Resource HUB Correspondents

Keystone Symposia "The Malaria Endgame"

Complete series

MESA Correspondents bring you cutting-edge coverage from the Keystone Symposia "The Malaria Endgame: Innovation in Therapeutics, Vector Control and Public Health Tools".

30 October – 2 November 2019

Hilton Hotel, Addis Ababa, Ethiopia

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Day 1: 30th October 2019

Grand Challenges: Where we go next: African leadership for African Innovation

The Keystone Symposia opened on Wednesday, October 30, with a joint session with the Grand Challenges Annual Meeting. The Master of Ceremonies **Kedest Tesfagiorgis** (Bill & Melinda Gates Foundation) kicked things off by welcoming **Abdoulaye Diouf Sarr**, the Senegalese Minister of Health and Social Action. He spoke about the importance of partnership in fostering innovation, giving the example of the Pasteur Institute and the Institute of Vector Borne Diseases in Senegal.

The Spotlight Talk was given by **Segenet Kelemu** (International Centre of Insect Physiology and Ecology, ICIPE, Kenya), who spoke passionately about the need to change misconceptions about Africa. She also gave an overview of ICIPE and how it combines health, agriculture and environment and their relationship with insects.

Albert M. Muchanga, a delegate for the African Union Commission, expressed his commitment to engaging stakeholders in tackling the health burden in Africa.

Panel: Genetically-Based vector control for malaria elimination

Helen Jamet (Bill & Melinda Gates Foundation) moderated a discussion of gene drive for malaria elimination with some of the key players involved in the design and implementation of genetically modified mosquito trials in Burkina Faso.

Abdoulaye Diabaté (Target Malaria) spoke about the importance of engaging those who are suffering from malaria, having government commitment, robust regulation, and capacity building in implementing the Target Malaria project.

Alkassoum Maiga (Minister of Higher Education and Scientific Research of Burkina Faso) shared his personal experience of having malaria and its devastating effect on the lives of individuals. He

described how the research team overcame challenges in implementation of the gene drive project through transparency and community engagement with scientific research.

Jerome Singh (University of KwaZulu-Natal, South Africa) discussed the ethical concerns related to implementing gene drive studies, highlighting the difference between stakeholder and community engagement, risk assessment and mitigation, and interests of cross-border countries.

Francine Ntoumi (Congolese Foundation for Medical Research) discussed how the gene drive project was selected for funding among many emerging technology applications. So much of this research has been conducted in Africa, by Africans, stimulating future researchers.

The second Spotlight Talk of the evening was given by **Faith Osier** (Kenya Medical Research Institute KEMRI), who shared how the SMART network of African scientists and the KILchip© came together to identify antibodies necessary for the development of a malaria vaccine against merozoites. Professor Osier highlighted the need for equity in health and education, citing her personal experience as a success story.

Patrice Matchaba (Novartis) highlighted the struggle of those with sickle cell disease and inequity in access to care. He presented new drugs that promise a higher quality of life and protection from comorbidities.

The closing conversation was led by **Trevor Mundel** (Bill and Melinda Gates Foundation), who discussed South-South collaboration for vaccine development with **Amira Elfadil Mohammed Elfadil** (African Union) and **Renu Swarup** (Indian Ministry of Science and Technology). The former gave an overview of the history of the African Union and a long-term strategic plan for the next 50 years, including the goal of "well-being for all Africans". She also stressed that the empowerment of women is essential to achieving African development goals. **Renu Swarup** discussed the journey of vaccine development and manufacture in India, and stressed the importance of partnership with international stakeholders and government. To achieve equity for women, she argued that training is not enough – cultural change is also necessary to bring women to the mainstream.

Trevor Mundel closed the meeting by thanking all the partners that made the Grand Challenges meeting possible.

