NEWS & VIEWS

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MERA-INDIA Newsletter
‘News & Views’ May 2021

Ending the neglect to attain the Sustainable Development Goals: A road map for neglected tropical diseases 2021–2030

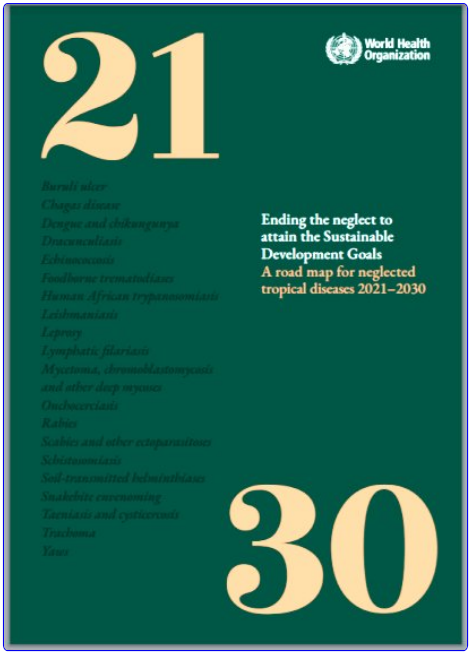


Figure 1: ‘Ending the neglect to attain the Sustainable Development Goals: A road map for neglected tropical diseases 2021–2030’. The recently released document by the WHO describes the necessary measures/approaches to be adopted in the immediate future for the prevention, control, eradication and elimination of 20 neglected tropical diseases including dengue, malaria, chikungunya, filariasis, chagas disease, *etc.*, that otherwise impose a huge socio-economic burden globally, particularly in the tropical and sub-tropical regions of the world. (Click Here).

ICMR-NIMR Activities: International Symposium on Malaria on World Malaria Day 2021 organized by MERA-India

On the occasion of **World Malaria Day *i.e.*, 25th April,** MERA-India organized one day virtual **international symposium on 26th April 2021,** which was attended by around 300 participants. The aim of the meeting was to bring together eminent malaria scientists from around the world on a common platform. The objective of the symposium was to connect bright minds to share and discuss their experiences and knowledge pertaining to various areas of malaria research. The speakers (shown in the panel above) discussed their groundbreaking research in the field of malaria which would be beneficial to the young minds working proactively in the field.

Dr. Amit Prakash Sharma, Director, NIMR, initiated the international malaria symposium by highlighting the research activities of NIMR in the field of malaria. He also discussed some of the critical strategies that need to be adopted to accomplish the goal of malaria elimination in India. He emphasized that although long-lasting insecticidal nets (LLINs) and artemisinin-based combination therapy (ACTs) are effective in the current scenario but we should be prepared for future challenges. He also expressed the importance of strengthening MERA-India and a new program, ICMR Malaria Mission (IMM).

This was followed by talk by **Dr. Bart G J Knols** (SCIE:NCE, Soneva Fushi, Republic of Maldives) who gave insights into how to close the gap between malaria control and malaria elimination. Dr. Knols pointed out the need to strategically apply multiple tools in an integrated fashion, which are adapted to local agro-cultural settings, vectorial systems and transmission dynamics. He added that walking the last mile is definitely hardest and most resource intensive in terms of people and funding sources. The need of the hour is to learn how to eliminate in different settings and we move from community based to strategy based elimination. Elimination also requires efficient larval source management, said Dr Knols.

Professor Utpal Tatu (IISc, Bangalore) talked about malaria parasite's response to oxidative stress. *Plasmodium falciparum* (*Pf*) lacks unfolded protein response (UPR). He explained that endoplasmic reticulum (ER) stress upregulates sexual stage specific genes and how UPR can be related to gametogenesis. Hence, *Pf* responds to ER stress by switching to gametocyte stage. Stress can be induced by nutrient deprivation, antimalarial drugs, cholera toxin, RBC lysates, but what specifically triggers gametogenesis is still an open question to be answered.

This was followed by talk by **Dr. Avadhesh Kumar** (Additional Director, NVBDCP) where he stressed that the major goals are to eliminate malaria completely from India by 2030 and to maintain this malaria free status consistently across the country. There has been shrinkage of malaria endemic areas over the years. Global funding supporting malaria elimination since 2005 has provided huge support to achieve the main goals of elimination. He indicated that malaria cases have declined by 85% and death rates by 83%. But key challenges still remain, for example, how to reduce the remaining 15% malaria cases in the country and it is possible to do it in the coming future.

