Malaria Molecular Epidemiology Unit

The scientific activity report of the Malaria Molecular Epidemiology Unit of the Institut Pasteur du Cambodge for the period January 1st to December 31st, 2012.
General presentation

1. Context
In Cambodia, malaria with an incidence of 4.07 per 1,000 population and 135 deaths in 2010 (data from public health facilities) continues to be a major cause for public health and economic burden. Its control is given high priority by the government and development partners. Forest villagers in the eastern and northern provinces are at high risk of malaria, with all age groups suffering infection; children under the age of five years are at highest risk of severe disease due to their lack of immunity. Elsewhere, malaria is an occupational disease with specific high-risk groups, including forestry workers, new settlers and mobile/migrant populations who have come into forested areas, and soldiers, and their families, serving in the forests.

The five Plasmodium species known to cause malaria in humans (P. falciparum, P. vivax; P. malariae, P. ovale and P. knowlesi) have already been described. Currently, P. falciparum remains the most frequent cause of malaria infections (prevalence of 63 % in 2011). However, distributions of Plasmodium species are changing since several years, with a particularly significant rising of P. vivax malaria cases (from 8% in 2000 to 37% in 2011). Moreover, in areas of low transmission, a proportion of P. vivax infections up to 50% is commonly found. This trend, probably related to various effective strategies implemented in Cambodia against P. falciparum malaria, shows clearly that we had significantly underestimated the burden of other simian Plasmodium species.
Although there has been a steady reduction in the total number of clinically diagnosed and treated malaria cases as well as in the severe case fatality rate (CMN Annual Reports 2000 – 2009) over the last thirteen years, morbidity and mortality due to malaria remain high compared to other countries in the region. Malaria in Cambodia is also a key contributor to anaemia, complications during pregnancy, low-birth weight and poor child growth.

In addition, multi-drug resistant strains of *Plasmodium falciparum* are common, particularly in the west of the country. As with earlier antimalarials, we are now facing to the emergence of artemisinin resistance in western Cambodia while no suitable alternative currently exists for first-line treatments of *P. falciparum* malaria. As previously observed with chloroquine resistance in the last century, artemisinin-resistant parasites represent a major threat to worldwide goals of malaria eradication and the potential to devastate sub-Saharan Africa by increasing childhood mortality.

2. Major Areas of Research

Scientific projects developed in the Malaria Molecular Epidemiology Unit are built around the concept of elimination of malaria in South East Asia.

They are mainly focused on three major areas of research:

1. Supporting and evaluating the impact of strategies against malaria implemented by National Malaria Control Programmes
2. Conduct researches focused on *P. falciparum* artemisinin resistant parasites.
3. Conduct researches on vivax malaria & other emerging *Plasmodium* sp.
They are conducted in close collaboration with the Cambodian National Malaria Control Programme (CNM), WHO Global Malaria Programme and others regional or international partners (RIIP, IPP, European and US institutes or universities).

**Major Areas of Research**

**General Goal**

Control/Elimination

Supporting and evaluating the impact of the strategies implemented by NMCPs

Conduct research focused on *P. falciparum* artemisinin resistance

*P. vivax* malaria challenges & other emerging *Plasmodium* sp.

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**The Team**

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Projects

1. Supporting and evaluating the impact of strategies against malaria implemented by National Malaria Control Programmes

As countries move towards malaria elimination, activities which aims to measure how public health programs operate over time and achieve their goals, will need to shift from measuring reductions in morbidity and mortality, to detecting infections (with or without symptoms) and measuring transmission. Thus, the monitoring and evaluation research needs to develop the tools that will replace passive surveillance of morbidity with active and prompt detection of infection, including confirmation of interruption of transmission by detecting present and past infections, particularly in mobile populations.

Our projects aim at

- developing and implementing high throughput real time PCR in the field (mobile laboratory unit)
- evaluating the structure of the parasite population to understand the parasite genes flow and monitor the spread of antimalarial drugs resistant parasites in Cambodia,
- developing tools to evaluate the malaria transmission, including serological markers and detection of gametocytes carriers,
- improving tools to detect G6PD deficiency which will facilitate the safety introduction of primaquine to treat falciparum malaria (gametocytes) or vivax malaria (hypnozoites)
- controlling the quality of malaria rapid diagnostic tests (RDTs) which allows the rational use of antimalarial treatments,
- developing evidence to guide the management of malaria parasite negative acute febrile cases, and guide priority setting for point of care diagnostics development to assist in such case management decisions.
2. Conduct researches focused on *P. falciparum* artemisinin resistant parasites

Among the available tools, antimalarial drugs are essential at all stages of malaria elimination. However, one of the major threats to sustained malaria elimination is the emergence of malaria parasites that are resistant to artemisinin derivatives, the most potent weapon in treating falciparum malaria which are used in association with partner drugs (Artemisinin-based Combination Therapies, ACTs).

 Evidence of resistance to artemisinins has been identified and confirmed in South East Asia, along the Cambodia-Thailand border. Resistance to previous generations of antimalarials spread rapidly around the world, resulting in increases in mortality, especially in Sub-Saharan Africa. In this context, this is absolutely critical to preserve efficacy in the areas where ACT are still fully active and to design and monitor containment measures to prevent spreading of the resistant strains out of the Southeast Asian endemic areas. It appears urgent to know the cellular and molecular mechanisms associated to artemisinin resistance in order to limit it geographically, but also to circumvent it by developing new drugs active against this new form of malaria resistance. Moreover, understanding and monitoring the declining efficacy of artemisinins is on the critical path to prevent them from jeopardizing the partner medicines.

