IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 25, Issue 2 Ser. 3 (February. 2026), PP 71-77
www.iosrjournals.org

A Brief Description on Malaria- Transmission and Clinical Trials

Anupal Chowdhury[1], Syeda Sagufta Sultana[2], Sharmishtha Banerjee Debgupta[3]
[1]*Assistant Professor, Basic Science and Humanities, Future Institute of Technology*
[2]*Department of Microbiology, West Bengal State University*
[3]*Assistant Professor, Basic Science and Humanities, Future Institute of Technology*
Corresponding author: Sabina Yeasmin, University of Calcutta

Abstract
Malaria, caused by Plasmodium parasites and transmitted by Anopheles mosquitoes, greatly impact public health and socioeconomic development, particularly in Sub-Saharan African countries. In recent years number of clinical cases and death increases after treatment and prevention of malaria. Due to complex life cycle and genetic diversity of Plasmodium parasites and a challenge development in vaccine development, resistant persist towards artemisinin. This review highlights the most recent research progress and understanding in Plasmodium biology, with a primary focus on P.falciparum and associated pathogenesis. Anti-malaria drugs are also taken for therapeutic targets have also been summarized. Artemether-Lumefantrine, Atovaquone-Proguanil and Primaquine are discussed and their benefits and limitations are highlighted in case of drug resistance. Some new vaccines like Sevuparin, Imatinib, Cipargain aredevelop against resistance vaccines. Overall, this review provides a detailed summary of the latest progress in malaria research and emphasizes the need for continous monitoring and innovation in malaria treatment.
Keywords: *Maaria, P. falciparum, merozoites, Sub-African, Cipargain*

I. Introduction

P. falciparum, *P. vivax*, *P. malariae, P. knowlesi* and *P. ovale* were some Plasmodium species causes malaria [1-6]. Mixed infections of *P. falciparum* with *P. malariae* and/or *P. ovale* in Africa [7] and *P. falciparum* with *P. vivax* and/or *P. knowlesi* in Southeast Asia have posed challenges in disease control [8,9]. In prediction to 2030 the number of cases of malaria increasing day by day nowadays [10]. According to WHO's report in the year of 2023 the cases of malaria increases continually. An estimated 263 million cases occur in Congo (12.6%), Uganda (4.8%), Mozambique (3.5%), Nigeria (25.9%) and in some other countries [11].

The sporozoites injected by Anopheles mosquito travel to liver for differentiation [8,12].

Merozoites infect RBCs (red blood cells) after 5-7 days of the infection. It multiplies in hepatocytes in thousands and infect the cells [13]. A recent study revealed that *P. falciparum* disproportionately infected school aged boys received a high number of mosquito bites. It highlight the interventions targeted malaria transmission [14]. The infection in RBCs result in coldness, shivering, sweating, headache, chills and vomiting [15]. Without confirm treatment, P. falciparum malaria can lead to severe illness and death with anemia, respiratory distress, or cerebral malaria [16].

Malaria treatment regimens are based on the parasite type, symptom severity and patient age [17]. For a decades classical drugs such as quinine, chloroquine, pyronaridine, pyrimethamine and piperaquine were widely used in the clinics. As antimalarial drug resistance arises *P. falciparum* ART based ACT has been recommended as the first line treatment. Chinese scientist discover special plant extract in the treatment of malaria patients [18]. Artemisia leaves extract have great potential in the treatment of malaria. Single drug treatment done by the plant extract to overcome the resistance [19]. The mechanism of overcome drug resistance *P. falciparum* have attracted tremendous attention, and gene mutations and duplications have been regarded as the main causes, whereas the specific mechanism of ART resistance is a debated issue that will be discussed later.

In this review at first we will discuss about the epidemiology of the disease. In epidemiology we will discuss about the global distribution of the disease, trends in malaria incidence and mortality. Next we will discuss about the parasite genomics. The clinical features of malaria will be discussed in detail, focusing on symptoms such as fever, cerebral and placenta-associated malaria. Then clinical section followed by pathogenic section.

Epidemiology of malaria

Malaria remains a significant global health challenge, with an estimated 263 million cases reported in 83 endemic countries across five WHO regions in 2023, reflecting a slight increase from 11 million cases in 2022,

according to WHO's World Malaria Report 2024 (www.who.int/teams/global-malaria-programme). In 2015, 93 countries were becoming malaria endemic. Among them 26% were becoming malaria free. It met the GTS morbidity milestone for 2023. Malaria case reduces by 34% and expected less than the target. 15% had similar incidence to 2015 and 26% experienced an increase in case incidence. Malaria can be control by several factors like proverty, funding gaps, and climate change. It sets a global efforts to reduce malaria transmission.