Next, **Dr. Marta Maia** (KEMRI Wellcome Trust Programme, Kenya) shared the findings of a Cochrane systematic review to evaluate the role of mosquito repellents (topical repellents, insecticide treated clothing or spatial repellants) in malaria prevention. Mosquito repellents can complement interventions like LLINs and insecticide-treated bed nets (ITNs). A meta-analysis of randomized controlled trials (RCTs) and cluster randomized controlled trials (cRCTs) was done, however, the quality of evidence was low across the studies to provide an evidence for efficacy of repellents. She stressed about the importance of conducting well-designed studies and producing high-quality data which can provide concrete evidence in order to enable the policy makers to take well-informed decisions.

Then, **Professor Ashis Das** (BITS Pilani) talked about the application of *in vivo* transcriptomic network analysis to provide clues to identify new drug targets against malaria parasites. He said that the role of proteins encoded by 50-60% of genes in *P. falciparum* and *P. vivax* are still not known. He showed studies from his group where *P. falciparum and P. vivax* samples from patients were used for transcriptome analysis using microarray. The transcriptomic data was further used to develop gene co-expression networks and disease specific modules, to identify the differentially regulated genes in different severe malaria conditions. Thus, using *in vivo* transcriptomic network analysis, the key conserved hypothetical proteins which are unique to the parasite and have no similarity to the human proteins can be identified, and these candidate proteins can be further targeted for different applications, for example to develop diagnostics or as drug targets.

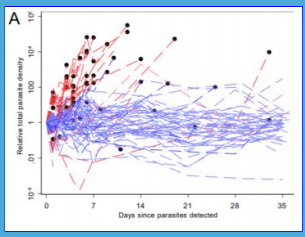
This was followed by a lecture by **Professor Sanjeev Krishna** (St. George's, University of London) who touched on the existence of malaria during current COVID-19 crisis. He indicated that advance planning and preparations of rapid distribution of ITNs, mass drug administration, stockpiling of Personal Protective Equipment (PPE) kits, diagnostics, sustained funding and integrated care pathways are must. He pointed out that certain alleles in ACE2 receptor can provide protection against malaria. G6PD (glucose-6-phosphate dehydrogenase) levels can enhance inflammatory responses in COVID19, but can provide protection against malaria as well.

Final talk was delivered by **Professor Richard Maude** (MORU, Thailand) who talked about mapping the anti-malarial resistance in Asia, with a focus on artemisinin resistance. He showed the data on the evolution and spread of the *P. falciparum* Kelch 13 (K13) mutations. Between 2002-2018, a steady increase in the number of geographical locations, and the proportion of infected people with validated artemisinin-resistance markers have been observed. However, he emphasized the need for a robust and frequent resistance surveillance to map the evolution and outspread of the resistance.

The symposium was concluded by a panel discussion which was moderated by **Dr. Manju Rahi** (ICMR Headquarters). The panel members discussed the current scientific and political problems and how they can be addressed to finally achieve malaria elimination in India by 2030. For example, continuous R & D strategies to achieve the elimination, strong public health schemes running in parallel with basic research themes, and making treatment and diagnostic strategies accessible at village level. Furthermore, importance of routine surveillances including insecticide resistance and entomological surveillances in larger geographical areas of India were also discussed.

Finally, **Dr Sachin Sharma** (Coordinator, MERA-India) concluded the meeting by extending thanks to all the distinguished speakers, participants and MERA-India team members. He mentioned that MERA-India is committed to organize more informative sessions and scientific meetings in future.

