RESOURCE HUB *Correspondents*

Malaria: From Innovation to Eradication

Complete series

MESA Correspondents bring you cutting-edge coverage from the Keystone Symposia "Malaria: From Innovation to Eradication"

February 19 – 23, 2017
Speke Resort & Conference Centre
Kampala, Uganda

MESA

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Background

There are a growing number of conferences being held globally where emerging evidence is shared in the field of malaria and related topics like entomology, parasitology, and health systems. These meetings offer the opportunity to hear cutting edge science and lessons learned from peers and mentors, in both broad and niche disciplines. As calendars and budgets are limited, those who could benefit from participating are often unable to attend. On the other hand, those who do participate, sometimes miss pertinent talks due to parallel scheduling of scientific sessions and side meetings.

With the overarching objective of sharing key findings with a global audience and also providing opportunities to emerging researchers, MESA identifies relevant conferences for the malaria community and reviews the scientific program to curate lists of talks to be covered by the *MESA Correspondents program*. Summaries of the highlights and technical content of the presentations are produced and shared through MESA's communication channels and those of strategic communications partners.

Day 1: Sunday, February 19th

Pre-Meeting Workshop for Global Scholars Shines the Spotlight on Surveillance

The Keystone Symposium meeting "Malaria: from Innovation to Eradication" in Uganda has kicked off with the pre-meeting workshop for Global Scholar Awardees, funded by the Bill & Melinda Gates Foundation. The workshop was organized to welcome and congratulate the 55 researchers from affected-countries selected for a travel award, plus the 40 scientists from Uganda that also received support to attend the conference.

Although the three workshop lectures covered very different topics, they all had one common denominator: surveillance.

The first talk by **Moses Kamya** (Makerere University School of Medicine, Uganda) introduced current malaria surveillance methods and metrics, and their use for measuring the impact of interventions, with examples from Uganda. He pointed out strengths and weaknesses of the various metrics. For example, parasite prevalence will vary according to the population sampled and the method of detection used (PCR being able to detect sub-microscopic parasitemia). Test positivity rates will vary depending on who seek care in the health clinics and the frequency of fever caused by other agents. He showed how these metrics have allowed evaluation of the impact of indoor residual spraying (IRS) in Nagongera, Uganda, where a dramatic reduction in symptomatic malaria was observed, but the reservoir of parasitemia, as measured by PCR, remained high.

Krijn Paaijmans (Barcelona Institute for Global Health, Spain) talked about the major contribution of effective vector control interventions (long lasting insecticidal nets (LLINNs) and IRS) in decreasing malaria prevalence worldwide. On insecticide resistance, he presented data from Southern Mozambique, where currently only 15% of mosquitoes die when exposed to pyrethroids as compared to 100% in 2002. He talked about residual malaria transmission, defined as persistence of transmission despite high coverage and quality of vector control measures and how it can be explained by the variety of vectors as well as changes in when, where and on whom the mosquito feeds, as well as changes in human behaviour. For example, mosquitoes biting early in the evening, or feeding or resting outside houses, or feeding on animals may help maintain transmission despite high IRS and LLIN coverage. To capture these trends and decide what tools to use, adequate and regular entomological surveillance is key.

"*The take home message is that mosquito control is difficult and complex and can only be achieved with adequate and regular surveillance. The entomologists should take more responsibilities*." **Krijn Paaijmans**

Sarah Volkman (Harvard T.H. Chan School of Public Health, USA) explained how genetics help us understand malaria and can contribute to surveillance. She gave an overview of genetic markers and approaches used to identify drug resistant loci. Molecular barcoding of parasites, using genes that express major and minor alleles, is a very useful tool to fingerprint parasites. It can help infer changes in transmission dynamics and predict what will happen in case of transmission reduction and rebounds. For example, as malaria transmission decreases, evidence from barcoding studies indicates that there is an increase in co-transmission of parasites (two different parasite types being transmitted by the same mosquito). It can also help assess the impact of interventions, such as LLINs (where all parasite types are expected to be affected), vaccines, or mass drug administration (where a few types may become predominant). Barcoding is also helping track parasites in space and time, and investigate the source of new infections and outbreaks, as well as of asymptomatic infections.

Each one of the lectures generated a great number of questions and discussion with the participants, which is one of the aims of the workshop.