In Sub-Saharan Africa about 94% of global cases in 2023 was observed. The burden concentration is highest in Nigeria (30.9%), Congo (11.3%), Niger (5.9%) and Tanzania (4.3%). In 2023, the region reported 246 million cases and 569000 deaths. The *P. falciparum* most virulent malaria species show vulnerable infection among young children, pregnant women and adults [20,21,22]. Young children also faces greatest risk of disease [23]. The environmental factors involve in support of breeding of Anopheles mosquitoes [24-26]. Low health infrastructure, limited access to diagonostic tools, high cost of insecticides lead to the spread of malaria [27].The rapid spread of artemisinin in Africa result in partial resistance which was a serious threat for both health and economic impacts. In South east Asia we were spreading the plants for the treatment of malaria that cannot be resistant [28].

In South East Asia 4 million cases in 2023 was reported in 2024. In some countries like Indonesia (27%), India (51%), Mayanmar (21%) and in Vietnam (370 cases only). These countries have made a reason for eliminating malaria in these zones. 48% of malaria spread due to P. vivax. In Asia antimicrobial resistace is observed in Cambodia, Thailand, Myanmar and Vietnam [29]. In recent years P. knowlesi infection has become an increasingly significant issue in malaria prominent in Indonesia, Malaysia, Thailand and Combodia. On an average 3290 cases of P. Knowlesi infection were documented in 2023, 2768 cases reported in 2022.

Malaria in the Americas is primarily confined to Brazil (33%), the Bolivarian Republic of Venezuela (26%), Colombia (21%), Guyana (6%), and Peru (4%) reporting the highest burden according to World Malaria Report 2024. In 2023, the region recorded ~505642 cases. *P. vivax* spreaded malaria in Guatemala and Mexico. Brazil, Colombia, French, Guiana, Panama, Peru, Nicaragua, Bollivia were the states where *P. vivax* spread across 60% to 92%. All indigenous cases reported here ncluding Dominician Republic and Haiti, 92% reported in Costa Rica in 2023, were related to *P. falciparum*. Malaria transmission is less intense in sub-Saharan Africa than other areas. In remote and rural areas healthcare access is still limited and migratory movements increase the risk of malaria transmission. To control malaria in South America mass drug administration (MDA) and indoor residual spraying program was done. To control further complications in drugs treatment *P.vivax* which was resistance to chloroquine was required for the first line treatment.

Malaria cases in the WHO Eastern Mediterranean Region were estimated to have decreased by 37.7% between 2000 and 2015, dropping from 6.9 million to 4.3 million according to World Malaria Report 2024. Reversed cases arised by 137% between 2015 to 2023 near about 10.2 million. In between the year of 2021 to 2023 large malaria outbreak occur in Pakistan. A rise of 3.7 million people affected by malaria following catastrophic flooding affected over 30 million people. Several countries experienced notable increases in malaria cases, with Afganistan seeing a rise in estimated cases from 288000 in 2022 to 424000 in 2023. In Afganistan and Pakistan P. vivax spreaded rapidly. In Sudan, Yemen the malaria spread slowly due to lower resident. WHO supported a subnatural estimated efforts to this nations to improve decision-making and guide malaria control strategies in regions with unstable conditions.

To control malaria in different region global challenges arises. The World Malaria report 2024 highlights the risk of climate change. It alter the risk of malaria vector transmission and their behavior. Extreme weather events such as floods and heatwaves, have been linked to increased malaria outbreaks, though the precise relationship between climate change and malaria transmission remains unclear [30,31]. The COVID-19 pandemic has also significantly disrupted malaria control efforts leading to delays in the distribution of mosquito nets, diagnostics tool and antimalarial treatments [32-37]. In each and every country it is very difficult to treat malaria for limited weapons.

The global malaria burden remains high due to introduction of some old medicine and vaccines. RTS, S/AS01g, r21/Matrix-M vaccine were some vaccines. The cases of malaria increases in 2024 in comparison to other years. The emergence of drug resistance, climate change, and the lingering effects of COVID-19 pandemic present significant challenges. We addressed these issues for crucial meeting and global elimination targets. Related to research, surveillance and development in innovative tools and strategies were essential for reducing the global burden of malaria and ultimately achievement of the eradiction.

