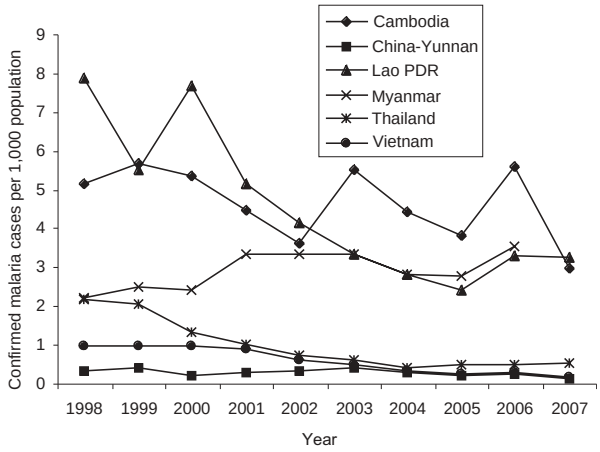
Trends in malaria incidence rates (Fig 4) indicate that progress in the malaria situation has also been varied among Mekong countries. Lao PDR and Cambodia have experienced notable improvements in the malaria situation, largely as a result of strategies implemented by the national malaria control programs and substantial support from the international community. However, the burden of malaria remains substantial in these two countries. The incidence of confirmed malaria cases recorded in 2007 was 2.96 and 3.26 per 1,000 population in Cambodia and Lao PDR, respectively, considerably higher than the malaria incidence recorded in Thailand, Vietnam and Yunnan Province (0.53, 0.17 and 0.13 confirmed cases per 1,000, respectively).

Myanmar is the only country in the Mekong Region where the incidence of con-

firmed cases has increased since 1998 (Fig 4). The incidence of confirmed malaria recorded in Myanmar was 3.6 cases per 1,000 population in 2006 compared to 1.8 cases per 1,000 in 1998. Possible explanations for the increase in the number of confirmed malaria cases in Myanmar are improvements in case finding and reporting systems, as well as the greater movement of migrant workers (ACTMalaria, 2005). Although Myanmar accounts for approximately one-fifth of the region's population, more than half of the malaria cases and approximately three-quarters of the malaria deaths in the GMS in 2006 occurred in this country.

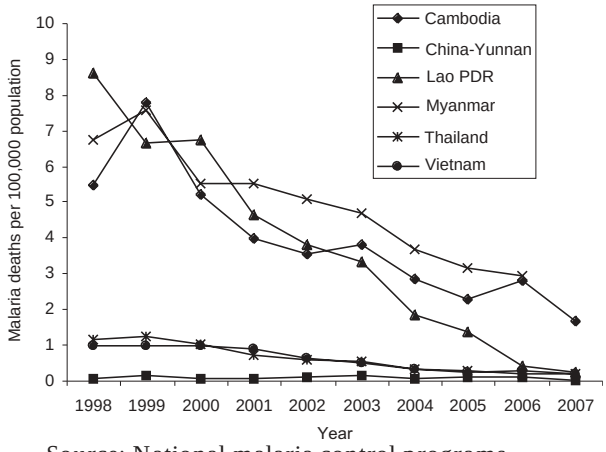
Fig 4 shows that the incidence of confirmed malaria cases increased in the GMS in 2006. Factors that contributed to the rise in malaria cases in 2006 over the previous year vary by country. In Cambodia, the number of confirmed cases increased in 2006 due to the increased movement of mobile populations from low malaria risk areas to high malaria risk areas in 2006; the establishment of many new villages in malaria endemic areas without malaria protection measures in place; and unusually early rainfall, which may have increased the mosquito density that year. The primary reasons for the increased incidence of malaria in 2006 in Lao PDR were the scale-up of Early Diagnosis and Treatment (EDAT) coverage, which resulted in increased case detection using RDTs, as well as improvements in reporting from peripheral sites (GFATM, 2007a).

