

MESA malaria eradication research grants 2012

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Targeting pregnant women to monitor malaria transmission.	Alfredo Mayor, CRESIB

Dr. Wendy O'Meara, Duke University

MESA project in health systems' readiness

Developing a rapid assessment tool to identify bottlenecks to malaria prevention for elimination

Project Summary: International efforts to scale up malaria control have achieved considerable success and have pointed toward the possibility of global malaria eradication. Achieving the long-term goal of eradication requires effective implementation of current tools, development of new technologies, and ongoing surveillance of the successes and failures of both. As malaria transmission declines and becomes increasingly heterogeneous, a finer-grained picture of malaria burden and intervention efficacy is required.

In Kenya, considerable reductions in malaria morbidity and mortality have been reported, but success has not been uniform. In Bungoma East district in western Kenya, data suggest that control efforts have not had the expected impact; despite the fact that ITN ownership exceeds 70%, malaria infection and morbidity remain high. The observation that malaria burden has not responded to control measures suggests a breakdown in effectiveness of ITN, but not due to simply to ownership, a common measure of 'coverage'. Breakdown in prevention of malaria may be due to a number of different factors in addition to coverage, including improper use and low adherence by households, changing vector populations and reduced susceptibility of the vector.

In the first phase of the proposed project, we want to answer the question of why malaria morbidity has remained alarmingly high in an area with high coverage of effective interventions. We will use the *efficacy decay framework* to quantify barriers to effective prevention. In the second phase, we want to apply the lessons from phase 1 towards developing a tool that can generate local, timely information in a cost-effective manner to identify and address barriers to elimination.

Aim 1: Quantify the efficacy decay at each step using case-control methodology. We will use a case control study to estimate the relative contribution of each step in the efficacy decay of ITNs to malaria prevention in an area where coverage is high but malaria burden has remained resistant to control measures.

Aim 2: Develop a rapid assessment tool that can be implemented at sentinel health facilities to identify local bottlenecks to malaria elimination. Based on the results of the efficacy decay analysis, we will develop a tool that can be used by community health workers to identify local barriers to effective prevention and stimulate local solutions.

Dr Rashid A Khatib, Ifakara Health Institute

MESA project in health systems' readiness

Responding to Efficacy Decay Analysis of Artemisinin-based Combination Therapy (ACT) for Malaria Treatment in Rural Tanzania: Intervening on Access

Rationale: Malaria remains the main cause of deaths in Tanzania. The government has harmonized its national program with the global malaria eradication agenda and case management with Artemisinin based Combination Therapy (ACT) is a key strategy for achieving this goal. However, improving the low effective coverage has been a major challenge that impedes health systems readiness for moving the strategy beyond control to elimination. We have developed a Systems Effectiveness Research Platform and conducted efficacy decay analysis on ACT case management in the country. Results revealed a 98% efficacy decaying to 18% effectiveness for effective treatment. This has further quantified specific weaknesses in local health systems and identified the gaps why efficacious treatments fail to bring full public health impact. Timely and appropriate access is a major driver of reduced ACT efficacy decay. As the introduction of AMFm quality ACTs is a major intervention to access and care seeking behavior we are proposing to test a set of low-cost interventions that also include private sector support and monitoring, in order to improve timely access and measure to what extent we can mitigate the baseline efficacy decay.

Goal: To test interventions to improve timely access to quality ACT providers in order to increase the system effectiveness of malaria case management and quantify its impact on efficacy decay of malaria treatment.

Specific objectives: 1) To introduce novel behavior change communications packages to the community that improve appropriate care seeking for fever within 24 hours at quality public and private ACT providers; 2) To monitor weekly AMFm stock levels in private accredited ACT providers using mobile technology; 3) To evaluate the contribution of improved access against the overall system effectiveness baseline in relation to malaria treatment.

Methods and design: The behavior change communications packages will be implemented over one year in the Rufiji Health and Demographic and Surveillance System (HDSS) site in southern Tanzania and will include school based programmes, distribution of IEC materials in public and private ACT outlets and community interventions. The "SMS for Life" program will be implemented in private accredited drug dispensing outlets to monitor weekly stock levels of AMFm products.

Within the routine HDSS household survey we will administer a detailed access questionnaire to a randomly selected sub sample of households. Each member from the sampled household reporting recent fever will be thoroughly interviewed to assess changes in treatment seeking decisions, patterns, pathways and costs compared with the baseline efficacy decay results. The Kilombero-Ulanga HDSS site will remain without intervention as a contemporary comparator.

