

Progress on the Containment of Artemisinin Tolerant Malaria Parasites in South-East Asia (ARCE) Initiative

I. Background

For many years, the border area between Cambodia and Thailand has been the source of *P. falciparum* resistance to several antimalarial treatments, including chloroquine, sulfadoxine-pyrimethamine and mefloquine. Resistance to chloroquine and sulfadoxine-pyrimethamine subsequently spread to other parts of Asia and Africa, causing a surge in malaria morbidity and mortality particularly in Africa. Currently, the most effective and widely used treatment for malaria is artemisinin-based combination therapy (ACT). Recently, routine national antimalarial drug efficacy surveillance systems in a few countries in South-East Asia, supported and coordinated by the World Health Organization (WHO), have shown that an increasing proportion of patients take longer to clear parasites following treatment with artemisinin combination therapy. Whereas previously, not more than 3-5% of patients showed parasites persisting in blood on the third day of treatment, in one border region between Cambodia and Thailand, over 20% of cases treated with ACTs in 2008 had parasites that persisted on the third day. The alarming possibility that parasites had developed resistance to, or at least become tolerant to, artemisinins was then considered.

The emergence of anti-malarial drug resistance in this region is not well understood. There are many factors that contribute to this:

- **Selection pressure.** Drug resistance can develop through genetic mutations of wild-type genes in the parasite rendering them no longer susceptible to antimalarial treatment. The use of antimalarial drugs in patients with parasites containing mutations can eliminate susceptible parasites, but leave resistant mutants to survive and reproduce.
- **Monotherapies.** Artemisinin monotherapies (single drug treatments) have been widely available and extensively used in Cambodia where a significant proportion of people seek treatment from the private sector. These artemisinin monotherapies are sometimes cheaper than ACTs, and are perceived as having fewer side-effects.
- **Irrational drug use, particularly in the private sector.** It has been estimated that up to 70% of Cambodian patients seek treatment for malaria

from the private sector. Private drug vendors are generally motivated to sell the drugs their customers seek and can afford. Despite the recent ban on the sale of artemisinin monotherapies in Cambodia, ensuring compliance and enforcement of this policy will remain a challenge.

- **Lack of compliance and adherence.** Multiple-day treatment regimens make it difficult for patients to finish their full course of treatment. This results in inadequate drug dosing which is likely to accelerate the development of drug resistance.
- **Counterfeit and substandard drugs.** Counterfeit and substandard drugs are widely available and well-documented in this part of the world. Inadequate dosing from ineffective or poor quality drugs can kill the patient, increase the potential for development of drug resistance and may also contribute to the prolonged infectiousness of a patient.
- **Mobile and migrant populations.** This region has a highly mobile population with people moving both internally and internationally, previously mainly for woodcutting, construction projects, military movement, land development, and more recently for seasonal agricultural work.

Without a well coordinated containment strategy, the resistant parasites could potentially spread beyond this region, just as with chloroquine and sulfadoxine-pyrimethamine in the past. Given that no other class of antimalarials is sufficiently far along in development to replace artemisinins over the next few years, their loss to drug resistance would present an enormous loss to global malaria control and elimination. In response to this critical situation, WHO, together with the governments of Thailand and Cambodia and committed experts and partners, promptly developed and began to implement a containment strategy to prevent the spread of artemisinin resistant parasites.

II. Response to artemisinin resistant malaria

A strategy for the containment of artemisinin tolerant malaria parasites in South-East Asia (ARCE) project began in November 2008. The initiative, which is funded mainly by the Bill and Melinda Gates Foundation (BMGF) but also by the Global Fund and the United States Agency for International Development / President's Malaria Initiative (USAID/PMI), aims to contain resistant parasites by

removing selection pressure and ultimately eliminating falciparum malaria from the area.



Zone 1 (purple) covers areas of the Thai-Cambodian border where there has been evidence of artemisinin tolerant *P. falciparum*. **Zone 2** (green) covers areas that are considered at risk.

The zones were defined on the basis of antimalarial drug efficacy data from the sentinel sites and some research data.