The number of deaths attributed to malaria per 100,000 population has declined dramatically over the past decade in Cambodia, Myanmar, and particularly in Lao PDR (Fig 5). Significant extra financial support of the Global Fund to Fight AIDS, TB and Malaria to scale up control interventions has contributed towards improvements in the malaria situation in Lao PDR in recent years. In Myanmar, the annual number of deaths attributed to malaria was almost halved over the same period, from 3,182 to 1,647 deaths. As of 2006, the estimated malaria mortality rate in Myanmar was 2.9 deaths per 100,000 population, down from 6.7 in 1998. The drop in malaria mortality in Myanmar might be partially attributed to greater private sector provision of rapid diagnosis tests and artemisinin-based combination therapies.



Source: National malaria control programs

Fig 4–Trends in the incidence of confirmed malaria cases, 1998-2007.



Source: National malaria control programs

Fig 5–Trends in the malaria mortality rate, 1998-2007.

In Cambodia, the annual number of malaria cases and deaths declined by 28% and 61%, respectively from 1998 to 2007. Reductions in morbidity and mortality have been due to multiple factors including environmental changes such as the continuous reduction of primary forest cover [Cambodia has been classified as having the third worst deforestation rate of primary forest in the world, (FAO, 2005)], the rapid scale-up of effective interventions including the expansion of bednet coverage in accessible areas (mostly in northeastern Cambodia), and the end of the civil war in 1998. As the political situation has stabilized since the late 1990s, widespread population movements have decreased and Cambodia's malaria control program has improved its ability to accelerate the scale up of curative and preventive measures throughout the country thanks to substantial funding from the Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM).

In Thailand, after the last epidemics were reported in 1999, malaria morbidity and mortality have declined substantially. In 2007, Thailand reported 33,178 confirmed malaria cases and 97 deaths due to malaria, a substantial improvement from the 125,359 cases and 740 deaths reported in 1999.

The burden of malaria in Vietnam has also decreased drastically with improvements in socio-economic conditions coupled with increased government investments in vertically driven malaria control operations all the way to the community level. The annual number of confirmed malaria cases decreased from 187,994 cases to 14,581 cases between 1991 and 2007. In 2007, the incidence of confirmed malaria cases was 0.17 per 1,000 persons as compared to 2.79 in 1991). The reduction in mortality was even more dramatic with only 20 deaths from malaria nationwide in 2007 compared to 4,646 deaths in 1991.

The malaria situation in Yunnan Province has also improved since 1999. However, progress has not been steady, with the number of cases and deaths increasing from 2001 to 2003, and the number of cases rising again from 2005 to 2006. In 2007, both the malaria cases and deaths dropped substantially: there were 6,085 confirmed cases for malaria and 9 malaria deaths throughout the province, a decrease from 11,064 cases and 32 deaths in 2006. While the malaria burden in Yunnan Province is very low compared to the rest of the Mekong Region, it is, along with Hainan Province, the most endemic province in China. In 2005, Yunnan Province accounted for 38% of malaria cases (all species) and nearly 80% of malaria deaths nationwide. In part, this can be explained by the continuous influx of migrants from Myanmar (GFATM R6 in China, 2006b) where *P. falciparum* infections are more prevalent.

Distribution of malaria cases and deaths within each country

Cambodia. Within Cambodia, the incidence of malaria is most pronounced in Mondulkiri Province in the East (44.7 confirmed malaria cases per 1,000 persons), which is the country's largest and most sparsely populated province. The provinces of Pailin and Preah Vihear in the western part of Cambodia, along the Thai border, also had very high incidence rates in 2007: 42.6 and 34.8 confirmed cases per 1,000, respectively. Large parts of these provinces are forested, with high malaria transmission and little access to public health services. Some parts of the western provinces are former strongholds of the Khmer Rouge.

Lao PDR. In 2007, the highest incidence rates of confirmed malaria in Lao PDR were recorded in the southern provinces of Attapeu, Sekong, Savannakhet, Champasack and Saravane. The provinces of Champasack and

Savannakhet also accounted for most of the 14 malaria deaths recorded in 2007, with 5 malaria deaths each. The most at-risk (or highest risk) groups are miners, forest and agricultural workers, pregnant women and children under five years of age (WHO, 2002).

