RESOURCE HUB *Correspondents*

ASTMH 2020 Annual Meeting - Virtual

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15 - 19 November 2020

Virtual Conference

The MESA Alliance would like to thank all the Organizers and Co-Chairs[1] of the symposia that collaborated with the program, and Valentina Mangano (University of Pisa, Italy) and Julie Chaccour (Independent Consultant, Spain) for providing senior editorial support.

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[1] *Complete list of names at the end of the report.*

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Day 1: 15th November 2020

Opening Plenary Session and Awards Program

The first virtual ASTMH annual meeting started with around 4000 people registered from over 100 countries on Sunday, November 15th. The conference kicked off with the opening plenary moderated by **Joel G. Breman** (ASTMH President, United States) and a welcome message from **Tedros Adhanom Ghebreyesus** (World Health Organization, Switzerland), which was attended by more than 600 viewers. Tedros talked about the importance of commitment and determination in fighting against devastating outbreaks and eradicating deadly diseases. Furthermore, he highlighted the need for people's trust in vaccines for the current COVID-19 pandemic.

The Opening Keynote was given by **Christiana Figueres** (co-founder of Global Optimism) who noted the huge financial infusion that is needed to combat the economic consequences of COVID-19, and raised the idea that depending on how these economic decisions are made, we could change the course of climate change or not. She also talked about the environmental crisis, the greatest risk to human health before COVID-19 and to remain so after it. She mentioned deforestation and pollution as important threats to both human and the planet's health, affecting disproportionately populations living in the tropics. Figueres encouraged global health professionals to use their recognized status reinforced during the COVID-19 pandemic to speak up and out in favour of planetary health and to sign the joint letter issued to the International Energy Agency in May 2020.

Anthony Fauci (National Institute of Allergy and Infectious Diseases, United States) was awarded for his outstanding service to the global public as a trusted voice in science. He talked about his genesis in times of the HIV/AIDS epidemic and how he became known as a reliable source of scientific information. He further emphasized the need to communicate accurately and honestly in the face of the present pandemic using data-driven evidence.

Afterwards, other prizes were awarded in several different categories such as the Annual Meeting Travel, ASTMH Postdoctoral Fellowship, Young Investigators, Clinical Research, 2020 Fellow of ASTMH

(FASTMH), ASTMH Distinguished International Fellows, 2020 Alan J. Magill Fellow and Communications.

This report is brought to you by the MESA Correspondents with mentoring and editorial support from Valentina Mangano (Pisa University Hospital, Italy) and Julie Chaccour (Independent Consultant, Spain).

Day 2: 16th November 2020

Symposium #3: Can We Ignore "Asymptomatic" Low-Density Malaria Any More?

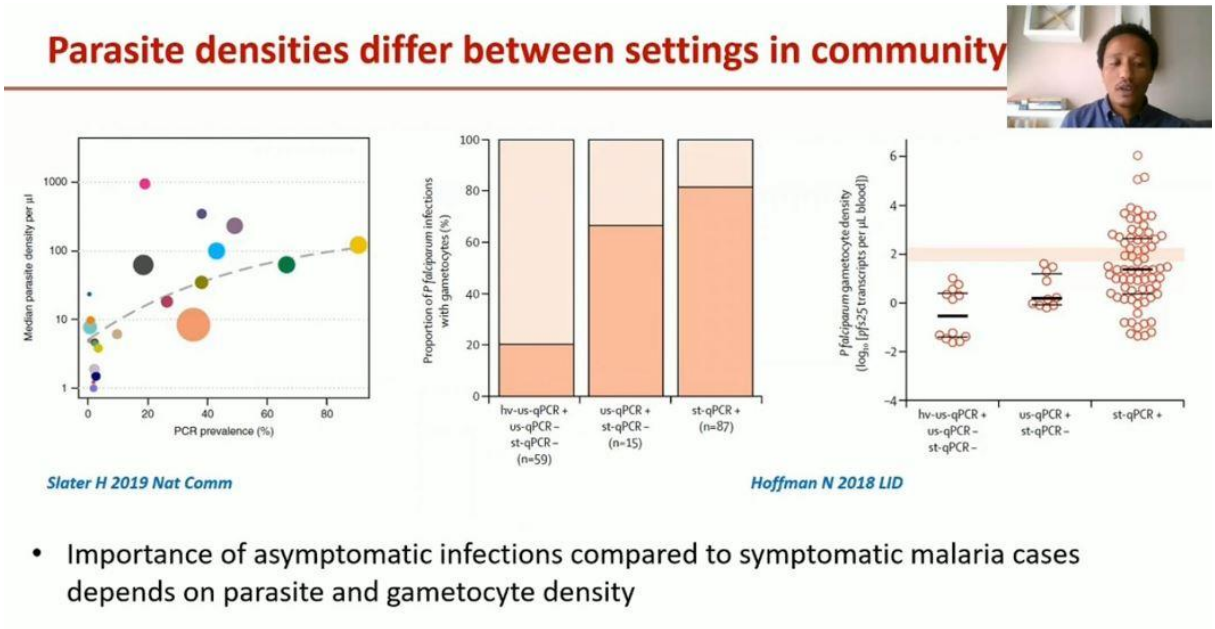
Lucy Okell (Imperial College London, United Kingdom) presented studies to highlight that detecting low-density malaria infections and identifying what factors drive infection in asymptomatic individuals are important elements in malaria elimination. Several studies have shown that low-density infections, undetectable by microscopy, are common in both *P*. *falciparum* and *P. vivax*. These low-density infections require ultrasensitive assays, e.g. qPCR, to be detected. Okell examined the relationship between the past and current transmission intensity in determining the relative abundance of submicroscopic infections in Africa and highlighted that low-density infections prevail in low-transmission areas. Explanations for this latter observation include 1) differences in the age distribution of infected populations with higher prevalence of infection being observed in older age groups in low transmission compared to high transmission settings; 2) low genetic diversity of the parasite in low-transmission settings favouring acquisition of protective immunity in the human population; 3) lower between parasite strains of low-transmission areas, where evolution may favour chronic low-density infections, reducing the parasite' chances of causing symptoms that require treatment.

Dylan R. Pillai (University of Calgary, Canada) presented work on the changing landscape of malaria diagnostics. For many years, microscopy has been the gold standard for detecting malarial infection, but it comes with various limitations. Rapid diagnostic tests (RDTs) based on immunochromatographic detection of the histidine-rich protein (hrp) have therefore played a key role in the last two decades. However, the emergence of Hrp2-deleted strains of *P. falciparum* limits the sensitivity of RDTs. Real-time polymerase chain reaction (PCR) emerged as a far more sensitive and specific tool to detect malaria parasites. PCR is however expensive and may not be applicable in low-income endemic areas. Recently, faster, cheaper and easier to perform loop-mediated isothermal amplification (LAMP) methods have been developed for malaria diagnosis, showing a limit of detection (LOD) of around 0.1 parasites per microliter. Also, it is possible to adapt in-house LAMP protocols enabling visual detection of samples' positivity, therefore not requiring using of fluorescence readers. Comparison of results obtained with LAMP and qPCR show similar sensitivity of the two methods both in non-endemic and endemic areas. In non-endemic areas, the high negative predictive value of LAMP methods allows to use it as a screening test, with no further examination needed for LAMP negative samples. In endemic areas, LAMP has proven useful in detecting low-density malaria infections in pregnant women, the treatment of which resulted in improved pregnancy outcomes in clinical trials.

Though often ignored, asymptomatic low-density malaria infection plays a crucial role in maintaining transmission of the disease, presenting a setback to global malaria elimination. **Gilles Cottrell** (Institute of Research for Sustainable Development, France) gave a presentation on the clinical effects of low-density malaria, which often goes undetected (submicroscopic) and causes asymptomatic malaria persisting from a few days to months. Asymptomatic infection could be beneficial by decreasing the risk of malaria illness. However, it also causes anaemia in children and expectant mothers, and moreover, it is associated with low birth-weight. Furthermore, in low-transmission settings, pregnant women are at increased risk of malaria, spontaneous abortions, stillbirths and premature births. Cottrell illustrated that submicroscopic prevalence is higher than microscopic prevalence in pregnant women, with the highest prevalence being detected during the first trimester. Additionally, intermittent preventive treatment in pregnancy (IPTp) does not fully prevent malaria infections, especially submicroscopic low-density infections. Women infected before conception are at higher risk of infection during their pregnancy and maternal infection increases infants' susceptibility to malaria. Therefore, monitoring during the early pregnancy period, or even before conception, is vital for optimal protection of both women and infants. Cottrell envisaged the

importance of carrying out longitudinal studies of malaria infection using highly sensitive diagnostic tools to fill the knowledge gaps in low-density asymptomatic malaria.

Fitsum Tadesse (Armauer Hansen Research Institute, Addis Ababa, Ethiopia) illustrated the relationship between asymptomatic malaria and parasite density distributions, gametocyte densities and malaria transmissibility. Especially in low-transmission settings, a large proportion of all malaria infections can be submicroscopic. Moreover, different *Plasmodium* species produce gametocytes at different rates: *P. vivax* produces them within 2-3 days, whereas *P. falciparum* takes 9-12 days. A study with 298 mosquito membrane feeding experiments demonstrated that infectivity positively correlates with parasitemia and gametocytemia. In humans, however, parasitaemia, gametocytemia and mosquito infectivity are correlated in asymptomatic *P. falciparum* infections but not in clinical malaria cases, where gametocyte carriers were more frequently detected by microscopy among subjects with lower parasite densities. In *P. vivax* infections, the level of gametocytes mirrors the asexual parasite density, both in symptomatic and asymptomatic infections. In endemic areas, patent *P. falciparum* infections were approximately three times more infectious than submicroscopic infections. Mosquito membrane feeding assays conducted in four African countries showed that the likelihood of mosquito infection is very low at gametocyte densities below one parasite per microliter and increases steadily from ten parasites per microliter. Therefore, the importance of asymptomatic infections compared to clinical malaria cases in *P. falciparum* transmission depends on asexual and sexual parasite densities, whereas the relative contribution to the infectious reservoir in a given setting depends on the frequency of asymptomatic infections in the population. Tadesse concludes stressing the importance of conducting longitudinal studies to assess the impact of different factors on parasite biomass kinetics and infectivity.

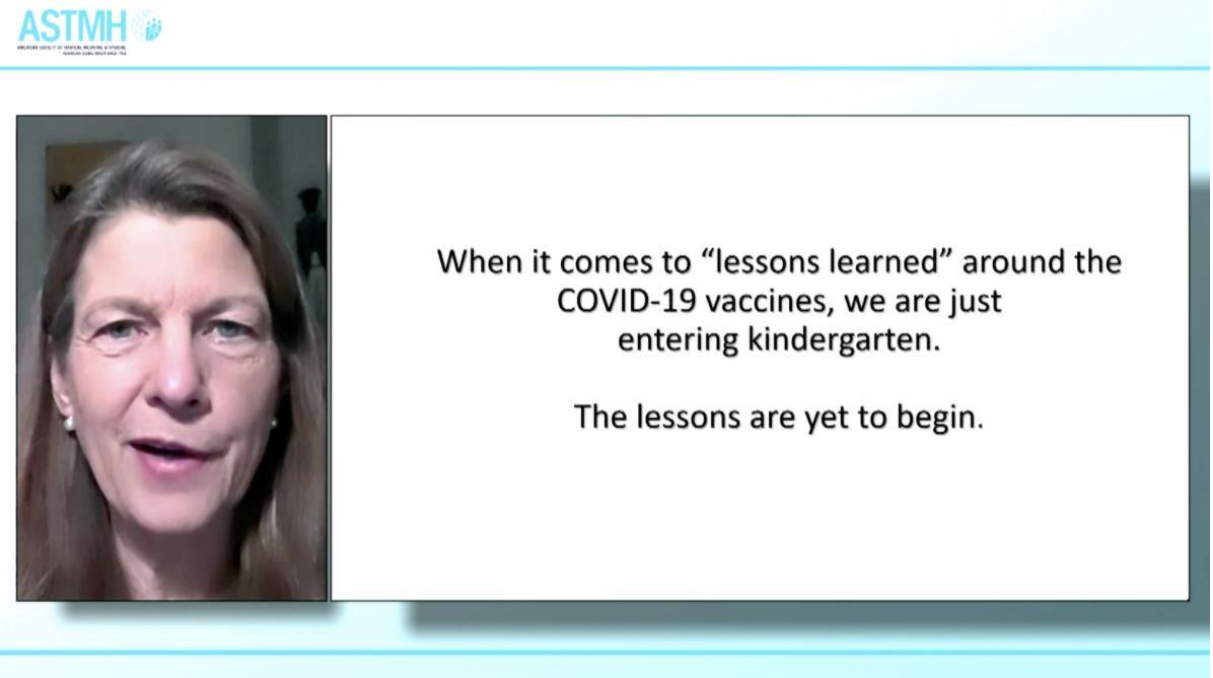


Plenary Session II COVID-19: Lessons Learned and Future Challenges

Anthony Fauci (National Institutes of Health, United States) started the session with a comprehensive overview of the basic aspects of the SARS-CoV2 infection: virology, transmission, clinical presentation and manifestations of severe COVID-19 disease, social determinants of risk, fundamental public health measures, and therapeutics and vaccines. He described COVID-19 as a pandemic that reached historical proportions not seen in the last hundred years. Fauci further mentioned that if adherence to the main public health response strategies were higher, we would not have seen a resurgence as dramatic as currently happening in the United States and Europe. Towards the end, Fauci described

recent events in vaccine development and said he is optimistic that first doses will be administered to priority groups before the end of this year.

John N. Nkengasong (Africa Centres for Disease Control and Prevention, Ethiopia) presented an overview of the COVID-19 response in Africa. The joint continental strategy was preventing transmission, death, and social and economic harm. He named several partnerships and initiatives that played a critical role in the response, such as the partnership to accelerate COVID-19 testing (PACT) in Africa. He further described epidemiological trends across African countries, which increasingly show concerning trends starting in the second half of the year. Key features in Africa's response to COVID-19 were unified leadership, along with a new public health order, partnerships, adaptive development and allocation of public health workers as well as investment in local manufacturing of medical interventions. As the way forward, he emphasized the need to maintain the gains achieved and to be prepared for the second wave in Africa by intensifying public health and social measures against COVID-19, including scale-up of testing and surveillance.



'*The lessons are yet to begin*' was the cautious introduction of **Heidi Larson** (London School of Hygiene and Tropical Medicine, UK) in her talk on "COVID-19: Lessons Learned and Future Challenges". She presented results from the Vaccine Confidence Project, which demonstrate the importance of confidence in products, providers, policymakers, and public health systems, in the public's willingness to accept a vaccine. Larson mentioned a wide variety of factors that would contribute to low acceptance and described vaccine hesitancy as a challenge not only in subgroups but also in the wider population. According to Larson, misinformation would be a serious obstacle to the acceptance of a COVID-19 vaccine and could be a 'tipping point phenomenon' towards achieving coverage levels required for herd immunity.

In the final talk of the session, **Richard Hatchett** (Coalition for Epidemic Preparedness Innovations - CEPI, United Kingdom) gave an overview of the role of CEPI in COVID-19 vaccine development and access. In partnership with the leading COVID-19 vaccine developers and non-governmental organizations, CEPI supports funding of nine vaccine candidates, eight of which are in clinical trials. Hatchett described various projects of CEPI that aim to ensure 'global access to vaccines to all countries at the same time regardless of income' and current efforts as well as challenges to achieving that goal. In the outlook for the future, Hatchett mentioned that CEPI aims to deliver two billion doses

around the world in 2021, and emphasized the need for better preparedness plans for the next pandemic and Disease X, for which their strategy could serve as a model.

Symposium #7: Human Landing Catches: Alternatives and Directions for the Future

As symposium organizers, Sarah Zohdy (Centers for Disease Control and Prevention, United States) and Jenny S. Carlson (United States Agency for International Development, United States) described human landing catches (HLC) and other mosquito collection methods for entomological surveillance and discussed imitations and challenges including standardization.

Heather Ferguson (University of Glasgow, UK) talked about the evaluation of the mosquito electrocuting trap (MET) in a region of Burkina Faso. Although METs caught 40-50% fewer *An. gambiae mosquitoes than* HLC, they provided a consistent representation of vector dynamics, species composition, biting behavior and infection rate. Therefore, despite limitations in sensitivity, METs could be a useful alternative collection tool. METs were also evaluated compared to BG-Sentinel traps for *Aedes* catches, with no significant difference between the two methods. However, the trial had limitations and more work for full evaluation was recommended. Challenges of METs were discussed and the development of a MET product following the identification of country-specific needs was envisaged.