The specific project objectives are to:

1. To eliminate artemisinin tolerant parasites by detecting all malaria cases in target areas (zone 1) and ensuring effective treatment and gametocyte clearance;
2. To decrease drug pressure for selection of artemisinin tolerant malaria parasites;
3. To prevent transmission of artemisinin tolerant malaria parasites through the use of mosquito control and personal protection;
4. To limit the spread of artemisinin tolerant malaria parasites by mobile/migrant populations;
5. To support containment/elimination of artemisinin tolerant parasites through comprehensive behavior change communication (BCC), community mobilization and advocacy;
6. To undertake basic and operational research to fill knowledge gaps and ensure that strategies applied are evidence-based;
7. To provide effective management, surveillance and coordination to enable rapid and high quality implementation of the strategy.

The efforts to contain artemisinin tolerant parasites in this area were undertaken in the full knowledge of some critical technical and operational challenges that had to be confronted in achieving this. These challenges included:

1. complete removal of artemisinin drug pressure from the area -which would have been ideal- was not possible, because there was no other suitable antimalarial medicine that could be deployed other than a different fixed-dosed ACT (dihydroartemisinin-piperaquine) to replace the co-blistered one (artesunate-mefloquine) that was being used;
2. the mosquito vectors in the area were exophilic (outdoor resting) and exophagic (outdoor biting), which makes them less vulnerable to standard vector control methods such as indoor residual spraying and insecticide-treated nets;
3. highly mobile populations in the area, which made it more difficult to track human infections and increases the chances of spreading parasites to neighbouring areas; and
4. the containment zone encompasses an international border between two countries, which makes co-ordination of strategies and implementation methods ever more complex.

The elements of the containment strategy, defined over the course of several WHO meetings, were considered the most optimal under these difficult circumstances (WHO 2007, 2008a, 2008b, 2008c). Activities to date have included a large-scale recruitment and training of health care workers at the village level; procurement and distribution of effective treatment, rapid diagnostic tests, long lasting insecticide treated ordinary nets as well as hammock nets to the residential and mobile/migrant population in the targeted zones of Cambodia and Thailand. In Cambodia, there has also been an active engagement with private drug sellers to combat counterfeit and substandard drugs and to enforce the ban on the sale of antimalarial monotherapies in collaboration with government agencies.

The initiative entails activities in three zones: zone 1 in which there are intensive containment activities aimed at the local elimination of malaria; zone 2 in which there are intensified malaria control activities; and zone 3, the rest of the country, in which regular malaria control activities are being carried out.

III. Monitoring progress and accomplishments

Monitoring of project progress is the responsibility of an independent panel of technical experts: the International Task Force (ITF), and two National Task Forces (NTF).

The NTF (for each country) is responsible for overseeing national project implementation, monitoring progress, coordinating the national containment project and advocating for high level commitment. The NTF informs the ITF of the progress of activities in each country. The ITF also provides guidance and technical advice, and advocates for high level political commitment. The ITF is represented by international malaria experts, and the two chairs of the national task forces. To date, two ITF meetings have been held, one in Phnom Penh in April 2009, and the other in Hanoi in February 2010. During the meetings the ITF members have provided critical guidance on technical issues, provided feedback on project progress and made the recommendations needed to ensure effective project implementation. Representatives from the national malaria control programme managers of affected and at risk countries, WHO, implementing partner organizations and donors were also invited to attend the meetings, as observers.

The International Task Force (ITF) has noted the progress made by the initiative in the following areas: rapid procurement and distribution of bednets, the quick deployment of village malaria workers for diagnosing and treating patients, and the effective behavioural change communication strategies. Innovative techniques were used in the project for microplanning and monitoring of bednet distribution.