Plasmodium Genomics

In aquatic invertebrates and some protozoa with chloroplasts lived in the intestine. Ancestors of Plasmodium parasite were reside in them [38]. This species involved in photosynthesis and adapted itself from ancestor to host [39]. Origins of Plasmodium parasites were closely linked to the host DNA sequence [40-42].For about 5500 years among 16 countries the comprehensive study of mitochondrial and nuclear genomics were expanded. The species were *P. falciparum, P.vivax* and *P. malariae respectively* [81]. This section will

explore the evolution of Plasmodium parasites, tracing their origins from free-living protozoa with chloroplasts to the complex parasites that depend on the apicoplast for host adaptation. GC/AT content, genomic sequences in genome size, organization were well defined genomic sequencing efforts listed in PlasmoDB. Comparative genomic analysis of different Plasmodium strains have been explored insights genomic diversity, parasite evolution and population genetics. Additionally the section will review rodent malarial parasites models, such as P. chabaudi, P. yoelii and P. berghei. They emphasizes on conserved core genomes and facilitate immune invasion. It also highlights on sigle-cell biology techniques that applied to Plasmodium research. Researcher understand the single –cell RNA sequencing to understand parasite development, transmission-blocking strategies and host-parasite interactions.

DNA sequences had done of Plasmodium species have genomes of 18-30 megabases (Mb) packaged into 14 chromosomes [43]. Multigene families were found near the telomeric ends of each chromosome, organized like a nucleus [44]. The *P.falciparum* 3D7 genome present in the malaria parasite genome was fully sequenced. The sequencing result was low GC content i.e near about 20% [45]. *P. relictum* and *P. gallinaceum* were some malaria parasites which have similar AT contents that like of P. falciparum [46,47]. Polychromophilus parasites, which infect bats, have compact genomes with a small number of protein-coding and RNA genes, highlighting their unique evolutionary adaptations [48,]. PlasmoDB is a public database where we can deposit genomic data after sequencing (https://plasmodb.org/).

Comparison of genomic sequences of Plasmodium species in different parasite evolution, genomic diversity, population genetics and drug resistance possibilities . *P. falciparum* NF54 isolated from patient f Netherlands, was one of the first strains used in clinical trials for malaria vaccine study [49,50]. Its genome size is ~ 23.40 Mb, with ~5273 proten-coding genes (PCGs), 229 noncoding RNA (ncRNA) genes, and 107 pseudogenes. A parent clone of *P. falciparum* NF54, was *P. falciparum* 3D7 strain widely used strain in laboratories worldwide . Its genome is ~23.33 Mb, comprising~5318 PCGs, 244 ncRNA genes, and 158 pseudogenes. The *P. falciparum* HB3 strain is a well-characterized Honduran chloroquine-sensitive strain [51,52]. Its genome is approximately 22.81 Mb, with ~5186 PCGs, 141 ncRNA genes, and 134 pseudogenes. The *P. falciparum* 7G8, a Brazilian isolate and genetically distinct from the West African parasite *P. falciparum* NF54 [53]. It genome is ~22.83 Mb, ~5183 PCGs, 161 ncRNA genes and 161 pseudogenes. Different strains of *P. falciparum* help in the vaccine development and drug resistance studies.

Malarial parasites that were rodents serve as a valuable models for studying species such as *P. falciparum* and *P. vivax* [54]. Three commonly used laboratory species were P.chabaudi, P.yoelii and P. berghei [54]. A conserved core genome present in both human and animal malarial parasites [42]. This includes essential genes for fundamental biological processes such as replication, transcription and basic metabolic pathways [55,56]. In addition, both human and animal Plasmodium species have chromosomal sub telomeric regions that contain large gene families involved in host–pathogen interactions and antigenic variation. These regions are prone to a high rate of recombination, aiding in gene diversity and

immune evasion. For example, the P. vivax (human) and P. yoelii (rodent) genomes both feature variable gene families in sub telomeric regions. However, P. falciparum has a unique gene family, the var gene family, encoding *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) proteins involved in cell adhesion and pathogenesis, which are absent in rodent and other primate malarial parasites. Similarly, rodent malarial parasites have their own unique gene families, such as the CIR/BIR/YIR families, which

are absent in human malarial parasites [56,57].

