New challenges for malaria control and elimination: the role of operational research for innovation in designing interventions

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INTRODUCTION NOTE

In over a decade, remarkable achievements in malaria control have been made. Malaria mortality rates have been reduced by 42% in all age groups worldwide, between 2000 and 2012, leading to an estimated 3.3 million malaria deaths averted during the same period. More than half of the countries that had ongoing malaria transmission in 2000 are meeting the Millennium Development Goal (MDG) target of reversing the incidence of malaria, and a vast majority of those countries are on track to meet Roll Back malaria (RBM) and World Health Assembly targets of reducing malaria case incidence rates by 75% in 2015. By the end of 2013, 19 countries are in pre-elimination or elimination phase, 7 countries are in prevention of re-introduction phase and 4 are recently certified malaria free (WMR 2013).

These successes have been made possible by a marked increase in international and domestic funding for malaria control, allowing increased deliveries of Long Lasting Insecticidal nets (LLINs) to population at risk; increased availability of rapid diagnostic tests; increased number of suspected malaria cases receiving a diagnostic test and increased deliveries of Artemisinin based Combination Treatment (ACT) to the public and private sectors. Despite these progresses there is still a need to improve access and use of LLINs, diagnostic testing before receiving an ACT, to increase availability and treatment of severe malaria with artesunate IV and to sustain adequate financing for these interventions, currently available for only half of the estimated global requirements.

Insecticide and anti-malarial drug resistance, identified in the last decade, are major threats to the sustainability of these progresses and monitoring of the resistance trends at country level is crucial to properly address those threats. Mosquito resistance to at least one insecticide has been identified in at least 64 malaria-endemic countries worldwide and it continues to rise in Africa, South East Asia and Latin America. WHO and RBM responded by releasing, in May 2012, the Global Plan for Insecticide Resistance Management (GPIRM) in malaria vectors.

Parasite resistance to artemisinin have been detected in five countries of the Greater Mekong sub-region: Cambodia, Thailand, Myanmar, Laos and Vietnam, and concerns are that it could spread further or emerge in South Asia and Africa. Although ACTs continue to cure patients, provided that the resistance level to artemisinin is not too high and that the partner drug is still efficacious. The K13 molecular marker recently identified will be an important tool for the surveillance of artemisinin resistance in South East Asia and further validation is needed elsewhere. The Emergency Response to Artemisinin Resistance (ERAR) framework was released in April 2013 and followed by the establishment of the Resistance Artemisinin Initiative (RAI) and of the WHO ERAR regional hub supported by the Global Fund to fight AIDS, TB and Malaria (GFATM) and by the Bill and Melinda Gates Foundation (BMGF). A multi donor trust fund supported by the Asian Development Bank (ADB) was also recently established to support the response to this issue.

In the last few years, new challenges have emerged, further complicating the potential solutions to the issue of drug and of insecticide resistance and to attain the goal of elimination:

• Large reservoirs of asymptomatic carriers have been identified by new diagnostic tools, maintaining undetected transmission (by microscopy) of malaria parasites, including drug resistant strains.
• Poor quality medicines are unfortunately circulating in most endemic countries. The consequences of using poor quality medicines range from prolonged sickness, treatment failure, side effects, loss of income, increased healthcare costs and death. Of particular current relevance, falsified or substandard anti-malarials containing subtherapeutic amounts of artemisinin derivatives or only one of the two active ingredients in ACTs are very likely to contribute to disastrous anti-marial artemisinin resistance.
• Population movement and migration from areas of drug resistance contribute to the potential spread of drug resistant parasites, it also potentially contributes to reintroduction of the parasite in areas where the disease has been eliminated or is no anymore a public health problem. Due to their mobility patterns, the remoteness of their location or the illegal aspects of their activity, these mobile and migrant populations, are often hard to reach with current malaria tools and interventions.
• Residual and outdoor transmission, falling out of reach of currently available prevention measures, particularly for mobile people, constitute another emerging challenge for which new tools and strategies are urgently needed, both in Africa and in Asia.

Operational research is critical to provide policy-makers and program managers with evidence based on rigorous research to improve program operations and performance. However, this crucial pathway from research to policy, the translation of research outcomes to actual policy changes still takes too much time when new interventions are urgently needed. Operational research offers the opportunity to address the challenges faced today for malaria control and elimination, when linked, in a timely manner, with proper field evaluation of current and future tools, interventions and strategies.

