RESOURCE HUB *Correspondents*

6th International Conference on Plasmodium vivax Research (ICPVR)

Complete series

MESA Correspondents bring you cutting-edge coverage from the 6th International Conference on Plasmodium vivax Research (ICPVR)

June 11 – 14, 2017
Manaus, Brazil

The MESA Alliance would like to acknowledge Rosalind Howes and Hernando del Portillo for their crucial role in the reporting of the sessions.

MESA

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Background

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

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

Day 1: Pre-meeting courses and Opening ceremony

Participants at this 6th international conference dedicated to *Plasmodium vivax* malaria research are being treated to the stunning surrounds of the Rio Negro, just upstream of the confluence with the Rio Solimões and the birth of the awesome Amazon river. This exceptional location is no doubt contributing to the buzzing atmosphere as a record 405 colleagues reunite for this conference, enabled in part by an impressive 41 travel awards for students and early-career scientists from across the world.

A busy day of diverse pre-meeting courses overseen by **Stefanie Lopes** and **Carmen Fernandez-Becerra** has whet the appetite for the main meeting. Dynamic session organisers triggered lively discussions reminding participants of the key and unique features of *P. vivax* malaria, and of the challenges and dilemmas confronting the *P. vivax* community and country programmes in particular.

A morning session led by **Rogério Amino**, **Mary Galinski** and **Letusa Albrecht** covered updates in parasite biology, animal models and imaging advances. Concurrently, sessions provided overviews of conducting epidemiological studies (**Ivo Mueller/Ingrid Felger/Wuelton Monteiro**) and clinical trials (**Quique Bassat/Ric Price/André Siqueira**), with participants being challenged to design studies of their own.

Afternoon sessions included guides to "omics" data and modelling studies (**Jessica Kissinger/Michael White**), with the latter emphasising the importance of epidemiological and biological parameters for appropriate model design. "Real-world" reality was also emphasised in relation to the effectiveness of tools available for *P. vivax* elimination (**Kevin Baird/Marcelo Ferreira/Paola Marchesini**). Finally, early-career scientists participated in a session led by **Marcel Hommel** and **Judith Recht** about scientific publishing and the importance to young scientists of learning to critically evaluate others' work.

The conference's official Opening Ceremony was warmly presided over by the conference host, **Marcus Lacerda**. The evening included an overview of the history of this *P. vivax* conference series, and a video documenting personal testimonials of the clinical and socio-economic impact of malaria on patients and healthcare workers in the Amazon region, an area of riverine communities dominated by *P. vivax* malaria. While the challenges remain significant, an optimistic outlook to the future concluded that is it now *#timetogoforvivax*.

The President of Brazil's most important health research institution, the Oswaldo Cruz Foundation (Fiocruz), **Nísia Trindade Lima**, shared that 2017 marks the centennial anniversary of Oswaldo Cruz's death, setting the fitting challenge to conference participants of addressing his vision of achieving development through improved health, and the importance of the translational alliance between scientific knowledge and public health policy. **Marcel Tanner**, as Chair of the WHO's Scientific Advisory Group on malaria elimination and eradication, reinforced this latter point to promote accelerated public health impact and the emphasised value of the research generated by conference participants on informing the group's analyses and recommendations.

Finally, **Kevin Baird** regaled the audience with his account of the historical legacy on the contemporary status of *P. vivax* in his plenary Grassi & Feletti opening lecture: "After seventy years of dormancy, *Plasmodium vivax* research awakens". While seven decades of vibrant and active research followed the parasite's original description, the parasite's clinical phenotype appeared constrained to the pre-Laveran label of "benign tertian malaria". Subsequent clinical data emergent primarily from the infamous neurosyphilis therapy era contradicting this label appear ignored by Kitchen's 1949 landmark publication, which, coincident with the emergence of antibiotics against neurosyphilis, DDT

for vector control and synthetic drugs for blood-stage infection marked the start of a seventy-year dormancy in *P. vivax* research funding and prioritisation.