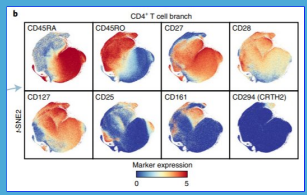
Scientific contributions by dedicated Scientists/Researchers in the field of Malaria Research



Higher gametocyte production and mosquito infectivity in chronic compared to incident *Plasmodium falciparum* infections

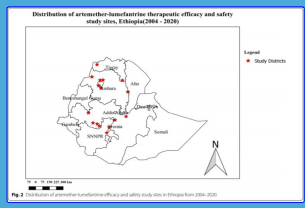
The infectivity and kinetics of *P. falciparum* gametocytes may vary between chronic and incident infections. In a recently published article Barry *et al.*, 2021, the parasite kinetics and infectivity to mosquitoes has been assessed among children (aged 5-10 years) with (a) incident infections following parasite clearance (n=48) and (b) chronic asymptomatic infections (n=60). Furthermore, the authors also reported that only 35% of those in the incident population contained gametocytes before being symptomatic and undergoing treatment, while all those with chronic infection have them or produced them during follow-up. In chronic diseases, antibody responses are higher and PMR (Parasite multiplication rate) is lower. In addition, reduced gametocyte infectivity to mosquitoes evokes symptoms and sexual stage immune responses. Most incident infections need to be effectively treated until the number of mature gametocytes is adequate to infect mosquitos. Chronic, asymptomatic diseases, on the other hand, are a major cause of mosquito infections.

Systems analysis and controlled malaria infection in Europeans and Africans elucidate naturally acquired immunity



In this particular study by Jong *et al.*, 2021, the authors showed that regulated human diseases enable researchers to investigate the immune system's association with malaria parasites, which is crucial for vaccine production. The authors have employed techniques such as mass cytometry, RNA sequencing, and data integration to compare immune markers of malaria-naïve Europeans and Africans with lifelong malaria infection such as variations in immune cell populations, antigen-specific responses and gene expression profiles before and 5 and 11 days after infection with *P. falciparum* sporozoites. The

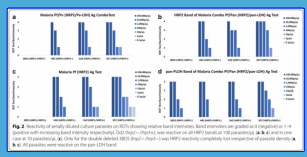
results of the study showed an activated/differentiated state of both innate and adaptive cells, including elevated $CD161^{+}CD4^{+}$ T cells and interferon-γ production, predicted Africans capable of regulating parasitemia prior to inoculation. Post inoculation, Africans capable of regulating parasitemia were distinguished from vulnerable population by the promptness of the transcriptional response and clusters of CD4+ T cells, plasmacytoid dendritic cells, and innate T cells. According to the authors, these results will help in the production of a malaria vaccine that might be successful in malaria-endemic areas, thereby lowering the incidences in such regions.



Efficacy and safety of artemether–lumefantrine for treatment of uncomplicated *Plasmodium falciparum* malaria in Ethiopia: a systematic review and meta-analysis

Anti-malarial drug efficacy must be monitored on a regular basis in order to develop rational malaria care recommendations to ensure satisfactory treatment results. Abamecha *et al.*, 2021, described the compilation all of the data obtained from meta-analysis on the effectiveness of artemether–lumefantrine for the treatment of uncomplicated *P. falciparum* malaria in Ethiopia from 2004 to 2020. Powerful conclusions cannot be drawn, however, due to the high probability of bias in the included studies.

HRP2 and HRP3 cross-reactivity and implications for HRP2-based RDT use in regions with *Plasmodium falciparum* hrp2 gene deletions



Because of abundance of *Plasmodium* species and their thermal stability, the *P. falciparum* antigen histidine rich protein 2 (HRP2) is considered as a popular candidate for global malaria rapid diagnostic tests (RDTs). Some species of *Pf* have reported deletions in *hrp2* and *hrp3* genes; also, antibodies against HRP2 antigen can cross-react with HRP3. Kong *et al*, 2021, described that multiple deletions and cross reactivity can affect clinical sensitivity of HRP2-based RDTs. It was found that parasites (1000/μL) with deletions in both *hrp2* and *hrp3* genes can be detected by all three test RDTs.

Malaria Scientists to watch

1. An interview with Dr. Sanjib Mohanty

Dr. Sanjib Mohanty, **Ex-director, Ispat General Hospital**, Present address- **Senior Consultant medicine**, CWS Hospital, Rourkela - 769 042, Odisha, India

1. How did your research career start, what has been the biggest motivation in life to become an efficient malaria scientist?