As a side event to the Roll Back Malaria Board Meeting, this one-day workshop, organized by France Expertise Internationale in the framework of the 5% Initiative, will convene a global community of researchers, representatives of malaria national control programs, of civil society organisations and financial and technical partners to discuss the new challenges for malaria control and elimination, the role of operation research for innovation in designing interventions, and to share results of projects supported by the 5% Initiative.
Resistance to Artemisinin and Artemisinin-based Combination Therapy in the Greater Mekong Sub-Region and in Africa: current and future approaches

Parasite resistance to artemisinin have been detected in five countries of the Greater Mekong Sub-region: Cambodia, Thailand, Myanmar, Laos and Vietnam, and concerns are that it could spread further or emerge in South Asia and Africa. Although ACTs continue to cure patients, provided that the resistance level to artemisinin is not too high and that the partner drug is still efficacious, failure rates to 2 major ACTs (mefloquine-artesunate and dha-piperaquine) have reached alarming levels in Thailand and Cambodia. The K13 molecular marker recently identified will be an important tool for the surveillance of artemisinin resistance in South East Asia and further validation is needed elsewhere. Large reservoirs of asymptomatic carriers have been identified by new diagnostic tools, maintaining undetected transmission (by microscopy) of malaria parasites, including drug resistant strains.

Elimination of Plasmodium falciparum parasites in South-East Asia is now considered a strategic option to address this situation and new therapeutic options are urgently needed. However considerable operational challenges remain to implement it and a clear consensus between policy makers, financial institutions and the research community is still lacking despite the urgency.

New surveillance strategies, tools and interventions are urgently needed both in South-East Asia and in Africa and operational research is crucial to move forward in this rapidly evolving context.

- Towards malaria elimination: effective strategies against transmission.
  The new challenges in South-East Asia
  Prof. Francois Nosten,
  Oxford, Shoklo Malaria Research Unit, Mae Sot, Thailand

The emergence and spread of artemisinin resistance (AR) in P.falciparum in South East Asia justify renew efforts towards accelerated elimination. The recent discovery of large submicroscopic reservoirs of AR parasite carriers and the high prevalence of G6PD deficiency represent significant obstacles to the reduction of transmission, the indispensable route towards elimination.

New approaches need to be deployed in the region that involves mass drug administration of ACT and low dose primaquine. A project supported by FEI in 4 countries of the sub-mekong region with the objective of mapping G6PD deficiency and gametocytes carriage is currently on-going, in support of pilot projects for the rapid elimination of P.falciparum.
Advantages of ultramobile laboratory in strengthening the surveillance of anti-malarial drug resistance in the Democratic Republic of Congo
Dr Veronique Sinou
UMR-MD3, Aix-Marseille Université, Marseille, France

The Democratic Republic of the Congo (DRC) is one of the countries most affected by malaria in the world. In 2005, due to the emergence and spread of the Plasmodium falciparum resistance to antimalarial drugs, the DRC has modified its therapeutic regimens by integrating in particular the artemisinin-based combination therapies, requiring a regular updating of the levels of resistance of the parasite populations that circulate in DRC so as to best adapt the treatments to the local realities.

The present project proposes to evaluate the level of sensitivity of the parasites to antimalarial drugs (ex vivo assay, genotypic markers of resistance) in the provinces of Bas-Congo and Kinshasa. What makes our project unique is the use of a transportable microbiology laboratory (K-LMP) which allows to bring closer to the patients the means necessary to the collection and processing of the samples, for the diagnosis and to the achievement of ex vivo assays. The feasibility of this strategy has been evaluated in other regions of the world, particularly in South-East Asia. In this project, this strategy is deployed on a larger scale since the long-term goal is to cover the entire Congolese territory.

Risk of anti-malarial drug resistance worldwide: are we ready?
Prof. Philippe Guerin
Worldwide Antimalarial Resistance Network (WWARN)

More than 50 years ago, chloroquine resistance emerged in South East Asia and spread across South Asia and into Africa. Thirty years ago, sulphadoxine pyrimethamine (SP) resistance also emerged in South East Asia and Latin America and spread across the world. As a result of the dramatic spread of resistance to these antimalarials, millions of malaria patients died. The tide began to turn when the malaria community developed, registered and deployed artemisinin combination therapies (ACTs) as first line treatments for uncomplicated malaria.