Entire research on Plasmdium genome an era in the development and application of single cell-biology represented here. In 1998, single-cell reverse transcription PCR was first applied to amplify PfEMP1 with degenerate primers. This lead to the discovery of multiple var genes in a single *P. falciparum. Parasite* [58]. In 2019, Howick et al. utilized single-cell RNA sequencing (scRNA-seq) and identified 20 transcriptional modules among 5156 key genes, revealing a high resolution transcriptional atlas during the life cycle of P. berghei. The application of this atlas led to the possibility of defining of Plasmodium developmental stages on the basis of stage specific transcription markers [59].

Clinical features of Plasmodium

Malaria present itself in a wide range of clinical complicated and uncomplicated manifestations [61]. The clinical features of malaria were primarily responsible for Plasmodium infection, diagnosis and treatment[60]. In this sections we were going to discuss about clinical manifestations. It is associated with *P.falciparum* infection, which mainly focuses on severe symptoms. Complex pathogenesis also necessary for comprehensive management strategies. The section will then focus on CM, detailing its definition. This section also going to deal about pregnancy-associated malaria (PAM). It depends on placental sequestration and its detrimental effects on both maternal and fetal health. In case of pulmonary complications both pulmonary

edema and acute respiratory distress syndrome (ARDS) were also presented. Both adult and children underlying immune responses. Then the clinical features of both malaria were summarized. Both direct parasite induced effects and indirect immune mediated processes were taken and granted. The potential therapeutic interventions aimed at mitigating these severe outcomes are reviewed.

Uncomplicated malaria contain such symptoms such as fever, headache, nausea, vomiting, muscle aches and general malariae [62]. In low malaria zone region influenza was observed. In malaria-endemic areas, these symptoms were self treatment or presumptive diagnosis. Some physical condition such as elevated temperature, sweating, weakness, splenomegaly, mild jaundice and hepatomegaly observed. By using microscopy identification of Plasmodium parasites confirmed in the blood samples. Laboratory findings often include mild anemia, thrombocytopenia, low platelet counting, elevated bilirubin and elevated liver enzymes (aminotransferases) [62,63]. In clinics rapid diagonostic test can be determined all the malaria parasites [64].

After severe infection malaria occur and organ failure occur and abnormalities observed in blood or metabolism [65].

Pathogenetic mechanisms

The pathogenesis of malaria, particularly P. falciparum infection,involves intricate molecular mechanisms that lead to severe clinical outcomes. This section highlights the role of cytokines like TNF-α and IFN-γ in activating endothelial cells, leading to the sequestration of infected red blood cells (iRBCs) via the PfEMP1 protein, a key factor in CM. It concludes how the PfEMP1 family enables the parasite to evade the immune system through antigenic variation, allowing it to adhere to host receptors such as

CD36, ICAM-1, PECAM-1, and EPCR, which are associated with severe malaria. The section also covers the immune response, noting the roles of innate immune cells like macrophages and dendritic cells in producing inflammatory cytokines, and adaptive immune components such as $CD4^+$ T cells, $CD8^+$ T cells, and antibodies. It further describes the challenges of antigenic variation and the difficulty in achieving long-term immunity and vaccine development.The primary processes of sequestration of P. falciparum-infected erythrocytes in the microvasculature involve the activation of endothelial cells mediated by various cytokines and the adherence of iRBCs to multiple host receptors via PfEMP1. Tumor necrosis factor-alpha (TNF-α) [66-68] and interferon-gamma (IFN-γ) [69-75] play critical roles in endothelial activation by upregulating the expression of endothelial adhesion molecules, thereby facilitating the sequestration of iRBCs . Additionally,the release of cytokines by immune effector cells contributes to the procoagulant state of the brain observed in patients with CM.[76] A recent study revealed that CD8+ T cells adhere to the endothelium and that their interaction with perivascular macrophages leads to the release of cytotoxic cytokines, further damaging the BBB and contributing to brain edema [77]. Mechanistically, the NH2-terminal head structure containing the duffy binding-like domain 1 (DBL1α), cysteine-rich interdomain region (CIDR1α) and DBL2δ of PfEMP1 mediates iRBC adherence to multiple host receptors,[78] including cluster of differentiation 36 (CD36), intercellular adhesion molecule 1 (ICAM-1), platelet endothelial cell adhesion molecule-1 (PECAM-1), and endothelial cell protein c receptor (EPCR), which are closely associated with the occurrence of CM.[79,80]. This is discussed in more detail in the following paragraph. The binding of iRBCs to these receptors triggers a cascade of inflammatory responses and endothelial activation, contributing to the pathophysiological changes observed in CM.[81,82]. The sequestration of P. falciparum-infected iRBCs in the micro vasculature has been recognized as the main cause of organ failure in patients with severe malaria [83]. As previously discussed, PfEMP1, encoded by the ~60 var gene family, is the principal molecule implicated in CM and has been extensively characterized in the context of malaria pathogenesis [84]. After synthesis, PfEMP1 is exported to the surface of infected red blood cells, where it forms knob structures that facilitate iRBC attachment [85]. Although multiple distinct var gene transcripts can be detected simultaneously in bulk cultures and in individual infected erythrocytes, only one var transcript is virtually expressed and translocated on the surface of an iRBC. Moreover, frequent expression switching of these transcripts, which is mutually exclusive [86] results in almost unlimited strategies for the parasite to escape immune recognition and clearance [87].