Dr Arantxa Roca-Feltrer, Malaria Consortium

MESA project in health systems' readiness

Understanding the feasibility and potential impact of screening for asymptomatic malaria in households where a febrile case of malaria has been reported

Cambodia is one of the countries where malaria transmission has dramatically dropped to the point of making elimination an attainable target. A national survey in 2010 showed that overall asymptomatic parasitaemia is as low as 1%, and a statistically significant eight-fold reduction in the malaria mortality rate from 5.2 per 100,000 population in the year 2000 to 0.65 per 100,000 population in 2011 has been reported (1). Currently, in the pre-elimination phase, it is imperative that screening for malaria becomes more focused, foci of transmission are actively identified and a prompt response is taken. From existing survey data, we know that in one out of six households where an asymptomatic case of malaria exists, other members of the household also harbor malaria parasites (Cambodia Malaria Survey unpublished data). This means that, a surveillance system that could alert the health authorities of the appearance of a symptomatic febrile case, could also trigger a response to screen and treat malaria infection in other household members. In order to anticipate the potential impact of such intervention, the key piece of information currently missing is the amount of asymptomatic infection that exists in households where a febrile case of malaria occurs. Fortunately, in an endemic area of Cambodia, a state-of-the-art surveillance system is already in place for the detection of febrile malaria cases. This consists of a network of the so-called village malaria workers (VMWs) and health facilities that report, via SMS, to a central information unit each case of malaria that is slide/RDT-confirmed. Such surveillance system offers a unique and inexpensive opportunity to evaluate the potential impact of Active Detection and Treatment (ADAT) at the household level.

Objectives:

- (i) To estimate the proportion of infected individuals with malaria parasites in households where a febrile malaria case occurs.
- (ii) To understand how the above estimate varies according to geography and other modifying factors.
- (iii) To understand the feasibility of interventions where members of households with a reported case of malaria ('index household') are screened for asymptomatic malaria and treated accordingly.

Dr Ivo Mueller, Walter & Eliza Hall Institute

MESA project in measurement of transmission

Defining mosquito-to-man transmission of *P. falciparum* and *P. vivax*: Evaluation of epidemiological, molecular and serological markers in longitudinal cohorts in Brazil, Thailand, Solomon Islands and Papua New Guinea. The TransEPI Consortium.

Rationale: In order to re-orient a malaria control program from reducing the burden of disease towards the interruption of local transmission, it is essential that transmission can be accurately measured and areas with residual transmission identified efficiently. Both epidemiological (e.g. API, incidence, prevalence) and serological measures (antibody prevalence and titres) have been used both in research and programmatic settings as surrogate transmission measures even though we lack a detailed understanding of how they are related to the force of infection (FOI) in different transmission scenarios. Recent studies in highly endemic areas have demonstrated that FOI can be accurately quantified by high-throughput genotyping of consecutive samples in longitudinal cohorts. molFOI has been proposed as the 'gold-standard' measure to determine efficacy of novel interventions and to evaluate the impact of programmatic efforts in reducing transmission. However, determining molFOI is labour-intensive and costly; it is not easily applicable to situations where actionable information is required in 'real-time' and down to a local level. We now propose to evaluate the performance of different epidemiological and serological transmission measures with respect to molFOI in a series of 5 longitudinal cohorts currently being conducted in different transmission settings.

General aim: To investigate the performance of classical epidemiological, molecular and serological measures as markers of recent exposure (as measured by molFOI) in 5 cohorts conducted at moderate, low and very low transmission intensity. **Objectives:** 1) To determine the molecular force of *P. falciparum* (Pf) and *P. vivax* (Pv) blood-stage infections (molFOI) and their relationship with age, transmission season, spatial variation, intervention coverage, incidence of clinical episodes and prevalence, incidence density and multiplicity/genetic complexity of infection. 2) To measure antibody levels to a panel of Pf and Pv blood-stage antigens and relate antibody prevalence and titre to epidemiological and molecular measures of transmission. 3) To investigate the performance of epidemiological, molecular and serological markers of mosquito-to-man transmission for identification of hot-spots of recent transmission in areas with moderate, low and very low transmission intensity

Methodology: In 2013, the TransEPI Consortium is conducting a series of longitudinal cohort studies to investigate the epidemiology of man-to-mosquito transmission in different transmission settings in Brazil, Thailand, Solomon Island and Papua New Guinea (PNG). In each cohort up to 1000 participants will be followed for 12 months with monthly active detection of infection and continuous passive morbidity surveillance. In all samples, the presence of asexual and sexual parasites will be determined using PCR/qRT-PCR-based methods to study the temporal patterns of parasitaemia and gametocytaemia. We now propose to measure the molFOI by genotyping all PCR-positive Pf and Pv infections in each cohort and to determine the antibody titres of plasma samples against a panel of 16 Pf and 14 Pv bloodstage antigens. Epidemiological and serological measures will be compared to molFOI estimates to determine the best performing measures (and cut-offs) in each site. Cross-site comparisons will permit determination of the effect of transmission intensity on the performance of each measure.