Myanmar. About 60% of the total malaria cases in Myanmar occur in forest or forest fringe areas (WHO and Myanmar Ministry of Health, 2007). Population groups at high risk of malaria are internal migrants, people who resettle in malaria endemic areas, subsistence farmers in forests and on the forest fringes, and forest workers (loggers, gem miners, etc), particularly non-immune migrants working in forested areas. The malaria burden is particularly high in the border areas that have experienced longstanding conflict due to the civil war. For instance the highest morbidity rates were recorded in 2006 in Rakhine State on the West coast (54.6 clinical suspected malaria cases per 1,000 population). Other provinces with high recorded incidence rates of malaria include Chin State, which borders Bangladesh, Kachin and northern Shan States on the border with China, and Tanintharyi Division, which borders Thailand. The highest mortality rates were recorded in Kayah (on the Thai border) and Kachin states (bordering India and China), with 9.4 and 7.8 deaths per 1,000 population, respectively in 2005.

Thailand. The prevalence of malaria in Thailand is also concentrated along its borders, which are largely forested areas with substantial population movements. Thailand is the primary destination for migrant labor from neighboring countries (Asian Migration Center, 2005). Much of the population movement in and out of Thailand occurs on the Thai-Myanmar border, which extends for about 2,000 km. Along this border, malaria is the leading infectious disease, and most cases and deaths are related to cross-border movements. The Mae Tao Clinic in Mae Sot District, Tak Province, which provides free health care for refugees and migrant workers, treated more than 8,000 cases of malaria in 2006, of which 75% were from Myanmar (Mae Tao Clinic, 2006). The clinic reported 30 deaths from malaria the same year.

Furthermore, confirmed malaria cases in Thailand have risen slightly since 2004, partly due to the escalation of civil conflict in the southern provinces of Yala, Songkhla and Narathiwat. These three provinces accounted for more than 40% of Thailand's confirmed malaria cases in 2007. The unstable political situation and high degree of violence have severely disrupted the access to health services in these three provinces.

Vietnam. A large proportion of Vietnam's malaria cases occur in forested mountain areas (Erhart *et al*, 2005). Among the nine provinces with the highest number of cases, many border Lao PDR or Cambodia, and are located in the central or southwestern part of the country. The central provinces of Binh Phuoc, Quang Tri, Gia Lai, Dak Lak and Dak Nong all recorded increased numbers of cases from 2005 to 2006, accounting for most of the rise in the number of cases nationwide in 2006. The number of malaria deaths also rose in 2006, most notably in Dak Lak (7 deaths). However, the number of malaria cases has since come down, particularly in Gia Lai and Dak Lak.

Yunnan Province of China. Yunnan Province shares a border of 4,000 km with Myanmar, Lao PDR and Vietnam. Malaria occurs mainly on these border areas, and in drainage areas of the Yuanjiang River. Ethnic minority groups living in forests and on forest fringes are at risk, as are mobile workers who cross the border frequently for economic purposes – logging, mining, farming etc – and have little access to routine health

services on either sides of the border. International population movements occur on a large scale in the Yunnan border areas, with substantial implications for the malaria burden. It is estimated that between 2001 and 2005, 25.6% of the total confirmed cases in Yunnan (64,943) were infected in neighboring countries, with Myanmar accounting for most of these cases (GFATM China, 2006). Located in western Yunnan along the Myanmar border, Dehong Prefecture has the highest malaria burden in Yunnan Province, accounting for over 40% of the total confirmed cases in Yunnan and with a reported malaria incidence rate of 2.36 confirmed cases per 1,000 persons in 2007.

