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NEWS & VIEWS

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Interview

Dr Ipsita Pal Bhowmick,
Scientist D, ICMR - Regional Medical Research Centre (RMRC), Dibrugarh, Assam, India

Upcoming

Lecture Series on Infectious Diseases 2.0: Lecture 10 by
Dr Aneta Afelt,
University of Warsaw, Poland

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MALARIA THROUGH THE LENS OF RESEARCHERS | UPCOMING EVENT

Editorial

Dear Readers,

Over the past century, efforts to control malaria have encountered significant challenges. The emergence of resistance in both mosquitoes to insecticides and parasites to drugs has had a profound impact on malaria control efforts. Hence, it is crucial to explore innovative ways of eliminating malaria. With this prelude, the MERA-India team brings you the thirty-fifth issue of our newsletter, "News & Views".

The MERA-India team recently organized a three-day, hands-on training session on monitoring insecticide resistance in malaria vectors at ICMR-National Institute of Malaria Research, New Delhi. The aim of the training was to promote prioritized research and facilitate capacity building, focusing on providing participants with an in-depth understanding of insecticide resistance. The session benefited individuals across all positions and helped equip and enhance the existing knowledge of the workforce dedicated to malaria control.

In another event, after 30 years of research, the University of Oxford has made a significant breakthrough in the global fight against malaria transmission. They have developed the R21/Matrix-M™ malaria vaccine, which has already been authorized for use in Ghana by its Food and Drugs Authority. The Serum Institute of India Pvt. Ltd. (SIIPL) has manufactured and scaled up the vaccine, which seems effective and can be produced in large quantities to meet the needs of the countries most affected by malaria.

In this month's lecture series, Dr Farah Ishtiaq (Principal Scientist, Tata Institute for Genetics and Society, Bengaluru) gave a talk on 'Island biogeography and population genomics to understand colonisation patterns in urban malaria vector *An. stephensi*', with a focus on Lakshadweep islands becoming a new breeding ground for mosquitoes. In the Distinguished Lecture Series, Professor Marcel Tanner (President, Swiss Academies of Arts and Sciences, Bern, Switzerland) delivered an interesting talk on 'How the corona pandemic develops global public health and strengthens malaria elimination'. The newsletter contains a summary of the highlights from the informational lecture. A glimpse of the MERA-India Insecticide Resistance Training is also showcased in the "ICMR-NIMR & MERA-India Activities" section.

The 'Malaria Scientists to Watch' section encompasses an insightful and edifying interview with a young malariologist, Dr Ipsita Pal Bhowmick (ICMR-Regional Medical Research Centre, Northeast, Dibrugarh).

The "Research in Spotlight" section covers the summary of three malaria-relevant research articles. The first article by Martinez *et al.* showed that recombinant PvDBPII, used in

combination with Matrix-M and GLA-SE adjuvants, can produce strong cross-reactive antibodies that may protect against heterologous *Plasmodium vivax* infection. In the second article, Russell *et al.* developed a genome-scale screen to identify genes for *P. berghei* sexual development and their impact on transmission. Lastly, Fola *et al.* reported a concerning situation in Ethiopia where there has been a recent emergence of *P. falciparum* resistant to artemisinin and diagnostics.

Further, the "Malaria Through the Lens of Researchers" section showcases an image submitted for the MERA-India Image Competition 2022 by Dr Juhi Mangesh Ruat, Department of Community Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, (DMIMS), Wardha, Maharashtra.