Day 2: 31ˢᵗ October 2019

Welcome and Keynote Address

Participants were welcomed to Day 2 of the Keystone Symposia by the conference organizers. **Thierry T. Diagana** (Novartis Institute for Tropical Diseases, USA) celebrated that participants came from over 40 countries. **Philip Welkhoff** (Bill & Melinda Gates Foundation) expressed his hope that this conference would allow people to find shared solutions to common problems across different contexts. Finally, **Flaminia Catteruccia** (Harvard T.H. Chan School of Public Health, USA) made special note of all the young researchers attending the conference (a third of the participants), and encouraged them to share their ideas and take advantage of social networking at the conference.

The keynote talk addressed a prominent emerging technology in the world of malaria control: gene drives for vector control. **Stephanie L. James** (Foundation for the National Institutes of Health, USA) discussed how gene drive technology could be implemented given the regulatory, ethical, and engagement hurdles that pose such a significant challenge. A diverse working group recently published guidelines that built upon the WHO's recommendations for ethical gene drive development. The overall message stressed engagement with stakeholders, communities, and regulators throughout all the development process. Transparency is also key to gain acceptance and support. She predicted that public mistrust is the single greatest threat to the development and ultimate deployment of this potentially game-changing technology.

Defeating Resistance I:

Chanaki Amaratunga (Mahidol Oxford Tropical Medicine Research Unit, Thailand) presented on Triple Artemisinin Combination Therapies (TACT). In 2007 and 2008 in some areas of Southeast Asia, studies observed delayed in parasite clearance in patients taking artemisinin based therapies. High treatment failure rates are now being reported in Cambodia, Thailand and Vietnam. She gave an overview of potential options to tackle malaria treatment failure associated with resistance, among which is the use of triple ACTs. In the Tracking Resistance to Artemisinin Collaboration II (TRAC II) project, her team revealed that the different TACTs tested were efficacious, safe and tolerable in adults infected with drug resistance parasites. Chanaki is now leading the Development of Triple Artemisinin-Combination Therapies (DeTACT) project, a randomized controlled trial comparing safety, tolerability and efficacy of two TACTs in Africa and Asia. She also highlighted the need to make this effort multidisciplinary, including bioethics, mathematical modeling, and market positioning components in the research that can highlight regional factors and speed up widescale deployment.

Wiweka Kaszubska (Medicines for Malaria Venture, MMV, Switzerland) introduced MMV as an initiative to discover, develop and deliver malaria medicines. She presented the target product profiles for treatment and prevention of malaria. Approaches to mitigating drug resistance include working on already-approved market products, examining potential drug combinations, and new drug candidates. One of these outcomes is a new ACT product, pyronaridine-artesunate, that has been developed to be used in areas where other ACTs are failing due to multiple drug resistance. She also stressed the need to understand resistance mechanisms using genotype, ex-vivo phenotype and clinical outcomes in drug selection for development.

Elizabeth A. Winzeler (University of California San Diego, USA) presented the Malaria Drug Accelerator (MaIDA), a consortium of 14 research labs that are working together to develop new types of drugs. A direction of research coming out of her lab is the use of a longer-than-typical assay to

identify new compounds with a delayed killing effect. Overall, her lab has found that similarities in compound structure are associated with similar mechanisms of action. Her lab has also worked to identify resistance mutations through the use of in *vitro* evolution showing similar results to *in vivo* experiments.

Rounding out the session, **Geoffrey Ian McFadden** (University of Melbourne, Australia) asked the audience if we could design "genetic traps" for drug resistant mosquitoes. Malaria parasites are exposed to a radically different environment when they are taken up by the mosquito. This change in fitness landscape, especially when switching from drug pressure to absence of drug pressure, can be used to minimize the spread of drug resistance. The mutations conferring resistance to certain drugs may be advantageous in the human blood stage, but can become disadvantageous in the parasite mosquito stages, with infected mosquitoes developing fewer oocysts and sporozoites and thus being less infectious. This means the resistant parasite is less likely to be transmitted onwards. These drugs may be useful as combination partners to protect the efficacy of the primary compound.