Critical challenges for malaria control in the GMS

In order to build on current successes and further reduce the malaria burden in the GMS, the six national malaria control programs must overcome important challenges that characterize the Mekong Region. Well known critical issues that currently undermine malaria control in the region are: 1) multi-drug resistance, 2) the prevalence of counterfeit and substandard antimalarial drugs and irrational drug use, 3) low coverage of malaria control interventions among remote/ethnic populations and in some countries, and 4) difficult access to and use of basic health services by migrant workers and ethnic minorities who are not citizens and therefore not afforded the same social benefits.

Multi-drug resistance. Resistance to antimalarial drugs has been a longstanding problem in the Greater Mekong Subregion. Since the 1970s, the Cambodia-Thailand border has been the global epicentre of emerging resistance to antimalarial drugs. It is in this region that parasite resistance to chloroquine was first documented, followed by resistance to sulfadoxine-pyrimethamine, which was later shown by molecular markers to have spread far outside the GMS (Roper *et al*, 2004), and finally to mefloquine (WHO, 2003). In response to rising resistance to these anti-malarials, Thailand in 1995 and Cambodia in 2000 adapted their national drug policies accordingly to begin using artemisinin-based combination therapies (ACTs) to manage uncomplicated falciparum malaria. Currently, all WHO-recommended treatment regimens for falciparum malaria are based on artemisinin derivatives combined with an effective partner drug (WHO, 2006a). All Mekong countries are strongly promoting the use of ACTs except China and Vietnam, although they have demonstrated a recent willingness to consider a shift in their antimalarial drug policies from artemisinin monotherapies to ACTs.

Recent results from surveillance sites on the Cambodia-Thailand border, however, have shown an increasing failure rate of *P. falciparum* to artemisinin-combination therapies. Slower parasite clearance times have been detected in Pailin, in western Cambodia with an increasing proportion of patients with persistent parasites on Day 3 follow-up blood studies (Wongsrichanalai and Meshnick, 2008). Decreasing therapeutic efficacy rates in sentinel sites coupled with increasing parasite clearance time are a serious cause for concern, could indicate the local emergence of falciparum parasites resistance to artemisinin derivatives (Noedl *et al*, 2008; White, 2008; Dondorp *et al*, 2009).

Further investigation is being undertaken to examine the underlying causes of decreased sensitivity of *P. falciparum* to artemisinin in the region in order to determine whether parasite resistance to artemisinin is in fact developing or whether other causes for treatment failure are predominantly responsible. A Mekong therapeutic efficacy network of 32 sentinel sites is active in the six countries to monitor

Table 2
First-line antimalarial drugs as per national guidelines in the GMS to manage uncomplicated falciparum malaria (2008).

Country	Antimalarial drugs
Cambodia	Artesunate 3 days + Mefloquine 2 days (co-packaged)
Lao PDR	Artemether + lumefantrine (coformulated) 3 days
Vietnam	Artesunate monotherapy 7 days or dihydroartemisinin + piperaquine (coformulated) 3 days
Myanmar	Artemether+lumefantrine (coformulated) 3 days or Artesunate 3 days +Mefloquine 2 days (copackaged) or dihydroartemisinin + piperaquine (coformulated) 3 days
Thailand	Artesunate 3 days + Mefloquine 2 days (loose tablets)
China (Yunnan Province)	Dihydroartemisinin + piperaquine (coformulated) 3 days or Artesunate monotherapy 5-7 days or various other antimalarials as monotherapies or in combination

antimalarial drug resistance through *in vivo* tests (WHO, 2007a). Efficacy of antimalarial drugs is tested in patients against clinical symptoms and parasites counting in blood during at least 28-day follow-up by following strict standardized entry criteria and cross-checked quality data analysis procedures. Re-infections or recrudescence during studies are determined thanks to the systematic use of routine polymerase chain reaction (PCR) techniques. *In vitro* assay techniques are also common practices in Mekong countries but there is still a need to standardize procedures which vary from country to country and between research institutions themselves to interpret and compare results over space and time. However, looking at the 50% inhibitory concentration (IC50) trends of selected drugs on cultivated parasites over time by using similar *in vitro* assays techniques might provide useful complementary information when conducted in parallel to *"in vivo"* studies (Basco, 2007). Additionally, supported by the BMGF and USAID, there is ongoing global and regional effort to establish or strengthen current laboratory capacities, laboratory networks and common database to study relevant genetic markers *eg*, linked to artemisinin drug resistance in the GMS (BMGF- and WHO- 2008; WorldWide Antimalarial Resistance Network, 2009). Activities of the global and regional network include standardizing methodologies and operating procedures, and developing reference laboratories for clinical/molecular testing in existing laboratories throughout the region so that *in vivo*, *in vitro* and molecular marker results on drug efficacy are comparable and useful for policy decisions at country and regional levels.