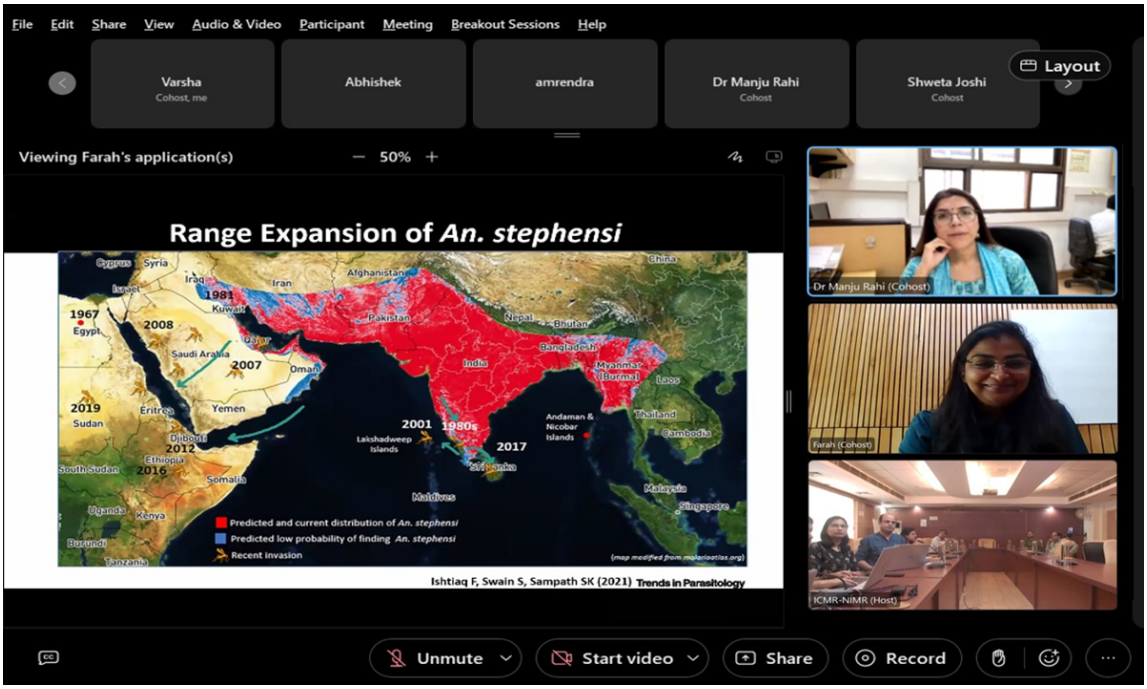
The "Upcoming Events" section comprises information on the tenth lecture in the Lecture Series on Infectious Diseases 2.0, to be given by Dr Aneta Afelt, University of Warsaw, Poland.

We hope that you will find this issue engaging and fascinating. Please write to us for any feedback or suggestions regarding the newsletter's content at meranewsletter@gmail.com.

With best wishes,
MERA-India team

ICMR-NIMR & MERA-India Activity

Lecture Series on Infectious Diseases 2.0: Lecture 08 by Dr Farah Ishtiaq



Dr Farah Ishtiaq was the eighth speaker of the Lecture Series on Infectious Diseases 2.0. She is working as a Principle scientist at the Tata Institute for Genetics and Society (TIGS) in Bengaluru. Currently, as a lead at the TIGS, she studies the field ecology and population genomics of key mosquito species involved in malaria and dengue transmission in India. Dr Manju Rahi, Scientist-F, ICMR, and Principal Investigator, MERA-India, welcomed Dr Farah Ishtiaq, and Dr Sachin Sharma, Chief Consultant, MERA-India, introduced her to the audience.

Dr Ishtiaq gave a lecture on the topic 'Island biogeography and population genomics to understand colonisation patterns in urban malaria vector *An. stephensi*'. At the beginning of the lecture, she provided a brief overview of the distribution of various vectors and the malaria situation in India. Through the lecture, Dr Ishtiaq explained how landscape genetics can be a powerful tool used to understand the influence of key environmental variables and human factors on the dispersal and spread of vector-borne diseases. *During the lecture,* she also discussed topics such as species richness and diversity, mosquito species turnover, larval abundance and niche overlap associated with natural or manmade habitats, and how vector ecology shows genetic variation between mainland and island populations. Dr Ishtiaq concluded the lecture by highlighting this approach together with spatial ecology, statistical modelling, and Geographic Information System (GIS) to help define the disease hotspots for public health interventions via evidence-based science.

The lecture was followed by an interactive question and answer session wherein the attendees raised their doubts and Dr Ishtiaq provided insightful responses to all the queries. The session concluded with a vote of thanks from Dr Sachin Sharma to the speaker and the attendees.

Distinguished Lecture by Professor Marcel Tanner

ICMR-NIMR and MERA-India conducted the Distinguished Lecture by Professor Marcel Tanner on Wednesday, 26th July 2023.

