International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Prevent the Spread of Malarial Disease for Sustainable Development

Abubakar Iliya

Department of Biotechnology, Molecular Biology and Genetic Engineering, School of Biosciences, Lovely Professional University, Pagwara, Punjab. India

Abstract

This article explores the intricacies of malaria, concentrating on the parasite *Plasmodium falciparum's* most harmful form. Malaria still poses a serious threat to world health, killing over 400,000 people each year and impacting mostly young children in Sub-Saharan Africa, despite decades of control attempts.

RTS, S, the first licensed malaria vaccine, is currently being tested in various African countries despite its low efficacy. There has been an overall fall in malaria infections, albeit the reduction varies geographically. Traditional control measures like bed nets and insecticides, combined with medical treatment, have helped.

It is essential to comprehend the biology of malaria transmission since asymptomatic cases help spread the disease and not all infections have severe symptoms. The complex mechanics of the parasite's life cycle are examined in detail in this article, with a focus on the function of PfEMP1 proteins in immune evasion. The wide variability of PfEMP1 complicates the creation of vaccines.

Hopes for a potential disease vaccine are increased by the attention paid to EPCR-binding phenotypes about cerebral malaria, although causal links still require explanation. The study emphasizes the need for cutting-edge methods, such as systems biology and machine learning, to decipher the intricate immunological and parasitological processes, and asks for a deeper comprehension of parasite-host interactions.

The paper also highlighted difficulties in accurately estimating disease frequency, particularly in low-transmission environments with common submicroscopic illnesses. For efficient surveillance and management, the significance of researching gametocyte dynamics, transmission volume, and parasite genetic diversity is emphasized.

The article's conclusion emphasizes the need for a holistic strategy, which includes a deeper comprehension of local vector ecologies, to fully address the problems caused by malaria and pave the way for more efficient control strategies.

Keyword: Malaria, Plasmodium, Transfection, And Vaccine

Introduction

The protozoan parasite *Plasmodium spp*. that is spread by mosquitoes is what causes malaria. Five species of malaria can infect people*: P. falciparum, P. vivax, P. malariae, P. ovale, and P. knowlesi. P. falciparum* malaria is the most virulent form of the disease and is responsible for the majority of human morbidity and mortality; as a result, it will be the focus of this article. Recent estimates place the annual malaria cases in the region at an estimated 247 million, and 619,000 deaths, primarily in young children living in

sub-Saharan Africa (Aheto, 2022). This is despite ongoing control efforts over the past 60 years or more. As a result of its insufficient efficacy (Power et al., 2014), the first licensed malaria vaccine (RTS, S) is only being used as a trial program in a few sub-Saharan Africa. Insecticide-treated bed nets, insecticide-sprayed homes, and other general mosquito control methods continue to be the mainstays of disease management in addition to the pharmacological therapy of patients. Over the past ten years, there has been a general decline in malaria infections due to a large-scale vector control program combined with artemisinin combination therapy (Bhatt et al., 2015). However, this reduction exhibits large spatial differences and does not always match up well with established control measures. For instance, significant reductions have been seen in Southeast Asia and the Western Pacific (Power et al., 2014). In contrast, recent years have seen little to no change or even a surge in cases in several parts of the Americas and Africa (Recker et al., 2018). The difficulties in controlling malaria are numerous, and even in areas where a significant decline in the disease has been attained and where local eradication is theoretically feasible, maintaining a state of disease-freeness without attaining a comparable decline in neighboring areas would be challenging. A lack of knowledge of the fundamental biology of malaria transmission and its connection to the epidemiological patterns of infection and illness in various transmission environments is at the root of these difficulties. Particularly, not all infections result in severe clinical symptoms, and the majority of infections causing transmission in a certain area are asymptomatic or just mildly unwell (Meibalan & Marti, 2017). Therefore, intervention-induced changes in parasite transmission will result in complicated alterations in the age distributions of certain age- and exposure-dependent disease symptoms (McCann et al., 2020). Therefore, it is necessary to have a deeper understanding of the causes of severe malaria as well as a better comprehension of who is currently infected and who contributes to transmission to predict the epidemiological outcome of control measures.