Defeating resistance II

The second drug resistance session began with a quick round-up of work being done in **Manu Prakash**'s lab at Stanford University, USA. The overall goal of his work is to enhance scientific tools, focusing on low-cost designs, such as a $1 foldable microscope, and also on technology that can be deployed on a flip phone. One such app allows people around the world to identify mosquito species by the sound they make. Another technology uses spectroscopy to identify parasites, reducing the human resources necessary for microscopy. This modular microscope can also be adapted for use in diagnostics for other diseases, and they are currently looking for field sites. Contact the Prakash lab if you are interested in using or testing any of these technologies in the field.

Abdoulaye Djimde (University of Science, Techniques and Technologies, Mali), presented on the status of artemisinin resistance in sub-Saharan African countries. He highlighted the origin of

artemisinin resistance in Southeast Asia and updated the audience on the methods to detect artemisinin resistance, both *in vivo* and by molecular methods. He presented the outcome of a study conducted in Mali in 2010-2011 assessing the efficacy of a 7-day artesunate monotherapy that had adequate clinical response. His team also continued to assess responses to the same regimen in 2015 in two sites, including the previous site used during 2011. They found that at the newly added study site, patients had much slower parasite clearance. He suggested that the difference in parasite clearance time between the two villages was not related to K13 mutations as none were found in either site. He concluded his presentation by mentioning that artemisinin-based therapy is still efficacious and slow parasite clearance time in Africa is not associated with K13 mutations.

Gordon A. Awandare (University of Ghana) reminded us that *P. falciparum* and *P. vivax* are not the only parasite species out there. *P. malariae* and *P. ovale* are poorly studied and are becoming more important. His PhD student, Felix Ansah, found that using cooperative primers led to improved detection of both species even at very low parasitemia, allowing for better detection of mixed infections. With improved detection, it appears that prevalence may be higher in areas of Ghana than previously reported. He also found that parasite clearance for *P. ovale* and *P. malariae* after treatment with ACTs is slower than for *P. falciparum.*

Charles Wondji (Liverpool School of Tropical Medicine, UK and Centre for Research in Infectious Diseases - CRID, Cameroon) presented on molecular genetics of insecticide resistance in different Anopheles populations. He remarked that the rebound of malaria coincided with the growing insecticide resistance in 2015 and described the need for urgent insecticide resistance management. His research team focuses on understanding metabolic resistance mechanisms in major malaria vectors and their impact on mosquito fitness and *Plasmodium* transmissibility. He noted the way forward for insecticide-based vector control that includes: 1) Detection of molecular markers of resistance improves the detection of resistance, 2) Prioritization shall be given to keep the current Long-Lasting Insecticidal Nets (LLINs) viable, 3) Resistance management should be proactive, and 4) Use of insecticide could be complemented with novel technology, such as the genetic manipulation of insects to block their ability to transmit disease.

Lemu Golassa (Addis Ababa University, Ethiopia) closed out the session with a discussion around the detection of asymptomatic and low parasite density infections with the available tools. He showed that ultra-sensitive Rapid Diagnostic Tests (u-RDTs) are more effective than traditional RDTs at detecting low-density infections. qPCR is the most sensitive diagnostic tool, followed by loop mediated isothermal amplification (LAMP).

Day 3: 1ˢᵗ November 2019

Leveraging Data Science to Defeat Malaria I

Lucy C. Okell (Imperial College London, UK) started off the "Leveraging Data Science to Defeat Malaria" session with an explanation of various modelling projects looking at the impact of antimalarial treatment and artemisinin resistance. The first project looked at the relationship between delayed treatment and the development of severe malaria. She also discussed a project led by Joe Challenger suggesting that the effectiveness of ACTs is fairly robust to poor adherence. Finally, she evaluated the potential for the development of DHA-P resistance if it is used for intermittent preventative treatment in pregnancy.

Emilie Pothin (Swiss Tropical and Public Health Institute, Switzerland) shared her experience on Data-Driven Operational Stratification for National Malaria Control Programs. She outlined the need for operational stratification to ensure efficiency of the malaria program. She described that data-driven operational stratification allows one to consider the heterogeneity associated with the decline in malaria endemicity and make evidence-based decisions. The iterative modelling process has data inputs and outputs that are continuously improved and discussed with policymakers. The outcome is a decision tool that can be used to allocate interventions in each stratum. The application of this model in Tanzania revealed the need to revise the national malaria strategic plan if the required impact on malaria burden in the country was to be met.