Nicodem J. Govella (Ifakara Health Institute, Tanzania) presented on the success of MET as an alternative to HLC for *Anopheles* surveillance. The target product profile used to develop METs was aimed at mimicking the set-up for HLC with no risk of exposure by the user and was tested for safety, quality and efficacy. Optimization was conducted as to the exact power needed to kill the mosquitoes while leaving them intact, after which the first trial was conducted in rural Tanzania. A sensitivity of 58% indoors and 20% outdoors, and a similar estimate of mosquito behavior relative to HLC was observed. Improvement of METs prior to the second trial in urban Tanzania resulted in better performance. The applications of METs included investigation of biting time and distribution of biting between indoor and outdoor environments in an experiment carried out in the Kilombero Valley, Tanzania. Moreover, MET was used to survey malaria vectors nationally and to assess how outdoor exposure to malaria vectors varied across diverse ecological settings of transmission in Tanzania in both dry and wet seasons over 3 years.

Krijn Paaijmans (Arizona State University, United States) talked about human-baited traps as an alternative to HLCs to accurately evaluate key medical entomological parameters with a caption on "*Nothing more attractive than a human*". Paaijmans described humans as excellent mosquito lures, pointed out the effectiveness of LLIN acting as a lethal lure in case of no resistance and highlighted the shortcomings of the human landing catches and why they should not be used. He talked about the Mozambican Alliance Towards Elimination of Malaria (MALTEM) project, which used the Centers for Disease Control and Prevention light trap (CDC light trap) deployed within human-baited tent traps indoors and outdoors. They generated evidence in Maputo province, Mozambique, to help the national malaria programs to design elimination strategies with significant achievements in Gaza and Inhambane. Paaijmans ended talking about the current development of next-generation human-baited tent traps.

Frances M. Hawkes (University of Greenwich, United Kingdom) introduced HLCs and their use for understanding mosquito biting behaviour in malaria pre-elimination settings and presented data on how HLCs might systematically under-estimate biting rate. She presented the findings obtained using the host decoy traps (HDTs) for outdoor malaria vector surveillance which caught ten times more *An.*

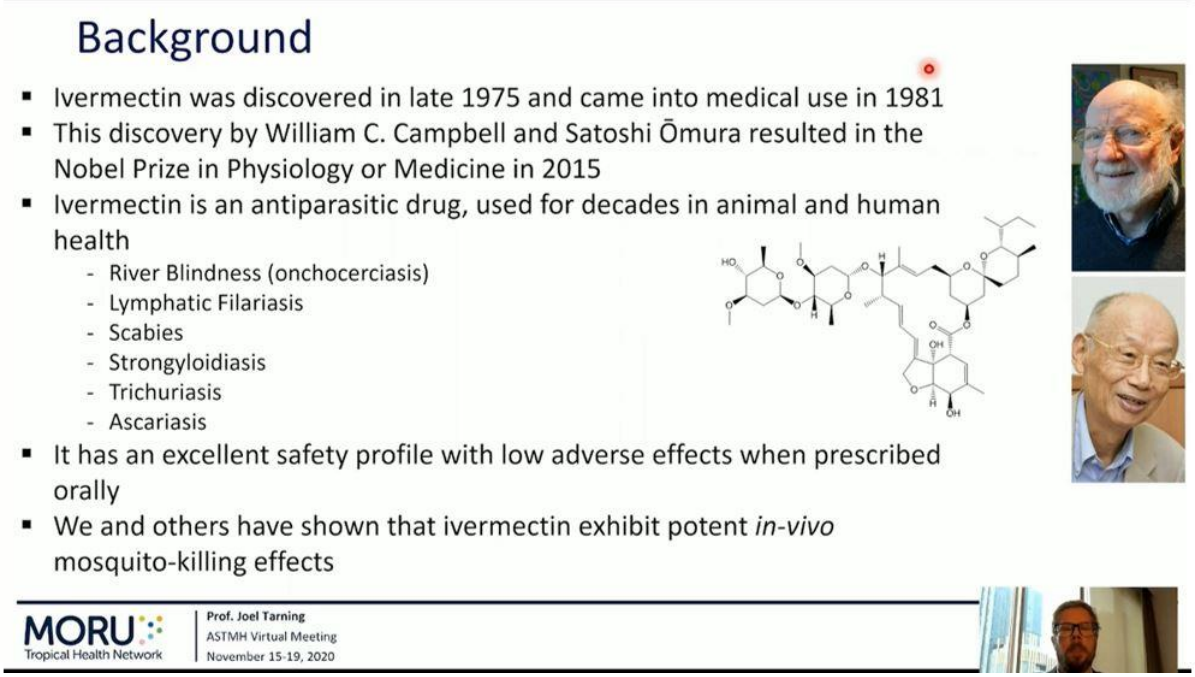
gambiae than HLC in Burkina Faso and Benin. Based on social and operational acceptability of the HDT, additional research was conducted across different settings in both highlands and lowlands. They also carried out qualitative assessments through interviews and focus group discussions to understand community responses to HLC. Field volunteers perceived HLCs as risky and difficult, associating it with disease and negative impact on their activities due to exhausting night work.

Brian D. Foy (Colorado State University, United States) presented on human-baited tent traps for sampling host-seeking malaria vectors in West Africa. The traps were tested in Malabo, Equatorial Guinea and in Senegal with satisfactory results compared to other catching methods. The human-baited tent traps did not result in exposure to any vector-transmitted disease since no mosquito bites occurred in the process of catching. Foy gave a brief discussion on the advantages and disadvantages of human-baited tent traps with battery-powered trapping signs. Foy ended talking about the RIMDAMAL trials I and II that assess the efficacy and risk of harm of repeated ivermectin mass drug administration (MDA) for malaria control.

John Gimnig (Centers for Disease Control and Prevention, United States) presented an overview of HLC, which remains the gold standard in entomological monitoring. Despite their shortcomings, human bait catches remain the most useful single method of collecting anthropophagic mosquitoes because there exists no replacement attractant for humans. Gimnig pointed out what could be learned about the biting behavior of the mosquitoes and the supplementary outcomes using HLC. He presented a pooled analysis for comparing trapping methods, identifying the different replacements for HLC with the CDC light trap indoors being the safest. He reviewed the analyses carried out on mosquito indoor and outdoor biting behavior with data from *An. funestus* biting times collected from different sites. Lastly, Gimnig emphasized the disadvantages and limitations of HLCs.

Symposium #19: Mechanistic Dose-Response Modelling of Antimalarial Drugs

Joel Tarning (Mahidol Oxford Tropical Medicine Research Unit, Thailand) presented a study on pharmacokinetics (PK) and mosquito-killing effects of ivermectin and its metabolites. Ivermectin showed potent mosquito-killing effects when the mosquitoes (*Anopheles dirus and A. minimus*) fed on blood from humans who had taken ivermectin, both in membrane feeding and direct feeding assays. Two clinical trials in human volunteers were pooled and analysed using a population PK modelling approach. Bodyweight and co-administration of dihydroartemisinin-piperaquine showed a significant impact on the pharmacokinetic properties of ivermectin. Predicted drug concentrations of ivermectin and its metabolites were linked to mosquito-killing effects and showed substantial differences between mosquito strains. Modelling and simulation suggest potent mosquito-killing effects for over 7 days after a standard 3-day oral dose of ivermectin. The developed model could be a valuable tool to inform dosing policy on transmission blocking and malaria elimination efforts.



Palang Chotsiri (Mahidol Oxford Tropical Medicine Research Unit, Thailand) presented on the topic "Primaquine pharmacokinetics and pharmacodynamics (PK/PD) modelling". Primaquine is an effective drug for treating *P. vivax* because of its activity on liver stage parasites. Chotsiri's presentation showed a population PK/PD modelling approach to predict PK properties of primaquine, and its effect on gametocytes and mosquito infectivity. In the gametocyte dynamics model, Chotsiri showed that primaquine killed gametocytes and higher doses of primaquine resulted in a shorter time to eliminate gametocytes from the blood. Mosquito infectivity was affected by both primaquine and gametocytes, resulting in a lower infectivity at low gametocyte density and high primaquine concentrations. Taken together, this model could be used to determine an optimal primaquine dose for blocking transmission of malaria.

Karen Barnes (University of Cape Town, South Africa) gave a talk focused on improving malaria treatment in vulnerable sub-populations (i.e. pregnant women, infants, hyperparasitaemic patients, or individuals with co-morbidities), which represent an important share of all malaria cases. Antimalarial drugs must be given at optimal dosages to ensure that all patients have an equal chance of being cured; however, during clinical drug development, vulnerable populations are usually excluded. Pooling already existing PK data and conducting individual patient data (IPD) meta-analyses can help to establish adequate dosages in these populations, achieving a sufficient sample size to reach the statistical power needed and increasing validity and generalizability of findings. Currently, this approach is being used to investigate artemisinin combination therapies (ACTs) for treating malnourished children with malaria. Malnourished children were observed to have an increased risk of delayed parasite clearance, recrudescence and re-infection, suggesting suboptimal dosing in this vulnerable population.

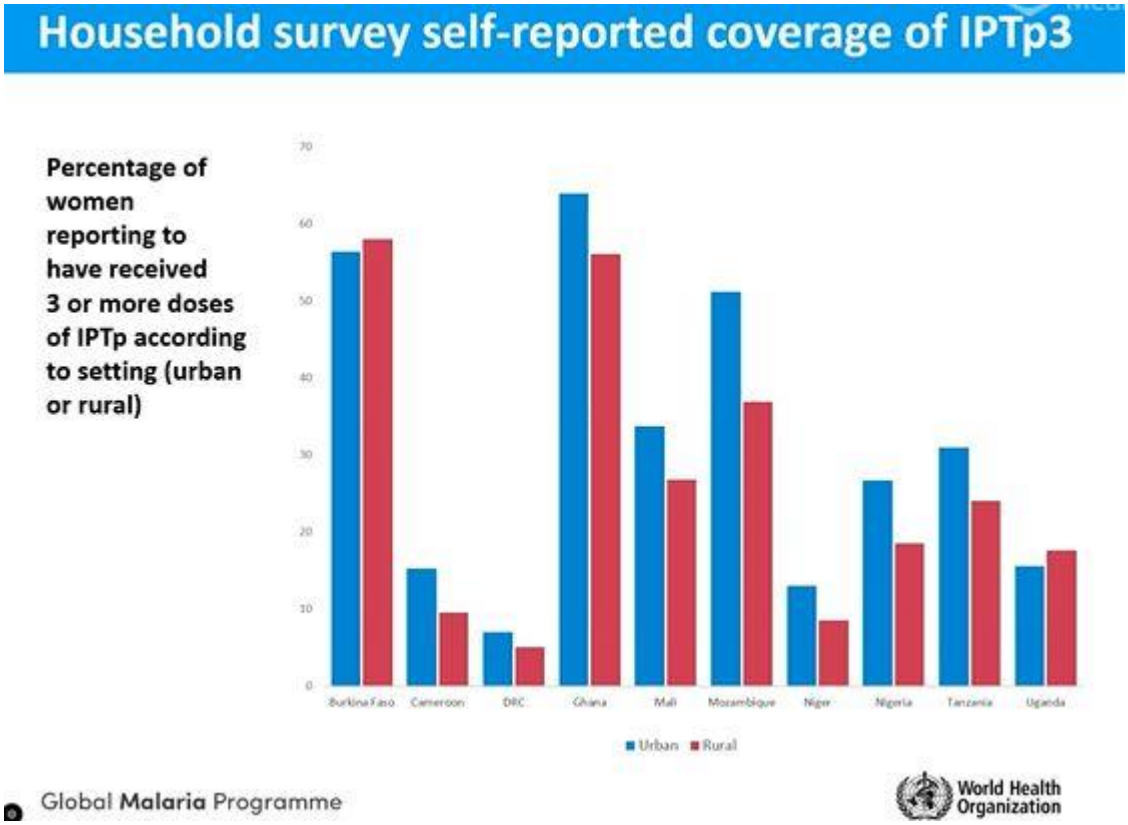
Julie Simpson (University of Melbourne, Australia) highlighted the significant declines in efficacy of ACTs in the Greater Mekong Subregion. Using within-host malaria models that capture the interplay between drug concentration and action, the efficacy of combination therapies can be predicted, providing a clinical decision tool for selecting dosing schemes and combination therapies for current and new antimalarials to be evaluated in clinical trials. One case study example is triple ACT (TACT), which combines dihydroartemisinin (DHA) + piperaquine (PPQ) + mefloquine (MQ). An *in silico* model was used to determine the optimal TACT dosing regimen to achieve ≥90% 42-day cure rates in regions where parasite resistance to DHA-PPQ has emerged. The model predicted the cure rates observed in

the TACT clinical trials and is available as an online clinical decision tool (TACT R Shiny App, www.qmalaria.org). Another case study example presented was within-host malaria modelling of the combination therapy OZ439-DSM265, using data from volunteer infection studies, which demonstrated an antagonistic interaction of the combined effect of OZ439-DSM265 and determined the minimum optimal dosing regimens required to achieve a 42-day cure rate ≥90%.

Symposium #20: A Fundamental Way to Prevent Malaria in Pregnancy: Improving Health Outcomes for Pregnant Women and Their Babies One Nurse and Midwife at a Time

Katherine Wolf (Jhpiego, United States) as a symposium organizer highlighted the fifth anniversary of the IPTp Call to Action. While progress has been made, the call is being renewed, particularly as the world faces the COVID-19 pandemic. Health continuity is critical, particularly for expectant mothers in malaria endemic areas. Wolf noted that nurses and midwives are adapting the care they give to pregnant women during COVID-19 to ensure that no pregnant women experience malaria. She invited participants to join the IPTp Call to Action.

Pedro Alonso (World Health Organisation, Switzerland) presented the WHO approach to speed up and scale up the fight against malaria in the pregnant women. WHO's three-pronged approach is encouraged during pregnancy; including the use of insecticide-treated bed nets to avoid women/vector contact, uptake of sulfadoxine-pyrimethamine (SP) and antimalarial preventive treatment and access to prompt diagnosis and effective treatment. Since 2010, an overall improvement was noted in the number of women who attend antenatal care (ANC) at least once and received malaria intermittent preventive treatment for pregnancy (IPTp). However, there are still barriers, such as transportation, level of education and wealth, which render unacceptable the level of ANC and IPTp coverage. Pregnant women cannot be considered as a forgotten group but a key vulnerable group. Thus, WHO is committed to continuing to put them at the centre of their fight against malaria.



Maud Lugand (Medicine for Malaria Venture, Switzerland) presented on quality measures used in manufacturing medicines used for intermittent preventive treatment for malaria in pregnancy. IPTp is a WHO-recommended intervention, which involves administration of a course of sulfadoxine-pyrimethamine (SP) at each antenatal care visit from the second trimester of pregnancy, as Alonso mentioned before. Its uptake is very low despite being an effective intervention; in 2018, only one third of eligible women in Africa were optimally protected. Sociocultural barriers for low uptake include medical pluralism, low patient acceptance and self-medication. Structural barriers included limited access to ANC services, non-availability of quality-assured SP and low health provider acceptance. MMV supported building GMP production capacity in the region in Nigeria and Kenya, and is currently in the process of developing a user-friendly IPTp-SP package to support local manufacturing companies. They field-tested the packaging to ascertain the use and acceptability, knowledge and perception of it. Results showed women and health care providers had positive experiences with the package.

Aissata Fofana (RTI International, Guinea) shared a study on bringing long-lasting insecticidal nets (LLIN) distribution closer to communities in Guinea through adaptive management, called StopPalu+. This project is to assist the government in reducing malaria-associated morbidity and mortality by helping increase LLIN distribution in the country through monitoring and evaluation. They discovered that distribution points were far and households lost their vouchers for net distribution, therefore the data collected was used to implement the following adaptation measures. Communities were split closer to distribution points, radio spots were used to encourage people to provide their names to get a copy of a voucher for an LLIN, and sensitization activities in schools and group discussions with women and youth associations were held. All these interventions helped increase the expected coverage of LLINs by 20%.