An optimistic **Kevin Baird** then bore witness to the impact of the current community's efforts since 2000 to reassess false perceptions regarding the significance of the relapsing malaria parasite. Nevertheless, important challenges remain for the future of *P. vivax* research, including optimisation of therapeutic and diagnostic tools to optimise case management at the peripheral level. Under-documented drug resistance, the complexities of G6PD deficiency and the management of patients non-eligible for primaquine therapy remain key challenges; while the recently identified role of variable CYP2D6 phenotypes further contributes to the reduction of therapeutic effectiveness of existing drugs. Current appreciation of the importance of *P. vivax*, as indicated by this conference's programme, suggests the next chapter in this parasite's history is now being written.

Official speeches were followed by an exuberant traditional Brazilian party. Thank you to all the conference's organisers and sponsors for this fantastic start to the 6th ICPVR. It is now *#timetogoforvivax*.

This blog was written by Rosalind Howes (University of Oxford) and Hernando del Portillo (Barcelona Institute for Global Health (ISGlobal) & Institut d'Investigació Germans Trias i Pujol (IGTP)) as part of the MESA Correspondent program, and is cross-posted on the MESA website and Malaria World.

Day 2: Monday 12th June

The conference's main scientific meeting got off to an impressive start with 33 talks covering a wide range of themes, grouped into the following topics.

Topic 1: Tackling the hypnozoite and relapse

This opening session put end to any lingering doubts of hypnozoites remaining "invisible" or "dormant".

Steven Maher presented his hypnozoite liver model, a primary hepatocyte liver-stage culture system which allows not only morphological characterisation of schizonts and hypnozoites but also candidate drug screening. A hypnozoite liver model is also being used by **Alison Roth** to screen pre-erythrocytic interventions and identify an antibody as a marker of liver infection.

Humanized mouse liver systems (>90% human hepatocytes) developed by **Sebastian Mikolajczak** are providing insight into hypnozoite maturation patterns, and visualisation of the impact of primaquine under optimised dosing regimens.

Impressive laser-capture microdissection is allowing **Roger Cubi** and **Shruthi Vembar** to isolate individual schizonts and hypnozoites of liver parasites in *P. cynomolgi* for single-cell transcriptomics. Similar transcriptomic evidence of hypnozoite non-dormancy in *P. cynomolgi* was presented by **Anne Marie Zeeman**. Further evidence of hypnozoite activity from detection of hypnozoite-derived exosomes in plasma was proposed by **Melisa Gualdrón-López** as an easily accessible biomarker of hypnozoite infection identifiable from a panel of protein markers.

Different immunological responses between primary infection and relapses presented by **Chet Joyner** showed the role of strain-specific B-cell memory; while deep sequencing of pvmsp1from successive *Pv* relapses indicate high multiplicity of infection in Cambodia, with differentiated waves of clonal activation through time, as discussed by **Jessica Lin**.

Finally, **Dennis Shanks** proposed a hypothesis grounded on historical military data of haemolysis as a trigger of relapse, with implications for the therapeutic mechanism of primaquine.

Topic 2: Achieving universal access to safe and effective radical cure

Lucio Luzzatto opened this next session with a historical overview of the "malaria-primaquine-G6PD deficiency" triangle. He highlighted common misconceptions around G6PD deficiency, including G6PDd being more frequent in males (in reality heterozygote females are roughly twice as frequent) and G6PDd being recessive. He discussed the need for quantitative phenotypic assessment of G6PD activity in females to predict haemolytic risks from primaquine as genotyping only conveys an incomplete characterisation. **Kevin Baird** developed this theme with discussion of the factors causing the "erosion of primaquine effectiveness in the real world" which represent important programmatic barriers to achieving safe radical cure of the hypnozoite reservoir. The heavy clinical burden of relapse, however, demands practical solutions to this treatment dilemma.