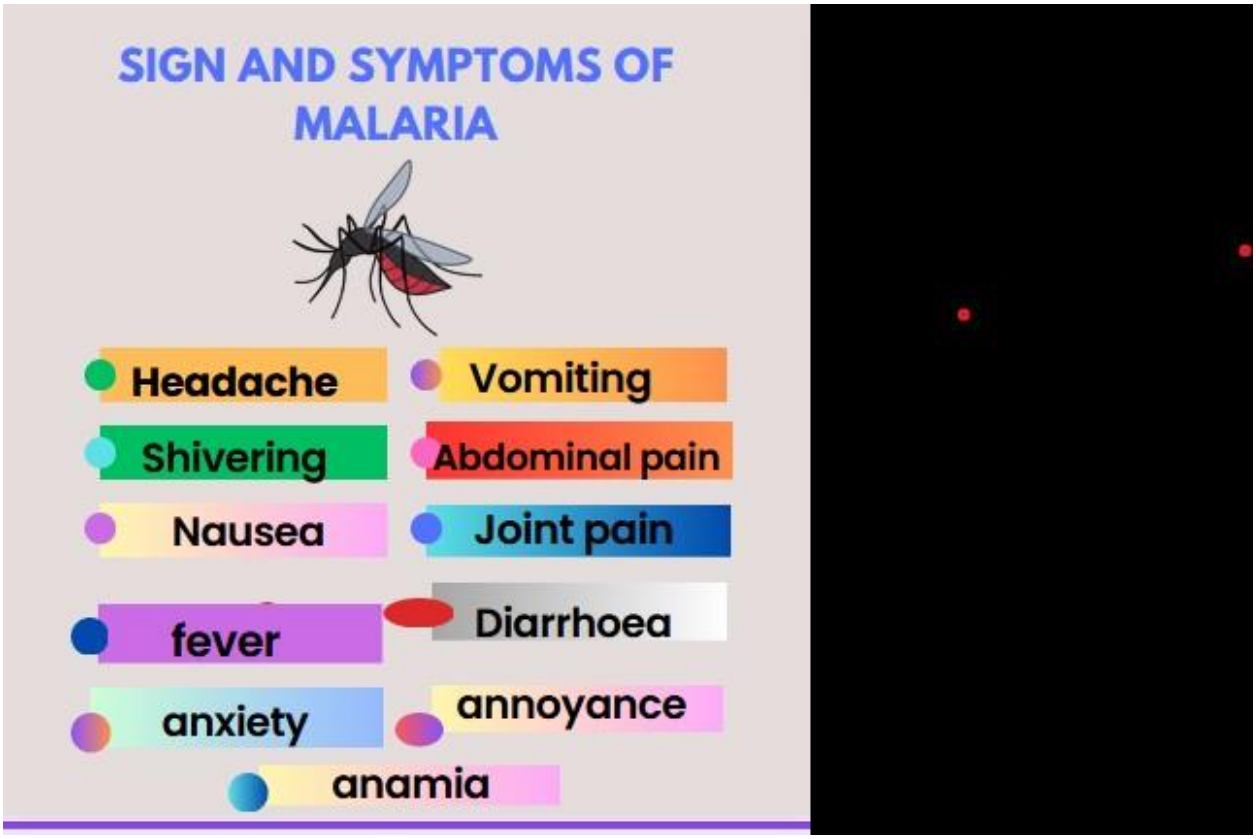

Figure:1 Common signs and symptoms of malaria

What are the leading factors to dangerous malaria?

An infectious mosquito bite causes *sporozoites* to be released into the bloodstream, where they go to the liver and differentiate into *merozoites*, which is how malaria infections begin. *Merozoites* are discharged into the circulation following several rounds of multiplication within infected liver cells, beginning a cycle of repeated invasion and multiplication among red blood cells (RBCs) that results in significant cell death both directly and indirectly (Molina-Franky et al., 2022). Malaria pathology is frequently brought on by parasites ensconced in the deep vasculature, which results in local inflammation, hemorrhages, tissue destruction, and obstruction of blood flow in addition to anemia as a direct result of RBC loss, splenic clearance of uninfected RBCs, and decreased RBC synthesis (Autino et al., 2012).