Our projects aim at

- identifying the molecular or cellular markers linked to artemisinin resistance and gaining fundamental knowledge on quiescence phenomena which has been described as a new mechanism of drug resistance in falciparum malaria parasites,

- developing new tools, currently strongly expected by the medical and technical teams in the field, such as relevant *in vitro* tests and molecular makers for monitoring artemisinin resistance,

- using our collection of present-day panel of Cambodian *P. falciparum* isolates with well-characterized *in vitro* drug resistance profiles for assessing the *in vitro* efficacy of new candidates antimalarial drugs.
3. Conduct researches on vivax malaria & other emerging Plasmodium sp.

In spite the considerable efforts undertaken to control and eliminate malaria in the world, it is still difficult to estimate the consequences of the reduction of *P. falciparum* transmission over the other *Plasmodium* species infecting humans and especially *P. vivax*. It seems increasingly evident that control measures initiated based on knowledge about *P. falciparum* (long-lasting insecticides impregnated bed nets, antimalarial treatments) are less effective for controlling vivax malaria. This difficulty has been exacerbated for several reasons: (i) the developmental biology of *P. vivax* is unique in early gametocytogenesis and the generation of hypnozoites in the liver that are responsible for relapses of the disease; (ii) the response of *P. vivax* to some antimalarials differs when compared with *P. falciparum*; (iii) the behavior and physiology of mosquito vectors, especially cryptic species, are largely unknown in many regions where *P. vivax* is endemic.

Progress had been slow, given inherent research challenges (i.e., developing a reliable long-term culture system to facilitate the understanding of its biology) and minimal financial supports.

In this context, the studies conducted in our unit aim at:

- estimating the global burden of vivax malaria in Cambodia, defining the risks associated to vivax malaria and assessing the parasite population structure.
- evaluating the *in vivo* efficacy of blood schizonticidal therapies (ACTs) for the treatment of vivax infections,
- developing *in vitro* tools to monitor antimalarial drugs resistance (phenotype and genotype) and developing reliable *in vitro* culture systems for blood-stage parasites,
- defining the distribution of red blood cell polymorphisms and inherited blood disorders linked to vivax malaria (Duffy antigen, G6PD deficiency, hemoglobinopathies) and determine the association with protection against vivax malaria
- improving our knowledge of biological mechanisms leading to *P. vivax* erythrocyte invasion with a particular focus on *P. vivax* Duffy Binding Protein/DARC interactions.
Publications - 71 publications

2013


2012

- Monidarin Chou, Saorin Kim, Nimol Khim, Sophy Chy, Sarorn Sum, Dany Dourng, Lydie Canier, Chea Nguon, Didier Menard (2012). Performance of "VIKIA Malaria Ag Pf/Pan"


**2011**

## Partners

### National level
- WHO Cambodia
- Malaria Consortium - [www.malariaconsortium.org/](http://www.malariaconsortium.org/)
- IRD Asie du Sud Est
- Université des Sciences de la Santé - [www.univ-sante.edu.kh/](http://www.univ-sante.edu.kh/)

### Regional level
- WHO regional office - [www.wpro.who.int/](http://www.wpro.who.int/)
- Eijkman-Oxford Clinical Research Unit - [http://www.tropicalmedicine.ox.ac.uk/j-kevin-baird](http://www.tropicalmedicine.ox.ac.uk/j-kevin-baird)
- Shoklo Malaria Research Unit - [http://www.shoklo-unit.com/](http://www.shoklo-unit.com/)
- Mahidol Oxford Research Unit - [http://www.tropmedres.ac/](http://www.tropmedres.ac/)
- Institut Pasteur du Laos
- Mahosot Hospital, Vientiane - [http://www.tropmedres.ac/departments-units/laos](http://www.tropmedres.ac/departments-units/laos)
- Hospital for Tropical Diseases, Ho Chi Minh - [http://www.oucru.org/](http://www.oucru.org/)

### International level

#### Europe
- Institut National de Transfusion Sanguine - [http://www.idf.inserm.fr/rubriques/structures-de-recherche/implantations/structures-de-recherche-paris-7/annexes2/umr-665](http://www.idf.inserm.fr/rubriques/structures-de-recherche/implantations/structures-de-recherche-paris-7/annexes2/umr-665)
- IMTSSA, Marseille
- Université Victor Segalen Bordeaux - [http://www.u-bordeaux2-medtrop.org/standard-436-1.html](http://www.u-bordeaux2-medtrop.org/standard-436-1.html)
- London School of Hygiene & Trap Medicine - [http://www.lshtm.ac.uk/](http://www.lshtm.ac.uk/)

#### Africa
- CERMES, Niamey - [http://www.cermes.net/cermes/](http://www.cermes.net/cermes/)
- Institut Pasteur de Madagascar - [http://www.pasteur.mg/](http://www.pasteur.mg/)

#### North America
- Case Western Reserve University, Cleveland - [www.case.edu/orgs/cghd/FacultyPages/ZimmermanPage.htm](http://www.case.edu/orgs/cghd/FacultyPages/ZimmermanPage.htm)
- Cleveland Clinic, Cleveland - [http://www.lerner.ccf.org/gmi/serre/](http://www.lerner.ccf.org/gmi/serre/)
- Department of Microbiology & Immunology, Columbia University - [http://www.microbiology.columbia.edu/faculty/fidock.html](http://www.microbiology.columbia.edu/faculty/fidock.html)
South America
Institut Pasteur de la Guyane - http://www.pasteur-cayenne.fr/spip/spip.php?article31