These overviews paved the way for much-anticipated presentations on the results of the GSK/MMV-driven Tafenoquine trials: DETECTIVE and GATHER, presented by **Raul Chuquiyauri** and **Marcus Lacerda**, respectively. The DETECTIVE phase III clinical trial demonstrated the efficacy of single-dose Tafenoquine (70% reduction in recurrence at the 6-month end-point relative to placebo), with GATHER demonstrating a good safety profile and no evidence of drug-induced adverse events. A limitation of GATHER was the low recruitment of heterozygous G6PD deficient *P. vivax*-infected

females, something subsequently addressed with primaquine by **Cindy Chu**. Her study assessed risk of primaquine-induced haemolysis in phenotypically normal G6PDd heterozygote females, finding that the standard dose (0.5mg base/kg daily for 14d) was well tolerated in all phenotypically normal G6PDd female participants.

Annette Erhart's work in Vietnam corroborated earlier findings of *P. falciparum* being a high-risk factor for subsequent *P. vivax* relapse, suggesting a benefit for more widespread use of primaquine.

Rob Commons' pooled analysis of the haematological profile of chloroquine and primaquine treatment identified differential Hb trends related to baseline Hb levels. Patients with lower baseline Hb levels (< 10g/dL) showed only an increase in Hb following treatment, contrasting with an initial marked drop seen when baseline levels higher.

Finally, a call was made by **Chansuda Wongsrichanalai** for simple and programmatically relevant case management algorithms for primaquine therapy, something currently very variable between countries.

Topic 3: Novel insights into parasite biology

This session was principally focussed on parasite invasion pathways, with **Wai-Hong Tham** presenting the structure of the PvRBP2 ligand which binds to reticulocyte transferrin receptor CD71 to achieve cell invasion. Blocking antibodies (anti-PvRBP2b) demonstrated to inhibit *P. vivax* invasion, varied in efficacy between samples, reminding us of the "everlasting host-pathogen arms race". **Benoit Malleret** followed this up with his announcement of identifying CD98, an erythrocytic amino acid transporter, as another important *P. vivax* invasion receptor, binding PvRBP2a in a dimer-dimer conformation. Selective inhibition of these receptors could be developed as an invasion-blocking intervention. **Usheer Kanjee** discussed methods using quantitative surface proteomics to identify potential new receptors, confirmed the well-known role of DARC, and demonstrated the use of knock-out technologies to down-regulate expression of TfR receptor to significantly reduce invasion.

Adeline Chua discussed her success with achieving up to 10% parasitaemia of *P. cynomolgi* in continuous culture, a valuable model for *P. vivax* drug screening.

Several speakers, including **Nicanor Obaldia**, then spoke to the role of bone marrow in harbouring *P. vivax* parasitaemia. **Marcelo Brito** identified 274 *P. vivax* genes from the bone marrow transcriptional profile with changing gene expression over time directly linked to erythropoiesis and potentially indicating an association with *P. vivax* anaemia.

Luis Carlos Salazar-Alvarez presented evidence of increased *P. vivax* gametocyte rosetting being associated with increased infectivity to *Anopheles aquasalis* vectors, and **Wanlapa Roobsoong** summarised results from Ethiopia relating PvDBP copy number with asymptomatic infection.

Topic 4: Systems biology

The day's final session featured studies using "big data" approaches for drug screening and parasite biology elucidation.