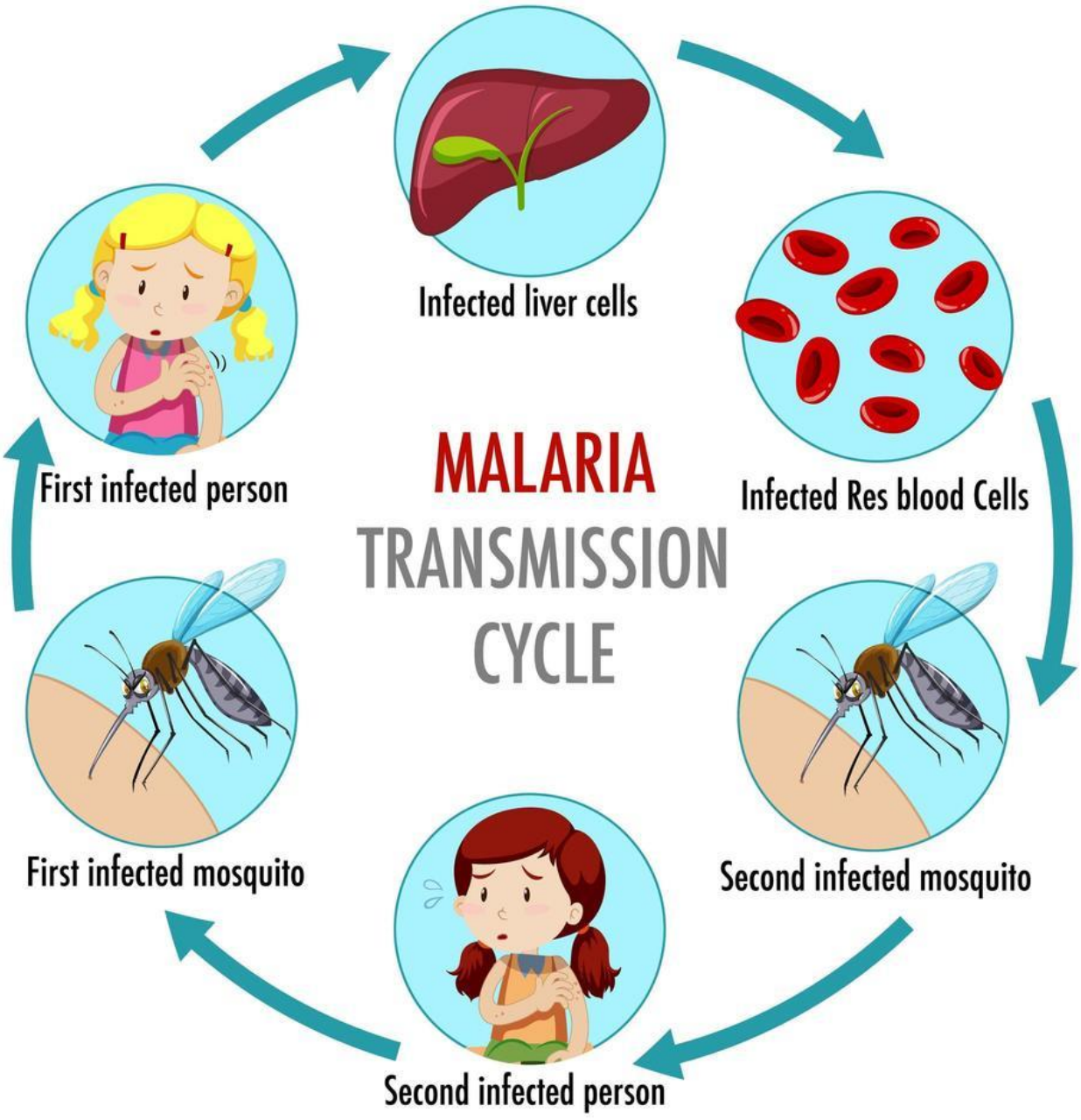

Figure:2 life cycle of malaria

Infected RBCs (iRBCs), which are highly polymorphic parasite proteins termed PfEMP113 that are expressed by the var multigene family and inserted onto the surface of iRBCs, adhere to a variety of host endothelium cell receptors as a result of sequestration (Melcher et al., 2010). The fact that these proteins are highly expressed on the surface of iRBCs makes them prime targets for adaptive immune responses, which the parasite evades by taking advantage of the enormous sequence variation of var genes between repertoires of var genes within parasite populations as well as between multiple variant var gene copies within individual parasites. Through a mechanism known as clonal antigenic variation, the parasite can switch between many PfEMP1 variants throughout infection, making it one of the most complex immune-evasion tactics yet studied. And below is host endothelium (Kirkland et al., 2022)

