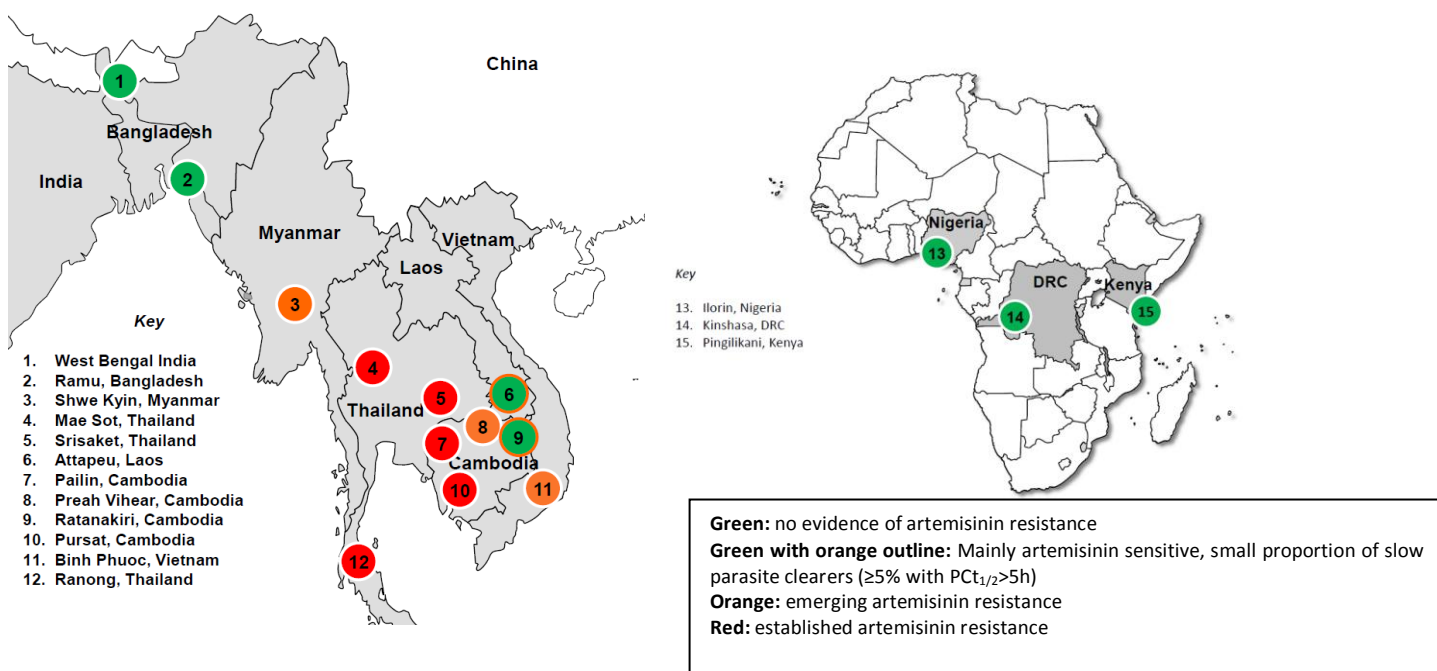


The emergence of artemisinin resistant *Plasmodium falciparum* malaria in South-East Asia poses the single greatest threat to current efforts to control and eliminate malaria. The Tracking Resistance to Artemisinin Collaboration (TRAC), funded by the UK Department for International Development, was set up in January 2011 with the goal of providing information and tools to slow or halt the spread of artemisinin-resistant malaria. The programme involves multiple institutions worldwide and is coordinated by the Mahidol Oxford Tropical Medicine Research Programme based in Bangkok (part of the University of Oxford). The Principal Investigator is Professor Nick White. The TRAC project has three main components: clinical research, assessment of demand factors and new approaches to vector control.

## Clinical Studies (Lead Institution: Mahidol Oxford Tropical Medicine Research Unit)

The principal aim of the clinical studies was to map the current extent and severity of artemisinin resistance.

### Maps showing location of TRAC study sites in Asia and Africa:



Between May 2011 and April 2013, 1241 adults and children with acute uncomplicated falciparum malaria were enrolled in an open-label trial at 15 sites in 10 countries (7 in South and Southeast Asia, 3 in Africa). Treatment was with 3 days oral artesunate followed by a full course of standard artemisinin combination treatment (ACT).

Slow parasite clearance reflecting artemisinin resistance was found in western and northern Cambodia, on the Thai-Cambodia and Thai-Myanmar borders, in southern Myanmar, and in southern Viet Nam. There are signs that resistance may also be emerging in Laos and eastern Cambodia. Patients with slow parasite clearance were more likely to carry gametocytes and thus are likely to possess a transmission advantage compared to drug-sensitive parasites. In western Cambodia, where standard 3 day ACT treatments are failing, the extended treatment course (3 days artesunate followed by 3 days of dihydroartemisinin-piperaquine) gave a cure rate assessed at 42 days of 97.7% [95%CI 90.9 to 99.4]. Several collaborative projects are ongoing using samples generated by the clinical studies which may produce vital information about the mechanism of artemisinin resistance and generate new methods to look for resistance in the laboratory.

