MESA research grants 2014

MESA operational research grant	Principal investigator
Mopping up and getting to zero: mapping residual malaria transmission for targeted response in urban Lusaka, Zambia.	Daniel Bridges, Akros
Using voice-based technology to improve access to malaria care and treatment among high-risk mobile population of forest-goers in Cambodia.	Justin Cohen, Clinton Health Access Initiative
Applying novel nucleic acid surveillance to malaria elimination in South Cotabato Province, Mindanao, The Philippines.	Colin Sutherland, London School of Hygiene & Tropical Medicine
Efficacy and safety of high-dose ivermectin in reducing malaria transmission.	Feiko ter Kuile, Liverpool School of Tropcial Medicine

MALARIA ERADICATION SCIENTIFIC ALLIANCE MESA

Daniel Bridges, Akros

Mopping up and getting to zero: mapping residual malaria transmission for targeted response in urban Lusaka, Zambia

Lusaka, Zambia is on the brink of malaria elimination. Malaria Indicator Surveys conducted in 2010 and 2012 found zero malaria parasite infections among children under the age of five during high transmission season. Confirmed malaria incidence still continues at health facilities however, likely due to pockets of residual malaria transmission and imported malaria from neighboring regions. These pockets must be eliminated to achieve zero transmission and imported malaria cases must not be allowed to re-establish transmission once malaria elimination is achieved.

Such low transmission levels do not warrant full coverage malaria interventions in Lusaka. It is well known that in low transmission settings any remaining malaria infections demonstrate a high level of micro-heterogeneity. Targeting the remaining transmission foci reduces costs and increases impact, however transmission foci need to first be identified. Approximately 85% of confirmed incident malaria cases in Lusaka report travel history in the previous month, suggesting that a simple map of malaria incidence may not reflect pockets of residual transmission. Furthermore, unless the vector is eliminated alongside the parasite there is always a risk of imported malaria infections re-establishing transmission. Elimination will only be achieved and sustained by knowing and targeting the location of these pockets of residual transmission and hotspots of re-introduction.

We aim to identify pockets of residual malaria transmission and hotspots of potential re-introduction in Lusaka by combining the spatial-genetic fingerprint of P. falciparum parasites presenting to health facilities, antibody reactivity to Anopheles salivary peptides among a sample of residents, and ecological measures of larval and adult Anopheles habitats derived from satellite imagery. The use of these type of measures to build high-resolution risk maps is a novel approach and will enable targeted malaria control measures within Lusaka to achieve and sustain zero transmission.

Objectives: 1) Develop risk maps of residual transmission and the risk of onward transmission from imported malaria cases through identifying the spatial and genetic clustering of circulating P. falciparum parasites and linking remotely sensed mosquito breeding sites to serological measures of exposure to Anopheles salivary peptides; and 2) Assess sensitivity of risk maps to target malaria interventions to stop the importation and spread of malaria transmission in Lusaka, Zambia.

This project builds upon 2 years of experience implementing a reactive case detection intervention as well as the establishment of a fully functional molecular lab in Lusaka. Answering these questions of how to specifically target and eliminate remaining reservoirs of transmission is absolutely crucial to eliminating malaria in Lusaka and other urban centers throughout Africa. The research team is tightly integrated with existing malaria elimination programs in Zambia, thus, research outcomes will immediately and directly inform current and future elimination programs in the region.

Justin Cohen, Clinton Health Access Initiative

Using voice-based technology to improve access to malaria care and treatment among high-risk mobile population of forest-goers in Cambodia

Recent malaria prevalence surveys in Cambodia have found the prevalence of malaria among mobile populations to be substantially higher than the general population. The frequent movement of these mobile populations into the remote forested areas, especially along the borders with neighbouring countries where malaria incidence is high, represents a major risk of malaria transmission and a challenge to Cambodia's plan on achieving pre-elimination by 2015 and elimination by 2025. Furthermore, this movement facilitates the spread of artemisinin resistant parasite strains throughout the region. Providing diagnosis and treatment services to the mobile and migrant populations (MMP) through trained Village/Mobile Malaria Workers (VMWs/MMWs) is part of the National Malaria Elimination Strategy Plan but identifying these groups and ensuring they contact health services remain challenging.