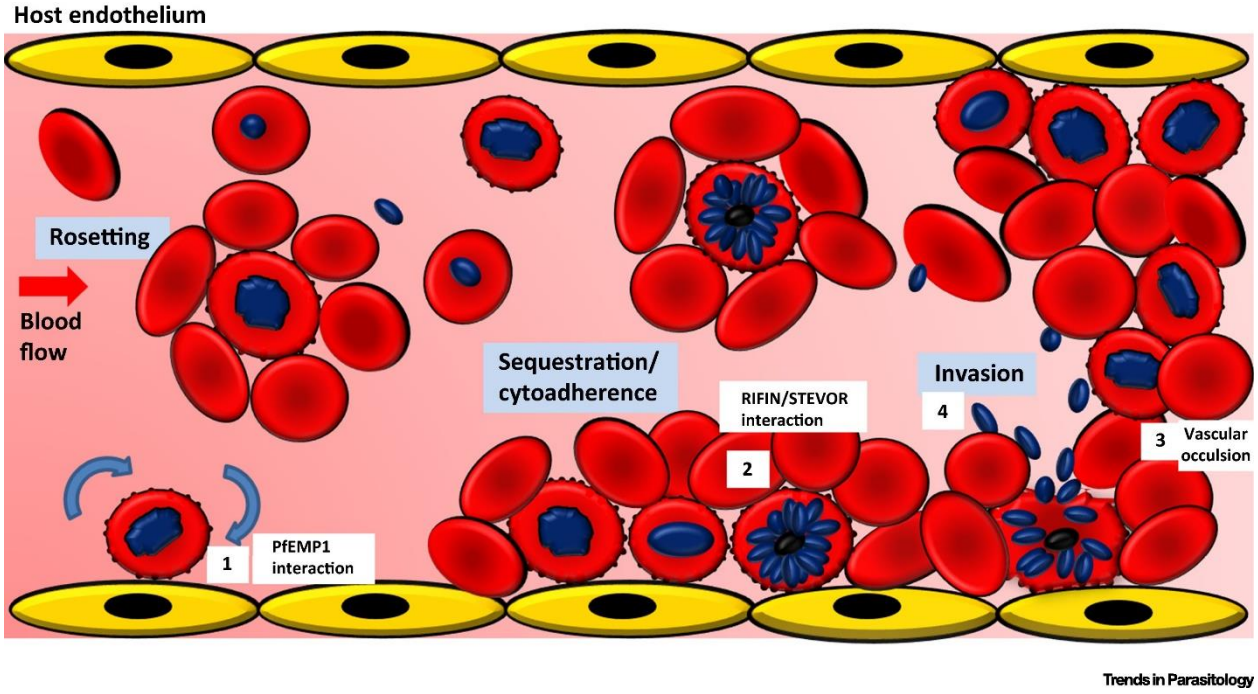

Figure:3

PfEMP1 is a key target of naturally acquired immunity (NAI), notwithstanding its variety. People who live in malaria-endemic regions build up a repertoire of PfEMP1 variant-specific immune responses during years of repeated infections, which are thought to offer protection from life-threatening illness (Bull & Abdi, 2016). Women in their first pregnancy who have grown up in malaria-endemic areas and have developed immunity to severe malaria momentarily lose this immunity because their placentas open up a unique niche for parasite sequestration, providing a stark illustration of the significance of PfEMP1 as immunological targets. Every parasite genome contains a unique, functionally, and immunologically distinct PfEMP1 type, VAR2CSA (see below and the above Figure3), to which immunity is quickly attained (Molina-Franky et al., 2022).