Professor Marcel Tanner is the current President of the Swiss Academy of Arts and Sciences and a board member of Fondation Botnar. He holds a Ph.D. in medical biology from the University of Basel and an MPH from the University of London. He was Director of the Swiss Tropical & Public Health Institute for 18 years and Professor Emeritus of Epidemiology and Medical Parasitology at the University of Basel. His research interests span the fields of global health, epidemiology, health systems, public health, and basic research in cell biology and immunology, with a focus on infectious diseases such as malaria, schistosomiasis, trypanosomiasis, and filariasis. Professor Tanner played a key role in developing malaria vaccines and implemented large programmes for health planning and training health workers. During his talk at MERA-India, he was welcomed by Dr Manju Rahi, and introduced to the audience by Dr Sachin Sharma.

Professor Tanner started his lecture with an interesting comparison between the research conducted in various fields during the COVID-19 pandemic and an old Indian story about three blind men and an elephant. Further, he explained how the COVID-19 pandemic has affected other diseases including malaria worldwide. During the presentation, he showed the progress made in malaria research, interventions, and implications from 2000 to 2015 and how intervening in complex disease and health systems can lead to translational

research. He also suggested the incorporation of mathematical tools to establish herd immunity, risk assessment, priority setting and resource allocation, risk-benefit analysis, and individual versus public health ethics. Professor Tanner talked about the years of research dedicated to malaria vaccine development followed by the designing of key responses such as diagnostics, surveillance, vector control, community engagement, interventions, and implementations for the effective elimination of malaria.

He concluded the lecture by highlighting the research priorities to empower the health systems by following the Global technical strategy by harnessing innovation, expanding research, and strengthening the enabling environment. The lecture was concluded by Dr Sharma with a vote of thanks to Professor Tanner and all the attendees.

The recording of this lecture can be found on the MERA-India website (https://www.meraindia.org.in/lecture-series).

MERA-India Insecticide Resistance Training

MERA-India organized a three-day hands-on training session at ICMR-NIMR, New Delhi, from August 2nd to August 4th, 2023. The training was aimed at providing capacity building at the institutional level for conducting studies on insecticide resistance. It was conducted for ICMR scientists and technical staff involved in the task force study on “Determination of resistance frequency and intensity among field populations of malaria vectors”. The training was intended to equip the site-specific scientist and technical staff for conducting the insecticide resistance study.

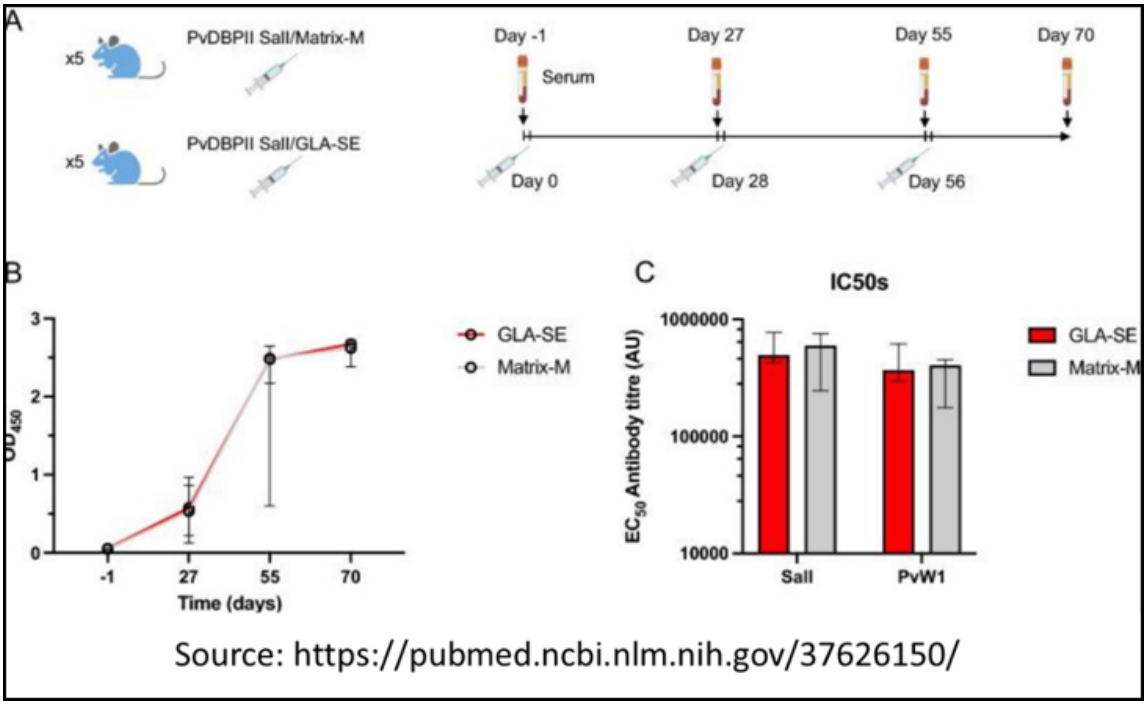
The training was carried out under the guidance of subject experts Dr P Jambulingam, Former Director of ICMR-Vector Control Research Centre (VCRC), Puducherry, Dr K Raghavendra, Former Scientist G, ICMR-NIMR and Dr K Gunasekaran, Former Scientist G, ICMR-VCRC, who served as the resource persons. A total of 18 participants from institutions including VCRC Puducherry, NIMR Field Unit Ranchi, NIMR Field Unit Raipur, ICMR-Regional Medical Research Centre (RMRC) Gorakhpur, and the ICMR-National