On the basis of sequence homology in the upstream regions, the var genes can be categorized into five subgroups: UpsA, UpsB, UpsC, UpsD, and UpsE [88]. These subgroups are distributed across

different locations on P. falciparum chromosomes. The UpsA subgroup var genes are located in the subtelomeric regions of the chromosomes; UpsB subgroup genes can be found in either telomeric or central regions; and UpsC subgroup genes are located primarily in the central regions of the chromosomes [89]. Severe malaria is frequently associated with the expression of A or B subgroup var genes,[90] whereas mild or asymptomatic malaria is linked to the expression of C subgroup var genes[91]. In the protein structure , PfEMP1 contains multiple Duffy-binding-like (DBL) domains and a cysteine-rich interdomain region (CIDR) in its extracellular sequence, along with a shorter acidic terminal

sequence in its cytoplasmic tail. CD36 is a receptor for most N-terminal DBL–CIDR domain cassettes across various PfEMP1 variants, a common feature of the majority of PfEMP1 variants

(types B and C) [92,93]. Another receptor common to the PfEMP1 A and B types is ICAM-1 [94,95]. Antibodies against the PfEMP1 NTSDBL1α domain can inhibit rosette formation and cyto adherence of iRBCs.[91] Moreover, antibodies against the PfEMP1 head structure DBL-CIDR domain are more indicative of malaria exposure than are those against the DBL-α tag,[94] offering insights into exposure and immunity dynamics. Moreover, the binding of PfEMP1 to nonimmune IgM and α2-macroglobulin (α2M) on the surface of immune cells hinders immune recognition of iRBCs, manipulates

host responses, and aids in immune evasion.[93] Additionally, experimental vaccines using virus-like particles (VLPs) conjugated to PfEMP1 domains have shown promise in inducing inhibitory

antibodies, offering a potential pathway for developing effective malaria vaccines [94]. Recently, the breadth of antibody responses to *P. falciparum* variant surface antigens on iRBCs, not to specific

PfEMP1 antigens, has also been implicated as a predictive factor for protection against malaria in controlled human malaria infection [95].

II. Conclusion

In Sub-Saharan Africa Malaria becomes a death threat among human beings for a prolong time being. Malaria generally caused by Plasmodium parasites transmission occur by anopheles mosquito. It is a global health challenge among people. The life cycle of plasmodium depend on laying eggs in human blood.i.e vertebrate host. Also drug resistant arises in *P. falciparum*. We are very glad to clinically isolates the strains. Studied their genetic stages,modifications and development of new strains. With side by side development of new strain new medicine also developed. These medicine we applied on human being on clinical trials. Under pathogenic section we understood how much pathogenic was the strain. We also study the mechanism of pathogenic.