The enormous variability of PfEMP1 has so far prevented this family of molecules from being taken seriously as a target for a vaccine. The question of whether a viable anti-disease or anti-virulence vaccination exists has been raised by the finding that specific illness symptoms are linked to the expression of specific subsets of PfEMP1 variations. The involvement of a specific PfEMP1 variation in pregnancy-associated malaria, which is caused by the binding of VAR2CSA-expressing iRBCs to placental chondroitin sulfate A (CSA), is one of the first and, so far, most convincing cases. The first placental

malaria vaccines, which are now undergoing clinical studies, are being developed by taking advantage of the protein's remarkably conservation (Dominique et al., 2019).

Figure: 4 Malaria vaccine

It is possible to include the genes that contribute to pediatric malaria in this functional segmentation of var genes. Var genes, for instance, can be divided into UpsA, UpsB, and UpsC groups according to the upstream promoter sequence (Ups). When there is a serious infection, UpsA genes are usually increased, especially in young children (Buckee & Recker, 2012). The UpA group's sequence diversification appears to be more restricted than that of other groups, despite their general richness. When endothelial protein C receptor (EPCR) appeared to be associated with cerebral malaria, there was initially a great deal of excitement. Because of its apparent importance in the outcomes of severe infections, this interaction is currently being pushed as a possible target for disease vaccines (Molina-Franky et al., 2022)

The main issue is that, rather than depending only on parasites enclosed in tissues, results are frequently dependent on correlations that have been seen between clinical consequences and the relative expression of gene variants in the population of infecting parasites that were obtained from peripheral blood (Lee et al., 2019). These investigations are made more difficult by the significant technological hurdle of accurately accounting for people's exposure histories and, by extension, their immune condition at the time of infection. Caution must be used when inferring causality, as recently highlighted by Azasi et al. (27), who found that in vitro iRBC attachment to endothelial cells is frequently independent of EPCR and can be quickly terminated under flow circumstances (Vandenbroucke et al., 2016).

Several strategies are proposed to overcome these issues: (1) Investigate associations between peripheral parasite gene expression levels and direct measures of sequestration through malarial retinopathy; (2) Improve understanding of the role of NAI in influencing the infecting parasite population; (3) Examine associations between peripheral parasite gene expression levels and direct measures of sequestration through mucosal surfaces; and (4) Enhance the assessment of parasite sequestration in tissues by directly observing parasites within capillaries through mucosal surfaces to correlate capillary congestion with disease consequence.

Who is sick, and who aids in the spread of the disease?

We must take into account variables such as an individual's past exposure to the parasite to comprehend and manage malaria. It is important to know who is affected right now, who spreads the sickness, and how much. However, determining the prevalence of an illness is difficult. Approximately half of all malaria infections are missed by the widely used technique of microscopy, particularly those with fewer than 100 parasites per microliter. Surprisingly, low-transmission zones have higher rates of low-density illnesses. Microscopy misses about 88% of infections in areas where the prevalence is less than 10%. A considerable reservoir of low-density infections is revealed by new, ultrasensitive PCR techniques, with a detection limit as low as 22 parasites per milliliter.

It's difficult to understand transmission. Numerous parasite clones are involved in many illnesses, and new infections frequently appear alongside asymptomatic parasitemia, leading to new outbreaks. The genetic variation of the parasite makes it difficult to define the incidence or force of infection, which is related to new infections throughout time, even when the percentage of infected persons is known. Tracking transmission chains is challenging due to a lack of trustworthy markers. The complexity of the infection is shown by advanced sequencing techniques, particularly in high-transmission areas where people may have up to 20 clones. By counting new genotypes acquired throughout time, the molecular force of infection (molFOI) assists in determining transmission networks and focal areas.