Yacouba Ouedraogo (Jhpiego, Burkina Faso) presented a pilot study on testing the feasibility of community-based IPTp (C-IPTp) provision in Burkina Faso. At only 17-22%, IPTp coverage was low in Burkina Faso in 2014 and 2015, calling for a high-impact intervention to improve the situation. The

study explored whether a community-based approach combined with promotion of routine ANC could increase IPTp coverage. Four health facilities in three districts with high malaria transmission were selected; with baseline and endline surveys conducted, in which the intervention was carried out by community health workers, who were trained and supervised by nurses. IPTp coverage was monitored, and results show an increase in ANC and IPTp4 in both intervention and control groups with IPTp3 and IPTp4 respectively at 50% and 22% in the control versus 64% and 49% in the intervention group at endline. However, no significant difference between controls and interventions was detected. The study revealed that community health workers (CHW) could be trained to provide C-IPTp and is still being implemented in some districts in Burkina Faso.

Jenipher Mukolwe Angaha (Jhpiego, Kenya) shared results from a study in Nigeria and Kenya on the effect of group antenatal care (G-ANC) versus individual ANC on IPTp and ANC attendance. During this study, G-ANC was embraced by both women and health care providers based on many aspects like patient-provider relationship, organisation of care, engagement and empowerment of women. It resulted in increases in ANC attendance and experience of care for women providers and supported further studies on G-ANC to improve coverage of other interventions. The study found the mean number of IPTp doses received was higher for the intervention arm compared to the control arm (Nigeria: 3.45 versus 2.14, $p < 0.001$; Kenya: 3.81 versus 2.72, $p < 0.001$).

Symposium #24: Aedes Surveillance in Africa: (Re-) Building Capacity to Address Growing Arboviral Disease Threats

In her talk on "*Aedes-borne arboviruses as an emerging public health threat in Africa and multi-sectoral approaches for prevention and control*", **Florence Fouque** (Special Programme for Research and Training in Tropical Diseases from the World Health Organization, Switzerland) highlighted the worrying re-emergence of arboviral diseases in Africa. Thus, severe surveillance and control networks have been set up against these often understudied diseases in Africa. To effectively do this, the study's main objective was to develop a reference and workable framework for the application of the multisectoral approaches in controlling vector-borne diseases (VBDs), identifying the best path to take in future collaborations among different sectors. The main findings demonstrated the effectiveness of a multisectoral approach in entomological surveillance to provide guidelines for the successful control and elimination of *Aedes* alongside other VBDs.

Presenting on "*The West African Aedes Surveillance Network (WAASuN)*", **Samuel K. Dadzie** (Noguchi Memorial Institute for Medical Research, Ghana) noted the need to have a surveillance system on the *Aedes* vector since reports have recorded arboviral diseases in 34 African countries. Increased surveillance would provide essential information and adequate preparedness against *Aedes*-borne parasites. Therefore, WAASuN was established in Sierra Leone in 2017 to enhance collaboration on *Aedes* surveillance between West African countries. So far, this network has successfully trained over 60 participants in insecticide resistance monitoring and geomapping, establishing good collaborations with international health organizations such as the Special Programme for Research and Training in Tropical Diseases from the World Health Organization (WHO/TDR), Centers for Disease Control and Prevention (CDC), Partnership for Increasing the Impact of Vector Control (PIIVEC), West African Health Organization (WAHO) and Emory University, among other achievements. Future prospects aim to further strengthen this collaboration and extend the network to cover the entire African region.

Rebecca S. Levine (Center for Disease Control and Prevention, USA) while addressing the capacity of entomological surveillance in Sierra Leone, pointed out the little attention paid to *Aedes*-borne viruses

in Africa. One reason is that these viruses constitute greater public health threats for immunologically-naïve non-African human populations. Secondly, the magnitude of the burden of malaria and many neglected tropical diseases in Africa detract attention from *Aedes*-borne infections. Over the years entomology capacity in Sierra Leone has greatly improved, as insecticide-treated bed nets (ITNs) distribution (2006), indoor residual spraying (IRS) trials (2010-2012), and the establishment of the IVM task-force (2016) monitoring insecticide resistance are important milestones in vector control activities in the country. This culminated in 2017 by the launch of the surveillance of *Aedes aegypti* in West Africa by the CDC and Emory University and the creation of the WAASuN. In 2018, under the USAID/CDC President's Malaria Initiative (PMI), monthly entomological monitoring and vector control interventions (ITN, IRS) were conducted. A partnership between the PMI and the *Aedes* project was hence established. With a budget of 16000 USD, the 12-month project began with sample collection in October 2019. Unfortunately, the COVID-19 pandemic has been a major impediment to the study. Notwithstanding, this project ultimately promises to bring to light the status of the *Aedes* population in the region.

Mawlouth Diallo (Dakar Institut Pasteur, Senegal) gave a detailed account of the *Aedes* surveillance system in Senegal. The programme objectives were to characterize the vectors and study their biology and ecology, to identify the vertebrate hosts and establish the transmission cycle, and investigate .the efficiency of vectorial transmission (vector competence, vector heterogeneity and distribution, virus-vector-host interaction dynamics. The research took a multidisciplinary approach, targeting the entomology, virology, and host (human/non-human primate) aspects in *Aedes*-borne arboviruses surveillance. Preliminary data showed a difference in the *Aedes* mosquito behavior in Africa compared to non-African regions of Asia and America. There was also a notable increase of insecticide resistance which needs to be closely monitored. Important to note was the fact that *Aedes* mosquitoes are governed by different conditions compared to *Anopheles* species, and the use of malaria vector control strategies as a reference point for *Aedes* control might not be as effective. New tools for vector control need to be developed, including increasing the capacity for vector surveillance at the district and community levels.

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Day 3: 17th November 2020

Symposium #32: Alan J. Magill Malaria Eradication Symposium - Basic Research in Africa for Sustained Malaria Elimination and Eradication

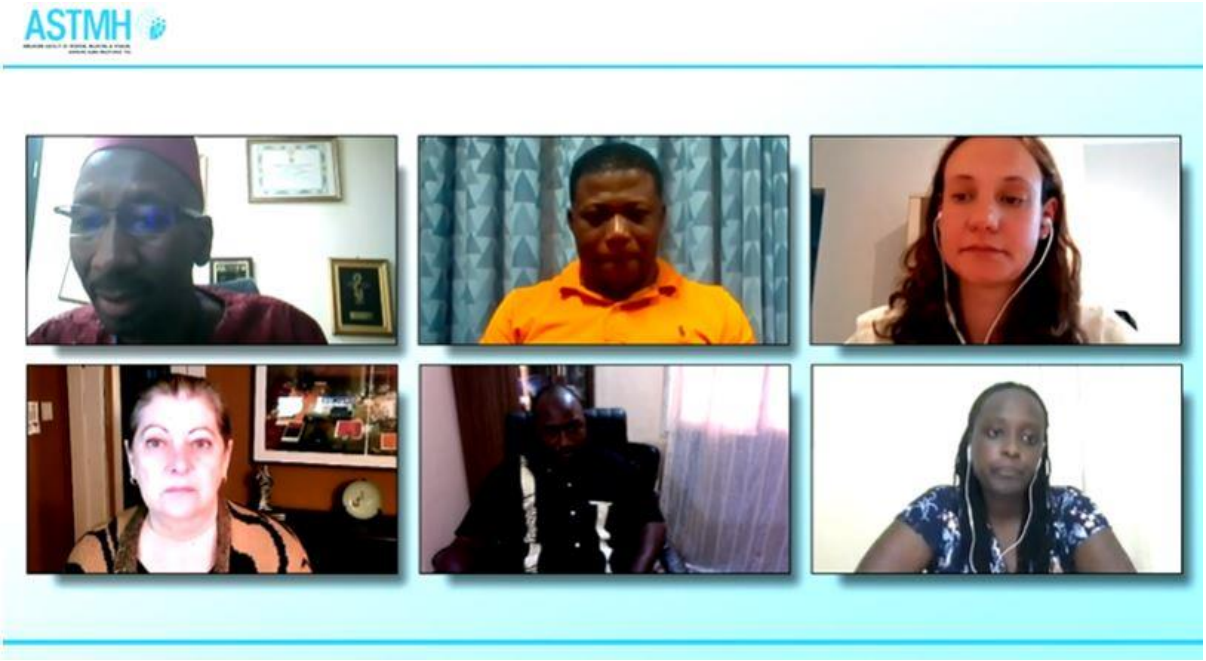
This session was chaired by Abdoulaye Djimde (MRTC-USTTB, Mali) and Janice Culpepper (Bill and Melinda Gates Foundation, United States), and was introduced by Joel Breman (Fogarty International Center, United States) and Janice Culpepper (Bill and Melinda Gates Foundation, United States).

Silvia N. Kariuki (KEMRI-Wellcome, Kenya) gave a riveting talk titled "Red blood cell tension protects against severe malaria in the blood group variant Dantu". In their study they aimed to characterize *P. falciparum* invasion into red blood cells (RBCs) and the RBC membrane structure across genotype groups (Dantu homozygous, heterozygous, and non-Dantu). They found that Dantu polymorphism inhibits the invasion of RBCs by *P. falciparum* and that the effect is mediated by membrane tension rather than membrane protein expression levels. Their research on membrane tension proposes a novel concept of tension thresholds for successful *P. falciparum* invasion. Kariuki closed her presentation by raising unresolved questions, such as the role of their model in explaining other features of *P. falciparum* invasion and its applicability to other polymorphisms protective against malaria.

In the second talk of the session, **Yaw Aniweh** (University of Ghana, Ghana) presented his work on the role of Plasmodium falciparum merozoite-associated armadillo protein (PfMAAP). Motivated by the question of what protective proteins they might find in a malaria-endemic setting, Aniweh had collected plasma in a study site in Ghana to investigate immunoglobulin G proteins. During the presentation, Aniweh described how they explored different features of the PfMAAP protein and its functional characteristics in detail. In the end, he highlighted a late-stage expression, dual localization pattern, and expression in gametocytes. Importantly, antibodies to PfMAAP inhibit merozoite invasion of erythrocytes.

Kathryn J. Wicht (University of Cape Town, South Africa), presented findings from a study on *P. falciparum* chloroquine resistance transporter (*Pf*CRT) point mutations and antimalarial drug susceptibility in the parasite. Their study aimed to investigate whether *Pf*CRT point mutations found in South East Asia could influence drug phenotypes and therefore piperaquine resistance in Africa. They found that PfCRT point mutations could decrease the sensitivity of African parasites to piperaquine, whereas specific mutations (F1451 and G353V) would increase susceptibility to common quinoline-based antimalarial drugs. Widespread DHA-PPQ use in Africa may therefore cause PPQ resistance. In their future work, Wicht is interested in exploring other newly emerging point mutations and editing them into African parasites, as well as conducting cellular transport studies.

In his talk 'Discovering new therapies for non-falciparum *Plasmodium* species from the field', **Laurent Dembele**, (MRTC-USTTB, Mali), addressed the urgent need for new candidate therapies for non-falciparum parasites, especially in sub-Saharan Africa. He presented findings from two studies, focusing on *P. malariae* and on *P. vivax*. Only piperaquine was found to be effective for *P. malariae*, whereas the effectiveness of artemisinin combination therapies was compromised. These results suggest a need to readjust the current *P. malariae* treatments. The second study presented found that plasmodium liver-specific protein 2 expression coincided with the beginning of liver-stage development and was a marker of active hypnozoites that cause relapses in *P. vivax* infections. The results add an important molecular feature to the definition of plasmodium hypnozoites and will be useful for designing novel *in-vitro* assays for measuring anti-relapse drug effects.



Symposium #33: Human Challenge Infections - Learning from Nature in Controlled Settings

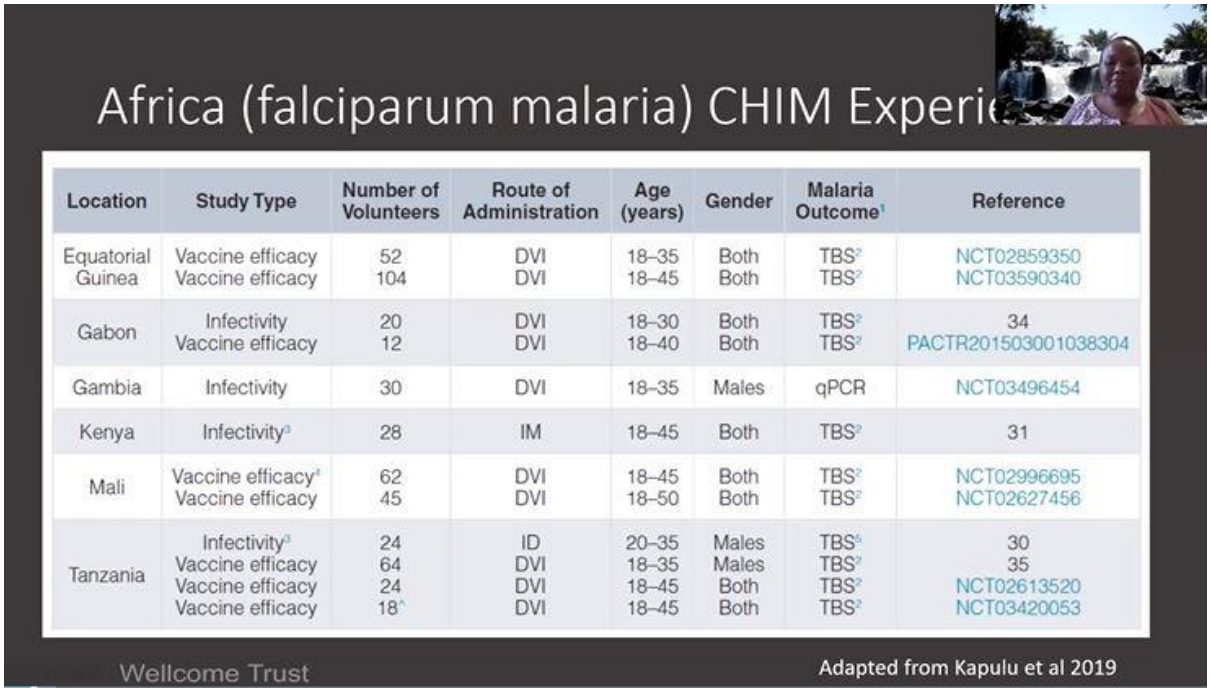
Opening the floor with a word of welcome the symposium organizer Siddhartha Mahanty (University of Melbourne, Australia) gave a brief introductory talk about each of the speakers.

Meta Roestenberg (Leiden University Medical Centre, Netherlands) addressed that “heterogenicity” is an important factor for drug and vaccine efficacy clinical studies. In controlled human malaria infection (CHMI) studies, the variability in the initial parasitemia or parasite growth rate affects vaccine efficacy results. Importantly, immunological aspects differ between two populations (from non-endemic and endemic regions) that need to be further unravelled and adjusted for in modelling. Roestenberg also showed a study with a controlled human hookworm infection model. This model suffers from variability in egg excretion within individuals as well as variability between individuals, affecting the power of the model. Nevertheless, egg counts were generally similar to the natural setting. The model can now be translated to endemic populations to understand the heterogeneity between non-endemic and endemic populations in their response to hookworm. Lastly, Roestenberg presented a model for schistosomiasis. Circulating anodic antigen released by the parasites was measured in human serum. The result showed little heterogenicity due to the stable antigen excretion from the parasite. The schistosomiasis model is highly sensitive but less representative of endemic populations because of low infection levels and the single-sex nature of the infection. Capturing heterogenicity is essential to bridging the gap to the field. Roestenberg concluded that "*controlled human infection is vital as it bridges the gap between animal models and targeted populations*".

The presentation by **James S. McCarthy** (University of Melbourne, Australia) on CHMI began with the history of CHMI for antimalarial drug testing. He showed that CHMI studies are a rational pathway for down-selecting drugs. For example, the CHMI approach was used to study PK/PD of Actelion-451840. Also, as mentioned earlier by Roestenberg, the approach is also helpful for testing candidate vaccines, such as recombinant *P. falciparum* circumsporozoite proteins. CHMI can tell us whether the selected antigen or the elicited immune response are right. Intriguingly, CHMI was used to evaluate the immunological protection against sporozoite inoculation in humans. Currently, CHMI is employed to study the protective efficacy of transmission-blocking interventions (drugs and vaccines). These include challenging people with genetically modified rodent malaria parasites to protect them from *P.*

falciparum infection, or chemically attenuated parasites to elicit an immune response in naïve volunteers. Finally, he addressed the usefulness of CHMI to study human malaria parasites that have no *in vitro* model such as *P. malariae*. The contribution of CHMI benefits our understanding of biology, immunity and pathogenesis of malaria parasites.