References:

1. Kwiatkowski, D. P. How malaria has affected the human genome and what human genetics can teach us about malaria. Am. J. Hum. Genet. 77, 171–192 (2005).
2. Miller, L. H., Good, M. F. & Milon, G. Malaria pathogenesis. Science 264,1878–1883 (1994).
3. Cowman, A. F., Healer, J., Marapana, D. & Marsh, K. Malaria: biology and disease.Cell 167, 610–624 (2016).
4. White, N. J. Severe malaria. Malar. J. 21, 284 (2022).
5. Phillips, R. S. Current status of malaria and potential for control. Clin. Microbiol. Rev. 14, 208–226 (2001).
6. Sato, S. Plasmodium—a brief introduction to the parasites causing human malaria and their basic biology. J. Physiol. Anthropol. 40, 1 (2021).
7. Mayxay, M., Pukrittayakamee, S., Newton, P. N. & White, N. J. Mixed-species malaria infections in humans. Trends Parasitol. 20, 233–240 (2004).
8. Bousema, T. & Drakeley, C. Epidemiology and infectivity of Plasmodium falciparum and Plasmodium vivax gametocytes in relation to malaria control and elimination. Clin. Microbiol. Rev. 24, 377–410 (2011).
9. Fornace, K. M. et al. Environmental risk factors and exposure to the zoonotic malaria parasite Plasmodium knowlesi across northern Sabah, Malaysia: a population-based cross-sectional survey. Lancet Planet Health 3, e179–e186 (2019).
10. Paintain, L. et al. Using donor funding to catalyse investment in malaria prevention in Ghana: an analysis of the potential impact on public and private sector expenditure. Malar. J. 21, 203 (2022).
11. Nonvignon, J. et al. Economic burden of malaria on businesses in Ghana: a case for private sector investment in malaria control. Malar. J. 15, 454 (2016).
12. Vaughan, A. M. & Kappe, S. H. J. Malaria parasite liver infection and exo erythrocytic biology. Cold Spring Harb. Perspect. Med. 7, a025486 (2017).
13. Ménard, R. et al. Looking under the skin: the first steps in malarial infection and immunity. Nat. Rev. Microbiol. 11, 701–712 (2013).
14. Markwalter, C. F. et al. Plasmodium falciparum infection in humans and mosquitoes influence natural Anopheline biting behavior and transmission. Nat. Commun. 15, 4626 (2024).
15. Milner, D. A. Jr Malaria Pathogenesis. Cold Spring Harb. Perspect. Med. 8, a025569 (2018).
16. Mousa, A. et al. The impact of delayed treatment of uncomplicated P. falciparum malaria on progression to severe malaria: A systematic review and a pooled multicentre individual-patient meta-analysis. PLOS Med. 17, e1003359 (2020).
17. Ashley, E. A., Pyae Phyo, A. & Woodrow, C. J. Malaria. Lancet 391, 1608–1621 (2018).
18. Su, X. Z. & Miller, L. H. The discovery of artemisinin and the Nobel Prize in Physiology or Medicine. sci. China Life sci. 58, 1175–1179 (2015).
19. Blasco, B., Leroy, D. & Fidock, D. A. Antimalarial drug resistance: linking Plasmodium falciparum parasite biology to the clinic. Nat. Med. 23, 917–928 (2017).
20. Eisele, T. Are investments in malaria control saving the lives of children? Challenges in using all-cause child mortality for measuring the impact of malaria control programs. Malar. J. 13, O27 (2014).
21. Adam, I., Khamis, A. H. & Elbashir, M. I. Prevalence and risk factors for Plasmodium falciparum malaria in pregnant women of eastern Sudan. Malar. J. 4, 18 (2005).
22. Kayiba, N. K. et al. Malaria infection among adults residing in a highly endemic region from the Democratic Republic of the Congo. Malar. J. 23, 82 (2024).
23. Phillips, M. A. et al. Malaria. Nat. Rev. Dis. Prim. 3, 17050 (2017).
24. Ashton, R. A. et al. Why does malaria transmission continue at high levels despite universal vector control? Quantifying persistent malaria transmission by Anopheles funestus in Western Province, Zambia. Parasites Vectors 17, 429 (2024).