The containment project was awarded in November 2008 and implementation activities began in early 2009. The project has already met some key milestones:

- More than 1300 village malaria workers and mobile malaria workers have been recruited and trained for the diagnosis and treatment of malaria patients, and are providing early diagnosis and treatment to at risk populations in zone 1 and 2 in Cambodia and Thailand.
- Rapid and large-scale procurement and distribution of long-lasting insecticidal nets (LLINs), long lasting insecticidal hammock nets (LLIHN) and insecticides have been achieved in the priority containment zones.
 - In Cambodia: 96% of LLINs delivered were seen at home during the assessment; 73% of the LLINs observed during the assessment (equivalent to 70% of those LLINs delivered) were currently in use; of the nets being used, respondents reported that 99.7% had been

used on the previous night; a national policy net coverage rate of 1.79 people per net was achieved.

- In Thailand: 100% coverage of LLINs in endemic villages; 73% of the population slept under an LLIN/LLIHN/ITN on the previous night; and among forest workers in 2009, 65% slept under a net the last time they slept in the forest. The target rate for 2010 is 80%.
- A ban on artemisinin-based monotherapies was issued on 23 March 2009 by the Cambodian Department of Drugs and Food (DDF) with support from the Minister of Health. All private pharmacies and shops dispensing drugs in Pailin have been registered and are regularly inspected.
- National Task Force meetings in Thailand and Cambodia and joint International Task Force meetings have been held to provide technical oversight and monitoring of the Project. The recommendations are implemented by countries and stakeholders.
- A robust Monitoring and Evaluation Framework for the Containment Project is in place with household and outlet surveys conducted in the first year of the project.
- Implementation of focal screening and treatment (FSAT) of high transmission villages in the containment areas is ongoing.
- Surveillance of patients who remain positive after three days of treatment and procedures for active investigation and follow-up are being piloted, particularly in Cambodia.
 - In Cambodia, a newly developed SMS-based reporting system for suspected artemisinin tolerant cases is being tested to detect, treat and follow up those cases that are still positive on Day 3.
 - In Thailand, all suspected malaria cases are diagnosed with microscopy or RDT and followed up to day 28. Mahidol BIOPHICS has developed an electronic surveillance system using smart phones; the system has the capacity to capture data on PCR, blood work, patient temperature, patient photos and GPS.
- Cross-border surveillance systems are being developed to share relevant information for action and follow-up.
- Situational analysis on migrants and other operational research is ongoing in Thailand and Cambodia.

- International advocacy (e.g., radio, print, video, new media) is encouraged to highlight containment efforts and malaria drug resistance.

IV. Impact

Given that the project implementation began in mid 2009, it would be premature to seek evidence of an impact on the malaria situation. Nevertheless,

1. In Cambodia, the malaria incidence in zone 1 has been sustained at a low level, whereas in zones 2 and 3 have increased from 2008 to 2009 (Figure 1). These figures are based on data from the routine health information system (HIS) of Cambodia¹. The decrease in cases in zone 1 began before the containment project was implemented, perhaps due to the fact that in selected districts the first-line medicine was changed from artesunate plus mefloquine to the more effective dihydroartemisinin-piperaquine some years before the project was implemented. The decrease in cases likely continued because of the expansion of community based diagnosis and treatment via village malaria workers, and a steady supply of antimalarial treatment. Given that, from 2008 to 2009, there was a major effort to actively search for malaria cases in zone 1, effectively increasing the detection of cases, the trend shown here probably underestimates the reduction in malaria transmission achieved in zone 1 as compared to zones 2 and 3.
2. The Health Information System (HIS) data on malaria incidence shown above is corroborated by more specific data from village malaria workers (VMWs) on the number of cases they diagnosed and treated (Figure 2). So as to avoid the bias introduced by the fact that the number of VMWs per population was increased in zone 1 during the intervention period, the number of malaria cases in Figure 2 have been expressed as an average per VMW, for comparison between zones. The average number of malaria cases detected per VMW decreased by half in zone 1 after the increased coverage of ITNs whereas little change was observed in the cases per VMW in zone 3, where ITN coverage remained unchanged (Figure 2).

¹ Routine health information system data on malaria incidence is not yet available at the health centre (HC) level, but only at the operation district (OD) level (see Figures 2, 3, 5-7). Ideally, data at the health center level is needed to assess impact, since some ODs incorporate health centres from both zones 1 and 2. The Ministry of Health is currently working on providing the data by health center, and will continue to collect data at this level in future.