Samson Kiware (Ifakara Health Institute, Tanzania) presented about a Mosquito Database Management System (MDbMS) applicable to diverse entomological studies. He pointed out the challenges encountered in most entomological studies related to variabilities in experimental design, which influenced the development of a data management system. The team developed the forms required, starting from field collection to sample observation and storage. They have made this available in an app for customization. He expressed his hope that countries will use this system if they lack well-designed generic paper-and/or electronic-based data collection tools.

Hannah Slater (PATH), the beloved senior editor of these MESA Correspondents reports, discussed modelling the impact of different stratification strategies in Senegal. This was a great practical example of the work discussed by Emily Pothin. She used the Imperial College malaria model to compare the effects of various combinations of Mass Drug Administration (MDA), Indoor Residual Spraying (IRS), Seasonal Malaria Chemoprevention (SMC), and high levels of treatment and found that all suggested packages besides MDA had comparable efficacies and cost-effectiveness. Finally, she called attention to the fact that the majority of cases in the low-transmission areas of Northern Senegal are occurring in only 20% of the facilities, an argument for understanding and targeting transmission at a very granular level.

Duncan Kobia Athinya (Vestergaard Frandsen Limited, Kenya) shared the Insecticide Resistance (IR) Mapper, a platform of insecticide resistance data that are freely available and can easily be filtered to answer different research questions. Data are updated monthly, and the database currently has over 32000 data points. Soon, it will also contain modelled resistance data from the Malaria Atlas Project. Please contact Duncan if you are interested in contributing data to this database.

Maria Tusell (MESA Alliance, Barcelona Institute for Global Health, Spain) presented the MESA Track platform and its goal to landscape research to showcase emerging evidence and guide the decision-making process. She expressed the need for objectively reviewing available data to develop policy recommendations. She shared with the audience the data sources for MESA TRACK, the magnitude of projects available in the database, and the types of information users can generate from the platform.

MESA TRACK is an important resource for different stakeholders such as researchers, research institutions, funders, and policymakers. The platform can help stakeholders to recognize the areas of research most in need of a response, enabling the malaria community to respond accordingly.

Michelle Hsiang (The University of Texas-Southwestern Medical Center and University of California San Francisco – UCSF, USA) talked about a randomized controlled trial of reactive focal mass drug administration (rfMDA) and reactive vector control (RAVC) that took place in Namibia. This study compared a controlled group with groups where each of the two interventions were done singly, and then a group where both interventions took place at once. She found that in an analysis adjusting for pre-intervention transmission levels and other confounders, all intervention combinations had a significant impact on clinical incidence compared to the control arm.

Maya Fraser (PATH, USA and one of our MESA correspondents) began the workshop session talking about how she had used routine surveillance data to conduct an impact evaluation of MDA in Southern Zambia. She concluded that while MDA had a significant impact on incidence, it was not enough to be an accelerant to elimination in the conditions under which it had been implemented. She also urged participants to think about how more routine data can be used to determine impact.

Laurent Dembele (University of Sciences, Techniques and Technologies of Bamako, Mali) shared with us approaches for novel antimalarial discovery against *Plasmodium* relapsing species, *P. vivax* and *P. ovale*. He stated that there was no robust model to conduct drug discovery targeting hypnozoites. His team validated *P. cynomolgi in vitro* model using *Macaca fascicularis* primary hepatocytes and characterized Liver-Specific Protein 2 (LISP 2) as marker of hypnozoite activation that is not expressed in dormant types. He also showed that LISP 2 negative forms are only susceptible to an anti-relapse drug, tafenoquine. The absence of this marker in dormant hypnozoites may be related to variabilities in activities of KDU691 on primary and secondary hypnozoites. These results provide novel biological insights in the hypnozoite activation and an early marker suitable for the development of drug discovery assays predictive of anti-relapse activity.