25. Andagalu, B. et al. Malaria Transmission Dynamics in a High-Transmission Setting of Western Kenya and the Inadequate Treatment Response to Artemether- Lumefantrine in an Asymptomatic Population. Clin. Infect. Dis. 76, 704–712(2023).
26. Kokwaro, G. Ongoing challenges in the management of malaria. Malar. J. 8, S2(2009).
27. Hossain, M. S., Ahmed, T. S., Sultana, N., Chowdhury, M. A. B. & Uddin, M. J.Examining the disparities of anti-malarial drug consumption among children under the age of five: a study of 5 malaria-endemic countries. Malar. J. 22, 370 (2023).
28. Martinez-Vega, R. et al. Regional action needed to halt antimalarial drug resistance in Africa. Lancet 405, 7–10 (2024).
29. Amato, R. et al. Origins of the current outbreak of multidrug-resistant malaria in Southeast Asia: a retrospective genetic study. Lancet Infect. Dis. 18, 337–345 (2018).
30. Boyce, R. et al. Severe flooding and malaria transmission in the western Ugandan highlands: implications for disease control in an era of global climate change. J. Infect. Dis. 214, 1403–1410 (2016).
31. Patz, J. A. & Olson, S. H. Malaria risk and temperature: Influences from global climate change and local land use practices. Proc. Natl Acad. Sci. USA 103,5635–5636 (2006).
32. Gao, L., Shi, Q., Liu, Z., Li, Z. & Dong, X. Impact of the COVID-19 pandemic on malaria control in Africa: a preliminary analysis. Trop. Med Infect. Dis. 8, 67 (2023).
33. Weiss, D. J. et al. Indirect effects of the COVID-19 pandemic on malaria intervention coverage, morbidity, and mortality in Africa: a geospatial modeling analysis. Lancet Infect. Dis. 21, 59–69 (2021).
34. Aguma, H. B. et al. Mass distribution campaign of long-lasting insecticidal nets (LLINs) during the COVID-19 pandemic in Uganda: lessons learned. Malar. J. 22, 310 (2023).
35. Kerr, G., Robinson, L. J., Russell, T. L. & Macdonald, J. Lessons for improved COVID-19 surveillance from the scale-up of malaria testing strategies. Malar. J.21, 223 (2022).
36. Dittrich, S. et al. Diagnosing malaria and other febrile illnesses during theCOVID-19 pandemic. Lancet Glob. Health 8, e879–e880 (2020).
37. Zawawi, A. et al. The impact of COVID-19 pandemic on malaria elimination. Parasite Epidemiol. Control. 11, e00187 (2020).
38. Dorrell, R. G., Drew, J., Nisbet, R. E. & Howe, C. J. Evolution of chloroplast transcript processing in Plasmodium and its chromerid algal relatives. PLoS Genet. 10, e1004008 (2014).
39. McFadden, G. I. & Yeh, E. The apicoplast: now you see it, now you don't. Int. J. Parasitol. 47, 137–144 (2017).
40. Siao, M. C., Borner, J., Perkins, S. L., Deitsch, K. W. & Kirkman, L. A. Evolution of host specificity by malaria parasites through altered mechanisms controlling genome maintenance. mBio 11, e03272 (2020).
41. Evans, A. G. & Wellems, T. E. Coevolutionary genetics of Plasmodium malaria parasites and their human hosts. Integr. Comp. Biol. 42, 401–407 (2002).
42. Su, X. Z., Zhang, C. & Joy, D. A. Host-malaria parasite interactions and impacts on mutual evolution. Front. Cell Infect. Microbiol 10, 587933 (2020).
43. Michel, M. et al. Ancient Plasmodium genomes shed light on the history of human malaria. Nature 631, 125–133 (2024).
44. Otto, T. D. et al. A comprehensive evaluation of rodent malaria parasite genomes and gene expression. BMC Biol. 12, 86 (2014).
45. Omelianczyk, R. I. et al. Rapid activation of distinct members of multigene families in Plasmodium spp. Commun. Biol. 3, 351 (2020).
46. Gardner, M. J. et al. Genome sequence of the human malaria parasite Plasmodium falciparum. Nature 49, 498–511 (2002).
47. Martinsen, E. S., Perkins, S. L. & Schall, J. J. A three-genome phylogeny of malaria parasites (Plasmodium and closely related genera): Evolution of life-history traits and host switches. Mol. Phylogenet. Evol. 47, 261–273 (2008).
48. Bensch, S., Hellgren, O. & Pérez-Tris, J. MalAvi: a public database of malaria parasites and related haemosporidians in avian hosts based on mitochondrial cytochrome b lineages. Mol. Ecol. Resour. 9, 1353–1358 (2009).