## Demand Factors (London School of Hygiene & Tropical Medicine; Dr Shunmay Yeung)

Preliminary results of the research into how demand factors may influence the emergence and spread of artemisinin resistance are presented below.

**In-depth epidemiological and behavioural studies of patients** recruited to the clinical studies have been completed in Cambodia, Laos and Bangladesh. Preliminary analysis of results suggest that the patients from Western Cambodia (Pailin and Pursat) where drug resistance is worst, tended to be mobile or migrants (79% permanent

resident in Pailin vs over 94% in other Cambodian sites;  $p < 0.0001$ ), more recently arrived (19% in the last 6 months in Pailin vs less than 9% in other Cambodian sites;  $p < 0.0001$ ) migrants, to have had more symptomatic malaria and taken more antimalarial drugs in the last year (82% in Pailin vs less than 45% in other sites  $p < 0.0001$ ). The results from the follow-up and mapping of patients suggests that the place of transmission of drug resistance was highly clustered in a few foci in, or close to the forest.

**Drug quality studies** have been undertaken in Cambodia, Laos, Thailand, Myanmar and Nigeria. No suspected fake antimalarials were found in the Cambodian national survey. This is a significant and important improvement associated with the implementation of a number of different interventions including the banning of oral artemisinins and the strengthening of regulatory and enforcement capacity. Sixty-eight percent of all artemisinin containing drug contained between 85% and 115% of the stated active ingredient and were considered “within standard”. Laboratory analysis of samples from the other sites is ongoing.

**Qualitative studies** have been undertaken in order to explore the reasons for the observed impact of the Village Malaria Workers (VMWs) programme on appropriate treatment seeking for malaria and antimalarial drug use patterns, to better understand the mobile and migrant population (MMP) and other childhood illnesses amongst the most vulnerable populations in Cambodia. Over 80 in-depth interviews were carried out with two categories of key users: mothers of children under the age of five and forest workers. Preliminary findings from the interviews with mothers indicate that key factors explaining the neglect of VMWs services in study locations were (1) scarce awareness of VMWs and the availability of free treatment for childhood illnesses in addition to malaria; (2) a preference for health professionals in the private sector, as these were often seen to provide more comprehensive and qualified health care.

**A conceptual and analytical framework for “Understanding demand”** has been developed in order to describe, understand and analyse factors (proximal to distal) affecting demand and access to antimalarial treatment and the emergence and spread of artemisinin resistance with an emphasis on identifying metrics for factors which can be realistically measured and acted upon, for example adherence to and quality of antimalarial drugs.

**Preliminary research related to the mobile & migrant population in Cambodia** has involved situational analyses of communities attracting the mobile and migrant population (MMP) in forested areas. Preliminary mapping and interviews with key informants have taken place and for 4 provinces a “Multi-sectoral provincial malaria profile” has been produced which brings together relevant demographic, socio-economic, land-use and malaria related data for the use of the provincial and district malaria control teams. In addition, in order to contribute to the development of strategies aimed at targeting the mobile and migrant population (MMP) in the context of malaria drug resistance and elimination, a Population Movement Framework was developed by a collaboration of researchers, key malaria stakeholders and policy makers in Cambodia, led by LSTHM-TRAC. This has become the cornerstone of the National Strategy for the control and elimination of malaria in MMPs.

## **Vector control** (Liverpool School of Tropical Medicine; Professor Janet Hemingway)

Malaria vector ecology in Asia is quite distinct from sub-Saharan Africa, with a greater variety of mosquito species acting as vectors, most of which exhibit different biting behaviours e.g. evening outdoor biting rather than the typical indoor night-time biting of the African vectors. Long-lasting insecticide treated bed nets are being deployed widely but the different vectors and the lower transmission intensity in most parts of Asia where malaria is frequently an occupational disease of young men means that they are unlikely to have such a marked impact on transmission as in Africa. The vector control component of the TRAC programme aimed to evaluate new approaches to vector control which might be suitable for scaling-up in target populations in Southeast Asia. After performing some baseline entomological surveys in collaboration with the national malaria control programme (CNM), studies in Cambodia have evaluated insecticide-treated clothing, insecticide-treated hammocks, and a repellent (metofluthrin) emanator (see Figure) on outdoor and indoor biting by local malaria vectors. To date none of the interventions tried have made any difference to biting rates of night biting insects outside at 3 sites in Cambodia. However metofluthrin reduced biting rates of an important vector of dengue at one site by 35%. Results to assess the effect of metofluthrin on indoor biting are awaited. In addition to the entomological survey, the LSHTM has conducted a mixed methods study to evaluate the feasibility of large-scale marketing and use of metofluthrin emanators in Cambodia.

For further information please contact the TRAC project coordinator Elizabeth Ashley ([liz@tropmedres.ac](mailto:liz@tropmedres.ac))

**Metofluthrin emanator  
(Sumitomo) being tested  
outdoors in western  
Cambodia**