Lauren Beth Arendse (University of Cape Town, South Africa) oriented us on pathways in establishing a *Plasmodium* kinase platform used in target-based malaria drug discovery. Whole cell phenotypic screening conducted by H3D resulted in a kinase inhibitor that has reached Phase II clinical trial. She shared with the audience a target-based drug design using *Plasmodium falciparum* phosphatidylinositol 4-kinase (P14K) and cGMP-dependent protein kinase (PKG). Using these approaches, they identified many molecules in a chemical class of imidazopyridazones that inhibit different kinases, which affect multiple stages and blood stages of parasites, respectively.

Monica Golumbeanu (Swiss Tropical and Public Health Institute, Switzerland) demonstrated why it is important to take vector species and behavior into account when modelling the potential impact of different interventions. As examples, she showed how three vector species had very different biting behaviour and resting patterns. When coupled with data about human behaviour, the *Anopheles* model (part of the Swiss TPH malaria model) can give us a more nuanced view. It will soon be released as an R package and will have an interface for easy access.

Steven Gowelo (Wageningen University, Netherlands) presented the outcomes of his project assessing the effects of sublethal doses of *Bacillus thuringiensis israelensis (Bti)* treatment in larvae on selected mosquito fitness parameters. His team conducted *Bti* assay and identified sublethal doses that were used in the experiment in fitness parameters of *Anopheles coluzzii* females. The study revealed a different impact on adult size and longevity across the sublethal doses of LC_{20}, LC_{50}, LC_{70} applied during larval stages. As the sublethal dose increased to LC_{70} longevity reduced and size increased. But oviposition was not associated with sublethal dose variation.

Kitty F. Cardwell (Oklahoma State University, USA) discussed the MicrobeFinder® (MiFi) tool, which allows researchers to design "e-probes" that aid in identifying particular stretches of DNA that could be markers of species, resistance, or anything else of interest. She estimates that doing detection for *Plasmodium* species would take about 5 minutes in the field with next-generation sequencers. They are currently looking for research partners, so let them know if you are interested.

Leveraging Data Science to Defeat Malaria I

Michael White (Institute Pasteur, France) spoke on a topic close to the forefront of many attendees thoughts: what is the impact of introducing tafenoquine (TQ) for radical cure of *P.vivax*? Specifically, he examined this question in Brazil, which just approved TQ this week. He combined the Brazilian malaria epidemiology with a mathematical model of *P. vivax* transmission to assess the potential public health impact of TQ treatment. He found that the additional impact of TQ would be dependent on the age distribution of *P. vivax* infections, the current availability and adherence to primaquine, and transmission intensity.

Melissa Penny (Swiss Tropical and Public Health Institute, Switzerland) described that models to date have been generated for specific stages of product development. She stressed the need to have models generating evidence in the whole development pathway from discovery research to translational research, extending to clinical development and implementation research. To this account, her team developed a new approach to use models and machine learning to inform target product profiles of new tools, and to identify key determinants of intervention impact in low transmission areas and other settings. Overall, she informed the attendants that a model is a useful tool for formalizing assumptions and providing outputs to inform decision making.

Daniel Neafsey (Harvard TH Chan School of Public Health, USA) spoke about techniques for determining relatedness in parasites and its potential applications. Specifically, older descent models used identity by state (IBS), which is often unable to tell recent changes and is not comparable across

different parasite populations. Instead, he suggested using identity by descent (IBD), which is now possible due to the development of Markov models such as hmmIBD. These models are informed by known allele frequencies in the parasite, they are transportable across studies, and can be used with any type of genetic marker (SNPs, micro-satellites, etc).

Mphasto Phiri (Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Malawi) discussed results from a randomized controlled trial in Burkina Faso and Mali that tested whether adding azithromycin (AZ) to seasonal malaria chemoprevention (SMC) would result in an additional mortality reduction. Children were given up to four cycles a year of either SMC+AZ or SMC+placebo. Though the researchers did not find an additional effect on mortality or hospitalization, they did find that there was a 15% reduction in respiratory and gastro-intestinal illnesses. He looked at the prophylactic effect of AZ on clinical malaria cases and found that it was quite modest, about 1-2 weeks only.