Melissa Kapulu (KEMRI-Wellcome Trust Research Programme, Kenya) reported on the role of the CHMI model as a potential solution for leveraging human infection studies and understanding immunity in endemic populations. Broadly, their CHMI model aims at understanding the role of pre-existing immunity in relation to parasite growth in addition to identifying key parasite targets that can be prioritized for vaccine development. Based on experience from Kenya where currently three CHMI and anticipated CHMI transmission studies are ongoing, many illuminating outcomes have already been noted through a view from the field. CHMI has shown that volunteers are either susceptible or resistant based on their antibody responses; this later could further be dichotomized in high immune and slow-growth parasitaemic patients. This model could also help in assigning participant susceptibility based on the residence in high- or low-transmission settings. The CHMI model was found to be a powerful tool in comparison to field cohort studies in examining correlates of infection. However, the contribution of pathogen exposure and modulation of endpoints to the outcome of human infection studies in endemic settings remains to be addressed.



The last speaker, **Anna Durbin** (Johns Hopkins Bloomberg School of Public Health, United States) discussed the COVID-19 human challenge models, which could quickly help in selecting efficacious vaccines or treatments against SARS-CoV-2. For the design of such trials, the World Health Organisation (WHO) recommends consideration of the volunteer's age, mental health condition, establishment of a robust informed consent process, designing facilities with a high level of containment and long-term monitoring of both volunteers and staffs, and conducting the trials with well-characterised challenge strains of SARS-CoV-2 virus. These precautions are mostly due to potential complications that include cardiovascular, respiratory or multisystem inflammatory syndromes which could occur during or after the trials. In addition, a more than six-month period of observation should follow for each cohort of challenged volunteers. Durbin reminded the attendees

that at present, 11 candidate vaccines against COVID-19 are at varying stages of evaluation, and preparations for large-scale manufacture are already in place for several of these.

This report is brought to you by the MESA Correspondents with mentoring and editorial support from Valentina Mangano (Pisa University Hospital, Italy) and Julie Chaccour (Independent Consultant, Spain).

Day 4: 18th November 2020

Symposium #65: Ivermectin and Antimalarial Mass Drug Administration for Malaria Control and Elimination: Preliminary Field Trial Results and Trial Designs

Umberto D'Alessandro (MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine Disease Control & Elimination Theme, Gambia) presented his work on combined mass drug administration (MDA) of ivermectin and dihydroartemisinin-piperaquine (DHA-PQ) as a potential intervention for malaria elimination in communities in The Gambia with high coverage of other vector control interventions. One objective of this study was to evaluate the impact of ivermectin (300 µcg/kg for three days) and DHA-PQ administration on malaria transmission by tracking clinical malaria cases and using qPCR to determine malaria prevalence over two transmission seasons. In the first transmission season, they did not achieve a good coverage of the intervention and malaria prevalence was higher in the intervention vs control villages. In year two, coverage around 80% was reached in all three rounds and malaria prevalence was reduced by 70% in intervention villages compared to controls. Additionally, incidence of clinical malaria in intervention villages was 80% lower than control villages in the second transmission season. Another goal of the study was to evaluate the effect of ivermectin on vector population density. Vector density was significantly lower in intervention villages and ivermectin significantly reduced mosquito mortality even 21 days' post-treatment although no effect on mosquito parity could be determined. D'Alessandro suggested that this study would ultimately reveal the cost and cost-effectiveness of this intervention and identify best practices for achieving and maintaining high coverage of MDA with these two tools. His group concluded that achieving high coverage was crucial for effectiveness. However, data from this study suggests that the addition of this intervention could be a game changer in efforts to eradicate malaria.

Brian D. Foy (Colorado State University, United States) presented the design and early results from the RIMDAMAL2. This is a double-blind, placebo-controlled, cluster-randomized, parallel-arm clinical trial conducted over two seasons (2019-2020) in Burkina Faso. The study consists of repeated ivermectin MDA to humans, added to the already supplied long-lasting insecticide-treated nets (LLINs) and existing monthly seasonal malaria chemoprevention (SMC). During the four months of the rainy season, ivermectin or placebo is given at a high dose (300 µg/kg) during a three-day course. The main objective of this study is to evaluate the impact of ivermectin on childhood malaria incidence. Modelling was extensively used for the study design and for the primary outcome statistical analysis. Study nurses conduct weekly active case detection for malaria in children ≤ 10 years old who, if febrile, are tested for malaria with a rapid diagnostic test (RDT). Children with positive results receive treatment with artemether-lumefantrine. Adverse effects are actively and passively detected in all study participants. Pharmacokinetic measurements and entomological sampling are also carried out for a subset of the study population. The study is still ongoing, but undoubtedly, will shed light on the benefits of using ivermectin MDA to prevent malaria in combination with other control measures.

The session closed with **Kevin C. Kobylinski** (Armed Forces Research Institute of Medical Sciences - AFRIMS, Thailand) presenting his work on the preparation and study plan of an ivermectin MDA to humans in Thailand. Since most *Anopheles* species in the Greater Mekong Region (GMS) feed outdoors, bed nets and indoor residual spraying are less effective. Ivermectin is a promising alternative for malaria control. In collaboration with Mahidol University and AFRIMS, Kobylinki's group is conducting ongoing field studies at rubber plantations in southern Thailand to assess parameters of malaria transmission at the entomological and epidemiological level. Many important *Anopheles* species tend to live in forest habitats, increasing the risk of malaria infection in individuals who live, work in, or visit these areas. So far, the group has found a *P. falciparum:P.vivax* ratio of 80:20 (contrary to what is commonly found in this area), and identified *Anopheles minimus* as the primary species in all three field sites. Interestingly, out of more

than 1,000 mosquitoes collected, none were *Plasmodium* positive. Besides, villages with the highest case burden were dominated by rubber plantations adjacent to the rainforest. These analyses allowed them to select study sites, train study personnel, and adequately plan a successful ivermectin MDA trial for 2021. The future study will be conducted in 20 clusters: individuals in 10 clusters will be administered 400 µg/kg of ivermectin in a single dose, while individuals in another 10 clusters will be given placebo instead.

Symposium #66: Lessons from the National Malaria Elimination Program in China

Before 1949, it was estimated that more than 30 million cases of malaria occurred annually in China with a 1% mortality rate. **Xiao-Nong Zhou** (National Institute of Parasitic Diseases at China CDC, China) presented the strategy and achievements of the national malaria elimination program in China. A five-phase malaria elimination program was launched back in 1949. The first four phases (1949-2009) involved various malaria control strategies using ITNs, early diagnosis and treatment, environmental modifications, health education etc. Phase 5 (2010-2020) targeted malaria elimination in all Type III counties and local transmission elimination in both Type I & II counties by 2015. 2020 has been set as a milestone year for malaria elimination in China. To achieve this milestone, county-specific elimination strategies were deployed. As a result, the total number of indigenous cases significantly reduced after launching Phase 5 and by 2017, zero indigenous malaria cases had been achieved. The "1-3-7" surveillance and response model has played a key role in Phase 5. In this model, cases are reported within 1 day, investigated within 3 days and focus investigated and responded to within 7 days hence "1-3-7". Currently reported malaria cases are a result of importation from returning individuals mainly from Africa and Myanmar.

Ying Liu (Henan Provincial Center for Disease Control and Prevention, China) presented a successful case study on malaria elimination with multi-province cooperation in China. Between 2005 and 2006, there was a 118% increase in *P. vivax* cases in the Huang-Huai plain of China. The majority of the infected were farmers (69%), those aged between 15 and 65 years (62%), and most cases were localized near water bodies (74.28%). A multi-province collaboration was key in responding to the outbreak between 2006-2010, with a mass drug administration as a major response to the outbreak carried out in April before the start of the "malaria transmission season". Response-case management was enhanced by carrying out early detection of three types of fever by blood smear and reporting cases to the National Notifiable Disease Reporting System within 1 day. Vector control was also carried out by spraying a larvicide with *Bacillus sphaericus* across villages every 15 days, resulting in a decrease

in *Anopheles sinensis* vectors. Training of medical personnel was also carried out and local residents were educated on malaria awareness. These responses led to a decrease in cases and no outbreak has happened since 2014. In conclusion, this case study highlights the need for multi-province collaboration in preventing malaria outbreaks.

Kay Thwe Han (Department of Medical Research, Myanmar) presented on a strategic plan for a malaria elimination project in China and Myanmar. Three bilateral workshops had been held in China and Myanmar alternatively in 2014 to eliminate malaria by 2020 in China and by 2030 in Myanmar. The project is a collaborative project called "Forge ahead together for elimination towards a malaria-free China-Myanmar border". So far their major achievement has been a feasibility assessment project to be completed in 2026. The project implementation, however, has been delayed due to government policy and practice and also the COVID-19 pandemic but will be completed, so the malaria elimination target can be achieved.

Prosper Pius Chaki (Ifakara Health Institute, Tanzania) presented a case study on Chinese-Tanzanian cooperation on malaria control in Tanzania. The main goal of the study was to reduce disease burden by 30% by combining the Chinese experience and the WHO T3 (Test, Treat, Track) strategy in pilot areas. The study was conducted in villages in Rufiji using the 1,7-malaria Reactive Community-based Testing and Response (1,7-mRCTR) approach. The implementation of the pilot project has been very successful with reduction of incident rates of cases in health facilities. The 1,7-mRCTR approach reduced the burden of malaria in intervention communities by 60%. Involvement of community health workers accelerated the process for malaria elimination. Their main challenge now is how to sustain gains and need for a proper exit strategy before integration into national malaria control program strategy. The pilot project will be extended for 18 more months, due to the impact of COVID-19, to address issues relating to data validation, as a demonstrating program before a national roll-out.

S #68: Triple Artemisinin Combination Therapies: A New Paradigm for the Treatment of Uncomplicated *falciparum* Malaria?

Chanaki Amaratunga (Mahidol Oxford Tropical Medicine Research Unit, Thailand) gave an overview of the "Development of Triple Artemisinin Combination Therapies (DeTACT)" project. In response to

increasing resistance of *P. falciparum* to both the artemisinin and partner drug components of several artemisinin combination therapies (ACTs) in the Greater Mekong Subregion and to prevent the spread of multidrug resistant parasites to other regions, a carefully selected second partner drug has been proposed to be added to the current ACTs. This way, even parasites resistant to artemisinin and the first partner drug are successfully cleared by the second partner drug. From the Tracking Resistance to Artemisinin Collaboration II (TRACII) project, two regimens of triple artemisinin combination therapies (TACTs) were found to be safe, well-tolerated and highly efficacious. The objective of the DeTACT project was to further assess the safety and efficacy of TACTs, including in African children, and to work towards a TACT that is ready to be deployed at the end of the project. The DeTACT project takes a holistic approach and includes clinical trials in Africa and Asia and studies on mathematical modelling, bioethics and marketing positioning.

Rupam Tripura (Mahidol Oxford Tropical Medicine Research Unit, Thailand) presented a study on safety, tolerability, and efficacy of TACTs. Rupam began the presentation by giving an overview of the current situation of artemisinin resistance, particularly in Western Cambodia and along the Thai-Myanmar border. Despite the emergence of drug-resistant parasites, there is a window of opportunity to tackle the parasites by deploying TACTs. Two regimens of TACTs, dihydroartemisinin-piperaquine plus mefloquine (DHA–PPQ+MQ) and artemether-lumefantrine plus amodiaquine (AL+AQ) were assessed for safety, tolerability and efficacy within the previously mentioned TRACII project. QTc prolongation is a concern with the use of some antimalarials but the study demonstrated that there were no clinically significant differences in QTc prolongation in patients receiving TACTs or ACTs. Rupam also presented another study, TACT-CV (unpublished data), from Cambodia and Vietnam where AL and AL+AQ were also highly efficacious and there were no serious adverse effects due to the trial drug in any of the patients. Overall, these results implied that the use of TACTs is safe, well-tolerated and efficacious.

Due to the risk of drug-drug interactions when the drugs are given together, pharmacokinetic and pharmacodynamic (PK/PD) studies are essential. **Richard Hoglund** (Mahidol Oxford Tropical Medicine Research Unit, Thailand) talked about PK/PD aspects of TACTs from studies conducted in healthy Thai volunteers and in patients with uncomplicated falciparum malaria from the TRACII study. Firstly, the results from the healthy volunteers showed that DHA absorption and exposure were reduced when DHA, piperaquine and mefloquine were co-administered. This interaction was reassessed in the clinical study, which showed a non-significant trend of lower DHA exposure. The results have prompted to adapt the DHA-piperaquine-mefloquine TACT, and further develop artesunate-piperaquine-mefloquine instead, in which dosing of artesunate (the parent drug of DHA) can be increased. From PD studies in both healthy volunteers and patients, an analysis of post-treatment changes in QTc interval showed that there was no further QTc prolongation when MQ was added to DHA-PPQ. Co-administration of AQ with lumefantrine resulted in lower exposure to lumefantrine but this did not affect lumefantrine concentrations on Day 7 and AL+AQ remained highly efficacious.

Maciej F. Boni (Pennsylvania State University, United States) began the presentation by questioning "how we could effectively treat and cure as many as people without driving drug resistance too strongly". Then, he addressed this question using mathematical modelling to predict the impact of TACTs in different settings of treatment coverage and transmission intensities. Preliminary results from the model indicated that TACTs will lower prevalence, reduce the burden and increase the chance of malaria elimination. In terms of evolutionary effects, deploying TACTs could delay the emergence of drug resistant parasites. A major concern is whether resistance to all 3 components of a TACT in a single area already exists in nature. In all three ACT scenarios, with the assumption that no triple resistance existed at baseline, AL+AQ was predicted to be better at delaying development of resistance because the short half-life of both partner drugs provides a shorter window of selection and also because there is no true triple resistance that is known to date. The use of PPQ and MQ could

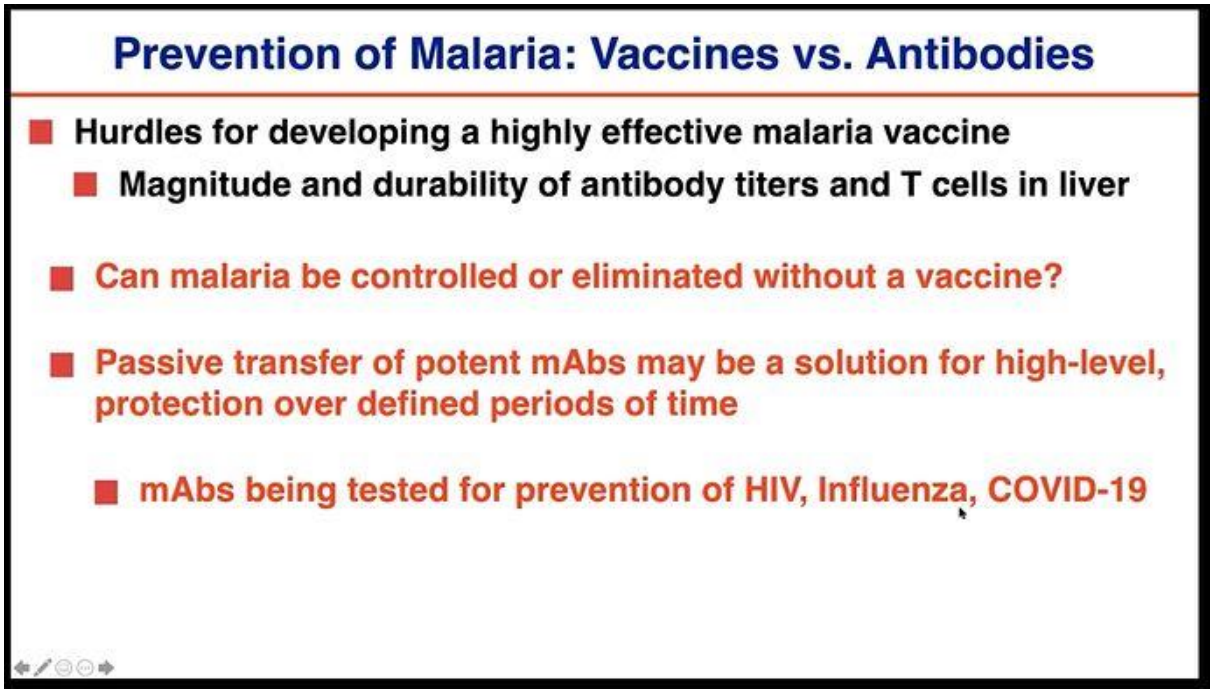
reduce prevalence given longer half-life of PPQ but this could increase the selective window. Future work will include scenarios where triple resistant parasites have already emerged before the introduction of TACTs and how that may affect the effectiveness of TACTs.