Elizabeth Winzeler's work aims to identify a universal marker of infection from the complex human transcriptome that is "switched on" by infection; results indicate that hsMUC13 may act as a universal biomarker for human malaria infection, though it is uncertain whether this responds to hypnozoites. **Mark Styczynski** presented data from a *P. cynomolgi* model in rhesus macaques that generates extensive "systems biology" datasets at repeated timepoints during primary and relapse infections (with relapses showing markedly lower upregulation), including proteomics, genomics, lipidomics and

metabolomics. He discussed solutions to "integrating the omics" in situations when expected correlations do not emerge; these complex relationships provide added insight into the underlying biology. **Luiz Gardinassi** investigated differential metabolic signatures to clinical outcomes through controlled human *P. vivax* infections of naïve and semi-immune hosts, finding that these varied between host groups at all time points during infection. **Karan Uppal** demonstrated the role of metabolomics in identifying biomarkers of chloroquine-resistant *P. vivax* malaria and an integrative network analysis combining the metabolomics with clinical outcomes.

Rosa Santana presented complimentary results from transcriptomes of *P. vivax*-infected *Anopheles darlingi* and *An. aquasalis* mosquitoes, demonstrating differential gene expression during invasion of the midgut epithelium by the two-vector species. **Alison Roth** also applied transcriptome analysis in the search for infectivity genes in *P. vivax* sporozoites in the study of the parasite's transition phases from vector into host.

Sonia Agrawal presented a method based on a whole genome capture technique for improved quality of *P. vivax* genome sequencing for samples with high levels of human DNA contamination.

"SPOTmalaria" was presented by **Cristina Ariani**, a collaborative MalariaGEN-led effort for genomic surveillance of the global evolution of malaria parasites. This open-access population genomics database uses state-of-the-art technologies to simplify and accelerate genetic data reporting to allow rapid identification of resistance emergence and other trends in parasite populations.

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Day 3: Tuesday 13th June

Topic 5: Epidemiology and surveillance

Reminding us of the importance of denominators and evidence-based risk assessment, **Ric Price** made a strong case advocating the life-saving benefits of primaquine and the need to "cleverly" expand access to safe treatment. Hospital records from Papua, Indonesia, make evident the delayed mortality from *P. vivax* infection associated with recurrent clinical episodes. A 5% risk of mortality for under-fives within 12 months of hospitalisation with *P. vivax* brings the mortality risk in line with that of *P. falciparum* hospitalisations.

Joe Vinetz presented an overview of the Peru ICEMR, discussing the concept of "resilient malaria" and the contribution of asymptomatic and sub-microscopic infections to transmission. Evidence of a potential "time-dependent transmission-enhancement" of *P. vivax* transmission was presented. A positive correlation between parasite load (and symptom intensity) and transmissibility was evident, something that later speakers would corroborate from other settings, including **Fitsum Tadesse** in Ethiopia where sub-patent infections are predominant. His membrane-feeding assays indicated a lesser role for sub-patent transmission of *P. vivax* relative to *P. falciparum*. **Jane Carlton**'s ICEMR in India emphasised the variable epidemiology of *P. vivax* between geographic sites, though with sub-microscopic parasitaemia and high gametocyte carriage widely observed. Given this "hidden burden", a genomics approach is attempting to ascertain the true burden of malaria. The hand-held MinION device allows real-time parasite detection and gene sequencing in the back of a tuc-tuc.

The next series of talks reminded participants of the continually evolving nature of malaria. **Priscila Rodrigues** investigated the origins and introduction routes of *P. vivax* into the Americas. mtDNA analyses indicate multiple waves of *P. vivax* importation from different continents, potentially explaining the parasite's relatively high genetic diversity in the Americas. **Ghyslaine Bruna** and **Fabián Sáenz** presented evidence of PCR-positive *P. vivax* infections in Duffy-negative hosts in Cameroon and Ecuador, respectively. And **Anielle Pina** warned of zoonotic malaria infection in the "malaria-free" Rio de Janeiro state from *P. simium* in the Atlantic Forest.

Topic 6: Understanding, mapping and novel interventions in transmission

Rhoel Dinglasan opened this session with an overview of the insights into fundamental biology and the development of novel transmission-blocking interventions which can be achieved through "omics" work. His searches for conserved parasite developmental pathways and parasite ligand-mosquito receptor interactions are identifying pan-malaria transmission-blocking vaccine targets. He also described a novel slow release vaccine delivery platform using virus-like nanoparticles.