Donnie Mategula (Malawi-Liverpool-Wellcome Trust, Malawi) presented his findings of geostatistical analysis of Malawi's changing malaria transmission from 2010 to 2017. He assembled 2237 *Plasmodium falciparum* parasite prevalence surveys and calculated population-adjusted prevalence and populations at risk by the district to inform malaria control program priority setting. He revealed that overall transmission was reduced in the country by 47.2% from 2010 to 2017 and that it had shifted to the south. The decline in prevalence was not equal across the country and was heterogeneous. He recommended the scale-up of malaria control interventions and identifying factors for heterogeneity.

Day 4: 2nd November 2019

Innovating to Enable Malaria Elimination I

Janice A. Culpepper (Bill and Melinda Gates Foundation, USA) welcomed participants for the last day of Keystone Symposia and moderated the morning session. She invited **Thierry T. Diagana** (Novartis Institute for Tropical Diseases -NITD, USA) who shared Novartis' antimalarial drug discovery and development pipeline. NITD has a drug portfolio for malaria, leishmaniasis and cryptosporidiosis. He gave the examples of projects targeting blood stages and chemoprevention targeting hypnozoites. His research team have two products, KAE609 which inhibits parasite growth, and KAF156 that is active against *Plasmodium falciparum* and *Plasmodium vivax* with an unknown mechanism, that have reached Phase 2 clinical studies. KAF156 targets both the hepatic and blood stages and can be a potential preventive, therapeutic and transmission-blocking product. His team is developing long-acting KAF156 to make it a candidate drug for chemoprophylaxis.

Lluis Ballell (GlaxoSmithKline, Spain) shared work from four areas of development: monoclonal antibodies (mAbs), long-acting injectables, dual-active agents (liver and blood-stage) and targeting mosquitoes with bacteria that prevent them from spreading *Plasmodium* parasites. The work in mAbs included the finding that CSP NANP mAbs are likely driving the improved protection of fractionally dosed RTS,S over the normal dose. He also discussed candidate molecules for a long-acting injectable preventative that could last up to five months, and a dual active agent that has a novel mode of action. Audience interest seemed focused on the mosquito-targeting bacteria, which were discovered after a GSK mosquito colony lost infectiousness.

Why, asks **Maria Mota** (Instituto de Medicina Molecular, Portugal) do some people progress to severe malaria while others do not, and why can this manifest as cerebral malaria, severe anemia, or respiratory distress? Her lab's work suggested that the human microbiome may play a large role in reaction to the parasite. They infected both germ-free and normal mice with parasites and found a higher mortality rate in the normal mice. When they conducted another experiment targeting bacteria found in lungs, they were able to reduce mortality after parasite infection. This leads to the conclusion that plasmodium-triggered lung microbiota dysbiosis may be an important factor in the development of severe malaria. In addition to the microbiota, her team pointed out the involvement of host response to trigger respiratory distress that may be mediated through IL-10.

Alejandro Llanos-Cuentas (Universidad Peruana Cayetano Heredia, Peru) presented about the clinical development and implementation of tafenoquine for *P. vivax* malaria, which is widespread in the Americas, the Horn of Africa and Asia. Tafenoquine, discovered in 1978 by Walter Reed Army Institute of Research, is a derivative of primaquine with a long half-life. Tafenoquine had similar efficacy in preventing recurrence as the standard regiment of primaquine in two multicenter studies. He also showed that tafenoquine had 100% adherence related to single-dose administration whereas the adherence of primaquine was 62%. He argued that tafenoquine improved cure rate in people without G6PD deficiency and adequate CYP2D6 activity.

Aissata Barry (National Center for Research and Training for Malaria - CNRFP, Burkina Faso) tested a hypothesis that mature gametocytes sequester in the dermis to maximize the chance of uptake by mosquitoes. She found high mosquito infection rate by direct skin feeding, and gametocyte densities were similar in skin fed and membrane fed mosquitoes. Additionally, she observed that gametocyte densities in different blood compartments were similar. Her finding s the absence of evidence for parasite sequestration.