Institute of Research in Tribal Health (NIRTH), Jabalpur, were actively engaged in this three-day training workshop. The program aimed to provide hands-on experience in insecticide resistance experiments. A pre-test was conducted on the first day to assess the existing knowledge of the participants. This was followed by informative and interactive lectures on diverse facets, encompassing the significance of insecticide resistance, relevant protocols, intensity assays, mortality calculation, and results interpretation.

Under the experts' guidance, the participants executed experiments, subsequent calculations, and data interpretation. The experts ensured the active involvement of each group member and rotated participants through different activities. The experts also shared practical insights and hacks to mitigate errors during experimentation, with particular consideration for field trips. The training comprised a lecture by Dr Vaishali Verma (Technical Officer B, NIMR, New Delhi) and Dr Gaurav Kumar (Technical Officer B, NIMR, New Delhi) to further illuminate the biochemical and molecular characterization aspects pertinent to the subject matter. This was followed by a result analysis of the experiments conducted during the workshop and several interactive quizzes under Dr Raghavendra, and Dr Gunasekaran's supervision. A post-test was also conducted to assess the impact and benefits of the lectures, tasks, and hands-on training. Ultimately, the outcomes were analyzed, shared, and elucidated by mentors during a comprehensive discussion, enhancing participants' comprehension. Notably, a performance shift of approximately 1.4 times was observed among participants, benefiting individuals across all positions. The training was concluded with the certificate distribution to all the participants and concluding remarks by the experts.

Research in Spotlight

Martinez FJ. *et al.*, *Sci. Rep.* 2023: Immunogenicity of a *Plasmodium vivax* vaccine based on the duffy binding protein formulated using adjuvants compatible for use in humans.