We are sending daily posts from Kampala, Uganda, during the week-long Keystone Symposia meeting, 'Malaria: From Innovation to Eradication', organized in collaboration with MESA. Additional funding was given by The Bill & Melinda Gates Foundation and the US NIH/NAIAD. This blog was posted simultaneously on ISGlobal's blog, the Malaria World website, and the MESA website.

Day 2: Monday, February 20th

Tackling the asymptomatic reservoir to achieve malaria elimination: the if, the why and the how

The Keystone Symposia meeting officially started today, with a welcome from the director of the National Malaria Control Programme of Uganda, **Jimmy Opigo**, who called for scientists to not stop at publishing papers: *"...work is needed after the science, to translate it into public health action and reap the benefits.*"

In his keynote presentation, the WHO Global Malaria Programme director, **Pedro Alonso**, underlined the unprecedented gains that have been achieved over the last decades thanks to increased funding, new tools, scaling up of core interventions (particularly vector control), and economic and social development. Today, the picture is heterogeneous; of the 91 countries with ongoing transmission, 10 countries account for 80% of the disease burden and reductions in disease mortality and morbidity are still lagging behind. On the other hand, the elimination targets defined by the WHO Global Technical Strategy for malaria 2016 - 2030 are on the right track (21 countries could achieve zero indigenous cases by 2020). Pedro Alonso concluded "*we're in for a long fight*" that needs to be sustained and taken over by the younger generation.

The rest of the morning session was dedicated to characterizing the parasite reservoir and measuring disease transmission.

Salim Abdulla (Ifakara Health Institute, Tanzania) shared an overview of the core interventions (LLINs, IRS, artemisinin combination therapies (ACTs)) which have had a great impact, yet none have reduced malaria to zero in Africa. Mixed interventions sustained over time will be necessary, particularly in high endemic areas.

Chris Drakeley (London School of Hygiene & Tropical Medicine, UK) presented the arguments to target – or not - the asymptomatic reservoir. We need to consider the imperative to target the reservoir and the capacity to do so. Although submicroscopic infections are transmitted to relatively few mosquitoes, they may predominate in low transmission settings; a big question for the field is to understand who infects mosquitoes.

Jetsumon Sattabongkot Prachumsri (Mahidol University, Thailand) presented data on *P. vivax* transmission in Thailand, where the majority of infections are low density and asymptomatic. Studies on gametocyte density and mosquito infection rate can inform the threshold for diagnostic sensitivity.

In a short talk, **Ana Maria Fonseca** (Barcelona Institute for Global Health, Spain) discussed how levels of malaria-specific antibodies in pregnant women can reflect changes in parasite exposure in the population. **Silvia Portugal** (University Hospital Heidelberg, Germany) addressed the characterization of the sub-patent of *P. falciparum* infections which persist during the dry season and the outcome of treating such infections.

The afternoon session focused on modelling. **Hannah Slater** (Imperial College London, UK) presented work done with the National Malaria Programme in Zambia and other partners to model the impact of various programmatic strategies. The model includes movement of mosquitoes and humans, thus takes into account imported malaria from other zones. The model suggests that increasing vector control interventions will have a greater longer-term impact than mass drug administration (MDA), which is transitory.

The use of different markers of exposure and transmission intensity to detect residual pockets of transmission was discussed by **Stephan Karl** (Walter and Eliza Hall Institute of Medical Research,

Australia). His data analysis shows that prevalence surveys provide a good approximation for the underlying force of infection even in low transmission settings, and that serological markers are good predictors of current infection.

The day's session closed with a short talk by **Levicatus Mugenyi** (Hasselt University and Infectious Disease Research Collaboration, Uganda) who described a statistical model to estimate parasite prevalence and the force of infection, taking into account host, vector and parasite heterogeneity, which can help to inform possible outcomes and impact of interventions.

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Day 3, Tuesday, February 21st

Tailored interventions not "prêt-a-porter" for malaria elimination

Today's morning session focused on tailoring packages of interventions to achieve the greatest impact in a specific setting.

In Zambia they say "*malaria ends with me*" and the national programme is implementing a step-wise approach to make this happen. **Kafula Silumbe** (Malaria Control and Elimination Partnership in Africa, PATH, Zambia) explained how, with a backbone of rapid reporting and a surveillance-response system, mass drug administration (MDA) has helped to rapidly reduce the number of cases in the Southern Province. Currently, most of the case reporting comes from the community health workers (CHW) and novel approaches to retain CHWs need to be tested.