I started my career as a young physician during early 1980's at the Ispat general hospital, Rourkela in western part of Odisha. Apart from many other diseases I encountered a lot of mild to severe malaria patients. It was indeed surprising to see many young adults with severe and complicated malaria and a high mortality. Our text books had taught that it is a severe disease of children leading to death in large parts of Africa, but after talking to our paediatrician colleagues we found out that children do suffer from severe malaria like cerebral manifestations and severe anaemia but the mortality was quite low. The patient load was much greater in adults particularly young adults between 15 to 45 years and deaths occurred in approximately 30 to 40% of them. These young patients had commonly multi-organ involvement in contrast to children. The quest for such discrepancies between the classical teaching and my own observation made me pursue my research in the field of malaria. The biggest motivation was observing differences between what had been described in literature and our findings which conflicted with the already established ones. Our findings were further substantiated after conducting autopsies in our cerebral malaria patients wherein not only we found brain capillaries packed with parasitized RBC but also inflammation and brain edema. Until then all the published papers mentioned the pathogenesis of CM was only due to aggregation of parasitized RBC to the capillaries of cerebral vessels and the edema of brain was an agonal event. More recently researchers have come to agree that parasitized RBC adhesion and inflammation leading to release of inflammatory mediators are responsible for cerebral malaria.

2. What has been the most crucial impact of your clinical and scientific research so far that is inspiring for young researcher?

The pathogenesis of severe malaria, particularly cerebral malaria is not well understood yet. There are many missing pieces in the puzzle. To unravel these phenomena, we have undertaken the help of imaging from CT scans to MRI. These advanced imaging techniques have thrown several new findings which have been published. The numbers of patients in these studies are quite large and well characterized as well. Recently published MRI features of brain in both adults and children have shown two distinct pathologies of adults and children. Whereas adults have features of cytotoxic edema mostly around basal ganglia, children have features of vasogenic edema in cortical and sub-cortical white matter. Some of the adjuvant agents like Manitol commonly used for brain edema was found to be deleterious in the largest series of adult cerebral malaria. Continuing with our imaging studies there is also a quest for effective therapy in malaria apart from the known anti-malarial drugs.

I would like to mention here that judicious fluid therapy in severe malaria is another clinically relevant finding where we have shown unlike in cases of sepsis fluid should be carefully administered in malaria patients even in malarial shock. Dehydrated patients have leaky lungs, so large volume fluids will lead to pulmonary edema. There are many unknown areas particularly in the mechanism of severe malaria that need to be explored both from clinical and basic science point of view. Younger generations of scientists have large unexplored areas to embark their journey upon and at the end of the day we need safe and effective agents to save lives.

Parasite developing resistance to current anti-malarial drugs is a huge challenge and big obstacle in malaria elimination. Triple drug combinations are being tried only to buy time before there is a new, safe and effective drug. There are not many in the pipe line, so development of a new drug targeting a different area of the parasite is one more area where lot of work needs to be done and fresh ideas and approach will be of relevance.

3. What are the research gaps you think require urgent attention in eliminating malaria from India?

The effort undertaken by institutions in India to eliminate malaria has been resounding success till date. There is always scope for improvement and course correction in all such programs. To me reliable data from each state and region is a very important element. I do not doubt the data that is put up by the government but in a huge and diverse population like in India, accurate and foolproof figures are the key to success. The present diagnosis is heavily dependent on RDTs which has its own drawbacks. It does not pick-up very low parasitemia and more so in asymptomatic malaria. So use of highly sensitive molecular tools like PCR will pick up this reservoir and help elimination. The other one is PfHRP2 gene deletion reported recently form Odisha, Madhya Pradesh and other parts of the world will render RDTs for *P. falciparum* malaria inaccurate. The last mile to elimination will certainly be difficult. SARS COVID 19 has given an opportunity and molecular diagnostic labs have come up in almost every district of India. This capacity can be well utilized in the post COVID times.

4. What other areas of research are you involved in?

Apart from research in malaria I was also an intensive care physician. In a collaborative work along with the physicians of resource limited settings, protocols were developed for sepsis and septic shock management. Guidelines were also developed for ventilator support and fluid management without state-of-the-art facilities. The organization and personnel were devised according to the availability of resources in the particular areas. All this work has been published at various time points in journals related to critical care.