Unfortunately, this progress is under threat because of the emergence of artemisinin resistance. Several drivers of artemisinin occurred long before the adoption of ACTs: use of artemisinins in monotherapy, inadequate formulations of certain products causing treatment with sub-therapeutic drug levels, poor adherence, and poor quality medicines.

Artemisinin resistance has now been reported in 5 countries within the Greater Mekong region, and the westward movement of the resistance is both spread of known resistant parasites and independent emergence of newly selected strains. The malaria community is proactively responding across the Mekong region, and is certainly better informed today about the risk, but do we have the right tools in place to monitor and respond to this new situation elsewhere? What are the barriers to being better prepared? How can we learn the important lessons from the past to improve our ability to collectively respond in the future?
**Access to treatment for most a risk and hard to reach populations and the need for evaluation of malaria intervention**

In South-East Asia, the people most at risk of malaria are often poor, living in rural areas and highly mobile. Population movement and migration from areas of drug resistance contribute to the potential spread of drug resistant parasites, it also potentially contributes to reintroduction of the parasite in areas where the disease has been eliminated or is not anymore a public health problem. Due to their mobility patterns, the remoteness of their location or the illegal aspects of their activity, these isolated mobile and migrant populations, are often hard to reach with current malaria tools and interventions.

More efforts are needed to reach all affected segments of the population in the malarious areas and to define the best strategies if we are to tackle the spread of resistance.

More operational research is needed to better understand the movement patterns and characteristics of those “people on the move” in different settings to be able to design the most appropriate interventions as well as new tools, especially for a better access to treatment and prevention of transmission.

Operational research is critical to provide policy-makers and program managers with evidence based on rigorous research to improve program operations and performance. Operational research offers the opportunity to address the challenges faced today for malaria control and elimination, when linked, in a timely manner, with proper field evaluation of current and future tools, interventions and strategies. New evaluation tools and strategies are needed to assess more comprehensively the impact of programs and to provide in a timely manner evidence-based feedback to policy makers and donor organizations.

- **The Global Fund Regional Artemisinin Initiative in the fight against resistant falciparum malaria**  
  Prof. Arjen Prof. Arjen M. Dondorp, Mahidol-Oxford Tropical Medicine Research Unit, Thailand

*Artemisinin resistance and high failure rates of ACTs in certain areas of the Greater Mekong Subregion are a major threat to the control of falciparum malaria in the region. The Global Fund has provided a large regional grant, the Regional Artemisinin Initiative, aiming to address this important problem. This talk will focus on the structure, activities and aims of this initiative. This includes an Inter-country Component, focusing on populations living in border areas, and mobile and migrant populations.*
In a global context of international funding plateauing, control programs are looking for innovative options to better perform with a constant budget. In absence of groundbreaking new control tools, the only option is to make the best use of the control measures that are already available. In order to guide policy making, we propose to carry out a broad and comprehensive evaluation of interventions deployed in a given setting, including an evaluation of their effectiveness and the identification of the key determinants affecting their effectiveness. We wrote and selected 20 Standard Operating Procedures (SOP) through a multi-country multidisciplinary workshop, including experts from Belgium, Benin, Cameroon, Côte d’Ivoire, France, Madagascar and Niger. These SOP cover the following fields: analysis of health systems (1), anthropology (1), biological diagnosis (4), drugs resistance (2), entomology (3), epidemiology (4), health economics (2), and immunology (3). All 20 SOP are combined in a single toolbox that is being implemented in Benin and Madagascar in 2014. Preliminary results will be presented. For each malaria control intervention the following indicators are evaluated: coverage, protective effectiveness against infection, protective effectiveness against morbidity, cost-effectiveness, socio-anthropological determinants of effectiveness, entomological determinants of effectiveness (vector behavior, insecticide resistance) if applicable, and in vivo and in vitro measure of antimalarial drug resistance. Results also include an analysis of health systems and management of malaria control in general. The toolbox –named PALEVALUT– will be further reviewed before and after implementation in Cameroon, Côte d’Ivoire and Niger in 2015. The whole tool will be soon available with free access on the internet.
Mosquito resistance to at least one insecticide has been identified in at least 64 malaria-endemic countries worldwide, affecting all major malaria vector species and all four existing classes of insecticides recommended by WHO. However, the extent and scale of insecticide resistance is still incomplete, and further operational research is needed to better understand the mechanisms of resistance and its geographical distribution in order to implement insecticide resistance management strategies.