Phaik Yeong Cheah (Mahidol Oxford Tropical Medicine Research Unit, Thailand) on behalf of Paulina Tindana (University of Ghana, Ghana) highlighted the ethical aspects of deploying TACTs in Africa. As mentioned earlier, although TACTs aim to provide added benefits of preventing or delaying the emergence of drug resistance, adding another drug to the current ACTs could expose patients to the side effects of three drugs instead of two drugs. This leads to the question of whether it is justifiable for those patients to take on these additional, albeit minor, risks? In Africa, a majority of patients are children who cannot make decisions themselves. Autonomy is also a matter of debate. If TACTs are found to be safe, tolerable, and efficacious, do the patients have a choice between ACTs or TACTs? The other aspects to be taken into consideration include when to change policy making TACTs first-line treatment, understanding of the rationale of TACTs, public engagement, resource allocation and investments and, importantly, views of stakeholders. These are being explored in a qualitative study that was conducted in Nigeria and Burkina Faso as part of the DeTACT project.

Symposium #83: Monoclonal Antibodies to Prevent Malaria Infection and Transmission – From Antibody Identification to Clinical Evaluation

Joshua Tan (NIAID/NIH, United States) began his presentation by emphasizing that IgA is the most abundantly produced antibody isotype in humans. The aim of his project is to investigate the circulating IgA response to *Plasmodium falciparum*. This led to the main focus of his talk concerning human malaria-induced IgA clones that target a novel functional site on the N-terminus of the *P. falciparum* circumsporozoite protein (PfCSP). PfCSP is required for parasite development in the mosquito, motility in human skin, and invasion of hepatocytes. Monoclonal antibodies (mAb) were produced from B cells isolated from two PfSPZ-vaccinated individuals who were PCR-negative for malaria and had sporozoite-binding plasma IgA. Clones were characterized for sporozoite binding, then tested for protective efficacy using an *in vivo P. berghei* mouse challenge model. Results showed significant protection ($P<0.0001$) by MAD2-6 IgA compared to no mAb control. Peptide mapping of this antibody clone revealed the N-terminus of PfCSP as its target site. Tan concluded that sporozoite infection induces immunity-conferring IgA production and that the N-terminus of PfCSP is a target of these functional antibodies.

In his presentation, **Robert Seder** (NIAID/NIH, United States) spoke about his group's work regarding two mAbs for preventing human malaria: CIS43 and L9. CIS43, a PfCSP-targeting mAb, was found to confer significant antimalarial protection against mosquito challenge in two mouse models. The group modified CIS43 by adding an LS mutation in the Fc region, which significantly increased the half-life of the antibody. This mAb is currently in phase I clinical trials for safety, pharmacokinetics and efficacy to prevent malaria following controlled human malaria infection (CHMI). Seder also shared news of the discovery and characterization of a new human mAb, L9, which binds NPNV minor repeats at the junction of PfCSP. This new mAb was shown to be more protective than CIS43 by mosquito bite challenge in mice and mediates the highest level of sterile protection versus three other human mAbs. Interestingly, the group found that mAb binding rPfCSP or SPZ does not predict protection. Using isothermal titration calorimetry to measure mAb binding to full-length recombinant PfCSP proteins, it was shown that the most protective mAbs bind rPfCSP in two steps rather than one. Seder's data reveals that potent mAbs such as L9 bind the junctional and repeat motifs CSP in two steps and prevent sporozoites from infecting hepatocytes in the liver.



Camila Coelho (NIAID/NIH, United States) began her presentation by reviewing the concept of transmission-blocking vaccines (TBV), which target the sexual stage of the parasite to prevent the spread of malaria. Her laboratory has been involved in the development of a mAb treatment to target parasites in the midgut of the mosquito. Now, they are seeking to define functional antibody repertoires in sera. Pfs230 is a gamete protein that was the target of mAb in the first clinical trial of TBV in an endemic area, Mali. The Pfs230 vaccine was able to reduce parasite transmission in standard membrane feeding assays (SMFA), and functionality was directly correlated with antibody titer. Using antigen-specific single B cells from study subjects, they sequenced the cells and expressed mAb to identify functional clones. LMIV230-01, which binds a broad, conserved epitope on *Plasmodium* gametes, was found to retain high activity even at lower concentrations. However, the group also found that LMIV230-01 titer does not correlate with functional activity, which, in Coelho's opinion, reveals the need to improve vaccine design. The laboratory used antigen-specific single cell BCR databases to match Pfs25-IgG plasma peptides from sequences of single B cells isolated from Pfs25 vaccine trial subjects. The cells expressing mAb IGHV4 were the most frequent gene subgroup of Pfs25-specific single B cells, and IGHV4 reduced parasite transmission by more than 80% in SMFA. This technique is very exciting in that it can be used to inform and improve vaccine and antibody therapies for malaria and other infectious diseases.

Saskia C. van der Boor (Radboud University Medical Center, Netherlands) presented on the safety and efficacy of the transmission-blocking humanized monoclonal antibody TB31F. This antibody targets Pfs48/45, a gametocyte surface protein that plays a key role in male gamete fertility and is a key candidate for transmission-blocking vaccines. Using SMFA, the group saw >80% transmission-reducing activity at a concentration of 3.3 μg/mL and significant activity in genetically diverse field strains. The aims of the project are to bridge SMFA and direct skin-feeding (DSF) assays to inform investments on transmission-blocking tools that currently rely on SMFA data, inform Pfs48/45 vaccine design, and investigate the potential of mAb as new transmission-blocking tools. These aims will be achieved by determining the safety and tolerability of TB31F in malaria-naive volunteers, evaluating functional activity via SMFA, and measuring serum pharmacokinetics. Results of this study found that intravenous administration of TB31F is safe at concentrations up to 10 mg/kg. Excitingly, IC80 is achieved at 3.8 μg/mL and transmission-reducing activity greater than 80% may be maintained for

more than four months. Future directions for this exciting project would be to explore subcutaneous administration of the treatment, modify the mAb to extend its half-life, and explore its application as a seasonal transmission-blocking intervention.

Symposium #84: Towards Regional Elimination of Malaria in Central America

Justin T. Lana (Clinton Health Access Initiative, Panama) as symposium organizer kicked off this session with a word on the malaria roadmap for the coming years in the Central America region.

His words were followed by a talk by **Blanca Escribano** (Pan American Health Organization, United States) on the "*Progress towards malaria elimination across Central America and ensuing challenges*". She gave highlights on the malaria morbidity and mortality trends in the Americas since 2015 showing positive progress from up to nine out of twenty-one countries which have been either certified malaria-free or already met the Global Technical Strategy for Malaria (GTS) targets within the 2015-2020 period. Half of the countries and territories (11/19) recorded less than 2000 indigenous cases and even zero cases for El Salvador and Belize in 2019 – a decline which seemed even more pronounced during the COVID-19 in most countries with high malaria burden. Currently, a new five-year plan of action (2021-2025) aims at eliminating malaria by interrupting local malaria transmission by *Anopheles* mosquitoes and maintaining an adequate surveillance and response system for preventing reestablishment of indigenous transmission. For implementation purposes, PAHO is supporting countries on six steps including 1) malaria risk stratification, 2) microstratification or foci identification and characterization, 3) microplanning or foci response plan, 4) adequate coverage of vector control interventions at targeted localities based on the malaria risk stratification, 5) minimum indicators at foci level and 6) an adequate environment to support malaria control efforts through advocacy, policy, collaboration and partnership. However, in order to effectively support operationalization, some key challenges should be considered and broadly concern biological/ecological or social determinants, health services and COVID-19.

Carlos Miranda (Ministry of Health, Honduras) importantly noted the drastic reduction of malaria in Honduras in recent years, now very concentrated in some areas, implying the feasibility of malaria elimination in the country. Miranda highlighted the strategic plan the country has in achieving zero cases by 2022. However, the COVID-19 pandemic is a limitation to this goal, with a few recorded coinfections and also for the attention it demands from the entire health sector and the limitations it has put on movement of malaria health workers. Honduras, despite increasing access to malaria diagnosis and treatment – for example, increasing the number of community health workers with RDTs – still faces some delays that contribute to the persistence of the disease. Therefore, they aim to continue improving access to diagnosis and treatment in particular areas to shorten the time from onset of symptoms to obtaining these services. Improvement of communication within the community is also expected to manage this problem. The existing challenge of insecticide resistance would also be a focus in the elimination program as well as coverage with indoor residual spraying (IRS), long-lasting insecticidal nets (LLINs) and monitoring of resistance in *Anopheles* mosquitoes. Rotation of IRS groups every two years to curb the growing insecticide resistance is additionally taking place. Stratification and microstratification methods to be used as surveillance is a huge part of the intervention. In closing, important policy changes in treatment, diagnosis, and vector control, alongside collaborations with the community and funding from regional and international sectors would greatly impact the malaria elimination program in the area. Honduras sits on a porous border with Nicaragua - a country with well over 10,000 cases this year, therefore cross-border collaboration will also be key to reach and maintain zero cases.

Thereafter, **Alejandra Acuña Navarro** (Ministry of Health, Costa Rica) shared experiences from the Costa Rican program with currently about 2 million inhabitants at risk of malaria. Costa Rica showed how strengthening interventions at the local level could bring significant success in malaria reduction, reaching zero cases in 2014 and 2015. However, in 2016 the country began to get out of control with nine indigenous cases detected, a number which continued to increase right to 96 indigenous cases in 2019, raising the alarm of malaria reestablishment in Costa Rica. Among the factors that contribute to the situation were migration, illegal gold mining, lack of national labour for agricultural activities and decreased surveillance, which caused delayed diagnosis and continuation of transmission. Highlights were also given about the country's renewed efforts towards elimination of malaria that combined both public and private actions all supported by PAHO-WHO. Costa Rica presented the 2019 risk stratification where four scenarios could be distinguished between localities. These include the non-receptive, the receptive but not vulnerable, the receptive vulnerable without indigenous cases, and finally, the receptive vulnerable with indigenous cases. In addition, they updated the foci registry, introduced RDT for hard-to-reach populations and strengthened local teams to improve detection, diagnosis, treatment, investigation and response. Costa Rica is also looking forward to an agreement with Nicaragua to improve cross-border collaboration.

Emma Margarita Iriarte (Inter-American Development Bank, Panama) broke down the strategies implemented on the "*Way forward: Sustainable financial mechanism to achieve malaria elimination*". Malaria elimination in the region by 2022 has mainly been set back by the ongoing global pandemic. Despite this, the regional malaria elimination initiative (RMEI) program is still actively working to reach this objective. The main approaches involved in this initiative focus on the interruption of malaria transmission, management of operational issues, and surveillance as intervention alongside other strategies to prevent re-establishment of transmission. Core elements of RMEI are a collective collaborative approach across the countries in this region that aim at elimination including having a single objective, similar plan and budgets, uniform management systems, effective team coordination, and continued communication. A result-based financing model has been established, in which programs receive funds from donors and national contributions. Progress is reviewed every few years to check if national goals have been attained before performance incentives are distributed. The finance-based model has admittedly eased malaria elimination programs in the area by promoting the implementation of the elimination strategies across the countries, maintaining accountability and leveraging domestic funding for the program, improving regional health systems, and reducing administrative burden for the countries.

Symposium #85: Host-Directed Therapeutics for Malaria

Alexis Kaushansky (Seattle Children's Research Institute, United States) talked about new approaches to elucidate host regulators and host-based inhibitors of *Plasmodium* liver infection. Key questions included whether heterogeneity of the liver contributes to differences of host signalling between infected and uninfected cells, and which unique properties of the hepatocyte facilitate the massive expansion of the liver stage parasite. Using kinase regression, a strategy that uses a small kinase inhibitor screen along with known properties of the molecules and a simple machine learning algorithm, the Kaushansky lab demonstrated that a broad range of host pathways, including those driven by host kinases are critical for *Plasmodium* liver stage infection. At least a subset of these phosphosignaling pathways are also regulated in non-canonical ways, paving the way for potential opportunities to target infected cells without damaging uninfected hepatocytes. Unique cell states, required for liver infection, present an opportunity for host-targeted intervention to eliminate liver stage malaria.

Emily Derbyshire (Duke University, United States) presented her lab's discoveries of druggable host factors that are critical to liver stage *Plasmodium* infection. In the talk, Derbyshire focused on one candidate that emerged from her screens, a gene called Aquaporin 3 (AQP3). AQP3 is not normally expressed in liver cells but was found to be one of the most upregulated genes after infection with *P. berghei.* The gene was demonstrated to be important for *P. berghei* development during the liver stage, where parasite size is significantly reduced in *AQP3* CRISPR-disruption cells. The host protein is recruited to the parasitophorous vacuole membrane in liver-stage *P. berghei*. Significantly, this recruitment is also observed in liver-stage *P. vivax* schizonts and hypnozoites. Further analysis revealed that the AQP3 inhibitor auphen inhibits multiple species and stages of *Plasmodium*, including the blood and liver stages of *P. vivax*. Finally, Derbyshire highlighted that the host liver would provide a rich source of genes and proteins that may play key roles in *Plasmodium* development. Elucidating the function of these essential host genes is important for advancing new drug candidates.

Joseph Smith (Seattle Children's Research Institute, United States) presented his work on using kinase inhibitors to protect endothelial cells from inflammatory damage. Vascular leak is a complication of cerebral malaria and currently, there are limited ways for treatment, calling for new host-directed malaria therapeutics. Drugs inhibiting the tyrosine kinase BCR-ABL were found to have opposing barrier-strengthening or barrier-disruptive activities on primary brain endothelial cell monolayers under resting or thrombin challenge. Polypharmacology and off targets were hypothesized to be essential, and kinase regression (KiR) was used to deconvolute. A screen of 28 kinase inhibitors identified differing barrier phenotypes. Machine learning predicted 50 kinase targets, including 20 kinases with known roles in barrier regulation and 30 novel candidates. The BCR-ABL drugs have partially overlapping and distinct polypharmacology and targeted many kinases involved in barrier regulation. Kinase inhibitors conferred early and sustained protection, although their pathways differ. Smith concluded that clinical drugs improved *in vitro* barrier properties and are promising leads for host-directed therapies for vascular leak syndromes.

Kevin Kain (University of Toronto, Canada) focused his talk '*New insights into microvascular injury to inform host-targeted therapeutics'* on how malaria infection in pregnancy (MiP) causes poor birth outcomes, for e.g. preterm birth (PTB), and brain injury in the developing baby. Such effects are caused, at least in part, by impairing the growth of placental blood vessels required for fetal growth and healthy birth outcomes. Moreover, Kain showed how these insights can be used to identify pregnant women at high risk of PTB, and to identify safe interventions to improve birth outcomes that are suitable for low resource settings (e.g. L-arginine). L-arginine is an essential amino acid in pregnancy that is required to make nitric oxide that regulates blood vessel growth. The research group observed that women at higher risk of PTB had a lower dietary intake of L-arginine during pregnancy. Also, in preclinical models of MiP adding L-arginine to the diet makes the placenta grow more blood vessels and improves birth outcomes. These findings have set the stage for a randomized clinical trial in western Kenya approach using dietary L-arginine/L-citrulline nutritional supplements to improve birth outcomes in pregnant women at risk of malaria. Finally, Kain pointed out that inequity starts in the utero, and that MiP is a modifiable risk factor for poor birth outcomes and neurocognitive impairment in children with a negative impact for 10s of millions of mothers and babies.

Symposium #86: Severe Malaria: Improving the Continuum of Care

John Phuka presented a randomized, parallel study in Malawi that evaluated the role that quality information, education and communication (IEC) toolkit played in the continuum of care, including patient referral. The study hypothesized that 1) community exposure to IEC influences caregiver presentation at the village health clinics (VHC) and acceptance of artesunate rectal capsules (ARC); 2)

health surveillance assistants' (HSA) exposure to targeted IEC increases appropriate assessment, administration of ARC and referral practices. Interventions involved poster-monitoring and infrastructure/commodity checks and sensitization of caregivers of children five years and under and resident HSAs working in difficult-to-reach areas more than five kilometres from a referral centre. Among HSAs, the intervention led to improved knowledge of severe malaria danger signs, increased ARC acceptability, increased perceived self-efficacy to administer ARC and manage danger signs. Caregiver knowledge of severe malaria and symptoms also increased in both groups. Messages on posters put up in the community did not influence the response to danger signs among caregivers of children presenting with danger signs, as this response to the emergency was already in place and ARC was already well-accepted in this population. However, HSAs exposed to the posters were more knowledgeable and aware of severe malaria management; hence they offered higher-quality assessment, care and referral. The care received at the point of referral was not included in the intervention, but on assessment revealed significant issues, affecting the continuum of care and the complete care of these sick children.

