



## The Science of Malaria Eradication

Complete series



*MESA Correspondents bring you cutting-edge coverage  
from the Keystone Symposia's 'The Science of Malaria  
Eradication'*

*February 2 - 7, 2014  
Mérida, México*



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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.

## Keystone Symposia Meeting: The Science of Malaria Eradication

This Keystone Symposia meeting provided a comprehensive look at the cutting edge of the science of malaria eradication as it advances. For the first time since the paradigm shift from malaria control to the interruption of transmission, research, development, innovation and lessons learned were all captured. The central goal of the meeting was to provide a unique and needed space for malaria eradication scientists to share new information and advance the scientific debate. As the field develops and results emerge, so too will the questions which need to be answered. The meeting facilitated cross-fertilization among multiple disciplines that have a role in advancing the science of malaria eradication.

In an environment conducive to creative thinking, an anticipated outcome of the meeting was the generation of ideas and the next priorities for the scientific community to tackle. Other disease eradication efforts, past and present, have taught us the critical role of research and development. The publication of the malaria eradication research agenda ([malERA](#)) in 2011 laid the foundation for this R&D effort. This meeting served as a significant milestone in the continual development of this research agenda. By showcasing new evidence, emerging data and new challenges, the meeting aimed to catalyze ideas across multiple disciplines as well as new research activities in the field.

## Day 1: Sunday, February 2<sup>nd</sup>

'The science of malaria eradication' Keystone Symposia celebrated its first day of activities in Mérida, Yucatan, with a workshop devoted to students and researchers from endemic countries that received a travel award to attend the meeting. This workshop offered the opportunity to interact with a group of international experts that discussed the role of a dynamic biomedical research agenda, including aspects relating to therapeutics, vector biology and vaccines to interrupt transmission.

During the workshop, **Lee Hall** (National Institutes of Health, NIAID, USA), introduced the particularities of the eradication approach and the role of R&D in achieving the goal. **Marcelo Jacobs-Lorena** (Johns Hopkins Bloomberg School of Public Health, USA) went deep into novel vector control techniques, including genetic modification both at the mosquito and the symbiont level. Finally, **Chetan Chitnis** (International Center for Genetic Engineering and Biotechnology, India) presented different vaccines that could have an effect in interrupting transmission, as well as current candidates and lessons from the past.

One of the main take home messages from this workshop is that research has to be an integral part of the malaria eradication effort and both basic research and applied research are required. Moreover, malaria eradication requires a number of steps such as the improved use and adaptation of the tools that are currently available, the development and evaluation of innovative tools and the integration of multiple interventions. In fact, according to Jacobs-Lorena words, *'unless we integrate the different tools, we will never eradicate malaria'*.

A number of challenges were discussed, and the point was emphasised that as we progress towards malaria eradication, the changes in the epidemiology of malaria will have implications for the R&D agenda. Therefore, there is a need to encourage a bidirectional dialogue between the R&D community and the public health programme.

The Keystone Symposia on the science of malaria eradication is organized in collaboration with the Malaria Eradication Scientific Alliance (MESA). During 5 days, it will gather more than 150 scientists that will share and discuss the most up to date research results. In total, 32 people from 13 different countries benefited from the travel award programme in this Keystone Symposia, which was made possible by a grant from The Bill & Melinda Gates Foundation.

*This blog was written by MESA Secretariat, and posted simultaneously on MESA's blog on MalariaWorld and ISGlobal's blog.*

## Day 2: Monday, February 3<sup>rd</sup>

From bioethical considerations, to mapping trends in malaria transmission with basic biology. From inspiring lessons in other eradication campaigns, to regulatory issues around tools which benefit populations, to novel genetic technologies which modify mosquitoes and the parasite life cycle. The first day of the Keystone Symposium on the science of malaria eradication set the scene for sharing and debating new discoveries and innovative approaches to malaria eradication.

Following the opening remarks, **Frank O. Richards** (Carter Center, USA) recounted elimination and eradication campaigns of three neglected tropical diseases. *'Start in the hardest places first; by definition they will be the ones that take longer'*, he suggested. Adding that, the need for surveillance and community-based approaches cannot be underestimated, and that only initiatives that address the problem from a regional perspective have any chance in achieving their goals.

**Dyann Wirth** (Harvard School of Public Health, USA) emphasized the need to understand the selective pressure at a biological level. Barcoding of Single Nucleotide Polymorphisms (SNPs) from parasite isolates was discussed as a key technology to evaluate trends in parasite evolution, and to assess trends in transmission, as well as the impact of interventions.

Vector biology was also addressed, with consensus that malaria eradication will not be successful without targeting the mosquito. The presentations focused on genetic tools with the potential to replace mosquito populations or to render them incapable of transmitting the parasite. Some examples involved genetic 'scissors' and others used bacteria symbionts through paratransgenesis.