Dr Bryan Greenhouse, University of California, San Francisco

MESA project in measurement of transmission

A molecular strategy to determine the origins of malaria cases and map transmission potential in countries approaching elimination

A critical need for countries attempting to eliminate malaria is the ability to distinguish infections locally transmitted by a mosquito bite from those imported into an area by the movement of people. Combating local transmission requires local, focused interventions, while combating imported transmission requires control at a distant focus of infection or at international boundaries. In addition, quantifying local transmission is critical in assessing progress toward elimination, efficacy of interventions, and eventual confirmation of elimination. A number of countries aiming to eliminate malaria, including Swaziland and Namibia, have instituted passive and active surveillance systems to better understand malaria transmission. While such surveillance systems may identify the location where both symptomatic and asymptomatic infections are detected, they are limited in determining the origin of infections by relying on reported travel histories and cannot quantify the number of malaria infections resulting from each source infection. We propose to add molecular genotyping of *P. falciparum* infections to these surveillance systems to reconstruct malaria transmission trees, thereby determining the origin of infections and quantifying local transmission potential.

While a number of methods have been used to genotype malaria parasites for various purposes, none have yet successfully tracked the origin and spread of malaria infections at a microepidemiological level. We have developed a novel genotyping method specifically to track the origin and spread of *P. falciparum*, overcoming earlier limitations. This method is designed to work robustly on dried blood spot (DBS) samples easily collected under field conditions, is relatively inexpensive, and provides high resolution genetic signatures at multiple loci through the *P. falciparum* genome, allowing for tracing of lineage through multiple transmission events. We will apply these methods to samples and data obtained from passive and active malaria surveillance in Swaziland and Namibia, two African countries poised to eliminate malaria. Taking advantage of high density sampling provided by our surveillance infrastructure and robust molecular genotyping methods, we will go beyond population level measures of genetic diversity to monitor transmission at the level of individual infections.

Goal: to implement a sustainable, field-friendly system for assessing and monitoring the microepidemiology of malaria transmission throughout Swaziland and in a district of northern Namibia.

Objectives: 1) classify individual malaria infections as locally transmitted (within the range of a mosquito) versus imported (requiring people movement); and 2) measure and map local malaria transmission potential, defined by the reproductive number under control (R_c , the number of secondary infections resulting from each infection).

Design: We will collect DBS samples and relevant epidemiologic data from existing passive and active surveillance systems in Swaziland and Namibia. We will perform multilocus genotyping on DBSs from every identified infection to determine genetic relationships between malaria parasites. These data will be used to develop and then fit a formal population genetic statistical model for calculating malaria transmission trees. Transmission parameters required to address our objectives will be obtained from this analysis. Results will be compared to those obtained from traditional epidemiologic investigation.

Dr Alfredo Mayor, Barcelona Centre for International Health Research

MESA project in measurement of transmission

Targeting pregnant women to monitor malaria transmission

Sensitive metrics of malaria transmission intensity (MTI) are needed to guide malaria eradication. Malaria-specific sero-conversion rates (SCR) estimated from the community have been shown to reflect medium- and long-term trends in MTI, but may not allow tracking recent changes and very low MTI, still require logistically complex collection of biological samples and does not take into account the effect of HIV infection on antibody responses. Serological measures in pregnant women may be a good approximation to monitor malaria in the general population, as suggested by studies conducted in Manhica (Mozambique) showing similar trends during the last decade in the burden of malaria in pregnant women and in the community, as well as in the levels of antibodies against VAR2CSA (the pregnancy-specific antigen that binds to Chondroitin Sulphate A in the placenta). Assessment of antibodies to VAR2CSA by regular sampling of pregnant women through antenatal clinics (ANC) has the potential to constitute an easy-to-implement surveillance tool of malaria transmission. Potential advantages of such a measure compared to other methods are: easy access of pregnant women through ANC; integration of malaria exposure over time (a pregnancy) that allows capturing both recent and past changes in transmission intensity by parity stratification; availability of information on maternal HIV status to correct serological measures by the impact of viral infection on antibody responses and high immunogenicity coupled with low serological diversity of VAR2CSA.

The aim of this project is to develop a robust and sensitive serological test for pregnant women at ANC that can be used to monitor trends of malaria transmission in the community. First, we propose to produce conserved regions of VAR2CSA to measure antibody responses in a cohort of HIV-positive and negative Mozambican pregnant women followed from first ANC visit to delivery. Immunogenicity of the antigens, longevity of the antibodies and the effect of HIV-infection on antibody dynamics during pregnancy will be assessed. We will select highly and poorly immunogenic VAR2CSA-based antigens as markers of transmission in areas of low and high endemicity, respectively; as well as antigens inducing long- and short-lived antibodies to be used as markers of exposure during previous (past) and current (recent) pregnancies, respectively. Secondly, we will determine the relationship between measures based on antibodies against the VAR2CSA selected antigens among Mozambican and Beninese pregnant women and standard estimates of MTI (entomological inoculation rates and community-based SCR). Finally, we will assess the value of VAR2CSA-based serology to detect recent reductions in exposure to *P. falciparum* associated with the use of Intermittent Preventive Treatment with different antimalarials among pregnant women from Mozambique, Kenya, Gabon, Tanzania and Benin participating in a multicentre clinical trial.

Results from this study may potentially lead to the development of a rapid test that can be used in maternity wards of countries with malaria transmission. This proposed project will also contribute to research capacity building through training and development of multicentre protocols to conduct pregnancy-specific serology.