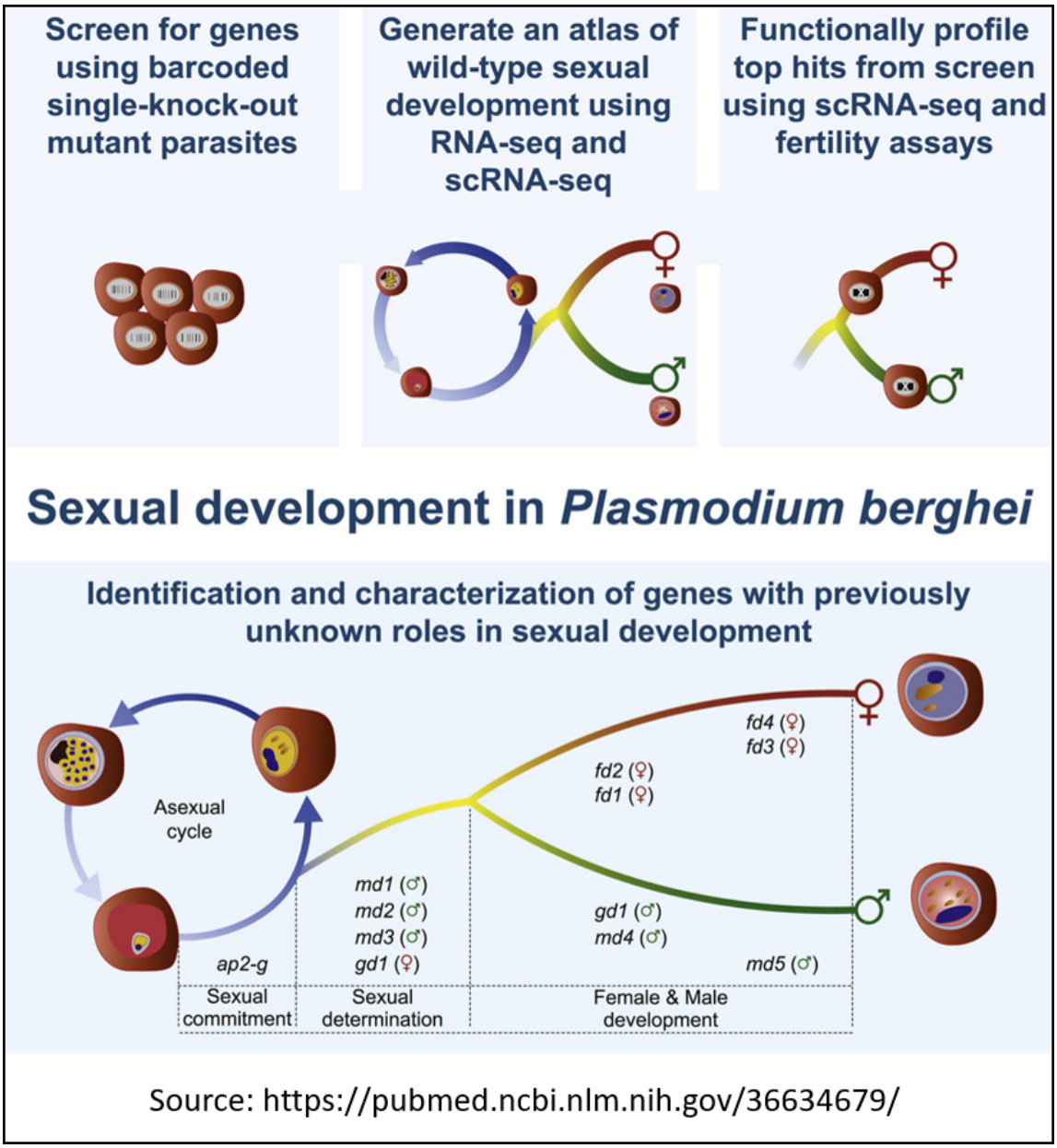
The blood stage of the *P. vivax* life cycle—which includes reticulocyte infection, intracellular replication, and outflow of next-generation merozoites—is solely responsible for the clinical manifestations of malaria. These *P. vivax* merozoites then invade newly formed reticulocytes. The invasion step is dependent on the interaction of the *P.* vivax Duffy Binding Protein (PvDBP) with the Duffy antigen receptor for chemokines (DARC). The N-terminal cysteine-rich region II of PvDBP (PvDBPII), which binds DARC, is a leading *P. vivax* malaria vaccine candidate.

In the present study, Martinez *et al.* explored the feasibility of formulating PvDBPII SalI with a saponin-based adjuvant, Matrix-M, in a pre-clinical mouse model and compared the immunogenicity with glucosylpyranosyl lipid adjuvant-stable emulsion (GLA-SE) formulation. Analysis of the antibody responses revealed comparable ELISA recognition titres as well as similar recognition of native PvDBP in *P. vivax* schizonts by immunofluorescence assay. Moreover, antibodies elicited by the two adjuvant formulations had similar functional properties such as avidity, isotype profile, and inhibition of PvDBPII-DARC binding. Furthermore, the anti-PvDBPII antibodies were able to block the interaction of DARC with the homologous PvDBPII SalI allele as well as the heterologous PvDBPII PvW1 allele.

The results validate the ability of recombinant PvDBPII formulated with both Matrix-M and GLA-SE to elicit potent cross-reactive antibodies that could potentially protect against

infection by the heterologous *P. vivax* challenge strain PvW1 by neutralizing reticulocyte invasion. Importantly, the DARC-binding inhibition of PvW1 also indicates that the PvDBPII-specific antibodies can potentially block the invasion of the *P. vivax* strain PvW1 that is used for blood-stage challenge trials with *P. vivax*. In conclusion, multiple antigens together are an appealing strategy to boost immunisation effectiveness.

Russell AJC. *et al., Cell Host Microbe*. 2023: Regulators of male and female sexual development are critical for the transmission of a malaria parasite.