Caterina Guinovart (ISGlobal, Spain and Malaria Control and Elimination Partnership in Africa, PATH, USA) compared different drug administration strategies (mass/population-based and focal/household-based) along a range of transmission settings in Zambia and Senegal, with the aim of determining whether drug-based parasite clearance and case investigation can take us to elimination. The results varied according to transmission setting and the coverage of vector control interventions.

Melissa Penny (Swiss Tropical and Public Health Institute, Switzerland) gave a comprehensive overview of how models can be used in various aspects of malaria research, from clinical development of new tools to examining different implementation strategies. For example, modelling predicts that the RTS,S vaccine will have the greatest public health impact in medium to high transmission settings. She emphasized that modelling provides a useful framework to guide thinking and must be an iterative process, using robust data from the field in collaboration with the programme partners.

The morning session closed with two short talks. **Gareth Jones** (Clinton Health Access Initiative, USA) presented an assessment of strengths and weaknesses of the malaria surveillance systems in Tanzania, Kenya and Uganda. Gaps were identified in data collection and reporting, particularly from the private sector facilities. **Krystal Lorna Nkusi Birungi** (Uganda Virus Research Institute, Uganda) presented the Target Malaria project. Her work includes characterizing the biology and behaviour, ecology and breeding sites for *Anopheles gambiae* and other species, which together provides a baseline to test new gene drive technology in the future.

The afternoon shifted its focus to health systems. **Irene Misuka Masanja** (Ifakara Health Institute, Tanzania) presented a study which evaluated the effectiveness of the health system and tested approaches to improve access to care. Cartoons and posters with malaria messages were developed by the communities themselves, and in the intervention group where these materials were used, there was an increase in access to malaria treatment. Only improving the quality of care does not directly translate into better access. Improving access requires an understanding of the socio-cultural, environmental and financial needs of the community.

Kathryn Roberts (University of California, San Francisco, USA) presented a practical approach to surveillance as an intervention as implemented through the Namibia Malaria Elimination Research Partnership, established in 2014. The surveillance system uses rapid case notification, robust data storage and management, and geographical reconnaissance. It is a powerful tool that allows the malaria programme to identify transmission foci and target interventions, but a number of challenges, including sustainability and internet access, remain.

Valentina Buj (UNICEF, USA) described UNICEF's malaria strategy, integrated community case management work and shared examples of integrated multi-sectorial approaches. Community engagement using radio shows and performance art, termed "edutainment" was a very successful and creative example from Madagascar.

The success story of Sri Lanka that was certified by WHO malaria-free on September 5, 2016, was one of the highlights of the session. **Sumadhya Deepika Fernando** (University of Colombo, Sri Lanka) talked passionately about the achievements as well as the challenges of avoiding reintroduction of transmission in a context of high receptivity and high vulnerability. She described the surveillance-response mechanisms in place to prevent the onward transmission of malaria infection imported by the armed forces returning from missions. One of the challenges, she said, is that "*malaria is becoming a forgotten disease*" but "*the job is not over once a country receives a certificate. We have a receptive vector and Sri Lanka must maintain its national surveillance system*".

The day ended on a high note with the presentation of a non-invasive malaria detection laser from **Vladimir Zharov** (University of Arkansas for Medical Sciences, USA). The concept is based on sampling the whole blood volume for parasite-infected cells which are travelling through blood vessels, using photo-acoustic flow cytometry. For the moment the technique has been tested in animal models, models for cancer and clinical prototypes will soon be developed. Many Keystone attendees rushed to exchange ideas with Vladimir over the poster session and light bites that followed.

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Day 4, Wednesday, February 22nd

Promising new candidates for the malaria tool kit

Today's sessions focused on tools for malaria elimination, including promising vaccine and drug candidates, and novel vector control.

Marcus Lacerda (Fiocruz, Tropical Medicine Foundation Dr. Heitor Vieira Dourado, Brazil) shared study findings and perspectives from clinical medicine in the Amazon. For *P. vivax* elimination, the Achilles heel is G6PD deficiency (G6PDd), since it limits the use of the 8-aminoquinoline primaquine, which targets the hypnozoite. He commented that investing in diagnostic testing for G6PDd would prevent haemolysis in patients and would also be cost-saving for the health system. Notwithstanding the G6PDd challenge, the antimalarial candidate tafenoquine has recently completed a Phase III trial and if results are positive could be recommended and registered in 2018.