Counterfeit drugs. The proliferation of counterfeit antimalarial drugs on the informal market, particularly along international borders, has been a major problem in the GMS. The intentional manufacturing and sale, and inadvertent use of fake drugs by unsuspecting patients, has caused deaths from malaria that may otherwise have been avoidable. Further more, the use of counterfeit antimalarial drugs prolongs illness and negatively

impacts the livelihood of those infected, and promotes a loss of confidence in malaria treatment and health systems. As these drugs are often sold for less than the standard price of recommended antimalarials, the most vulnerable populations (poor, hard-to-reach, mobile population) are particularly affected.

Although no precise estimate is available on the proportion of counterfeit antimalarial drugs throughout the GMS, several studies have been conducted in the region. A survey conducted in sites in Cambodia, Lao PDR, Myanmar, Thailand and Vietnam in 1999/2000 (using convenience sampling) found that 38% of 104 samples marked as oral artesunate were counterfeit, containing no active ingredient (Newton *et al*, 2008). A similar survey conducted in 2002-2003 found that 53% of the 188 artesunate blister packs collected were counterfeits (Dondrop *et al*, 2004).

To combat the distribution of counterfeit and substandard drugs, a drug quality monitoring network was established in the Mekong region in 2002, which samples antimalarial drugs in selected provinces of all six countries two to three times per year. In 2006-2007, an international multi-disciplinary group consisting of WHO officials, physicians, pharmacists, scientists, and INTERPOL conducted a joint investigation on counterfeit artesunate in the Mekong countries. From a sample of 391 artesunate tablets collected between 1999 and May 2006 in Vietnam, Cambodia, Lao PDR, Myanmar and the Thai-Myanmar border (mostly using convenience sampling), the group identified a wide variety of fake artesunate as having been manufactured in at least two sites in China (Newton *et al*, 2008). The evidence was presented by INTERPOL to the Chinese authorities, who in turn, carried out a criminal investigation on the manufacturing sites and conducted arrests. This investigation provides a successful model of collaboration between the health sector, INTERPOL and national authorities in combating the trafficking of counterfeit drugs in the Mekong region.

Accessing hard-to-reach and mobile populations. The malaria burden remains high among hill-tribe people and ethnic minorities, of whom about one third live in remote, often hilly, and forested areas where malaria transmission is high. Mobile population and (unrecorded) migrants constitute another high-risk group, especially those lacking citizenship who are therefore unable to access and use national health services at reasonable cost. Of this latter group, unrecorded migrant workers (without work permits) are particularly vulnerable, and in Thailand constitute a large proportion of the mobile population with estimated numbers between 500,000 and 2 million depending on sources (Regional Thematic Working group, 2008).

Ensuring quality diagnosis and appropriate treatment, however, is particularly difficult in the remote areas of the GMS, which are often where these vulnerable groups are found. In these regions, access is difficult due to poor roads (especially during the rainy season) increasing difficulties to bring ITNs. It is difficult as well to maintain a cold or "cool" chain for rapid diagnostic tests and antimalarial drugs. Supervision at the village level and exchange of information between villagers and district teams are often inadequate (WHO-ADB, 2008). A recent study on access to ACTs for malaria in Cambodia found that in remote areas the coverage of appropriate diagnosis and treatment for malaria was very low, and there was widespread use of artemisinin monotherapies (Yeung *et al*, 2008). The main reason for the low coverage of appropriate ACTs was the predominant use of the private sector for malaria services (such as *"informal"* vendors), where treatment is unregulated

and often inappropriate. However, results from the study also suggest that the provision of malaria diagnosis and treatment through trained and supervised Village Malaria Workers (VMWs) is an effective means of increasing access by remote population to malaria control interventions in certain remote settings.