Deficiencies in our knowledge of vector biology and vectorial capacity also hinder public health efforts for malaria vector control. Residual and outdoor transmission, falling out of reach of currently available prevention measures, particularly for mobile people, constitute another emerging challenge for which new tools and strategies are urgently needed, both in Africa and in Asia.

- **Towards a better understanding of insecticide resistance in malaria vectors in South-East Asia: the MALVEC project**
  
  *Dr. Vincent Corbel, Institut de Recherche pour le Développement*

The use of insecticides in public health has increased dramatically in the past decade through the scaling up of insecticide-treated bednets and indoor residual spraying for malaria control. Inevitably, the major malaria vectors have developed resistance to all public health insecticides and the resistance alleles are now spreading at an exceptionally rapid rate worldwide. Although decades of extensive research and substantial progress have been made on understanding the causes of insecticide resistance in “African” malaria vectors, remarkably few studies have focused on the distribution and mechanism of insecticide resistance in “South East Asian” malaria vectors. The MALVEC project conducted jointly by IRD (France), Kasetsart University (Thailand), Pasteur Institute and CMPE (Laos PDR) aims at investigating the current status and dynamic of insecticide resistance in anopheles vectors in hot spots for malaria transmission in Laos and Thailand and to address the possible causes of emergence. This project follows the recommendations of the global malaria action plan against malaria (GMAP), which calls for member states to implement an active system of insecticide resistance monitoring in vectors in order to improve preventive strategies and the fight against malaria worldwide.
Speakers

- **Dr. Sébastien Boyer** has an « Environment and Health » PhD. He did its PhD study in Grenoble (France) at the “Laboratoire d’Ecologie Alpine (LECA). He studied the resistance mechanisms of mosquito larvae to insecticides. He was then in China (Huazhong Agricultural University) for its postdoctoral studies on the microbiota of Anopheles sinensis. In 2008, he lead a work package on the biology and the behavior of Aedes albopictus in order to implement knowledge for the Sterile Insect Technique. Currently, he’s the Head of the Medical Entomology Unit in “Institut Pasteur de Madagascar” where the main scientific axes are focused on malaria, arbovirus and plague vectors.

- **Prof Marc Coosemans** has longstanding research experience on insects, vectors of diseases and their control. He evaluated the first pyrethroid insecticides sprayed indoors against malaria vectors in Burkina Faso in the late seventies. He designed and evaluated a strategy minimalizing the number of rounds of indoor residual spraying (IRS) in the low and high land of Burundi. He is involved in operational research in Vietnam, Laos, and Cambodia since 1996. Prof Coosemans has chaired the working group of the WHO Pesticide Evaluation Scheme (WHOPES) for several years and is now chairperson Vector Control Advisory Group of WHO.

- **Dr. Vincent Corbel** is a medical entomologist having 15 years’ experience in leading research and training programmes in medical entomology in Africa and Asia. His research activities focus on the genetic basis of insecticide resistance, vector control and vector biology & transmission. He is the chairperson of the WHOPES working group and a member of the RBM Vector Control Group since 2004. He is currently leading the international research programme STOP-VEC (supported by the Institut de Recherche pour le Développement, the Thailand International Development Cooperation Agency and the French Ministry of Foreign Affairs) and the Vector Biology & Control network (WHO collaborating centre) at Kasetsart University, Bangkok Thailand

- **Prof. Arjen M. Dondorp** trained as an infectious diseases and intensive care physician in the Netherlands. He is a Professor of Tropical Medicine at the University of Oxford, U.K., and a visiting Professor of Clinical Tropical Medicine at Mahidol University in Bangkok, Thailand. He is the Deputy Director and Head of Malaria Research at the Mahidol Oxford Tropical Medicine Research Unit in Bangkok, Thailand. He chairs the Regional Steering Committee for the Global Fund Regional Artemisinin Initiative and chairs the Technical Expert Group on Antimalarial Drug Resistance and Containment for the World Health Organization.