Presentations were followed by lively Q&A and discussions at the poster sessions. In such a multidisciplinary environment, the importance of integrating strategies was highlighted. As an example, one participant suggested that we could start by reducing mosquito populations through genetic approaches, and then bring in Mass Drug Administration to finalize the job.

A number of questions remain open, however. What drives the parasite selection process, and which parasites or genomes persist over time? Are all parasite strains equally transmitted? What is the correlation between gametocytes and transmission and what are the determinants of infectiousness? How can vector biology strategies be implemented to sustainably reduce malaria transmission?

The good news is that malaria elimination and long-term eradication is not perceived as unachievable. Nelson Mandela was quoted to reinforce this message: *"It always seems impossible until it is done"*.

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## Day 3: Tuesday, February 4<sup>th</sup>

The Keystone Symposium on The Science of Malaria Eradication entered its second day of activities with a focus on drug-based strategies and health systems research in the elimination context. The evidence for use of single dose primaquine to clear *P. falciparum* infections, the new K-13 artemisinin resistance marker, and how clearing asymptomatic infections in children can improve cognition and reduce transmission all featured in the animated discussions.

**Elisabeth A. Winzeler** (University of California San Diego, USA) opened the morning session. She spoke about technologies that encompass the use of phenotypic screens coupled with genomics for drug discovery. The aim is to identify compounds that are active against all stages of the parasite (including hypnozoites) and discover targets for radical cure and transmission blocking.

**Tim Wells** (Medicines for Malaria Venture, Switzerland) challenged the audience to think about the drug pipeline in new ways. According to Tim, in the studies that evaluate the efficacy of the antimalarial drugs "*it is equally important to measure when the parasite goes away and when the parasite comes back*". Finally, he highlighted the need to design novel ways of using today's antimalarials as well as the development of future drugs.

Audience and speakers discussed the potential use of primaquine for clearing *P. falciparum* gametocytes and thereby reducing transmission with a single dose; something that has been already used and documented in several parts of the globe. And **Marcus Lacerda** (Tropical Medicine Foundation, Brazil) reminded us that many knowledge gaps in drugs for *P. vivax* have still not been addressed, namely the ability of to kill hypnozoite without a partner drug; the different primaquine dosage regimens in different parts of the world; and G6PD deficiency management.

The audience later learned about exciting new results and the discovery of a novel molecular marker, the K-13-propeller, associated with resistance to artemisinin. Speakers pointed to potential uses in surveillance and elimination of artemisinin resistant parasites in the Greater Mekong subregion.

Speakers **Marcel Tanner** (Swiss Tropical and Public Health Institute) and **David Smith** (Johns Hopkins Bloomberg School of Public Health, USA) delivered very animated presentations relating to the critical role of the health system in driving down infections and keeping them out. 'Surveillance' was the key word: to inform interventions and adapt programmes to real needs. Research needs include understanding what the minimal essential data are for an elimination effort, and to understand where health system effectiveness is lost in a given socio-economic environment. The positive news from historical patterns studied with mathematical modelling is that once eliminated, malaria seems to stay eliminated. The strength of the health system being key to keeping malaria out.

To end the day, the focus shifted to school-based operational research in Mali, where drugs to clear parasites in children showed encouraging results. Data suggests that children perform better in schools after taking drugs that clear their malaria (even those with very low parasitaemia) and that such interventions can play a role in transmission reduction. **Sian Clarke** (London School of Hygiene and Tropical Medicine, UK).

This all provided food for thought over lite bites and discussions continued at the stimulating poster session.

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## Day 4: Wednesday, February 5<sup>th</sup>

The third day at the Keystone Symposium on The Science of Malaria Eradication was an action-packed day of exciting discussions on vaccines and tools to measure transmission, with an interlude to the Mayan ruins of Mayapan, where the malaria community rhetorically climbed the 'Mayan pyramids' of eradication.

A passionate **Stephen Hoffman** (Sanaria, USA) opened the morning session with encouraging results on the safety and efficacy of the irradiated sporozoite vaccine candidate (PfSPZ) and plans for future work. In the context of transmission blocking vaccines (TBV), **Patrick Duffy** (National Institute of Health, USA) shared the positive outcomes on safety and transmission blocking activity of the vaccine candidate based on the Pfs25 antigen. Other vaccine targets were presented by **Veronique Beiss** (Fraunhofer Institute, Germany) and **Daria Nikolaeva** (National Institute of Health, USA) based on sexual-stage proteins. Participants discussed that studying transmission-blocking vaccine targets also helps our understanding of how transmission actually works and could open doors to identifying immunological biomarkers of transmission activity in populations.

In the related field of immunology, **Carlota Dobaño** (CRESIB-ISGlobal, Spain) exposed a series of studies currently underway to better characterize the immune responses to the RTS/s vaccine candidate, and consequently identify surrogates of protection. **David Kaslow** (Malaria Vaccines Initiative, PATH, USA) finalized the session with a reflection on the regulatory path to licensure of vaccines to interrupt malaria transmission (VIMTs) and suggested the direct feeding assay was potentially a critical tool in the regulatory strategy.