Kelly Chibale (University of Cape Town, South Africa) presented exciting work from the H3D drug discovery centre in collaboration with Medicines for Malaria Venture (MMV). They have discovered that an aminopyrazine (UCT943) has potent activity across the different stages of the life cycle of both *P. vivax* and *P. falciparum*. Their data show that it is efficacious in vitro and in humanized mouse models of malaria, selectively targets the PI4K kinase, has good pharmacokinetic and safety data, and is soluble.

Stephen Hoffman (Sanaria, USA) offered a sobering reminder that there are more cases of malaria today than there were polio cases when the polio eradication campaign began. Innovation and tenacity in the field of malaria elimination are essential. He presented data from an iterative set of studies on the sporozoite-based vaccine candidate, which led to optimising protective efficacy through dose escalation. The work is progressing in partnership with many international researchers and stakeholders, particularly those in endemic countries.

With five different parasite species, genetic diversity, and highly differentiated stages of the life cycle, developing vaccines against the malaria parasite is not for the faint hearted. **Louis Schofield** (James Cook University, Australia) presented data on a new target antigen that is highly conserved across all stages of the parasite life cycle: GPI (glycophosphatidylinositol). Data show that GPI induces high titers of antibodies and prevents severe disease in animal models, reduces blood stage replication and blocks transmission to mosquitoes, possibly by interfering with parasite mobility.

Itziar Ubillos (ISGlobal, Spain) gave a short talk on the characterization of antibody responses to the parasitic antigen circumsporozoite protein in children and infants in Sub-Saharan Africa participating in the Phase III trial for the RTS,S/AS01E malaria vaccine. Her work will allow a better understanding of the mechanisms of protection induced by the vaccine.

Umberto D'Alessandro (Medical Research Council Unit, The Gambia) shared work on a pilot study the characterization of residual transmission after one round of MDA with dihydro-artemisinin-piperaquine in several villages. The evidence suggests that there are parasite flows from the east to the west of the country, and that local transmission can be rapidly re-established after the MDA intervention period.

Didier Leroy (MMV, Switzerland) shared key points about testing for resistance as part of the development of the next-generation of antimalarials. He underlined the need to integrate new mutants from the field in laboratory parasite test panels, to test compounds against field isolates as

well as known resistant parasites, and to generate artemisinin resistance in vivo to mimic the situation in the field.

The afternoon session focused on vector control, the cornerstone of malaria prevention. **Charles Wondji** (Liverpool School of Tropical Medicine, UK) highlighted key questions in insecticide resistance: what is the resistance profile and intensity; what are the molecular drivers; and what is the actual impact on malaria transmission? Analysis of the gene expression indicates that different resistance mechanisms have arisen in different regions. The need for new active ingredients on LLINs is crucial to prevent multiple resistance mechanisms developing in the same mosquito populations.

John Lucas (Sumitomo Chemical Company, Japan and UK) underlined that currently there are limited options in the insecticide toolbox, and emphasized the critical role of insecticide resistance management starting from the development process right through to implementation in the field, so that we can maintain susceptibility of the vector to these hugely effective vector control tools

Krijn Paaijmans (ISGlobal, Spain) presented surveillance results in Mozambique indicating that vector composition, densities and insecticide resistance differ between and within villages. He underlined the need to go back to the drawing board and rethink entomological surveillance by reassessing when and where vectors and humans interact. He emphasized the responsibility of entomologists to obtain good quality data and ensuring that the maximum number of people are protected for every dollar spent on vector control.

Closing the session on vector control, **Sheila Ogoma Barasa** (US Army Medical Research Directorate, Kenya) presented early data on novel vector control tools, which aim to protect people in public and outdoor spaces where IRS and LLINs do not prevent mosquitoes from biting. Shelia and colleagues have been testing transfluthrin-treated mats for sitting or sleeping on and transfluthrin-treated decorations to hang inside homes, bars or restaurants. Data suggest that they can provide long-term and long-distance protection against mosquitoes. However, further testing is needed and resistance to the pyrethroid class of insecticide needs to be addressed.

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Day 5, Thursday, February 23rd

Exciting new science and big challenges for the next generation of malaria scientists

This morning was full of exciting science on the malaria parasite and its interaction with human and mosquito hosts. A common message from the presenters was the dynamic nature of parasite populations. Today's parasites are adapting to evolutionary pressure and will not be the same in the future. As countries reach elimination, tools and strategies need to adapt as well.