The focus of surveillance is on asexual parasites that produce symptoms. A very small proportion develop into gametocytes, which mosquitoes disperse, during the sexual stages. Uncertainties surround gametocyte dynamics, their relationship to transmission, and the transition to sexual development. Recent research casts doubt on the notion that infectivity and asexual parasitemia are directly related. Asymptomatic infections cast doubt on early beliefs by contributing more to transmission than previously thought. For example, research conducted in Ethiopia revealed that just 15% of the population gives blood. A gametocyte might collect beneath the skin and affect transmission. Although there is a connection between the prevalence and the intensity of transmission of gametocytes to infectious *sporozoites*, there are still issues because mosquito behavior during sexual change is unknown.

Development of transfection technologies for Plasmodium parasites

- **1993**
  - Temporary transfection(Fus-Kujawa et al., 2021)
- **1995**
  - Stable transfection (DHFR selectable marker for P. berghei)
  - Temporary transfection using CAT reporter (Carvalho & Ménard, 2005)
- **1996**
  - Toxoplasma gondii DHFR selectable marker stable transfection, and DHFR selectable marker for T. gondii with stable episomal transfection (Robert G et al., 1993)
- **1997**
  - Human DHFR is a novel selectable marker, and GFP reporter (Böhme et al., 2018)
  - Knockout genes
- **1998**
  - GFP reporter (Soboleski et al., 2005)
- **1999**
  - 151 New selectable markers (BSD, Neo)
  - Luciferase reporter
- **2000**
  - Human DHFR sequence modification via sequencing (Liu et al., 2013)
- **2001**
  - Enhancement of gene knockout
  - New PAC (selectable marker) (Xu29427645, et al, 2011)
- **2002**
  - Selection in opposition (TK and CD, 2011)
- **2004**
  - Conditional gene deletion system 155 FLP–frt (Maltzman & Turka, 2007)
- **2005**
  - Amaxa high-translucency transformation and Selection vs (yFCU)
  - Bxb1 integrase system (Knuepfer et al., 2017)
- **2007**
  - DD post-translational suppression mechanism (Gough & Sadanandom, 2021)
- **2008**
  - CAD post-translational shutdown mechanism (Zhong et al., 2023)
- **2011**
  - Recombineering, GIMO61,111,11, piggyBac transposon mutagenesis
  - New selectable marker (DHODH), Cre-loxP and FLP-frt conditional gene-deletion systems, and DDD post-translational knockdown system (Habibi et al., 2022)
- **2012**
  - System 105: Zinc-finger nuclease genome editing and ATc conditional knockdown mechanism of transcription (caroll, 2011)
- **2013**
  - DiCre conditional gene deletion system and the riboswitch post-transcriptional knockdown system (kudyba et al., 2021)
- **2014**
  - Recombineering PlasmoGEM112, 103,109 CRISPR-Cas9 genome editing system and Systems TetR-aptamer 10 (Tahir et al., 2022)

Moving forward

The discovery of EPCR-binding phenotypes and their conceivable participation in cerebral malaria have sparked interest and inspired some hope for the creation of a disease vaccine. However, one still needs to clearly show the causal relationship between host receptor binding and certain illness presentations to make a compelling case (Maltzman & Turka, 2007).

It's important to noter that every parasite has at least some of these "disease-causing" or rather "disease-associated" variations in its repertoire. That is, if the parasite is allowed to express the whole range of PfEMP1 antigens during infection, what happens? PfEMP1 expression has been demonstrated to be hierarchical and host immune responses can affect which variations are produced throughout an infection (Health, 2012). This, however, does not account for why an infection causes severe malarial anemia in one child but cerebral malaria in another. Additionally, the observed hierarchical expression of the var genes may simply be the result of the parasites using different molecular tactics to circumvent immune responses in people with varying levels of immunity. Group A-like var genes that were previously linked to severe malaria have been shown to express highly in asymptomatic infections, which suggests that the PfEMP1 antigens they encode may be involved in the upkeep of chronic infections. Currently, more comprehensive (i.e., systems and -omics) approaches should be able to provide more information about the precise immunological and parasitological processes involved in the development of disease, particularly when taking into account the makeup of the infecting parasite population about the host's immune history.(Natama et al., 2021).