After a relaxing lunch and tour to the Mayan ruins, the Symposium continued with a series of presentations on tools to measure parasite transmission intensity. **Rick Steketee** (MACEPA, PATH, USA) provided an explanatory summary of the different tools available and their advantages and disadvantages in different transmission settings. He emphasized on the need to constantly update research to inform ongoing elimination programmes. **Ivo Mueller** (Walter and Eliza Hall Institute, Australia and CRESIB-ISGlobal, Spain), highlighted the particularities of measuring *P. vivax* transmission in low transmission settings. Considerations ranged from asymptomatic individuals, increasingly prevalent sub-microscopical positive samples, and the challenges in the relationship between gametocytemia and infectiousness. **Sarah Volkman** (Harvard School of Public Health, USA), then presented her barcoding tool that takes advantage of the parasite's responses to selective pressure to measure transmission intensity and evaluate the impact of interventions in the context of elimination programmes. Further work will help understand if the barcoding tool will be able to distinguish imported and autochthonous cases. The short talks highlighted innovative research in measuring pregnancy-specific proteins as indicators of transmission. **Ana Maria Fonseca** (CRESIB-ISGlobal, Spain) shared initial results on the VAR2CSA pregnancy protein as a potential candidate to estimate malaria transmission in the population. Another innovative tool, the magneto-optic detection of parasite haemozoin, was presented by **David Newman** (Exeter University, UK).

The combination of these topics led to a series of discussions ranging from the role of asymptomatic individuals and relapsing cases on transmission; to the need for research to inform target product profiles, such as profiling immunogenicity to help identify new vaccine targets; and the need to better understand the mechanisms of transmission in different human and parasite populations in order to support programs moving towards elimination.

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## Day 5: Thursday, February 6<sup>th</sup>

The Keystone symposium 'The science of malaria eradication' ended with a common appreciation of bringing together scientists from completely different disciplines, but whose work is led by the singular goal of clearing malaria infection from the entire world. "*We need to put our own work in perspective and identify what really needs to be done*", said **Chetan Chitnis** (International Centre for Genetic Engineering and Biotechnology, India), one of the three scientific co-organizers, during the closing remarks that followed an inspirational talk by **Peter Agre** (Johns Hopkins Malaria Research Institute, USA).

The day's sessions were devoted to parasite-host interactions, and surveillance for eradication. The morning session started with **Robert Sinden** (Imperial College London, UK) who presented an overview of a number of basic biology research questions. Pending questions include, identifying the small parasite populations which mediate transmission across the dry season, understanding how immunity is induced and assessing the weakest points in the parasite life cycle. He also referred to innovative work looking at multiple transmission cycles, and male-female parasite sensitivity to antimalarial compounds.

With a specific focus on *P. vivax*, **Hernando del Portillo Obando** (CRESIB-ISGlobal, Spain) followed with insights into reticulocyte-derived exosomes and their potential significance in the science of malaria eradication. Contrary to the dogma, he showed new evidence that almost every cell of the immune system involved in the response to *P. vivax* can produce exosomes and that they are likely to play a role in remodelling the spleen. Promising applications will be explored in future work such as therapeutics and rapid diagnostic tests.

Other talks focused on the biology of gametocytes. **Oliver Billker** (Wellcome Trust Sanger Institute, UK) talked about the function of APiAP2 genes and calcium signalling pathways in gametocyte activation and development; **Gabriele Pradel** (RWTH Aachen University, Germany) unveiled the role of perforin-like proteins in gametocyte egress, and finally **Abhinav Sinha** (Gardi Medical College, India) presented work on gametocyte non-producer mutations and the discovery of a transcriptional regulator which could be taken forward as a transmission-blocking target.

Jumping from the basic biology in laboratories, to operational challenges in the field, in the afternoon session speakers and participants discussed the role of surveillance for elimination. Based on the premise that "*each case identified has a source that can be identified*", the importance of active and passive surveillance and the concept of 'effective reproductive number' were discussed.

The meeting closed with amusing and thoughtful perspectives from Nobel Laureate **Peter Agre** (Johns Hopkins Malaria Research Institute, USA). "*Science brings people together*", said Peter Agre, who reflected on his personal experiences in research. His talk made particular note of the role of young researchers, from all parts of the globe, as well as science's ability to scale international barriers and the importance of creative thinking.

Overall, 170 people from 37 different countries attended the meeting. Encouraging the audience to "*evaluate what we are doing and see how we can do better*", **Chetan Chitnis** trusted that the multidisciplinary dialogue on the science of malaria eradication will continue, and that the Malaria Eradication Scientific Alliance (MESA) will be there in the future to encourage it.

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