The talk by **José Martins** will be available soon.

Anitta R. Kamara (National Malaria Control Programme, Sierra Leone) shared her country's progress in preparing the rollout of artesunate rectal capsules (ARC). The implementation process started in October 2019 until March 2020 when the COVID-19 pandemic surfaced; this caused delays in the artesunate rectal capsule roll out to the five PMI/IM-focused districts. The training was conducted in September 2020 at national and district levels. In October 2020, after the district peripheral health units (PHU) staff cascade training, the artesunate rectal capsule was successfully rolled out to the five districts. The training was conducted in July 2020 at national and district levels, and in October 2020, district cascade training on ARC and implementation started. The US President's Malaria Initiative through the PMI Impact Malaria Project is supporting the national malaria control programmes with the training of trainers and cascade training for health providers before rollout. Rapid review and assessment at hospitals will be conducted to identify weaknesses and strengths to inform phase 2 of the rollout for six months. Limitations encountered during the rollout of phase 1 were the expiry of commodities due to delays, overstocking or understocking in some facilities due to quantification challenges. Assessment challenges included the use of routine records and forms.

Mauricette Andriamananjara Nambinisoa (National Malaria Control Programme, Madagascar) shared a Madagascar experience from cascade training, implementation and process evaluation related to a pre-referral intervention for severe malaria patients. ARC implementation was launched in 2019 with focus on 8 regions supported by the Medicines for Malaria Venture (MMV) at the community level. Implementation was a phased process from April 2019 to July – August 2020. It involved training of investigators and an evaluation process. Analysis of the implementation revealed high community acceptance during the implementation process with availability of inputs for trainees. However, one weakness was the need to improve on availability of data for severe malaria cases. Local authorities were also strengthened in the fight against malaria. The implementation will continue and be evaluated, and findings will be shared with other countries.

Symposium #104: Accelerating New Tools for Radical Cure of vivax Malaria from Clinical and Operational Research to Policy

Allison L. Golden (PATH, United States) talked about the new diagnostic tests for *P. vivax*. The challenge to case management and elimination of *P. vivax* is that the liver stage of the parasites, the hypnozoite, cannot be detected yet. Commonly, rapid diagnostic tests (RDTs) have been used to detect human malaria, but the antigens utilized in the RDTs are expressed at a lower concentration by *P. vivax* compared to *P. falciparum,* rendering lower sensitivity. Golden pointed out that current RDTs may not fully support *vivax* malaria case management. The physical hemozoin detection method employs the magnetic property of hemozoin to detect the presence of *P. vivax*. Although showing improved sensitivity, this technique can only detect the blood stage parasite in symptomatic patients. For asymptomatic patients carrying hypnozoites, serological testing may be indicated, leading to a greater percentage of treated patients. She underlined that "new biomarkers are always needed" for *P. vivax* diagnostic tools with higher sensitivity.

Daniel Yilma (Jimma University, Ethiopia) was in charge of presenting the study that assessed the performance of the STANDARD™ G6PD test across Brazil, Ethiopia and the US. The glucose-6-phosphate dehydrogenase (G6PD) status of patients should be used to guide administration of primaquine, according to WHO. However, this is challenging because of limited access to the test and because accurate tests require higher laboratory infrastructure. A quantitative, point-of-care G6PD test is needed for radical treatment. The test had good discriminatory power for G6PD-deficient and intermediate cases. When comparing the test with the reference assay, the G6PD activity values correlated well in the clinically relevant range. The hemoglobin measurement is comparable to the reference assay. However, interpretation errors were common with intermediate and deficient results. This highlighted that additional training and supervision is required to support the successful introduction of the test.

Relapse infection frequently occurs in people infected by *P. vivax*. The infection by the parasite poses a complexity in case management because of the hypnozoite stage of the parasite, G6PD status in patients receiving primaquine or tafenoquine, treatment adherence and age and pregnancy restrictions. **Michael White** (Institut Pasteur, France) and his group adopted a mathematical model of *vivax* transmission developed for Papua New Guinea to examine the potential impact of tafenoquine on *P. vivax* in Brazil. It is projected that after 5 years of introduction of tafenoquine in 2021 the proportion of effective radical cure would increase from 43% to 53%. This will also reduce local transmission, and the local transmission rate will be greater if the use of single-dose tafenoquine can be expanded to children. Owing to the number of cases averted increases, the number of doses and G6PD tests will reduce.

Marcus Lacerda (Tropical Medicine Foundation Dr. Heitor Vieira Dourado, Brazil) gave an update of TRUST (Tafenoquine Roll-oUT Study) in Brazil. The study investigated the safety of tafenoquine for treatment in patients with normal levels of G6PD activity. The study plan includes study design, site selection, screening for acute hemolytic anemia, duration of the study, and data management. He highlighted that national treatment guidelines are getting updated since it is mandatory to perform G6PD test before treatment with tafenoquine while the test is required for treatment with primaquine where testing is available. The group has developed visual materials such as comic books of patient information. The study has now ethical approval and it is projected to start in November 2020.

Wint Phyo Than (Ministry of Health and Sports, Myanmar) provided the information about the steps and methods for implementation of a better *P. vivax* radical cure policy in Myanmar. Myanmar's strategic plan is to eliminate *P. falciparum* by 2025 and all malaria cases by 2030. This can be achieved by ensuring a safe radical cure of *P. vivax* from all service providers. The actions to accelerate radical cure include a generation of evidence on the feasibility of the introduction of new tools, registration of tafenoquine, strengthening the pharmacovigilance system, and monitoring progress.

Symposium #109: Using the Data You Have: Innovative Methods to Enhance Vector Control Evaluation and Decision-Making

The vector control landscape has become increasingly complex due to changing resistance patterns, and transmission heterogeneity. At the global level, randomized controlled trials that evaluate novel interventions or approaches are prioritized to guide policy recommendations. However, at the national or subnational level, additional evidence may be helpful to customize vector control approaches to local contexts to maximize impact. This symposium presented different scenarios to illustrate how multiple approaches can help to provide information for subnational decision-making around targeting and tailoring vector control interventions.

Jules Mihigo (US President's Malaria Initiative, Mali) noted that it is essential to know 1) what insecticides should be used for indoor residual spraying (IRS) and insecticide-treated bed nets (ITNs), 2) where the next generation of ITNs and IRS should be deployed, and 3) what the epidemiological impact of these interventions is. Nevertheless, data is often not easily available and accessible, not summarized at the required levels, as well as not easily digestible and actionable. Mihigo exemplified some case studies from Mali where using routine data was useful for guiding national vector control decision-making. In all these case studies, data from multiple sources were integrated (e.g. malaria incidence, socio-demographic, and interventions coverage data). However, data quality is essential. Thus, efforts have been made to improve the completeness and consistency of data in Mali. Future use of routine data is expected to continue helping in the evaluation of deployed vector control interventions and in maximizing their impact.

Dorothy Echodu (Pilgrim Africa, United States) illustrated how locally available data, both entomological and epidemiological, can be combined with modelling. This approach can provide important insights into how different components of the vector control toolbox can be deployed for improved disease control. Echodu described two paired studies conducted in Uganda. At first, the goal was to achieve an acceleration in the reduction of malaria using different combinational strategies including IRS, LLINs and mass drug administration (MDA) depending on the study arm. Later, the interventions were interrupted with the goal of maintaining the effects using different community case management strategies. Routine data was coupled with modelling, which was key to optimizing the timing of multiple interventions for maximizing impact and evaluating impact itself accurately.

Ellie Sherrard-Smith (Imperial College London, United Kingdom) discussed how models can be used to assist in decisions for insecticide-treated net placement, as well as other vector control interventions. The epidemiological impact of any vector control intervention depends on a myriad of factors, including mosquito ecology and human behavioral characteristics, which differ from setting to setting. Therefore, collecting local routine data can help validate and strengthen the models. Only then, it will be possible to achieve models parameterized and calibrated to local data, able to predict the impact of interventions more accurately in each location. Examples of useful data to quantify include the physiological resistance to pyrethroids in mosquitoes and mosquito feeding behaviors. Besides, Sherrard-Smith also pointed out that the capacity of a transmission model to predict an epidemiological effect can be validated using randomized controlled trial data.

Molly L. Robertson (PATH, United States) gave an overview of the various methods of using existing data to assess the effectiveness of vector control interventions. She noted that routine data is increasingly important as particular studies cannot cover the whole range of possible mixes and stratifications, and models need to be refined with local data. Robertson also highlighted the challenge of using routine data with variable quality. It is crucial to understand the data used, be aware of the limitations of each dataset and disaggregate it in a meaningful way. Thus, overinterpretation can be avoided and focused investigation of the root causes of observed trends can be initiated. She also proposed opportunities for strengthening these approaches, which include using antenatal care (ANC) surveillance data for comparison and collecting more disaggregated entomological and anthropological data. Understanding what data is used and useful to model stratification and impact can help focus new data collection efforts.

This report is brought to you by the MESA Correspondents with mentoring and editorial support from Valentina Mangano (Pisa University Hospital, Italy) and Julie Chaccour (Independent Consultant, Spain).

Day 5: 19th November 2020

Symposium #117: Vaccines Against Placental Malaria

The organizers, Stephanie Yanow and Nicaise Tuikue Ndam, introduced this discussion topic by emphasizing the importance of developing a vaccine against placental malaria. Pregnant women are especially susceptible to malaria which affects infant birth weight alongside maternal anemia and can lead to abortions. The unique sequestration of *Plasmodium*-infected erythrocytes to the placenta poses detrimental risks to the mother and baby and therefore vaccines suitable for pregnant women are necessary.

Arnaud Chêne (French Institute of Health and Medical Research, Paris, France) updated the audience on progress in the development of a placental malaria vaccine. About 30 million women become pregnant in malaria-endemic areas annually, and this malaria-susceptible group requires some form of protection. He further noted that primigravidas have little immunity to placental malaria while multigravidas do. Previous reports demonstrated that infected erythrocytes express the VAR2CSA variant of P. falciparum Erythrocyte Membrane Protein 1 (PfEMP1) which allows them to bind to chondroitin sulfate A (CSA) during parasite sequestration in the placenta and that this process is essential to the pathogenesis of maternal malaria. A VAR2CSA-based vaccine could therefore offer potential protection to improve pregnancy outcomes, the main goal of the PRIMVAC project. Different vaccines were formulated using different constructs, expression systems, and adjuvants. Immunogenicity was assessed, and elicited antibodies were evaluated for their specificity and affinity to VAR2CSA cross-reactivity, and cross-inhibitory capacity against heterologous strains. The most suitable candidate spanned the Duffy binding-like domains 1 and 2 (DBL1-2) from 3D7 expressed in *E. coli* SHuffle (PRIMVAC). Phase 1 clinical trials on women aged 18-35 were conducted showing that PRIMVAC did not elicit serious adverse reactions, was highly immunogenic and induced good reactivity and inhibitory activity against the homologous VAR2CSA-expressing strain. In contrast, it had only weak cross-reactivity and no cross-inhibition against heterologous strains.

Nicaise Ndam (University of Ghana, Ghana) gave an overview of the "*Malaria Vaccine Technology Roadmap*" from 2015 to 2030 and prospects for vaccines against *P. falciparum* and *P. vivax*. These vaccines should have more than 70% efficacy against clinical malaria, reduce parasite transmission and significantly decrease the incidence of infection to achieve elimination in several areas. The vaccine candidate PAMVAC is based on the minimal CSA binding domain (DI1-ID2a) of VAR2CSA from FCR3. PAMVAC was evaluated in Phase I clinical trial with two cohorts, one in Germany and another in Benin. Antibodies from vaccines recognized the homologous parasite FCR3 but had limited cross-reactivity to heterologous VAR2CSA strains. Ndam discussed the limitations and obstacles for further clinical development of the vaccine, particularly the challenges posed by VAR2CSA polymorphisms, the need for inducing long-lasting immunity and the logistical challenges of measuring vaccine efficacy in pregnant women.

Following these highlights, **Justin Doritchamou** (National Institute of Allergy and Infectious Disease, USA) in his presentation "*Aotus* model is superior to rodent models in predicting human immune response to VAR2CSA vaccine" described a different animal model to measure the efficacy of VAR2CSA-based vaccines. *Aotus* is biologically closer to humans compared to mice and rabbits and is, therefore, a suitable model for vaccine studies. IgG elicited to the PAMVAC and PRIMVAC vaccine candidates was studied in the *Aotus* model with similar results to those observed in the human trials. The antibodies had good functional activity against homologous parasites but little cross-inhibition to heterologous parasites. The study also showed that malaria infection in pregnant vaccinated animals failed to boost functional antibodies. Based on these findings, *Aotus* is a preferred model compared to rodents and may provide a more accurate prediction of vaccine efficacy in humans.

Finally, **Stephanie Yanow** (University of Alberta, Canada) discussed a cross-species vaccine approach to elicit VAR2CSA antibodies. Analyses from her lab showed that, unlike in African women, antibodies to VAR2CSA are not parity-dependent in Colombian women. Serum antibodies from men and children could recognize VAR2CSA. In addition, a blocking parasite adhesion effect to *in vitro* CSA was noted with antibodies from Colombian men and children. These two last observations raised the question of how VAR2CSA antibodies are acquired outside of pregnancy and suggested immunogenicity and potential cross-reactivity with *P. vivax* proteins. She presented data mapping a conformational epitope in the *P. vivax* PvDBP protein that mediates cross-reactivity to VAR2CSA. This epitope was recapitulated using a conformationally constrained peptide. When conjugated to a carrier protein, this peptide elicited cross-reactive antibodies to VAR2CSA in mice and rabbits, and shows promise as a vaccine candidate against placental malaria.

Symposium #119: Cross-Disciplinary Sciences to Understand Malaria Vaccine Immunity

Carlota Dobaño (ISGlobal, Spain) in her talk "RTS,S vaccine immunity and immune system development in African children" presented findings from a phase III multi-centre trial with around 2000 children (age 6-12 weeks and 5-17 month) in seven countries. The findings showed that RTS,S/AS01E-induced protection against malaria involved IgG against the C-terminal region besides the NANP repeat region of the circumsporozoite protein (CSP). CSP-specific Th1 cytokine signatures were associated with RTS,S/AS01E-induced protection against malaria, while Th2 signatures correlated with risk. Importantly, immunogenicity was shown to be lower in infants than children. Another finding was that the baseline cellular activation status was associated with RTS,S/AS01E antibody response. Lastly, interferon transcriptional signatures were associated with vaccine-induced protection.

Stephen Hoffman (Sanaria Inc., United States) in his talk on "Progress towards understanding and harnessing the complexity of protective sporozoite vaccine immunity against malaria" called for a new cross-disciplinary approach and advancement in immunological insights. Although phenomenal progress has been made, the understanding of the immunological mechanisms of protection induced by whole *Pf*SPZ vaccines has changed little in the past two decades' due to being mostly based on animal studies. Hoffman presented results from vaccine studies in terms of efficacy, protection, and duration. Four studies conducted in Mali and Burkina Faso showed achievement of 50% efficacy and sustained efficacy for 18 months in Burkina Faso. In 2021, a phase III trial with the PfSPZ vaccine will start aiming for licensure and marketing authorization. Although not yet achieving 100% efficacy, a foundation would be laid out for further improvements. To move forward, it would be key to understand induction and effector phases of protective immunity and to establish biomarkers of protection, being able to interrogate the immune responses in liver, spleen and essential lymph nodes. To do so, Hoffman proposes a different approach with, firstly, studies on *P. knowlesi* and *P. falciparum* in rhesus macaques and *Aotus* species to establish mechanisms and biomarkers of induction and protection t, and then clinical trials in humans to further corroborate the findings.