We also need to use more sophisticated methods to enhance our comprehension of NAI to malaria. Importantly, this calls for

- ✓ a precise description of what protection entails and
- ✓ strong and quantifiable correlates of protection, neither of which are simple.

As was previously said, NAI must be viewed as a multi-stage process, if not a continuum, in which the severity of the infection typically lessens with repeated contact with the infection. countless studies have used prospective cohort studies to uncover correlates of protection by correlating the occurrence of clinical episodes with people's immune responses to predetermined panels of antigens. These studies frequently have modest effect sizes, which results in inconsistent findings and poor reproducibility. This is made even more difficult by the absence of accurate indicators of how frequently an individual has been tested in the past, which is crucial to take into account given that cumulative exposure to infection increases both the needle of protective responses and the haystack of non-protective responses, as well as NAI itself. Furthermore, reducing this complicated process to a binary phenotype (protected or not) skips over some of the complexity that underlies NAI and malaria pathophysiology, making it unlikely to give a complete view of the multiple processes at play. In that regard, it is also crucial to use more advanced techniques to analyze ever-more complicated datasets. In their capacity to extract non-linear correlations and interactions from high-dimensional data in a hypothesis-free way, machine learning systems provide a variety of advantages over more conventional, univariate analyses. For instance, in a recent study, were applied machine learning to protein microarray data including thousands of observed immunological markers to uncover predicted signals of clinical protection. In another study, Helb et al. estimated recent exposure to the malaria parasite using a predictive approach based on machine learning. These effective methodologies do, however, heavily rely on comprehensive and reliable datasets that allow for the proper cross-validation and verification of study findings. The use of ensemble datasets across numerous

investigations, which has lately been encouraged to more precisely characterize the infectious reservoir and evaluate transmission, is a significant step in that direction.

Last but not least, a deeper comprehension of the biology of mosquito-human and human-mosquito transmission requires a greater understanding of regional vector ecologies. Surprisingly, we still know relatively little about how shifts in mosquito species distribution and abundance over the past few years and decades—some of the most crucial factors influencing malaria epidemiology—might have not only influenced but actively shaped some of the observed shifts in malaria incidence. Unfortunately, there are only a few vector species for which comprehensive and long-term surveillance data on vector dispersal are available likewise epidemiological conditions. Therefore, to develop a fine-grained and holistic understanding of malaria epidemiology that takes into account the Plasmodium parasite, the human host, and the mosquito vector, large-scale vector sequencing initiatives, like the malariaGEN 1000 genomes project, as well as more in-depth investigations into the behavioral and ecological factors underlying this part of the transmission cycle, will have a crucial role to play.