Ensuring an adequate coverage of vector control and personal protection measures is also particularly challenging in the isolated, forested areas of the region (such as in central Vietnam or on the Thai-Myanmar border, where many ethnic minorities and migrant workers live). Moreover, ITNs are not always appropriate, for example in forest settings where *An. dirus* bites early in the evening (Erhart *et al*, 2005). This highlights the need for operational research in remote settings to develop and use relevant case management and vector control measures that are appropriate for the population being targeted and the forest environment.

DISCUSSION

This paper highlights progress made in the GMS in malaria control during the last 10 years based on official epidemiological data annually reported to WHO by Member States. There are limitations to this data for many reasons (WHO, 2000, 2008a), and there is recognition by countries themselves and the international community that improvement in reporting and measurement methods of malaria burden estimates are needed in almost all countries (Guitran *et al*, 2006; Cibulski *et al*, 2007; WHO-MEASURE Evaluation, 2008; WHO, 2008a). During a recent informal consultation in Bangkok in September 2006 (WHO, 2006b), the need for increasingly simple yet effective methods for data collection and reporting were discussed as well as increasing country ownership of the data by building capacity to measure and map the burden of malaria. International efforts are also focusing on fine-tuning methodologies to accurately map malaria transmission and infections such as the Malaria Atlas Project (Hay and Snow, 2006). In addition to data routinely generated by the national information system, many tools have been developed by various institutions to fulfill reporting and auditing requirement from donors when significant non-domestic funds are used in malaria control. These tools, while well-intentioned, often contribute to parallel systems that increase confusion and the burden of data management and reporting at country level (WHO-MEASURE evaluation, 2008). Standardization and consistency among indicators and proposed methodological guidelines are needed, bearing in mind that despite the limitations, data routinely collected through the national information system remain the basis for measuring malaria trends over space and time. This routinely collected information should be complemented by indirect methods cross check data accuracy (Cibulski *et al*, 2007). The WHO Mekong Malaria Programme along with partners is facilitating the M&E surveillance network activities in the GMS. The Mekong malaria M&E Network aims to harmonize and simplify needed indicators and improve data management tools to be consistently used across Mekong countries (WHO-MEASURE Evaluation, 2008). The Global fund, which is providing substantial funding for malaria programs in the GMS is also looking to better document the impact of its investment (WHO *et al*, 2006 under revision), and encouraging more investment in operational research (GFATM-TDR, 2008).

Malaria transmission in the GMS is increasingly recorded in fewer and fewer "hot spots" or occupational situations. Detection and control of such foci where local transmission may occur need more innovative and technology advanced surveillance

approaches. New internet-based comprehensive surveillance technologies should be able to precisely identify and locate confirmed malaria positive cases in order to actively investigate for potential secondary infected patients (so-called active foci). Such active surveillance systems need strong linkages in reporting and consolidation of confirmed malaria cases from both public and private health care facilities and from community health workers under strong malaria national leadership as described in recent guiding manuals on malaria pre- elimination and elimination by WHO (WHO, 2007a, 2008b). Sophisticated surveillance tools tracing positive cases at household level will be piloted while looking at containing artemisinin resistant malaria parasites on the Cambodia-Thailand border (WHO, 2008c,d).