- Both severe malaria cases (Figure 3) and malaria deaths (Figure 4) have decreased in Zone 1 from 2008 to 2009 in absolute terms, as well as in comparison to in zones 2 and 3. The case fatality rate of malaria likewise was sustained at a low level in zone 1 compared to zones 2 and 3, reflecting the provision of early treatment to patients in the former (Figure 5).

Thus, there is preliminary evidence to indicate that the transmission of malaria in zone 1, where the full set of interventions are being rolled out, has been controlled, but not yet eliminated. Diagnosis and treatment and management of malaria has improved in zone 1 compared to that in zones 2 and 3 where the incidence of uncomplicated and severe malaria and malaria deaths, as well as the case fatality rate of malaria, have increased from 2008 to 2009. This may reflect a significant achievement, given that the artemisinin tolerant parasites in zone 1 have an inherent survival advantage over sensitive parasites and would have, without intervention, spread much faster given their greater propensity to be transmitted compared to drug sensitive parasites in zones 2 and 3.

The strategies, activities and interventions within the containment project are being continuously reviewed, evaluated and updated by a range of internal and external experts and observers.

References

World Health Organization (2007). Containment of Malaria Multi-Drug Resistance on the Cambodia-Thailand border: report of an informal consultation. Phnom Penh, 29-30 January 2007.

http://www.who.int/malaria/publications/multi_drug_resistance_en.pdf

World Health Organization (2008a). Global malaria control and elimination: report of a meeting on containment of artemisinin tolerance, 19 January 2008, Geneva, Switzerland. http://whqlibdoc.who.int/publications/2008/9789241596817_eng.pdf

World Health Organization (2008b). Development of a strategy towards elimination of *Plasmodium falciparum* parasites with altered response to artemisinins. Report of an informal consultation: Bangkok, Thailand. February 2008.

World Health Organization (2008c). Minutes of an informal consultation on resource mobilization for the containment of artemisinin tolerant malaria on the Cambodia-Thailand Border. June 2008.

http://www.wpro.who.int/internet/resources.ashx/MVP/Min_Inf_Con_ResMob_Cont+of+Art_FINAL_19-Dec-08.pdf