Results from **Kevin Kobylinski**'swork with ivermectin offer clear hope of an additional vector control intervention for interrupting transmission by shifting the vector population survival curve to reduce abundance of infectious anophelines. Further study is exploring the observed benefit of co-administration with piperaquine, and a possible hypnozoiticidal effect. **Paulo Pimenta** described the effect of ivermectin on *P. vivax* transmission with key vectors of the Americas, reporting a reduction in oocyst abundance together with significant inhibition of *P. vivax* asexual development in ex vivo cultures.

Mathilde Gendrin discussed the influence of the mosquito microbiota on parasite transmission, finding the nature of the microbiota variable between specimens and in time, with no core subset of species universally detected. Experimental antibiotic treatment of the microbiota increased parasite transmission.

An important road-block to *P. vivax* basic research is the lack of in vitro continuous culture of *P. vivax*, and the associated supply of stage-specific parasites. Addressing this limitation, **James McCarthy** described optimisations to his human challenge models which provide unique opportunities for basic research as well as drug and vaccine screening. To date, 42 individuals have been infected, with high levels of onward mosquito transmission and subsequent production of infectious sporozoites. **Gissella Vásquez** described the laboratory-breeding of *Anopheles darlingi* at NAMRU-6 in Peru which provides an important supply of sporozoites for many studies presented at the meeting.

Marta Moreno took us to Iquitos, and compared membrane-feeding methods with direct feeding to assess the transmissibility of low parasitaemia infections. Data confirmed the role of patent asymptomatic hosts in transmission, but found no evidence of transmission from sub-microscopic infections, with no significant difference between the feeding methods.

Finally, **Muzamil Hamid** presented a study of *P. vivax* vectors in Sudan. Although dominated by *Anopheles arabiensis*, results suggested a broader range of vectors may be involved.

Topic 7: Immunity, pathogenesis, vaccine discovery and development

This session took us through different stages of the vaccine discovery chain, with insights from the natural processes of the host immune response helping to guide vaccine candidate searches.

First off, **Chris King** discussed using human monoclonal antibodies (mAbs) to identify potential vaccine targets. mAbs targeting PvDBPII have been isolated from individuals with acquired *P. vivax* immunity which inhibit parasite binding. These mAbs recognise a conserved epitope at the binding interface of DARC, and evidence of cross-strain recognition from Cambodian mAbs to Madagascar parasites points to strain-transcending blocking activity. Next, **Arturo Reyes-Sandoval** described his identification of "Rv21" as a candidate pre-erythrocytic vaccine. This RTS,S-like vaccine is a virus-like particle presenting PvCSP, which shows promising activity against sporozoites. He described ongoing efforts to identify a multi-antigen vaccine, with "Rv21+Ad-M-TRAP" currently the lead candidate. He also advocated using transgenic murine *P. berghei* parasites expressing *P. vivax* antigens to avoid Aotus pre-clinical phases, thus representing significant cost savings. **Noah Sather** then discussed the special implications of relapse in the context of vaccine development, demonstrating that even a relatively low efficacy (<50%) vaccine against primary infection could still significantly reduce the incidence of relapses by preventing the development of hypnozoites.

Camila Barbosa presented her in silico work screening peptides presented by infected reticulocytes for potential immunogenic properties. She is using this approach to unravel the HLA Class I antigen presenting pathway in *P. vivax*-infected reticulocytes.

The role of complement-fixing antibodies in severe malarial anaemia was discussed by **Damian Oyong**. Unlike with *P. falciparum*, there appears to be no significant association of complement activity with *P. vivax* and severe anaemia. Evidence presented by **Steven Ko** however, suggests that platelets play a major role in killing blood-stage parasites, with greater impact on *P. vivax* infection than *P. falciparum* or *P. malariae*. **Stephanie Yanow** also described studies of the host immune response guiding vaccine target identification. She discussed cross-reactive PvDBP antibodies against Var2CSA and the protection acquired by *P. vivax*-induced antibodies to *P. falciparum* infection.