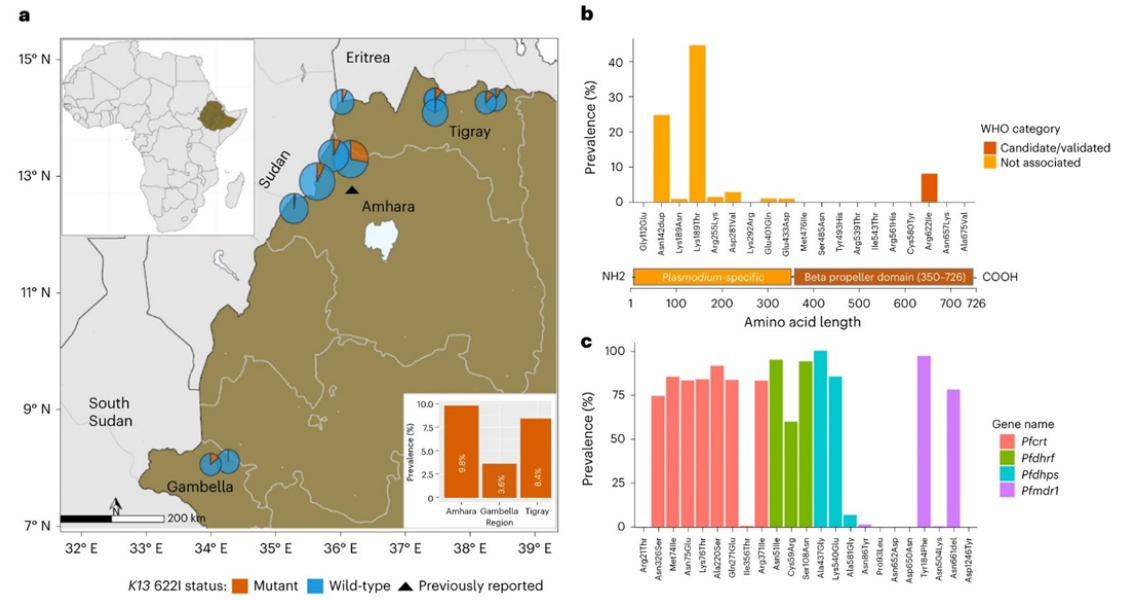
Source: https://pubmed.ncbi.nlm.nih.gov/36634679/

The transmission of malaria to mosquitoes entails a transition in blood-stage parasites from asexual division to sexual reproduction. The transcription factor AP2-G is necessary and sufficient for this switching in the case of *Plasmodium berghei*, but it is not yet known how specific sex is determined in a haploid parasite.

Herein, Russell *et al.* have used a global screen of barcoded mutants for the identification of genes involved in the formation of either male or female sexual forms and for the validation of their significance in transmission. In addition, single-cell phenotyping and protein interactions were performed to distinguish between functions in sex determination and development and generate initial insights into the mechanisms by which male and female sex are determined in a divergent eukaryote.

A diverse group of putative RNA-binding proteins, including the maleness-inducing factor MD1 and the early response genes MD4, MD5, and FD1, have been identified that are co-expressed downstream of AP2-G and whose deletion affects either the determination of or differentiation along a male or female cellular trajectory. The protein interactors of a zinc-finger protein that controls female development and a male-determining gene with a LOTUS/OST-HTH domain demonstrate that transcriptional processes are complemented by germ-granule-like ribonucleoprotein complexes in the regulation of both male and female development of a malaria parasite. Data from the current work indicate that comparable principles might have a role in the case of *P. berghei*. Sex determination mechanisms evolve rapidly but often involve RNA-dependent regulation, for example, through differential splicing or translational repression, and data from the present study suggest similar principles operate in *P. berghei*.

Fola AA. *et al.*, *Nat. Microbiol.* 2023: *Plasmodium falciparum* resistant to artemisinin and diagnostics have emerged in Ethiopia.



Source: https://www.nature.com/articles/s41564-023-01461-4

In spite of increased control efforts for malaria globally, the ever-evolving drug resistance and the emergence and spread of resistant strains have faltered the progress towards malaria elimination in recent years. Since diagnosis and treatment of *Plasmodium* infections are key components of effective malaria control, monitoring the emergence, evolution, and spread of drug- and diagnostic-resistant parasites has become essential.

In this study by Fola *et al.*, comparative genomic analysis of drug resistance among pfhrp2/3-deleted and non-deleted parasites collected across three regions of Ethiopia was performed using molecular inversion probe (MIP) sequencing for highly multiplexed targeted genotyping. The prevalence of key drug-resistance mutations was assessed, and the co-occurrence with the pfhrp2/3 deletion was checked in three regions.