Figure 1. Treated malaria cases by containment zone (Cambodia), 2005-2009

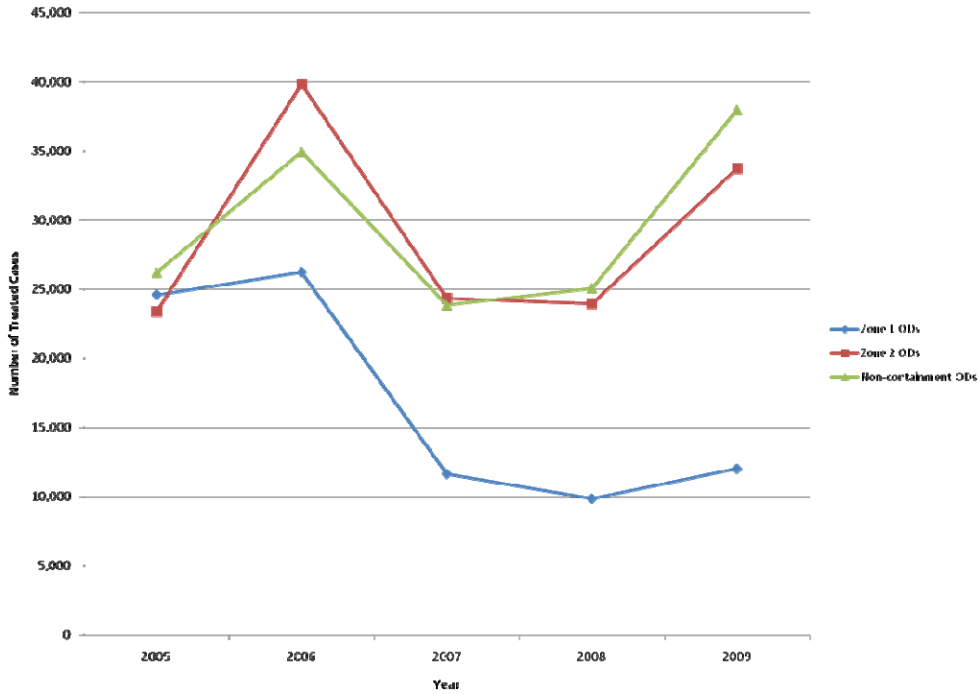


Figure 2. Pf cases per VMW report (Cambodia), 2009

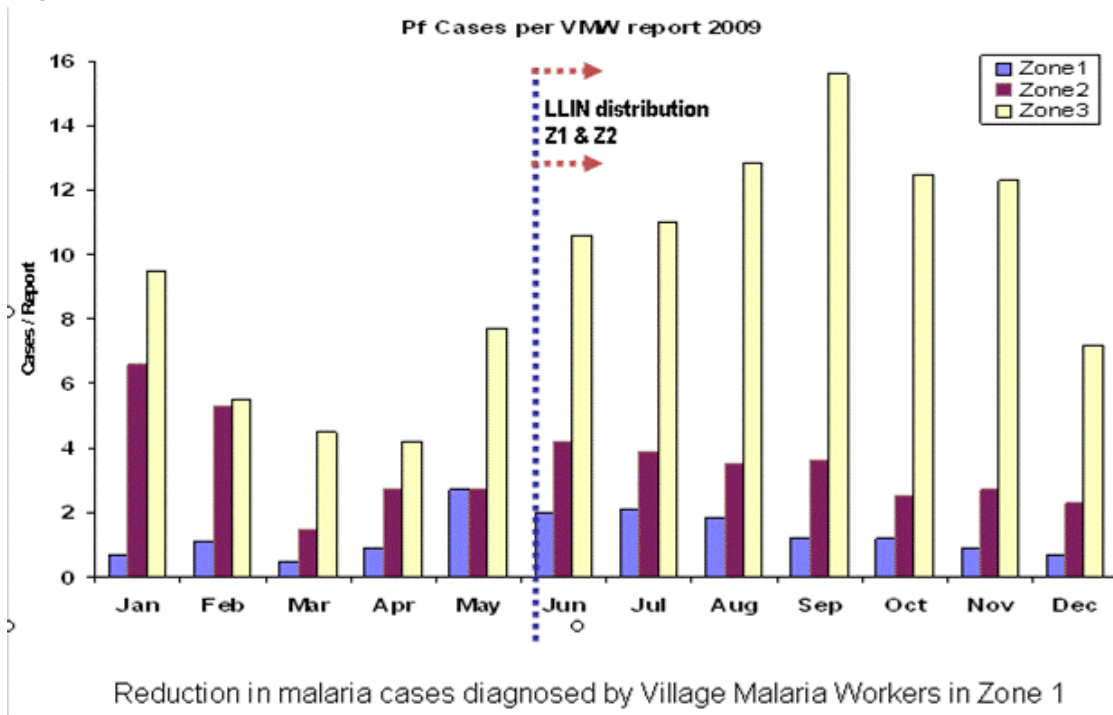


Figure 3. Severe malaria cases in referral hospitals, by containment zone (Cambodia), 2005-2009

