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ASTMH 2020 Annual Meeting (virtual): Day 4

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Day 4: Wednesday, 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.

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.


D4_Image 1

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.

D4_Image 2

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.

D4_Image 3

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 g/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 g/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.

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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. Senior editorial support has been facilitated by the Organizers and Co-Chairs of the symposia, Valentina Mangano (University of Pisa) and Julie Chaccour (Independent Consultant). This report is cross-posted on the MESA website and on MalariaWorld.

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ASTMH 2020 Annual Meeting (virtual): Day 3
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ASTMH 2020 Annual Meeting (virtual): Day 1
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2019 Aug - 2021 Sep | $1.08M

A quasi-experimental study to assess the effectiveness of Malaria Camps as part of the Odisha State malaria elimination drive (India ICEMR)

National Institute of Allergy and Infectious Diseases (NIAID), NIH, New York University (NYU) | Jane Carlton | India

2013 Jan - 2015 Dec | $668k

Studies to demonstrate the feasibility of the use of the malaria LAMP kit for population screening in Zanzibar

Kreditanstalt für Wiederaufbau (KfW), Swedish Research Council, Karolinska Institute, Sweden, FIND | Anders Bjorkman, Iveth Gonzalez | Africa, Eastern, Tanzania

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