In the presentation "Do differences make a difference: using systems immunology to dissect natural and engineered adjuvants", **John Tsang** (NIAID/NIH, United States) addressed questions on predictability of immune response outcomes, type of predicted parameters and shared mechanism across different types of immune responses. The presented data suggest the existence of a baseline predictor that can be shared across different vaccines. Evidence on yellow fever indicated that the baseline predictor would not include pre-existing immunity. To further investigate this, they applied cellular indexing of transcriptomes and epitopes by sequencing (CITE-seq). The results suggested a two-stage immune response model with high and low responders. Applying CITE-seq and other methods provided a better understanding of baseline predictive signatures and allowed the discovery of natural adjuvants. Moreover, the application of multimodal single cell analyses allowed for easier interpretation of immunological cell clusters, for virtual sorting and denoising, as well as linking clinic to cell surfaces and transcriptomic phenotypes.

Purvesh Khatri (Stanford University, United States) shared in his presentation "Leveraging biological, clinical and technical heterogeneity in public data to accelerate translational medicine" a new framework for predicting clinical outcomes prior to treatment or vaccination in heterogeneous populations. He described the traditional approach that strives for reduced heterogeneity as a 'fundamental flaw' of the current paradigm in biomedical and translational research. There is no technical variation and most research does not capture heterogeneity of the disease and therefore results produced cannot be generalized. Khatri's proposed solution to this phenomenon is to embrace heterogeneity by using different publicly available datasets, different treatments, and different technologies, so results can be generalized. He has developed a model that leverages heterogeneity of biological data available online. The model was applied and validated in several use cases, leading to new discoveries that currently move toward commercialization. In the end, Khatri emphasized the need for sharing data in order to unravel biological, clinical and technical heterogeneity and to provide the opportunity to identify new signatures/biomarkers and develop new interventions.

Symposium #121: Comprehensive Surveillance in the Setting of a Dramatic Decline in Malaria Following Sustained Control Interventions in a Historically High Transmission Area of Uganda: From Mosquito to Human and Back Again

Alex K. Musiime (Infectious Diseases Research Collaboration, Uganda) presented work on the changes in malaria vector biology and bionomics following intensified vector control in Tororo, Uganda, an area

with a high malaria transmission rate. In the study, malaria transmission indoors and outdoors, before and after intensified vector control were analysed along with vector behaviour. Two cohort studies i.e. Program for resistance, immunology, surveillance, and modelling of malaria 1 (PRISM 1) (2011-2017) and PRISM 2 (2017-2019) were carried out with all participants given long-lasting insecticidal nets (LLINs) at the start of the study. Results showed that indoor residual spraying intervention resulted in a sustained decrease in human-biting and infective rates. However, the intervention resulted in a shift to early evening biting parallel with an increase in outdoor biting. The vector control had a negative effect on numbers *An. gambiae s.s* and *An. funestus* but resulted in an increase of *Anopheles* species. Although successful in decreasing vector abundance, the study also highlighted the need to incorporate tools that reduce outdoor biting in the fight against malaria transmission.

Joaniter I. Nankabirwa (Makerere University, Uganda) presented work on malaria transmission, infection and disease following sustained indoor residual spraying of insecticide in Tororo, Uganda. To curb the high transmission rate in this district vector control measures were scaled up, long-lasting insecticide nets (LLIN) in 2013and indoor residual spraying (IRS) in 2014. The study set out to evaluate the impact of intensive vector control on various clinical metrics in two serial cohort studies. Results showed that in children between 0.5 to 10 years, IRS intervention led to a decrease in monthly malaria incidence from 2.66 to 0.05 after 5 years. Also, there was a decline in the prevalence of anaemia, from 34.6% to 5.1%, in both microscopic and submicroscopic infection. However, a significant proportion of the population remained parasitaemic, providing a potential reservoir for malaria transmission.

Jessica J. Briggs (Univerity of California San Francisco, USA) and her group sought to characterize malaria infections using amplicon deep-sequencing to longitudinally track *P. falciparum* clones within individuals with the goal of determining molecular force and duration of infection in the cohort. qPCR was performed on a blood sample taken every 28 days at routine visits as well as at non-routine visits during which malaria was diagnosed. All qPCR positive samples would be subject to a hemi-nested PCR to amplify a highly variable region of apical membrane antigen 1 (AMA-1), then use the bioinformatics pipeline SeekDeep to determine single-nucleotide polymorphisms (SNP) and haplotypes. Infection timeline plots were given for each individual to track the overall molecular force of infection (mFOI), which takes into account the number of new blood stage clones detected, number of susceptible people exposed, and duration of exposure. This statistic captures additional ongoing transmission that is not reflected by malaria incidence. The group found that both malaria incidence and mFOI increase after an increase of mosquito population. Interestingly, the study found that females' clear infections faster than males across all age groups. School-aged children were found to have higher complexity infections, higher parasite density, and the longest duration of infection. Briggs discussed the usefulness of amplicon deep-sequencing in providing detailed information on within-host parasite dynamics, which can be used to estimate mFOI and duration of infection.

Chiara Andolina (Radboud University Nijmegen Medical Centre, Netherlands) presented on the kinetics of gametocyte production and human infectiousness to mosquitoes. The objectives of the study were to longitudinally quantify the contributions of different populations to the infectious reservoir through transmission assessments in the PRISM2 study cohort. The group tested individuals for malaria infection by microscopy, var gene acidic terminal sequence (varATS) qPCR, and gametocyte qRT-PCR. Participants who were qPCR positive the previous month or microscopy positive at the routine checkup were recruited for membrane feeding. Venous blood was drawn from 107 participants and used in a membrane feeding assay during which 60-80 mosquitos fed, then were dissected 10 days' post-infection to assess the presence of oocysts. Only 7.2% of 538 total experiments resulted in infections. Adults had lower gametocyte densities than subjects of younger age. Symptomatic individuals were more infectious to mosquitoes compared to symptomatic ones. In a longitudinal assessment of infectiousness, it was found that 4 "superspreaders" were responsible for an astounding 62.6% of all infected mosquitoes. Andolina concluded that since asymptomatic super

spreaders likely sustain transmission, identifying these populations is the key to controlling the spread of malaria and eliminating infectious reservoirs.

Symposium #122: The RTS,S Malaria Vaccine Pilot Implementation in Africa: Generating Data for Decision-Making

Public health specialists and scientists engaged in the RTS,S Malaria Vaccine Pilot Implementation Programme (MVIP) presented the key components of pilot evaluation activities that are generating data to inform a WHO policy recommendation on the broader use of RTS,S/AS01 in sub-Saharan Africa.

Mary Hamel (World Health Organization, Switzerland) opened the symposium with a review of the malaria context, noting the stall in global progress to reduce malaria illness and death and the need for new interventions to get malaria control back on track. Hamel summarized results from the RTS,S/AS01 Phase 3 trial (2009-2014) that confirmed the vaccine significantly reduces malaria incidence in children, including severe malaria. Three safety signals were identified during the trial whose causal relationship to the vaccine are unclear and may be chance findings – an excess in the number of meningitis cases, excess cerebral malaria cases, and, in post-hoc analysis, excess female deaths. The malaria vaccine pilot – recommended by WHO in 2016 – supports the pilot introduction of the malaria vaccine in routine childhood vaccination by the ministries of health in Ghana, Kenya and Malawi and the evaluation of the vaccine in routine use. The pilot evaluation will assess the programmatic feasibility of delivering a four-dose schedule, the vaccine's impact on child mortality, and its safety in the context of routine use, with an emphasis on the safety signals seen in the phase 3 trial. Hamel noted that more than 1 million doses of vaccine have been administered and 430,000 children have received their first dose of the vaccine. An initial WHO recommendation on broader use of the vaccine may be considered as early as 2021, based on safety and impact data accrued in the pilot evaluation.

Rose Jalang'o (Ministry of Health, Kenya) presented the progress of the malaria vaccine pilot in Kenya, and a timeline of the Kenya MoH's consideration of the malaria vaccine over the last decade: from the formation of a national malaria vaccine subcommittee; the expression of interest by MoH to participate in the MVIP; the finalization of vaccine introduction plans; national regulatory authority approval of the vaccine for use in the pilots; vaccine introduction preparation, pilot initiation in 2019 and through the first year of implementation in 2020. Jalang'o highlighted some key challenges, including early misunderstanding among health workers of eligibility for the 4-dose vaccination schedule and how to catch up children who come late for vaccines; and, a decline in immunization coverage during the COVID-19 pandemic. Coordination and EPI support through remote means (virtual meetings) helped to mitigate the COVID-19 situation. She noted areas of pilot success: political and goodwill at all levels, strong MoH-partner collaboration, improved vaccine acceptability, mitigation strategies resulting in minimal disruptions during COVID-19, and strong county-level ownership of the pilot. Jalang'o noted some health system benefits of the pilot, including strengthening of pharmacovigilance systems, and more active collaboration between national immunization and malaria control programmes.

Sam Akech (KEMRI/Wellcome Trust, Kenya) described the sentinel hospital surveillance system, which is assessing safety signals identified in the Phase 3 trial, including meningitis and cerebral malaria, and the vaccine's impact on severe malaria. Akech presented key elements of the evaluation, which builds on an established clinical information network (CIN) that supports hospitals to improve patient documentation and uptake of evidence-based pediatric clinical practice. Akech explained that the surveillance system in Kenya includes six public hospitals, located in different counties and serving

children living in areas where RTS,S vaccine is offered and comparator areas, where the vaccine has not yet been introduced. A clinical protocol is established as part of the CIN, to guide clinicians on how to identify, diagnose, and manage patients. Some clinical equipment, materials and personnel were provided to hospitals in order to meet safety and impact objectives. Additional data quality assurance measures were introduced to ensure complete and high-quality data collection. Akech concluded that the CIN is an effective way to improve compliance with evaluation processes in a hospital-based study and that high-quality safety data to inform a recommendation on the wider use of RTS,S vaccine is being obtained.

Kwaku Poku Asante (Kintampo Health Research Centre, Ghana) described the community mortality surveillance system, another essential component of the malaria vaccine pilot evaluation. The approach to collect data to evaluate the impact of the RTS,S vaccine on child mortality. Asante explained that existing mortality data sources (such as vital statistic systems) have limited and sometimes unreliable data. Evaluators aimed to augment and scale up the existing vital statistics infrastructure to collect reliable, timely and accurate mortality data to meet the evaluation objectives. Primary approaches included the mapping and sensitization of key mortality data stakeholders; training of health personnel and community volunteers to strengthen data collection; provision of logistical support for data collection; and development of a data management system that captures data on mortality. A quality assurance system is established and includes regular data reviews and visits to communities with no deaths reported. Successes of the programme were reported: the scaled system established a network of 7,000 community volunteers to identify and report deaths; 66 district health directorates are better able to conduct community mortality surveillance with a verbal autopsy, and there is improved data on vaccination status related to reported deaths. Surveillance was sustained throughout COVID-19, following national health and research guidelines.

Nicola Desmond (Malawi-Liverpool-Wellcome Trust, Malawi) presented an overview of the Health Utilization Study (HUS) that will evaluate the feasibility and community acceptability of the malaria vaccine pilot introduction in Malawi. Study questions include: how is RTS,S promoted and delivered through existing health systems; how do community members learn about and understand the vaccine; what social dynamics shape adoption of the 4-dose schedule; and, how does RTS,S uptake affect malaria prevention and treatment behaviors. The study methodology (observations, interviews, longitudinal design, and iterative approach) can help understand of how to make RTS,S vaccine introduction feasible in communities. Study areas in Malawi encompass a mix of rural and peri-urban areas with varying levels of literacy, access to health services, and access to media and social media. Study teams explored knowledge of the vaccine, vaccine adherence, community engagement strategies, health worker training gaps, and how to integrate the vaccine with routine services. Desmond reported a generally positive response to RTS,S in Malawi, based on initial survey data. Primary caregiver exposure to RTS,S messages was at health facilities. Some confusion was reported among health providers and caregivers as to the age at which a child can receive the vaccine doses. Desmond noted that caregivers have generally high confidence in vaccines and health systems.

Paul John Milligan (London School of Hygiene and Tropical Medicine, United Kingdom) presented on the analysis approach for the Malaria Vaccine Pilot Evaluation (MVPE). The results of the RTS,S vaccine Phase 3 trial were reviewed, showing RTS,S vaccine safety and efficacy when provided in a 4 dose schedule, and the safety signals whose clinical significance was unclear. The objectives of MPVE include estimating the effect of RTS,S introduction on the incidence safety, impact and feasibility measures. The evaluation aims to assess the population effects of vaccine introduction in routine use, and since the expected impact or detectable safety measurements depends on vaccine coverage, the evaluation has been powered with that consideration. The analytic approach will compare the risk ratio of events of interest (e.g. meningitis, severe malaria) in children age-eligible to receive the RTS,S vaccine to children not age-eligible (older or younger) in vaccinating areas compared with the event

risk ratios in comparator areas. This approach adjusts for differences between RTS,S vaccinating and comparator areas in access to a hospital; and the analysis does not require estimates of population denominators. It is anticipated that sufficient events will have accrued by 2021 for analysis of key safety outcomes and of the initial impact against severe malaria. A recommendation for broader vaccine use across sub-Saharan Africa could be made by WHO towards the end of 2021, if safety signals are satisfactorily resolved, and data indicate a positive impact. By the end of 2023, results will include coverage of the 4th dose, and impact on mortality.

Symposium #140: Spatial Intelligence to Optimise Public Health Interventions

Starting off the discussion, Anna Winters (Akros, Zambia) as symposium organizer explained the need to improve spatial intelligence in the fight against malaria, neglected tropical diseases, COVID-19 and others to achieve the SDGs as quickly as possible. She importantly noted that, despite having the most effective health treatments, high disease rates and mortalities were still being recorded majorly due to the gap in reaching target populations. It is important therefore to develop a better and more efficient system to ensure full coverage of disease interventions through the use of spatial intelligence.

Kafula Silumbe (PATH – MACEPA, Zambia) gave a presentation on *"Spatial Intelligence for malaria elimination in Southern Province, Zambia"* where he highlighted the use of the open-source platform called Reveal in identifying regions where mosquito control and malaria interventions could be effectively reached. The tool would be useful in optimizing indoor residual spraying (IRS) across the region. He pointed out that the IRS had previously faced several challenges including poor planning and budgeting and Reveal has been instrumental in curbing these setbacks. This was mainly due to the capacity of the Reveal tool to perform real-time monitoring and ultimately improve planning and decision-making in implementing malaria control strategies such as IRS. One of the main challenges faced by the program was the time-consuming programming and software development. Collaborations would therefore be important to improve the entire system's efficiency in implementation. Plans for Reveal (2020-2021) are to implement IRS across seven districts in the region monitoring true coverage and redirecting resources as necessary through the support of the spatial intelligence platform. Finally, they plan to incorporate the use of the GRID3 datasets in the platform to allow mapping of areas that require interventions and estimating resources needed for the implementation.

Olatunde Adesoro (Malaria Consortium, Nigeria) shared his country's experience from piloting Reveal for use in seasonal malaria chemoprevention (SMC) in Nigeria. SMC is the administration of full courses of antimalarial medication in areas of high seasonal transmission. This has been implemented since 2013 and ten million children have been covered in 2020. Challenges faced by SMC implementation include inaccurate coverage data and difficulty in reaching the aimed program coverage. The Reveal platform is expected to bring improvements through spatial mapping. Reveal deployment included a baseline assessment, usability testing, a pilot study, and operational research. Preliminary findings from usability testing showed the accuracy of data, easy monitoring and supervision, and easy drug reconciliation due to the ability to uniquely identify treatment history for children. The COVID-19 pandemic made most activities virtual so implementation and technical teams could not work together physically, but did so remotely. They also encountered internet connectivity issues in the field, security challenges, flooding, and bad terrain during the rainy season. Usability testing will guide the national malaria control programme on its uses for SMC.

Olena Borkovska (Columbia University, United States) in her talk titled "*High-Resolution Population and Settlement Data for Impactful Malaria Interventions in Sub-Saharan Africa"*, demonstrated GRID3's implementation. The program aims to create efficient spatial data hence ensuring all areas are fully covered and development goals reached. This would be made possible by integrating enough details on pinpointing inhabitants in remote areas and utilizing this data to deliver resources and services for disease monitoring and control. Through the GRID3 project, Olena noted, high-resolution population maps are developed that would show the contrast in predicted population counts. This has been helpful for effective planning of malaria interventions in Zambia, under collaboration with Akros and the Ministry of Health. Objectives of GRID3 are to create planning maps and operationalize these with Reveal to create an implementation model and capacity building. This would ensure all remote areas are fully accounted for in service delivery, resources are efficiently distributed, and monitoring improvement of coverage from previous years. Future work will involve improving data accuracy, using Zambia as a reference point to expanding implementation of GRID3 workflows to other countries and integrating GRID3 into the Reveal tool in other countries.