Recently we have been coming across Scrub Typhus patients in our area and we are documenting their clinical profile. Though it is an old disease in Asia, in India it is a re-emerging disease. In this part of Odisha, this is a novel disease and I along with my team am still learning about its various manifestations. We intend to document and publish about Scrub Typhus in the near future. To conclude, my journey as a clinician and clinical researcher particularly in malaria has been satisfying and quite fulfilling.

2. An interview with Dr. I. P. Sunish

Dr. I. P. Sunish, **Scientist-E, ICMR-Regional Medical Research Centre (RMRC)**, Dollygunj, Port Blair - 744 103, Andaman & Nicobar Islands, India

1. Please describe your scientific background and journey that contributed to you becoming a skilled malaria scientist?

Subsequent to my post graduate course in Medical Entomology from ICMR-VCRC, Puducherry, I was able to join the same line of research in ICMR-VCRC field unit (then it was Centre for Research in Medical Entomology) at Madurai, under the leadership of renowned mosquito taxonomist, Dr. (late) Rachel Reuben. I was fortunate to pursue my doctoral programme under her guidance, on the vectors of Japanese encephalitis virus, which was the stepping stone into field related works on vector borne diseases. My studies on malaria vectors began at ICMR-RMRC, Port Blair. In Andaman & Nicobar Islands, various aspects on the bionomics of *Anopheline* mosquitoes were investigated. The valuable support from the local staff of malaria department (in Tamil Nadu as well as A&N Islands), was a boost to carry out various field studies.

2. Significance of your most valuable research that can be inspiring to young researchers working in the field of public health research?

My maximum tenure at ICMR during the past 30 years was field based research in field units at various remote/ rural areas. Working in the field/ villages was inspiring and made me learn new aspects, even though there were many instances where it was not possible to approach the villages for field work. Contacting the villagers regularly created a valuable relationship with them, making the field works more effective. During the studies on the vectors of JE virus in rice field ecosystem, an observation which could have missed in normal circumstances helped me to gain better understanding on the role of fertilizer in the breeding of these vectors. The adjunct role of vector control in LF elimination programme was demonstrated in the villages of Tamil Nadu. Similarly, the additional advantage of albendazole (when combined with DEC) for LF elimination was observed in a large scale study, which paved the way for making DEC with ALB combination as an MDA strategy.

3. Additional scientific interests other than malaria research?

Other than malaria, I had worked on various other vector borne diseases, especially on mosquito vectors, *viz*., Japanese encephalitis, Lymphatic Filariasis, Dengue and Chikungunya.

4. Finally, on a lighter note, do you have hobbies other than science that have always kept you motivated during your research career, especially during tough times?

I enjoy reading books, mainly fiction, watch movies and travel, to obtain new experiences from new places, having travelled to numerous places in lieu of my official work. Moreover, philosophy is another great aspect of interest to me.

Recent publications

The Indian burden of malaria in pregnancy needs assessment. 2021, Med 2, 456-504.

MiP remains unexplored in the country which in turn poses threat to the overall national public health by adversely affecting mother and their new born. Therefore, urgent improvements in the areas of stringent surveillance and health management are required to address this problem and reduce its occurrence from the country, thereby, significantly contributing to mission of malaria elimination from India in the near future.

Relapses of *Plasmodium vivax* malaria threaten disease elimination: time to deploy tafenoquine in India? 2021, BMJ Global Health, 6:e004558.

Plasmodium vivax infections accounted for ~53% of total malaria cases in India in the year 2019. After infection by mosquito, some *P. vivax* sporozoites can form hypnozoites which can remain in the liver in a dormant state, and can reactivate at a later stage to cause bloodstream infections resulting in relapse. Primaquine (PQ) is the only drug against hypnozoites, and the current treatment protocol in India is chloroquine for 3 days and PQ for 14 days. However, there are several hindrances in the successful implementation of this treatment regimen, one of which is the poor compliance of the recommended course of PQ by the patients. Tafenoquine (TQ) is a synthetic analogue of PQ and has a longer half-life than PQ, and can thus be used as a single-dose drug. TQ is currently approved for use in different countries and several clinical trials have shown the efficacy of TQ against *P. vivax* hypnozoites. Thus, the adoption of TQ in the treatment guidelines for *P. vivax* infections in India can reduce the infection burden as well as overcome the challenge of infection relapses.

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