Antibody kinetics and longevity against *P. vivax* antigens were investigated in Thai patients for a year after infection by **Zoe Shih-Jung Liu**. She identified a range of antibody lifespans, with most being short-lived, but some persisting longer than 6 months even in the absence of boosting exposure. Combination antigens would provide a valuable surveillance tool.

Topic 8: Late breaker turbo talks

This fast-moving session (each talk lasted only 5 mins) jumped around a range of themes:

Daniel Bargieri presented "Ookluc", a new high-throughput screening tool for identifying transmission-blocking targets; **Lilia Gonzalez** presented evidence of vector selection on *P. vivax* populations in Mexico, with different parasite strains adapted to different vector species; **Gabriel Rangel** described using KCl Percoll enrichment of very low parasitaemias of cryopreserved parasite isolates (<0.02%) to screen antimalarial sensitivity; **Camila França** screened antibody responses to recombinant *P. vivax* antigens looking for possible interactions between panels of antibodies, demonstrating that combinations of up to five antibodies could boost efficacy; **Andre Siqueira** summarised large-scale serological screening and treat activities that achieved elimination in southern Brazil in the 1980s; and finally **Miriam Diaz-Varela** explained that exposure to exosomes can induce long-term immunity in mice, and she is now performing studies of human reticulocyte-derived exosome proteomics to help understand the mode-of-action of this novel vaccine platform.

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The day ended at the Parisian-modelled Manaus Opera House. A truly stunning venue for a beautiful concert of emotive Brazilian music entitled "Vivace" by the Amazonas Guitar Orquestra. Surprise guest appearances were the evening's highlight, with our conference's great Scientific Committee President, **Hernando del Portillo**, pulling out all the stops in a sensational vocals and guitar rendition of Girl from Ipanema; while **Joe Vinetz** performed on clarinet a beautiful composition by his own son, **Max** – truly remarkable from both father and son! The evening ended with a reception on the Opera House's balconies overlooking the old buildings of the city of Manaus. Thank you to **Marcus Lacerda** and all the organisers for such a special evening!

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Day 4: Final scientific sessions & Krotoski closing lecture

Topic 9: Are current control strategies aimed at *P. vivax* working?

This morning's opening session was focussed on diagnostics for *P. vivax* parasitaemia and G6PDd. **Ingrid Felger** discussed the pros and cons of available high-sensitivity diagnostics, which differ in suitability depending on the diagnostic objective: e.g. maximising detection sensitivity vs. quantifying parasitaemia. She discussed the negligible benefit of gametocyte detection for programmatic surveillance and the trade-off between false-positives and increased sensitivity, urging a conservative approach to avoid potentially alarmist results. **Iveth Gonzalez** (FIND) discussed refinements to RDT diagnostics, including a new combination RDT for *P. falciparum* and *P. vivax* currently in development. She emphasised that improved diagnosis requires not only technological innovation, but also increased patient access to treatment in terms of treatment-seeking behaviour and test availability. **Anna Rosanas-Urgell** demonstrated the operational feasibility of mobile LAMP-based detection of asymptomatic infections using pop-up laboratories in remote Amazonian riverine communities near Iquitos.

Kevin Baird presented on behalf of Ari Satyagraha a study of G6PDd in 2056 females from Sumba, Indonesia. Almost all females with <70% enzyme activity were heterozygote G6PDd with a range of variants. Qualitative diagnostics set to the routine threshold of 30% residual activity would fail to identify most heterozygotes. **David Sebba** (industry representative from BD) presented a hand-size portable diagnostic device that provides rapid, temperature-corrected, quantitative measures of G6PD activity and Hb levels. Tight correlation with the Trinity diagnostic reagent was found in field evaluations on the Thai-Myanmar border, and a high concordance between samples from venous and capillary blood. **Angela Devine** presented a scenario-based cost-effectiveness model of G6PD diagnosis for *P. vivax* patients. Her model predicted that on the Thai-Myanmar border, G6PD testing could avert DALYs by reducing recurrences and reducing haemolytic risk in G6PDd patients at low costs or cost savings. An online tool allows model parameters to be adjusted to local settings.