In his talk on interventions that block parasite transmission to the mosquito, **Rhoel Dinglasan** (University of Florida, USA) highlighted the complex yet largely unknown interactions between parasite ligands and mosquito receptors in the midgut. He shared ongoing work from his lab, e.g. testing parthenin as a "chemical condom" that inhibits male gametogenesis and other research to cure infected but not yet infectious mosquitoes. A promising target for vaccine development is the mosquito ligand (AnAPN1). Results show that antibodies to AnAPN1 can block its interaction with the parasite and data from mouse models show that it can be delivered as nano/microparticles. Could this be the basis for a future pan-malaria transmission blocking vaccine?

Sara Volkman (Harvard T.H. Chan School of Public Health, USA) gave an overview on how genetics, and in particular molecular barcoding of parasites, can contribute to surveillance-response in malaria elimination. Data from Senegal show that genetic parasite signatures reflect transmission intensity and patterns. As intensity of transmission declines, the complexity of infection shifts from polygenomic to clonal, and parasite relatedness increases. Genetic tools termed "identity by descent" may help to differentiate local from imported parasites and detect which infections are contributing to transmission.

Alfred Cortes Closas (ISGlobal, Spain) explained how parasites of the same genetic background can increase their diversity by activating or silencing some genes (a strategy called bet-hedging). He showed data indicating that parasite adaptation occurs at the non-genetic level, and that these stochastic epigenetic changes could have an impact on drug resistance, transmission or virulence. Other work from Alfred's lab shows that a transcription factor is critical for parasites to transform into sexual stage gametocytes and that some drugs can stimulate this sexual conversion.

Abdoulaye Djimdé (University of Science, Techniques and Technologies, Mali) presented recent data from the *Plasmodium* Diversity Network Africa (PDNA) network that screens for parasite diversity and markers of resistance to drugs. Initial work has started by looking at the K13 gene and a study performed in Mali indicates that artemisinin monotherapy (tested in the research protocol) remains effective but heterogeneity in parasite clearance time requires further investigation.

Didier Menard (Institut Pasteur, Cambodia) presented approaches to identify molecular signatures for monitoring antimalarial drug resistance in Cambodia. Six artemisinin resistance-associated mutations in the *P. falciparum* K13 gene have been described. Two main foci in Asia were identified and data show that one of the six mutations in the K13 gene (C580Y) has become fixed. On the other hand, K13 mutations in Africa are rare and not associated with drug resistance and other world regions seem to be free of resistance-related Asian alleles for the moment.

Moses R. Kamya opened the afternoon session, which turned its attention to surveillance strategies at the programme level. Moses is a senior Professor at Makerere University College of Health Sciences, Uganda where Keystone attendees had enjoyed a site visit earlier this week. Researchers in bacteriology, mycobacteriology, molecular biology, immunology and translational research explained their projects and many collaborations with African and international institutions. The hope is that the

interactions between Makerere researchers and Keystone attendees may be the start of collaborations to come. In his presentation, Moses shared a series of studies performed by the ICEMR (The East African International Centre of Excellence on Malaria Research) to evaluate the impact of the scale up of the core interventions in Uganda. Great strides have been made, but pyrethroid resistance remains a challenge.

Abdisalan Mohamed Noor (WHO Global Malaria Programme, Switzerland) presented a realistic and sobering picture on the current state of surveillance in many African countries, where the greatest burden of malaria exists. He emphasized that action is what distinguishes surveillance from monitoring. Problems (such as too many indicators, registers and reports) and recommendations (such as strengthening human resources) were discussed. "*It may be boring and difficult, but it is the single most important thing we have to do to move to the next step, and the only one for which we have the tools*", he said. In the words of D. A. Henderson, "*surveillance is the neurological system of public health*".

Marcel Tanner (Swiss Tropical and Public Health Institute, Switzerland) closed the meeting with a keynote lecture on the impact of travel and migration on the risk of malaria reintroduction. Echoing Noor, he stressed the need for strong and responsive surveillance systems which utilize minimal essential information and collect data in near real time to enable rapid responses. The challenge is not only increasing the effectiveness of the core interventions, but achieving "equity effectiveness" so that interventions reach all vulnerable groups. This is especially pertinent at during this time of social fragmentation.

In their concluding remarks, the scientific organizers highlighted the excellent quality of the questions from the young scientists, the added value and rich discussion by hosting the meeting in Uganda and announced their goal for a future Keystone Symposia on malaria elimination and eradication in Asia.

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