It was found that 8% of malaria cases were caused by *P. falciparum* carrying the candidate artemisinin partial-resistance kelch13 (K13) 622I mutation, which was less common in diagnostic-resistant parasites mediated by histidine-rich proteins 2 and 3 (pfhrp2/3) deletions than in wild-type parasites. Identity-by-descent analyses showed that K13 622I parasites were significantly more related to each other than to the wild type. Of concern, 8.2% of K13 622I parasites also carried the pfhrp2/3 deletions. The Pfhrp2/3-deleted parasites were also highly related, with evidence of clonal transmissions at the district level. Overall results suggest the recent clonal spread of the kelch 622I mutation in three regions of Ethiopia, leading to the development of partial resistance towards artemisinin.

Malaria Scientist to Watch:
An interview with Dr Ipsita Pal Bhowmick

Dr Ipsita Pal Bhowmick
Scientist D,
ICMR-Regional Medical Research Centre, NE,
Dibrugarh, Assam

1. Please share your journey and experience in malaria research with the readers.

Coming from a background in Chemistry, my fresh journey in the biological fields began in the path of Malaria as a graduate student at the Tata Institute of Fundamental Research (TIFR) in India and then as a Post-Doctoral fellow at the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health, US. At NIAID, I explored the unique biochemical, and structural properties and the moonlighting functions of different Malarial glycolytic enzymes to explore their role as therapeutic and vaccine targets. During my stay at NIH and later as a fellow at the Department of Public Health, Johns Hopkins University, I started getting exposure, experience, and training in the public health aspects of malaria. I decided to embark upon a career where I can have the flavour of both basic as well as translational research. My career started with my stints as a Scientist and Site Manager for the North-East Site of Malaria Evolution in South Asia- International Centers of Excellence for Malaria Research (MESA-ICEMR) team at the Regional Medical Research Centre, NE, and Model Rural Health Research Units (MRHRU), Tripura, and is now continuing as Scientist at ICMR-Regional Medical Research Centre, NE, Dibrugarh, Assam. I'm now conducting several projects in different parts of North-East India where I am assessing the overall malaria situation in different Tribal communities dwelling mostly in the hilly forested terrains, covering all the epidemiological, entomological, ecological, meteorological, and socio-behavioural aspects. Based on the findings, I am also designing and imparting targeted and customized interventions. Additionally, I am involved in designing and deploying real-time, pictorial, and local language-based mobile applications in these areas for overall fever surveillance and management by grassroots-level health workers and volunteers.

2. Malaria parasites can exist in the human host at various densities. What are some of the key differences and challenges in studying low-density infections compared to high-density infections?

Key differences and challenges in studying low-density infections compared to high-density infections are in the detection, as low-density ones are by definition missed by the point-of-

care rapid diagnostic tests, very difficult to detect even by manual microscopy, often missed if the technician is not highly skilled or experienced or cannot afford enough time to scan several fields to detect low density or if the density is beyond the human limit of detection. The only option remaining to detect low-density infections is sensitive molecular methods which are expensive, time-consuming, and can be mostly performed only in a few settings, subject to the equipment and skilled personnel availability.

Even among the molecular techniques, the expense increases with the increase of sensitivity targeted. Last but not least, the majority of the low-density infections, being asymptomatic, often remain hidden as people without symptoms do not come under the routine surveillance system, or even if they are targeted for screening in mass surveys, they are often reluctant to give blood without any symptoms.

All these reasons combine to make the asymptomatic infections the huge non-tip part of the iceberg.

The detection of the gametocyte, i.e. the infectious stage detection in the low-density infections, can be even more challenging due to the added challenge of detecting them with even lower density and because of the requirement to see at the transcript level, rather than the DNA level. RNAs, being very fragile, are hard to detect, especially from distant areas.

3. One of the challenges in low-density infections is their potential to contribute to ongoing transmission. How do you assess the role of low-density infections in sustaining malaria transmission within a community?