Mariusz Wojnarski presented results of a trial in a military cohort in Cambodia comparing monthly prophylaxis including weekly primaquine against PCR-based monthly FSAT. High rates of recurrence were seen with the FSAT approach, promoting monthly prophylaxis with primaquine. G6PDd individuals in the prophylaxis arm were treated with weekly primaquine and closely monitored with no patients showing >25% Hb drop.

Nathália Siqueira presented evidence of successful nested PCR analyses from 10 year old thick blood smears off archival microscopy slides, identifying higher proportions of mixed infections than by microscopy diagnosis.

Topic 10: Towards elimination of P. *vivax* malaria

Scott Miller shared the Bill & Melinda Gates Foundation's outlook on *P. vivax* tools for achieving elimination. No single silver bullet is anticipated but instead elimination will be achieved incrementally through a combination of improved interventions. In his broad-ranging presentation of priority interventions, he included the asymptomatic reservoir, the role of modelling for evidence-based planning, R&D priorities for higher sensitivity RDTs, biomarkers of recurrence risk, G6PD diagnostics, simpler guidelines to increase access to primaquine and Tafenoquine, endectocide treatment for vector control as well as broader vector control innovation, non-haemolytic radical cure drugs, vaccines... He emphasised the need to maintain a user-focussed perspective (i.e. NMCPs) and the development of innovative delivery planning and financing to increase access to diagnosis and treatment.

Brice Campo presented MMV's liver-stage drug pipeline. Although considerable efforts are going into identifying new drug candidates, Tafenoquine remains MMV's only current liver-stage drug, with ongoing support for its programmatic roll-out. Important hurdles to novel drug discovery against *P. vivax* include restricted sporozoite supplies and the lack of in vitro blood stage culture systems. Liver-stage assays, however, have seen impressive development, with several teams developing systems which have already screened 1000 compounds for prophylactic and radical cure activity, and should process 15,000 this year.

The next series of talks described the benefits of integrating parasite population genetic surveillance into elimination policies.

Wang Nguitragoo presented on behalf of **Veerayuth Kittichai** evidence of a spatially clustered *P. vivax* population structure between sites in Thailand based on microsatellite variation. Sources of parasites implicated with regional outbreaks can be determined, supporting the country's 2024 target for elimination. **Zuleima Pava** presented the impact of the universal ACT policy on *Plasmodium* parasite diversity in Papua, Indonesia. A significant reduction in polyclonal infections was identified, with *P. falciparum* parasites displaying greater genetic differentiation over time than *P. vivax*, which remains relatively diverse. **Pablo Fontoura** discussed reactive case detection in the Amazon region and the use of molecular genotyping to infer local parasite population structure. This has revealed high *P. vivax* diversity consistent with complex transmission networks and multiple sources of infection within clusters, potentially complicating malaria elimination efforts.

Topic 11: Is modelling accelerating elimination?

Michael White opened this final session with a presentation of a model he has developed to simulate the impact of intervention combinations on *P. vivax* transmission in different provinces of Papua New Guinea and help determine locally-specific intervention packages for achieving elimination. The model is parameterised by substantial datasets including cross sectional surveys, longitudinal case surveillance, entomological data, host demography, host genetics etc. Extending the model to other settings will be contingent on epidemiological data to inform the model parameters.