Ashenafi Assefa (Ethiopian Public Health Institute, Ethiopia) presented study outcomes comparing short course and standard 14-day regimen primaquine for the radical cure of *Plasmodium vivax* malaria. The study involved patients from Ethiopia, Afghanistan and Indonesia to assess symptomatic recurrences over 12 months and risk of hemolysis. The study arms were: primaquine 7-day, primaquine 14-day and control with placebo. Incidence rate of *P. vivax* infection was 0.96% in control arm, PQ 0.18% in 7-day and 0.16% in 14-day arms. Patients assigned in all arms had similar tolerability. In general, 4 serious adverse events were recorded in intervention arms, 3 in 7-day and 1 in 14-day arms and he explained that this adverse event was due to G6PD heterozygous trait in female participants which were missed at the time of enrollment to the study. He concluded that the 7-day regiment is not inferior to 14-day regimen in efficacy to prevent relapse and speculated advantage of the 7-day regimen in improved adherence and effectiveness for radical cure of *P. vivax* infection.

Innovating to Enable Malaria Elimination II

Flaminia Catteruccia (Harvard TH Chan School of Public Health, USA), beloved senior editor of these MESA Correspondents reports, spoke about her lab's work experimenting with antimalarials in mosquitoes. In theory, if we can treat mosquitoes with antimalarials, without affecting mosquito reproduction and longevity, there will be no selection pressure in mosquitoes against these compounds. Her lab performed a proof-of-concept experiment using atovaquone. They exposed infected mosquitoes to an atovaquone-treated surface and found that all parasites were killed, even with only six minutes of exposure. This still works 12 hours' post-infection, meaning that IRS is a potential formulation for this solution. Finally, her team experimented with adding atovaquone to attractive targeted sugar baits, which resulted in the killing of all parasites within the mosquitoes. To avoid contributing to parasite resistance, the team has begun to screen novel compounds that could be used as antimalarials in mosquitoes.

Nicholas M. Hamon (Innovative Vector Control Consortium – IVCC, UK) gave an overview of the Zero by 40 initiative, a partnership between six large chemical partners to work towards eradication by 2040 through the development of new vector control tools. IVCC works as an organizing body for this development agenda, mitigating risk for companies and providing technical expertise. This research agenda has resulted in four new potential insecticides, with one back-up. Their three most important areas of focus moving forward are getting dual-active ingredient nets to market, stopping outdoor transmission, and creating next-generation approaches to IRS. The speaker stressed that IVCC believes that eradication is possible by 2040, and that these new tools will be a necessary component of reaching that goal.

Austin Burt (Imperial College London, UK) talked about gene drive and the importance of translating it from bench to field. He gave the current context of malaria control and elimination and stressed that Africa will not eliminate malaria by 2030 if the current achievements are maintained with the same pace. This rationalizes the need to have new tools to eliminate malaria, among which is the use of gene drives that suppress mosquito populations. After explaining how gene drives can spread in field populations, he discussed that a successful gene drive system requires not only the appropriate gene construct, but a wider recognition of implementation challenges including support from the regulatory authority, support from the public and communities, and sufficient local capacity to release the gene drive mosquitoes.

Lilian Mbaisi Ang'ang'o (International Centre of Insect Physiology and Ecology – ICIPE, Kenya) gave a detailed account of how a novel microsporidian blocks *Plasmodium falciparum* transmission in *Anopheles arabiensis* mosquitoes. She stated that *Microsporidia* prevalence across different

regions of Kenya varies and found that there was no coinfection with *P. falciparum*. Her team observed that the symbiont is transmitting vertically from the infected mother to its progeny at high efficiency (45-100%). Their field observation on lack of coinfection was validated in laboratory: microsporidia infection blocked *Plasmodium* development inside the vector by arresting plasmodial development at oocyst stage without having any host fitness cost.