One of the high-risk groups in MMP includes forest-goers who are usually poorly connected to routine public health interventions and community based surveillance systems. The Cambodia Malaria Survey 2010 found that forest-goers have a three-fold increased risk of malaria compared to those who do not go to the forest. This population represents a critical group for malaria elimination efforts, yet there is little known about the malaria care and treatment adopted by forest-goers. Targeting this group of MMP require different approaches than current malaria control and elimination activities.

The use of mobile technology to establish communication with MMP has great potential in Cambodia considering the fact that more than 90% of the population has access to a mobile phone and mobile coverage is good in rural areas. There are currently several SMS-based projects being implemented in Cambodia but these projects are limited by the absence of Khmer script in the phones typically available to the local population. Additionally, these projects are implemented with VMWs and private sector facilities which forest-goers may not contact. Verboice, a free and open-source tool which uses interactive voice response (IVR), provides an opportunity to overcome these barriers. Verboice allows users to listen and record messages in their own language and dialect or answer questions with a phone keypad. Thus Verboice can be used to establish or improve communication with communities previously inaccessible due to both geography as well as illiteracy. Further, the voice feature makes it possible to reach out and interact with ethnic minority groups, located in remote regions of Cambodia, in their own local languages. The technology has been successfully implemented by other organizations in Cambodia.

The primary objective: assess the potential of automated voice calls (Verboice) in: (i) identifying forest goers; (ii) delivering education and behavior change communication messages; and (iii) improving access to care and treatment among the mobile population of forest-goers in Cambodia by linking them with the closest VMWs or health facility staff. The secondary objective is to better understand the movement patterns, existing malaria care practices, and treatment-seeking behavior of these mobile populations.

Colin Sutherland, London School of Hygiene & Tropical Medicine

Applying novel nucleic acid surveillance to malaria elimination in South Cotabato Province, Mindanao, The Philippines

In endemic areas where malaria control efforts are successful in reducing the numbers of symptomatic cases, a larger proportion of the remaining malaria parasite population will be harboured by asymptomatic individuals. Novel methods are required to identify those individuals carrying such infections, which are usually of low density in the peripheral blood and thus harder to detect. In 2013, a cross-sectional sampling of several villages in South Cotabato Province in Mindanao, with parasite detection by nested PCR, identified a handful of people carrying such infections. These included individuals harbouring P. vivax, and others infected by P. falciparum. No symptomatic cases of malaria were seen, and overall parasite prevalence by PCR was less than 5% in each village. Such infections may represent a reservoir of parasites which successfully maintains a low level of transmission year to year in this remote part of the Philippines. Reduction or elimination of this reservoir is probably necessary for malaria elimination to be achieved in this setting.

The parasite detection methods available to field teams in South Cotabato, rapid diagnostic tests based on detection of circulating parasite antigens, and microscopic examination of stained blood films, lack the sensitivity to detect low density infections, but can be used in, or close to, real time for near-patient diagnosis. These asymptomatic cases were previously identified post hoc and therefore could not be given antimalarial therapy at the time. The DNA extracts for nested PCR were prepared from dried filter-paper blood spots shipped back to LSHTM, UK, and results were obtained months or even more than a year after sample collection. A portable molecular diagnostic test that could travel to, or nearby, the communities of interest and deliver rapid, sensitive parasite detection would overcome this problem, and permit infected individuals to receive antimalarial treatment within several hours, or at most a few days, of identification.

A recent study in Uganda described the application of a new, commercially available molecular diagnostic test, Malaria LAMP, for real time diagnosis of malaria infections in a rural clinic.[1] This test was also found to perform with excellent sensitivity and specificity in a UK clinical setting.[2] The provision of LAMP parasite detection less than one day's travel from the villages of interest would provide an opportunity to evaluate a "test and treat" strategy in South Cotabato. However, the performance of LAMP under these conditions has only been demonstrated once, and never in an Asian setting where P. vivax is prevalent. Some form of retrospective quality control step, performed after completion of the "test and treat" phase and using a different methodology, would be of great value and would permit determination of the sensitivity and specificity of the LAMP strategy in South Cotabato.