Gonzalo Domingo (PATH) described a model to support service delivery planning for G6PD diagnosis. The model is informed by the Malaria Atlas Project *P. vivax* endemicity map, from which case numbers per health facility are estimated. These are adjusted to generate G6PD diagnostic market size estimates by country, accounting for a range of parameters including treatment seeking rates, *P. vivax* diagnostic sensitivity, asymptomatic parasite carriage rates, among others, as well as product-specific parameters including diagnostic cost and shelf-life. The model forecasts annual commodity needs and the associated economic cost of implementing G6PD screening.

James Watson's model capitalises on the kinetics of haemolysis to determine a daily primaquine dosing regimen that can be safely tolerated by G6PDd *P. vivax* patients. The natural decay of G6PD enzyme activity puts older cells at greatest risk of haemolysis. Haemolysis triggers erythropoiesis, leading to a hypothesised period of primaquine-insensitivity associated with the overall younger red cell population. The model identifies the primaquine dosing regimen (with variable daily primaquine dose) associated with triggering the lowest overall haemolysis and Hb drop. A "regimen-finding" clinical trial will investigate the impact of this modelled dosing in healthy G6PDd volunteers. The model is highly variant-specific, and currently parameterised to the Viangchan G6PDd variant.

Rodrigo Corder ended the formal conference sessions with an overview of his model of *P. vivax* transmission in Brazil. The model is informed by cross-sectional surveys of asymptomatic carriage, malaria case data, household census information, as well as environmental variables including

breeding sites and housing quality. His model aims to account for heterogeneity in local transmission to optimise intervention policies.

Closing ceremony

The Krotoski Closing Lecture was given by **Nick White**. Amid gentle banter, Nick shared a glorious overview of the history of *P. vivax* relapse research.

Human challenge studies, including by Manson on his own son, helped demonstrate "recurrence of malaria" in 1900. This was pursued during the early twentieth century by teams in different parts of the world defining the frequencies of relapse. Different strains were associated with long or short-latency relapse phenotypes, labels which persist to this day (with perhaps also an intermediate-latency phenotype). These early studies also evaluated the association between sporozoite load and relapse, one of this week's themes.

A particularly detailed documentation of the characterisation of relapse comes from the 1938 text "Malaria in the Netherlands" by Swellengrebel and de Buck who define the 9 month relapsing rate of the Dutch long-latency strain. Nick recommended this textbook as one of the best available on malaria, having valuable insights for our current elimination-focussed era. As part of their scrupulous patient monitoring, microscopy was performed with sensitivity equivalent to that of today's PCR-based techniques by reading up to 6,000 leucocytes. Very low density and asymptomatic infections, important themes at this present conference, have therefore been known of for about a century.

Nick's fascinating exploration of the literature that incrementally described the biology of relapse made evident the treasure-trove of historical data. While a little dismaying to realise how many of today's "new" observations are actually meticulously documented in the early 20th century literature, the thoroughness of reporting from that period provides a uniquely rich dataset of the biology of *P. vivax*. Further, some of the dubious experiments permitted before the establishment of ethical boundaries provide rare data that could never be collected today. Despite decades of research, important unknowns remain, including the triggers of hypnozoite activation and the mechanisms of radical cure antimalarials.

Nick concluded that while the science was all very interesting, parasite elimination remains our task, something requiring the use of radical cure.

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Voicing everyone's thoughts, Nick White said the meeting was one of the best he'd ever attended. He thanked Marcus Lacerda and Hernando del Portillo, as Conference and Scientific Committee organisers, and their teams for their fantastic efforts making this ICPVR 2017 such a successful meeting, striking a perfect balance between exciting science and Brazilian hospitality.

The meeting ended with **Marcus Lacerda** passing the baton to **Chetan Chitnis** and colleagues **Georges Snounou** and **Ivo Mueller** who will host the next ICPVR in June 2019 at the Institut Pasteur in Paris, France.

And then the caipirinhas flowed…Obrigado Manaus, et à bientôt Paris!

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