To improve the monitoring of malaria parasite resistance to antimalarial drugs in the GMS, the WHO Mekong Malaria Programme is consolidating the therapeutic efficacy study (TES) network in the GMS. The Mekong TES Network provides evidence-based information and accurate data on the efficacy of first line antimalarial drugs in the region to malaria program managers on which to base timely modifications to their drug policy (Vestergaard and Ringwald, 2007; WHO, 2007a). In addition to the WHO Mekong-supported network, regional and international research institutions are conducting studies validating new antimalarial combinations, testing new regimens and dosages of existing regimens, and assessing their use at field level. Recent findings from therapeutic efficacy studies conducted in the GMS and other regions have prompted researchers and donors to invest increasing resources to contain *P. falciparum* resistance to artemisinin in the GMS (WHO, 2007b, 2008d; BMGF and WHO, 2008; Noedl *et al*, 2008; Enserink, 2008).

Circulation and use of substandard and counterfeit drugs is not new in the GMS and increasing efforts have been made by National Drug Regulation authorities, WHO, INTERPOL, the International Custom Organization and field researchers to document the magnitude of the problem and advocate for strong action from national Governments. Recent successes to shutdown factories producing substandard and counterfeit drugs with government support are encouraging, but there is still a need for additional global and regional concerted multi-sector approaches and a stronger commitment from affected countries. WHO is encouraging Member States to look at and strengthen their regulatory and supervision mechanisms (WHO, 2002) with particular attention to private sector practices, and encouraging donors to increase their direct investment in the problem (*eg*, GFATM R6 Cambodia).

According to epidemiological data, malaria (and other communicable diseases) remains at unacceptably high levels in border areas (Fig 1), and in hard-to-reach populations including ethnic minorities and mobile population. Exclusion of such populations from basic health services (ADB, 2001), even in countries with effective control interventions, sophisticated tools, good health infrastructure, and sufficient funding, will hamper efforts at isolation of tolerant parasites (WHO, 2007b) and overall elimination. More harmonized and aligned multi-country malaria control and pre-elimination strategies and proposals are needed to address inclusion of vulnerable populations. Efforts are ongoing to mobilize Ministries of Health and Governments to increase their support, attention, and investment to assure access in hard-to-reach locations for marginalized populations to health care services including malaria prevention and control tools (WHO, 2008; GFATM round 7 in Vietnam (2007) and Thailand (2007b) and Rolling Continuous Channel in Cambodia (2009).

Efforts have been made to document and improve communicable diseases control and prevention in migrants and mobile population in certain health programs, particularly HIV/AIDS programs (Asian Migrantion Centre, Mekong Migration Network, 2005; FHI-USAID, 2006; Regional Thematic Working group, 2008). However, efforts have to go beyond the health sector as part of human security concerns and must then include other Ministries with potential conflicting interest such as the Ministry of Interior, Labor, Defense and Foreign Affairs.

The Mekong Malaria Programme is increasingly involved with national programs and partners to better document internal and cross-country migratory patterns, migrant health status, and to monitor transmission of malaria in mobile population. Surveillance systems have to incorporate such vulnerable populations to increase their performance and usefulness for action (BMGF and WHO, 2008; GFTAM R9 in Cambodia, Myanmar and Thailand under development, 2008).

Importantly, there is evidence in areas where microscopy is widely used for diagnosis, such as Thailand, of the increasing importance of *P. vivax* infections. This is partially due to the success of controlling falciparum infections and also due to the lack of effective tools to manage relapses which are responsible for maintaining vivax transmission (Galappaththy *et al*, 2007). More research is needed in this yet neglected area to, for instance, validate the most effective dose and regimen of primaquine, and to identify alternative safe drugs in areas where G6PD deficiency is highly prevalent (WHO, 1989; Beutler and Duparc, 2007). The Vivax network, established in Shanghai in 2006, is expected to link researchers and international donors organizations to develop a research agenda on vivax infections (WHO, 2006). In the overall context of malaria elimination, increasing investment on research targeting *P. vivax* infections was emphasized by experts participating in the launching of the Asia-Pacific Malaria Elimination Network (APMEN) in Brisbane in February 2009 (APMEN, 2009).

The discussed challenges require sustained attention and support from individual countries, and increased interaction and strategic technical cooperation between international and national organizations. WHO must provide strong technical leadership in malaria control and research to support these efforts (Anonymous, 2008).

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