REFERENCES

1. WHO Malaria Report: World Malaria Report 2022
2. F1000Research 2018, 7(F1000 Faculty Rev):1159 Last updated: 01 AUG 2018
3. Aheto, J. M. K. (2022). Mapping under-five child malaria risk that accounts for environmental and climatic factors to aid malaria preventive and control efforts in Ghana: Bayesian geospatial and interactive web-based mapping methods. *Malaria Journal*, *21*(1), 1–15. https://doi.org/10.1186/S12936-022-04409-X/FIGURES/8
4. Autino, B., Corbett, Y., Castelli, F., & Taramelli, D. (2012). Pathogenesis of malaria in tissues and blood. *Mediterranean Journal of Hematology and Infectious Diseases*, *4*(1). https://doi.org/10.4084/MJHID.2012.061
5. Bhatt, S., Weiss, D. J., Cameron, E., Bisanzio, D., Mappin, B., Dalrymple, U., Battle, K. E., Moyes, C. L., Henry, A., Eckhoff, P. A., Wenger, E. A., Briët, O., Penny, M. A., Smith, T. A., Bennett, A., Yukich, J., Eisele, T. P., Griffin, J. T., Fergus, C. A., … Gething, P. W. (2015). The effect of malaria control on Plasmodium falciparum in Africa between 2000 and 2015. In *Nature* (Vol. 526, Issue 7572, pp. 207–211). https://doi.org/10.1038/nature15535
6. Buckee, C. O., & Recker, M. (2012). *Evolution of the Multi-Domain Structures of Virulence Genes in the Human Malaria Parasite , Plasmodium falciparum*. *8*(4). https://doi.org/10.1371/journal.pcbi.1002451
7. Bull, P. C., & Abdi, A. I. (2016). *The role of PfEMP1 as targets of naturally acquired immunity to childhood malaria : prospects for a vaccine*. 171–186. https://doi.org/10.1017/S0031182015001274
8. Fus-Kujawa, A., Prus, P., Bajdak-Rusinek, K., Teper, P., Gawron, K., Kowalczuk, A., & Sieron, A. L. (2021). An Overview of Methods and Tools for Transfection of Eukaryotic Cells in vitro. *Frontiers in Bioengineering and Biotechnology*, *9*(July), 1–15. https://doi.org/10.3389/fbioe.2021.701031
9. Health, G. (2012). *THE AMERICAN JOURNAL OF Annual Meeting Public-Private Partnerships Innovation*. *87*(November).
10. Kirkland, T. N., Stevens, D. A., Hung, C. Y., Beyhan, S., Taylor, J. W., Shubitz, L. F., Duttke, S. H., Heidari, A., Johnson, R. H., Deresinski, S. C., Lauer, A., & Fierer, J. (2022). Coccidioides Species: A Review of Basic Research: 2022. In *Journal of Fungi* (Vol. 8, Issue 8). https://doi.org/10.3390/jof8080859

11. Lee, W., Russell, B., & Rénia, L. (2019). *Sticking for a Cause : The Falciparum Malaria Parasites Cytoadherence Paradigm*. *10*(June), 1–15. https://doi.org/10.3389/fimmu.2019.01444
12. Maltzman, J. S., & Turka, L. A. (2007). Conditional gene expression: A new tool for the transplantologist. *American Journal of Transplantation*, *7*(4), 733–740. https://doi.org/10.1111/j.1600-6143.2006.01685.x
13. McCann, R. S., Cohee, L. M., Goupeyou-Youmsi, J., & Laufer, M. K. (2020). Maximizing Impact: Can Interventions to Prevent Clinical Malaria Reduce Parasite Transmission? *Trends in Parasitology*, *36*(11), 906–913. https://doi.org/10.1016/j.pt.2020.07.013
14. Meibalan, E., & Marti, M. (2017). *Biology of Malaria Transmission*. 1–15.
15. Melcher, M., Muhle, R. A., Henrich, P. P., Kraemer, S. M., Avril, M., Vigan-Womas, I., Mercereau-Puijalon, O., Smith, J. D., & Fidock, D. A. (2010). Identification of a role for the PfEMP1 semi-conserved head structure in protein trafficking to the surface of Plasmodium falciparum infected red blood cells. *Cellular Microbiology*, *12*(10), 1446–1462. https://doi.org/10.1111/j.1462-5822.2010.01481.x
16. Molina-Franky, J., Patarroyo, M. E., Kalkum, M., & Patarroyo, M. A. (2022). The Cellular and Molecular Interaction Between Erythrocytes and Plasmodium falciparum Merozoites. *Frontiers in Cellular and Infection Microbiology*, *12*(March), 1–21. https://doi.org/10.3389/fcimb.2022.816574
17. Natama, H. M., Rovira-Vallbona, E., Krit, M., Guetens, P., Sorgho, H., Somé, M. A., Traoré-Coulibaly, M., Valéa, I., Mens, P. F., Schallig, H. D. F. H., Berkvens, D., Kestens, L., Tinto, H., & Rosanas-Urgell, A. (2021). Genetic variation in the immune system and malaria susceptibility in infants: a nested case–control study in Nanoro, Burkina Faso. *Malaria Journal*, *20*(1), 1–14. https://doi.org/10.1186/s12936-021-03628-y
18. Vandenbroucke, J. P., Broadbent, A., & Pearce, N. (2016). *Causality and causal inference in epidemiology : the need for a pluralistic approach*. *January*, 1776–1786. https://doi.org/10.1093/ije/dyv341