The role of low-density infections in sustaining malaria transmission within a community can be ideally assessed via mosquito feeding assays where *Anopheles* vector mosquitoes will feed on the *Plasmodium-infected* blood carrying low-density parasites, and the parasite development till the infectious stage to be monitored to determine the infective potential of the low-density infections. However, in many settings, especially in hard-to-reach areas, these kinds of studies are non-feasible because one requires fresh infectious blood for the feeding of the mosquitoes. The alternate, if not the best, strategies in these situations are to assess the presence of gametocytes, i.e. the sexual stages of the parasites responsible for the transmission of the disease by microscopy or more sensitive methods like real-time reverse transcriptase PCR techniques. The studies on the presence of the infectious stages of the parasite in the vectors in low-density infection-dominated areas, and comparison to the high-density areas can also give an indirect assessment of the role of low-density infections in sustaining malaria transmission within a community.

Furthermore, though at the individual level, the low-density infections usually are less transmissible than their high-density counterparts, at the community level, the former can have equal or more impact on the transmission with a higher abundance in population and for remaining untreated to give sufficient time to develop gametocytes. In contrast,

symptomatic high-density infections mostly get detected and treated quickly, sometimes before the mature gametocyte development, especially for *P. falciparum*. Hence, the prevalence of low-density infections in different communities and transmission settings will also determine their role in the transmission.

4. What strategies or interventions do you believe are most promising for targeting low-density malaria infections as part of broader malaria control and elimination efforts?

Targeting low-density is difficult mainly because of the diagnostic challenges of detection, limitation, and refusal for tests and can be overcome by planned, systematic population-wide interventions in selected areas, e.g. mass drug administration (MDA) is one of the promising tools to clear the infectious reservoir harboured by the asymptomatic population. However, not overlook the fact that MDA can have its own challenges and limitations like people having the reluctance to consume the medicine in the absence of symptoms and more challenging for *P. vivax* low-density infections where convincing asymptomatic people to maintain a 14-day radical treatment regime, can be a highly arduous task.

5. From your perspective, what role does MERA-India play in advancing India's goal of malaria elimination, and how crucial is its contribution in this context?

The MERA-India has contributed considerably in bringing the different aspects of malaria research relevant to India’s goal of malaria elimination by 2030 under one umbrella, covering several important topics having implications in the programmatic implementations. It has also played a commendable role in organizing the distinguished lecture series followed by the vibrant interactive discussion, bringing the World leaders in Malaria together with their pioneering research, creating an excellent resource for Malaria researchers and program personnel.

It has also been very instrumental in the capacity building of the researchers by organizing several short training courses and workshops in different areas of Malaria, which will benefit immensely in the long run.

Malaria Through the Lens of Researchers

In the current edition, we are featuring another selected entry from the MERA-India Image Competition 2022, which was submitted by Dr Juhi Mangesh Ruat from the Department of Community Medicine at Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, (DMIMS), Wardha, Maharashtra.

Image title: “Development of cities & manmade malaria: someone’s boon, somebody’s bane?”

A brief description of the image is as follows:
India has committed to eliminate malaria by 2030. Development Projects in cities like Cement road construction have triggered the rural “push” (for earning a livelihood) and “urban pull” (for availing this job opportunity to migrant workers) phenomenon. Resultant poor housing and sanitary conditions promote vector breeding and can result in malaria outbreaks in the short term and endemic malaria with risk of *P. falciparum* resistance strains in the long term to all people staying around the breeding site. The image depicts the Road construction material-making site and the resultant mosquito breeding site (rainwater puddle) created due to the movement of trucks & machines and nearby settlements.

Upcoming Event

Lecture Series on Infectious Diseases 2.0: Lecture 10 by Dr Aneta Afelt

The tenth lecture in the ICMR-NIMR and MERA-India "Lecture Series on Infectious Diseases 2.0," will be delivered by Dr Aneta Afelt from the Interdisciplinary Centre for Mathematical and Computational Modelling, University of Warsaw, Poland. Dr Afelt's work is concentrated in the areas of health geography and environmental science with an emphasis on one health. She also holds a membership in the Polish Academy of Science's COVID-19 ThinkTank. Additionally, Dr Afelt has been an active participant in international projects in the fields of epidemiology and public health, including those of the World Health Organisation (WHO).

More information on the lecture will be made available through the ICMR-NIMR and MERA-India's official website (https://meraindia.org.in/) and social media accounts. Be sure to keep an eye out on these platforms to stay informed about this event. We look forward to your participation in this upcoming session.

To receive regular updates about the events being organized by MERA-India, please subscribe at https://www.meraindia.org.in/event_sub.

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