The project would visit three villages found to harbour asymptomatic individuals in 2013, and test for parasites cross-sectionally, using a temporary molecular diagnostic lab with local LAMP capacity. Everyone found to be positive would then be treated with artemether lumefantrine. Each sample taken would then also be tested, post hoc, by RNA detection methods (Singapore) and by species-specific nested PCR (London), to generate an estimate of the diagnostic accuracy of the field-based LAMP. A follow-up LAMP survey would then be carried out in the same villages 12 months after the initial test and treat, to evaluate parasite carriage one year after the original intervention. [1] Hopkins H et al. 2013. J Infect Dis 208: 645 – 652, [2] Polley SD et al. 2013. J Infect Dis 208: 637 – 644.

Feiko ter Kuile, Liverpool School of Tropcial Medicine

Efficacy and safety of high-dose ivermectin in reducing malaria transmission

Substantial progress has been made in malaria control through the use of insecticide treated nets (ITNs), intermittent preventive treatment, indoor residual spraying (IRS) and case management with artemisinin combination therapy (ACT). In western Kenya the prevalence of malaria in <5 year olds has fallen from 70% in 1997 to 40% in 2008, where it has now stagnated, despite sustained interventions. Innovative approaches are needed to interrupt transmission. Ivermectin (IVM) is a broad spectrum antiparasitic endectocide widely used for the control of onchocerciasis and lymphatic filariasis. It is also active against a range of exoparasites and has potent mosquitocidal properties resulting in a high mortality of Anopheles mosquitoes taking blood meals from humans recently treated with IVM. This makes IVM a potent novel tool for malaria transmission reduction strategies including for mass drug administration (MDA) when provided in combination with ACTs. It has the potential to target outdoor feeding mosquitoes that escape the effects of ITNs or IRS, and kill vectors that are resistant to pyrethroids and other insecticides used for IRS. The standard dose used for onchocerciasis and lymphatic filariasis MDA is 150-200 mcg/kg. IVM at this dose has a potent, but short-lived effect for 6-11 days on mosquito survival and parasite sporogony. Higher doses are needed to prolong the mosquitocidal period. Regulatory studies have shown IVM is very well tolerated and safe even up to 2,000 mcg/kg. A dose of 400 mcg/kg is used for head lice and for MDA against W. Bancrofti in the Southwest Pacific; 800 mcg/kg was successfully used in clinical studies in Africa involving 750 individuals with onchocerciasis. Combined clinical, entomological, and laboratory investigations of these higher doses are now required. We will conduct dose finding studies to evaluate the mosquitocidal properties of high-dose IVM to define the optimal dose for future use of IVM in combination with ACTs for MDA for malaria in Kenya. Primary objective: To determine the effect of single doses of 0, 200, 400 and 800 mcg/kg of IVM on day-10 mosquito survival, when provided with dihydroartemisinin-piperaquine (DHP) for uncomplicated malaria. Secondary objectives: a) To determine the safety of single doses of 200, 400 and 800 mcg/kg of IVM, in combination with DHP, by assessing the occurrence of adverse events in each study arm in comparison with adverse events with DHP plus placebo. b) To determine the effect of single doses of 0, 200, 400 and 800 mcg/kg of IVM with DHP on vector malaria transmission capacity measured by sporozoite rates in malaria vectors.

Hospital outpatient-based, double-blind, randomized placebo controlled trial. 164 non-pregnant adults with uncomplicated malaria will be allocated to one of 4 arms (41/arm): DHP plus either 0, 200, 400, or 800 mcg/kg IVM. Mosquitoes will be fed through membrane feeding on patients' blood taken at 0, 1, 3, 7, 10, 14, 21, and 28 days post-IVM; mosquito mortality and parasite sporogony will be measured. Primary outcome: comparison of mosquito survival. The studies benefit from parallel membrane feeding studies of the effect of low-dose primaquine on malaria transmissibility.

This study explores a research question of global relevance. Should IVM impact on malaria transmission, it could have substantial consequences for malaria control in the next decades. We expect the results to inform the national regulator in Kenya, national malaria control programs in malaria endemic countries, to inform WHO guidelines, and to contribute to the regulatory process. This is a collaboration between the Kenya Medical Research Institute, the Kenyan Ministry of Health, the US Centers for Disease Control and Prevention, PATH-MACEPA, and the Liverpool School of Tropical Medicine.