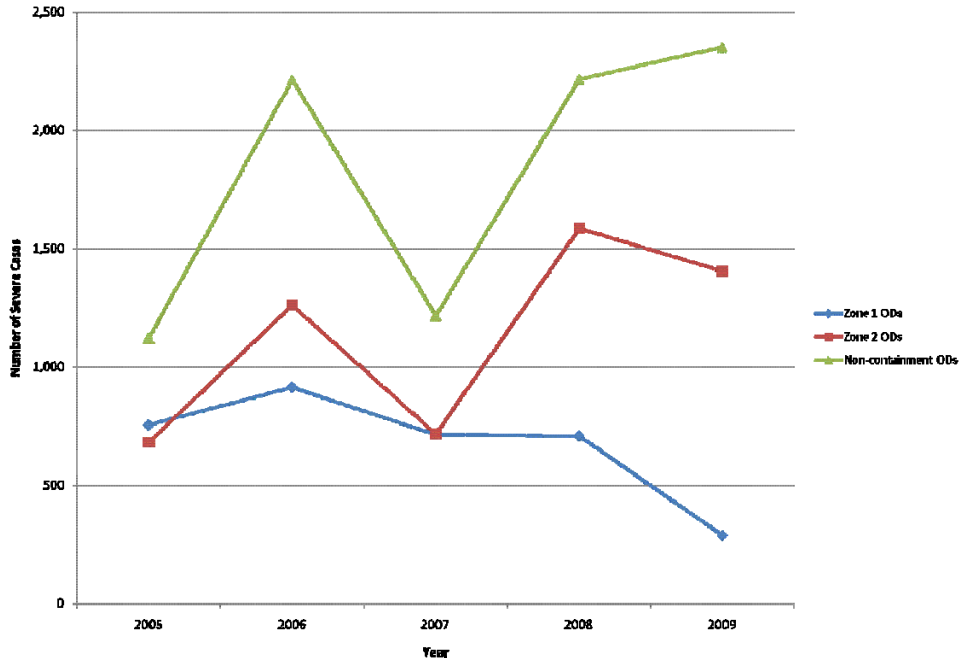


Figure 4. Malaria deaths by containment zone (Cambodia), 2005-2009

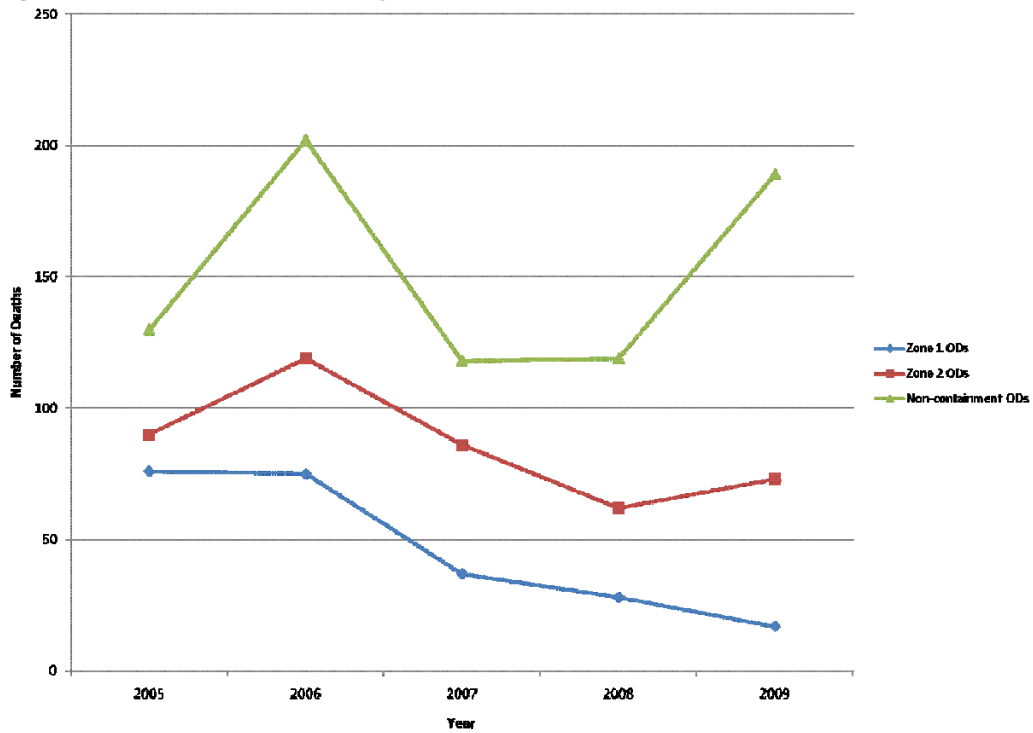


Figure 5. Case fatality rate in referral hospitals, by containment zone (Cambodia), 2005-2009