Tibebu Habtewold (Imperial College London, UK) came out with tough questions for those of us working with mosquitoes: why are our mosquito husbandry practices so different from what occurs in the wild? What implication does this have for our evaluation of transmission blocking tools? Specifically, he pointed to the common practice of feeding an infected blood meal to mosquitoes and then only feeding them sugar until oocysts are counted. In the wild, the mosquito might feed multiple times in that interval, and would then lay eggs. He found that the relationship between oocysts and sporozoites was different with and without multiple blood meals, calling into question the current Standard Operating Procedures (SOP).

Helen V. Jamet (Bill and Melinda Gates Foundation, USA) discussed future approaches to vector control. She argued that an ideal vector control product should have four characteristics: not disrupting day-to-day life, inexpensive, not need to be re-applied frequently, and accepted and valued by the people who must use it. This last characteristic has often been lacking in the history of vector control due to poor communication between developers and end-users. She gave two examples of excellent community engagement leading to success: human African trypanosomiasis (HAT) eradication efforts resulting in the introduction of "Tiny Traps" and the Target Malaria project which engaged communities around the first initial sterile male releases that might eventually lead to gene drive testing. Finally, she discussed the replication crisis, and called for improvements in vector control testing and SOPs to ensure high-quality evidence.

Fitsum G. Tadesse (Armauer Hansen Research Institute, Ethiopia) presented about the contribution of asymptomatic infections to transmission from his studies based in Ethiopia and Uganda. From a previous cross-sectional study, it has been known that high rate of mosquito infection in Africa was from asymptomatic cases whereas in a study from Cambodia transmission is from symptomatic cases. His current study involves running a longitudinal assessment of the infectious reservoir using repeat membrane feeding assays on infected individuals. It was evident that infectivity to mosquitoes was related to parasite density. A decline in the contribution of asymptomatic infections throughout the study was observed, and minority of individuals, called by the research team super-spreader, remained infectious throughout the study. He concluded that *P. falciparum* infection can persist for many months at fluctuating asexual densities and can continue to produce gametocytes throughout.

Philip Welkhoff (Bill and Melinda Gates Foundation - BMGF, USA) discussed how the BMGF malaria strategy has changed to adapt to new challenges. In particular, they are pivoting to take a pathway towards eradication that minimizes deaths along the way. Taking lessons from polio, he stressed three elements that will help both reduce burden and work towards eradication: good surveillance, better case management, and vector control. As an integral part of these efforts, countries should be empowered to use data and make subnationally tailored plans to achieve their goals. Finally, he raised the difficult question of what we should *not* do. He compared our situation to the trolley problem: any resources we use in one place are resources that we cannot use somewhere else. For example, universal bednet coverage in low-transmission areas may not be a solution that will have the greatest effect on the amount of money spent. Ultimately, the balance of resources is a difficult problem that will require extensive thought within the malaria community.

Kristine Werling (Harvard TH Chan School of Public Health, USA) talked about how *Plasmodium* development in the *Anopheles* mosquito builds an adaptable relationship that

shapes malaria transmission and control. She said that mosquito egg development and *Plasmodium* development were linked. *A .gambiae* did not suffer reproductive costs of infection with *Plasmodium falciparum*. While *A. gambiae* egg and *P. falciparum* oocyst numbers were positively correlated in both laboratory and field *P. falciparum*, oocyst mean size (a proxy for parasite growth rates) was inversely correlated with egg development. Suppression of mosquito reproductive processes accelerated parasite development, increasing chances of parasite transmission. She concluded that *P. falciparum* development is responsive to physiologic changes in *A. gambiae*, with implications for mosquito control strategies.

Flaminia Catteruccia, who moderated the last session, acknowledged participants and handed over the mic to **Thierry Diagana**. He thanked all the speakers, appreciated the energy and enthusiasm of participants and valued the conversations and wished all to keep it up. He stressed everybody to reach out and keep learning basic biology of the parasite and vector. **Flaminia Catteruccia** thanked Keystone symposia organizers and all participants. **Philip Welkoff** appreciated the connection people will have after this symposium.

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