Echoing the preceding presenters, **Hugh Sturrock** (Locational, United Kingdom) described the need to improve access to data and artificial intelligence to ultimately improve global health. Data availability has greatly improved with the development of programs and platforms to operationalize and visualize mapping data such as Reveal and DHIS2. Collaboration with data scientists would be useful for descriptive analysis and to extract the most relevant information. As an example, he pointed out that mapping malaria data fundamentally helps in designing disease prediction models and the effective distribution of disease-intervention resources across communities. To be able to understand and interpret this data, expertise in data interpretation would be a prerequisite. This could be quickly achieved via the use of algorithms-as-a-service such as locational.io. This organization builds and applies algorithms and proper tools, documentation, and expertise to enable quick interpretation of raw data by non-experts. This would play a key role in the speedy interpretation of data and implementation of disease-control strategies, thereby improving global health.

Symposium #163: Responding to the challenge of vector borne diseases in the context of urban expansion

Regina Rabinovich (MESA, ISGlobal, Spain), co-chair of the session together with Lee Hall (National Institute of Allergy and Infectious Diseases, National Institutes of Health, United States), introduced the concept of the symposium by highlighting that when thinking about the urban context, the first challenge is how to define "urban". She also noted that to address this complex landscape and its

challenges, we will need to involve many different sectors that are not normally involved in vector control. Lee Hall noted that this area has received attention from the International Centers of Excellence for Malaria Research (ICEMR) programs, but further work is needed to better understand both risk and emerging interventions.

Peter Gething (Curtin University and Telethon Kids Institute, Australia) started his talk by saying that, according to the United Nations Development Programme (UNDP), by 2050 two thirds of the world's population will live in urban areas. The implications of this urbanization process for malaria are still unknown. He then presented the work that the Malaria Atlas Program (MAP) undertook in an effort to answer this question: a descriptive analysis to discern the observable effects that urban areas are currently having in malaria transmission, and geostatistical modelling analysis to capture the current relationships between malaria prevalence and urbanicity and simulate the potential impact that urbanization may have in the future. Both analyses demonstrated malaria transmission and burden decline with increasing urbanicity, but Gething noted that caveats to this outcome are reliant on the accuracy of predicted trends for urbanization and continued relevance of present-day relationships.

The relationship between housing improvement and the built environment and vector control was discussed by **Lucy Tusting** (London School of Hygiene and Tropical Medicine, United Kingdom). The fact that the population in sub-Saharan Africa is predicted to double by 2050 creates a huge demand for new homes. Given the estimation that around 90% of malaria transmission occurs indoors, any features that block mosquitoes from entering the houses, such as closing eaves or screening windows and doors, can have a great impact. A systematic review published in 2015 concluded that improved housing could lower the risk of infection by 50%. Similarly, a survey across 29 national health systems in sub-Saharan Africa in 2017 saw 9-14% reductions in malaria linked with modern housing. Good housing also protects from other vector-borne diseases such as dengue, sleeping sickness or leishmaniasis. Tusting concluded by saying that Africa's housing transition is a major opportunity, but we must link with sectors beyond health.

Abdisalan Noor (World Health Organization, Switzerland) started his talk by also asking the question 'what is urban?'. As Rabinovich, he emphasized that a good definition becomes very important when we encounter huge differences between settings, cities and countries. When thinking about the urban malaria problem we are confronted with huge diversity, and some of the interventions that are normally applied to rural settings may not be useful for urban areas. He also posed additional questions that need to be addressed, such as the governance system in urban areas, the current and future of urban planning and sustainable living, and our current knowledge about urban health, health systems and service delivery in malaria-endemic countries. The answers to all these questions entail integrating malaria into surveillance and control of other vector-borne diseases, as well as characterizing and stratifying malaria risk in urban areas. The evidence to determine next steps in this area needs to be evaluated, and WHO is planning a series of consultations in the coming year.

Symposium #164: Integrating Functional, Population Genomic and Transcriptomic Data to Decipher Antimalarial Drug Resistance and Guide Drug Discovery

The employment of population genomic studies has led to discoveries of molecular markers and mechanisms underlying artemisinin resistance. The symposium began with **Shannon Takala Harrison** (University of Maryland School of Medicine, United States) showing that many genes identified in functional screens are supported by previous results from population genetic studies, including genes involved in endocytosis and proteasomal degradation. Harrison also showed that integrated selection of allele favoured by evolution (iSAFE) analysis could pinpoint favoured mutations within *P. falciparum* selective sweeps to identify new artemisinin resistance or compensatory mechanisms that could be validated by forwarding genetic approaches.

Resistance to antimalarial drugs, most recently to artemisinin drugs threatens malaria elimination and eventual global malaria eradication. Population genomics and transcriptomics have been used to identify regions of the parasite genome or gene expression patterns associated with both clinical and *in vitro* drug resistance phenotypes. **Zbynek Bozdech** (Nanyang Technological University, Singapore) presented a study on *P. falciparum* population transcriptomics in the context of evolving multidrug resistance in the Greater Mekong Subregion (GMS) to understand patterns that underlie artemisinin resistance in *P. falciparum.* A current study from the TRACII project from 15 different sites showed physiological relevance of artemisinin resistance-associated transcriptional profile (ARTP) including proteotoxicity, exported proteins, oxidative stress and gametocyte commitment. Bozdech showed that biological pathways linked to expression quantitative trait loci (eQTL) overlapped with ARTP. Remarkably, this led to a functional study of Cyclophilin B19 (CYP19B) which could drive significant resistance to artemisinin.

Jenna Oberstaller (University of South Florida, United States) presented recent findings that might explain how *P. falciparum* evolved resistance to artemisinins. A random, genome-scale subset of *P. falciparum piggyBac*-mutants selected from the saturation mutant-library was used to identify genes allowing parasites to survive the human fever. Pooled screening for mutants' sensitive to heat shock enabled high-throughput characterization of gene function, identifying a number of genes involved in protein folding, vesicle-mediated transport, and host-cell remodelling driving the heat-shock response. Interestingly, apicoplast genes were highly responsive to febrile temperatures. Connecting these findings to previous and concurrent studies, the apicoplast isoprenoid biosynthesis pathway drives vesicular trafficking, which plays a critical role in host-cell remodelling, haemoglobin transport and digestive vacuole function. Interestingly, this study further linked heat-shock response to artemisinin resistance, leading to the integrative hypothesis that pathways gained through the algal endosymbiont-derived apicoplast allowed parasites to survive host fever—and they are now being utilized by the parasite to survive artemisinin treatment.

Stanley C. Xie (University of Melbourne, Australia) began his presentation by giving an overview of our current understanding of the mechanisms of artemisinin resistance and mode of action that are still under debate. From recent studies, dihydroartemisinin (DHA) has been shown to induce oxidative stress and proteotoxicity, leading to parasite death. This study led to the evaluation of proteasome inhibitors as promising potent antimalarials. In corroboration with Takeda and MMV, proteasome inhibitors were further examined by a hit-to-lead program where MPI-5 was found to be efficacious and well-tolerated in mice. Cryo-EM was used to solve the fine structure of the Pf 20S (Proteasome subunit) and reveal its interactions with inhibitors. He noted that this advanced technology could be used to guide rational drug discovery.

Symposium #166: Current Knowledge of Mosquito-Stage Malaria Parasite Biology: Implications for Developing a Robust in vitro Culturing System

During this session, the Co-Chair Flaminia Catteruccia (Harvard TH CHAN, USA) questioned the panellists on *why we do not have a reliable in vitro system yet and what we could achieve if we had one*. Potential answers to these questions were brought by the speakers.

Shirley Luckhart (University of Idaho, USA) reported on host factors in the blood meal as regulators of vector-parasite interaction and transmission in malaria. She addressed questions on why mosquitoes feed on blood, which constitutes a high risk, but also a high payoff. If there were more to it than reproduction, this characteristic could be used to prevent malaria parasite infection of and transmission by mosquitoes. A mosquito blood meal contains pathogen-derived factors as well as nutrients. Luckhart talked about insulin and mitogen-activated protein kinase (MAPK) signalling as ancient regulators of homeostasis in invertebrate and the insulin/insulin-like growth factor signalling cascade components controlling the biosynthesis of coenzyme A (CoA). Their findings showed that *P. falciparum* activates c-Jun N-terminal kinase (JNK) signalling to inhibit mosquito use of pantothenate, increasing available substrate to its own CoA biosynthesis. Luckhart suggested the exploitation of blood as a source of signalling mediators.

Marcelo Jacobs-Lorena (Johns Hopkins Bloomberg School of Public Health, USA) discussed the gametocyte-to-oocyst transition as a most valuable target for setting-up the *Plasmodium in vitro* system. One of his key points was that malaria did not exist without the mosquito vector. An understanding of the development of *Plasmodium* parasites in mosquito vectors is needed, especially in the midgut which seemed to be the best place to target the parasite in the mosquito due to the existence of an "oocyst bottleneck". The team designed a plasminogen activation inhibitor (PAI) which could selectively inhibit tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA) that are required for ookinete formation. Through the fibrinogen/fibrin network of the mosquito midgut blood bolus, fibrinogen promotes red blood cell (RBC) aggregation and could be useful in inhibiting midgut development of *P. falciparum*. These findings could be translated to the field by

introducing transgenic mosquitoes expressing huPAI. As the *P. berghei* in vitro development from gametocyte to ookinete is well established, this knowledge could help the development of an in vitro system for high-throughput screening for *P. falciparum*.

Ashley M. Vaughan (Seattle Children's Research Institute, USA) presented on "*Take it and make it: oocyst development required nutrients uptake and de novo biosynthesis*" with emphasis on oocyst development and generation of infectious sporozoites. They knocked out the Abcb5 transporter in *P. berghei* and found that oocyst development was delayed and no sporozoites were produced and linked this phenotype to a possible role of Abcb5 in the uptake of mosquito lipids. He also addressed the question of whether parasites make their own nutrients presenting published data on the *P. falciparum* fatty acid synthase (FAS) II, which is essential for oocyst maturation and the knockout of which produces oocysts that mature but fail to form. *P. falciparum* oocyst development, therefore, requires uptake of blood meal-associated nutrients and the *de novo* synthesis for sporozoite production. Oocysts appear to sense nutrient levels and can enter a dormant state. He concluded by pointing out the fact that in *vitro* sporozoite production is possible but still challenging.

Photini Sinnis (Johns Hopkins Bloomberg School of Public Health, USA) explained how sporozoite migration from mosquito to mammalian host is associated with a series of bottlenecks, including midgut phase, skin phase, blood phase and liver phase. Quantitative approaches such as the Ross-MacDonald Model could help in understanding mammalian malaria transmission and the probability that a sporozoite-carrying mosquito will feed upon and infect another person resulting in malaria infection. The use of the *P. yoelii*/mice combination already showed that infection likelihood depends on the sporozoite load in the mosquito salivary glands. Interestingly, blood meal acquisition has no impact on the likelihood that an infected mosquito will initiate malaria transmission. Even though sporozoite-based vaccines have been the only ones to show some efficacy in the field, uncertainties concerning the skin phase of *Plasmodium* infection persist. An *in vitro* system for producing human-infectious sporozoites would be a huge advance to these efforts.

Symposium#167: Tracking the Threat of pfhrp2/3 Gene Deletions and Future Alternatives to HRP2-based Malaria Diagnosis

P. falciparum parasites with histidine-rich protein 2 and 3 (hrp2/3) gene deletions are a growing problem, diminishing the performance of HRP2-based RDTs currently used for malaria case management and surveillance in affected areas. The symposium provided a comprehensive overview

with presentations on the global distribution, country experiences on high throughput screening, hrp2/3 deletion characterization and reporting, as well as alternative diagnostic tests.

Jane A. Cunningham (World Health Organization, Switzerland) spoke about how PfHRP2/3 gene deletions are actually being tracked by the WHO. A majority of malaria rapid diagnostic tests (RDTs) target PfHRP2 because of its stability. PfHRP3 is another protein that shares some epitopes with HRP2, which allows antibodies on some brands of RDTs to bind HRP3. This is important for detection of malaria parasites that have HRP2 deletions. The first clinical isolates lacking PfHRP2/3 were found in Peru, but have since been found across the globe. In response to these findings, WHO built an international network of laboratories to assist countries in identifying, tracking, and mapping parasites with gene deletions. Another impressive development was the WHO Malaria Threat Maps, an open source tool for interactive data visualization of global malaria threats such as drug resistance and gene deletions. Data is extracted from published reports and maps are updated every 4-6 weeks. However, Dr Cunningham pointed out that the original source for each data point is critical for properly interpreting these data. In a systematic review of 38 publications, only 5% of studies met the 7-point criteria for accurate investigation and reporting of deletions. Therefore, in order to plan appropriate interventions and decrease morbidity and mortality, the quality of many surveillance studies must be improved.

Eric Rogier (Centers for Disease Control and Prevention, United States) began his presentation by providing a review of malaria rapid diagnostic tests (RDTs), which mainly probe for histidine-rich protein 2/3 (HRP2/3) and/or lactate dehydrogenase. Diagnosis by RDT involves assessment of the absence or presence of target proteins, with multi-target RDTs sometimes providing combinations of positives and negatives that make diagnosis more challenging. Rogier presents a different method for screening parasites lacking HRP2/3 which starts with a phenotypic screening using a bead-based multiplex antigen detection panel, followed by molecular characterization using PCR. Multiple sample types can be screened for *Plasmodium* antigens by using antibody-bound beads to capture the corresponding antigen and detect it with a fluorescently labelled antibody. Using a phenotypic screen is advantageous because it can be used in a high-throughput format, is relatively inexpensive, detects the same proteins as RDTs, and can specify those samples that truly require further molecular characterization. Addition of targets to a hypothetical multiplex panel can expand the potential for interpreting phenotypes and better describe an individual's *Plasmodium* infection status.

Jonathan B. Parr (University of North Carolina, United States) presented "*The evolving approach to pfhrp2/3 deletion characterization*". Confirming the absence of a gene is not straightforward and several steps and methods are required to make a deletion call. Initial evidence can be obtained via microscopy, RDT and PCR, whereas for confirmatory evidence multiple PCRs are required per current guidelines. However, even with these approaches, it remains challenging to be confident in the absence of a gene. Parr gave an example from work in the Democratic Republic of the Congo (DRC), where they conducted multiple PCR assays and identified eight individual deletions using an established PCR-based approach. However, whole-genome sequencing indicated intact genes and a bead-based antigen screen confirmed circulating antigen, leading to the conclusion that the false-negative RDT results among symptomatic subjects in DRC were not due to deletions. This example demonstrated the value of using multiple approaches to overcome weaknesses of single methods, and for improved rigor. During the talk, Parr shared three key PCR workflow changes they made that improved their performance (maximizing DNA template, using AmpliTaq Gold polymerase and using additional cycles (>45) of amplification). He further briefly described new emerging technologies (molecular inversion probe (MIP), Oxford nanopore technologies, and digital droplet PCR). He shared a recent example of hrp2/3 MIP sequencing applied during a large cross-sectional survey, which enabled deletion calls, visualization of deletion breakpoint regions in the parasite's chromosomes, and initial assessment of the evolutionary forces impacting parasites in the regions sampled. He closed

with a reference to a WHO reference laboratory network that is available to support hrp2/3 deletion surveillance.

Dionicia Gamboa (Universidad Peruana Cayetano Heredia, Peru) presented options, performance and affordability of promising alternatives to HRP2-based rapid tests. Alternative tests include automated microscopy and cell phone-adapted systems for parasite detection, ultrasensitive RDTs, multiplex immunoassays, and high-throughput screening systems for antigen detection, loop-mediated isothermal amplification (LAMP) for DNA detection, and urine or saliva samples as non-invasive methods. Automated microscopy, tested in a study in Peru, was found to have the same performance as microscopy by trained professionals, however, it requires good quality of the blood slides. LAMP, also tested in Peru, identified four times more individual infections than microscopy, whereas sample preparation and storage requirements outweighted the advantages. Multiplex immunoassays were useful for identifying hpr2/3 deletions and play an important role in the development of ultra-sensitive RDTs. The immunoassays use both frozen blood samples and dried blood spots. The development of new RDTs and accuracy trials, with genomic characterization for hrp2/3-deleted samples, is part of Gamboa's ongoing work. Moreover, new biomarkers used for sero-surveillance are promising but need further validation (glutamate dehydrogenase, MSP10).

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