- **Dr. Didier Fontenille** is Director of the Institut Pasteur in Cambodia. As Head of the Medical Entomology Laboratory at the Institut Pasteur in Madagascar from 1982 to 1990, Didier Fontenille carried out research into the vector-borne transmission of arboviruses and malaria. After a period at the University of Quebec in Canada, he worked for seven years in Senegal as Director of the Medical Zoology Laboratory at the Research Institute for Development (IRD). From 1998 to 2001, Didier Fontenille was Head of the Medical Entomology Laboratory at the Organization for Coordination in the Control of Endemic Diseases in Central Africa (OCEAC) in Yaoundé, where he focused his research on the biology and genetics of malaria vector populations. He returned to France in 2001, coordinating research on the characterization of vector populations in research unit 016 at the Montpellier Research Institute for Development (IRD). He became Director of the research unit in 2005. In 2011, he was appointed Director of the MIVEGEC joint research unit. The same year he was also appointed Director of the French National Center of Expertise on Vectors (CNEV). He is a member of several advisory boards and review panels.
Prof. Philippe Guérin was appointed WWARN Director in January 2009. Guérin has extensive experience working in the field for the French Government and Médecins Sans Frontières in several countries in Africa and Asia. Following three years as a Senior Advisor to the Department of Infectious Disease Epidemiology at the Norwegian Institute of Public Health, Philippe Guérin joined Epicentre in Paris - a World Health Organization (WHO) Collaborating Centre for Research in epidemiology and response to emerging diseases. Prof Guérin served as Scientific Director for six years at Épicentre before moving to the WWARN network. He is Professor of Epidemiology and Global Health at the University of Oxford and visiting Professor at the French School of Public Health (EHESP).

Dr Philippe Guyant has over 15 years experience in public health and malaria control in Cambodia and has managed and coordinated projects related to malaria and dengue prevention and control, primary health care, health system strengthening, health staff capacity building and communicable disease surveillance system. He has been in the last few years involved in research and projects related to drug resistance issues on the Thai-Cambodia border with a focus on operational research related to the issue of malaria, mobile and migrant population in the context of anti-malarial drug resistance in South East Asia.

Prof. François Nosten is professor of Tropical Medicine in Oxford and the director of the Shoklo Malaria Research Unit. He works on the Thai-Myanmar border since 1986. As part of the Mahidol-Oxford University Research Unit program, Prof. Nosten has conducted large clinical trials on the treatment of malaria in the displaced populations living on the Thai-Myanmar border. He is leading the recent projects of malaria elimination supported by the Wellcome Trust, the Global Fund and the Bill & Melinda Gates Foundation.

Dr Veronique Sinou, PhD, of the National Museum of Natural History (Paris), is researcher at the University of Aix-Marseille, in the UMR-MD3 infectious diseases research unit. Her research focuses on the epidemiology of drug resistance and on the development of new innovative tools for field investigations. In particular, she has been involved in collaboration with industrial partners, in the design and development of an ultramobile microbiology laboratory to support surveillance and monitoring of drug resistance in the field.

Dr Siv Sovannaroth was trained as a Medical Doctor Assistant in Phnom Penh, and then as a Medical Entomologist in Malaysia. He holds a MSc of parasitology and disease vectors from the Liverpool School of Tropical Medicine, UK. He currently holds the position of Chief of Technical Bureau and Malaria Program Manager of the National Center for Parasitology, Entomology and Malaria Control in Cambodia. He is a member of the RBM Vector Control Working Group and of the WHO Technical Expert Group on anti-malarial drug resistance.

Dr. Prof. Nicholas White’s diverse interests include the epidemiology, pathophysiology and management of uncomplicated and severe malaria, melioidosis, enteric fever, tetanus, dengue haemorrhagic fever, Japanese encephalitis and tuberculosis. His particular interests at present include the pathophysiology and treatment of severe malaria, the prevention of antimalarial drug resistance using artemisinin-based combinations, and the biology of relapse in vivax malaria.

Dr. Shunmay Yeung is a pediatrician and has a background in health economics and operational research. She is the LSHTM lead investigator for the Tracking Resistance to Artemisinins Collaboration (TRAC) and Deputy Director and a core scientist for the Artemisinin Combination Therapy Consortium (ACTc). She is active clinically as consultant in Pediatric Infectious Disease at St Mary's Imperial College Hospital, London. She maintains a strong affiliation with the Mahidol-Oxford Research Unit in Bangkok and was the coordinator for the Artemisinin Resistance Confirmation, Characterization and Containment (ARC3) consortium. She has worked for the WHO Global Malaria Programme and sits on a number of expert committees and advisory boards.