49. Schaer, J. et al. High diversity of West African bat malaria parasites and a tight link with rodent Plasmodium taxa. Proc. Natl. Acad. Sci. USA 110, 17415–17419 (2013).
50. Walk, J. et al. Modest heterologous protection after Plasmodium falciparum sporozoite immunization: a double-blind randomized controlled clinical trial. BMC Med. 15, 168 (2017).
51. Bojang, K. A. et al. Efficacy of RTS, S/AS02 malaria vaccine against Plasmodium falciparum infection in semi-immune adult men in The Gambia: a randomized trial. Lancet 358, 1927–1934 (2001).
52. Sanchez, C. P., Wünsch, S. & Lanzer, M. Identification of a chloroquine importer in Plasmodium falciparum: differences in import kinetics are genetically linked with the chloroquine-resistant phenotype. J. Biol. Chem. 272, 2652–2658 (1997).
53. Valderramos, S. G. et al. Identification of a mutant PfCRT-mediated chloroquine tolerance phenotype in Plasmodium falciparum. PLoS Pathog. 6, e1000887 (2010).
54. Drakeley, C. J. et al. Geographical distribution of a variant epitope of Pfs4845, a Plasmodium falciparum transmission-blocking vaccine candidate. Mol. Biochem. Parasitol. 81, 253–257 (1996).
55. De Niz, M. & Heussler, V. T. Rodent malaria models: insights into human disease and parasite biology. Curr. Opin. Microbiol. 46, 93–101 (2018).
56. Frech, C. & Chen, N. Genome comparison of human and non-human malaria parasites reveals species subset-specific genes potentially linked to human disease. PLoS Comput. Biol. 7, e1002320 (2011).
57. Kooij, T. W. A. et al. A plasmodium whole-genome synteny map: indels and synteny breakpoints as foci for species-specific genes. PLoS Pathog. 1, e44 (2005).
58. Hall, N. & Carlton, J. Comparative genomics of malaria parasites. Curr. Opin. Genet. Dev. 15, 609–613 (2005).
59. Chen, Q. et al. Identification of Plasmodium falciparum erythrocyte membrane protein 1 (PfEMP1) as the rosetting ligand of the malaria parasite P. falciparum. J. Exp. Med. 187, 15–23 (1998).
60. Howick, V. M. et al. The Malaria Cell Atlas: single parasite transcriptomes across the complete Plasmodium life cycle. Science 365, eaaw2619 (2019).
61. Afriat, A. et al. A spatiotemporally resolved single-cell atlas of the Plasmodium liver stage. Nature 611, 563–569 (2022).
62. Severe malaria. Trop. Med. Int. Health 19, 7–131 (2014).
63. Daily, J. P., Minuti, A. & Khan, N. Diagnosis, treatment, and prevention of malaria in the US: a review. JAMA 328, 460–471 (2022).
64. Lalloo, D. G. et al. UK malaria treatment guidelines 2016. J. Infect. 72, 635–649 (2016).
65. McMorrow, M. L., Aidoo, M. & Kachur, S. P. Malaria rapid diagnostic tests in elimination settings-can they find the last parasite?. Clin. Microbiol. Infect. 17, 1624–1631 (2011).
66. Trampuz, A., Jereb, M., Muzlovic, I. & Prabhu, R. M. Clinical review: severe malaria. Crit. Care 7, 315–323 (2003).
67. Mita-Mendoza, N. K. et al. Dimethyl fumarate reduces TNF and Plasmodium falciparum-induced brain endothelium activation in vitro. Malar. J. 19, 376 (2020).
68. Fiedler, U. et al. Angiopoietin-2 sensitizes endothelial cells to TNF-α and has a crucial role in the induction of inflammation. Nat. Med. 12, 235–239 (2006).

69. Tchinda, V. H. M. et al. Severe malaria in Cameroonian children: correlation between plasma levels of three soluble inducible adhesion molecules and TNF- α. Acta Trop. 102, 20–28 (2007).
70. Pais, T. F. et al. Brain endothelial STING1 activation by Plasmodium-sequestered heme promotes cerebral malaria via type I IFN response. Proc. Natl. Acad. Sci. USA 119, e2206327119 (2022).
71. He, X. et al. RTP4 inhibits IFN-I response and enhances experimental cerebral malaria and neuropathology. Proc. Natl. Acad. Sci. USA 117, 19465–19474 (2020).
72. Belnoue, E. et al. Control of pathogenic CD8+ T cell migration to the brain by IFN-gamma during experimental cerebral malaria. Parasite Immunol. 30,544–553 (2008).
73. Chen, Q., Schlichtherle, M. & Wahlgren, M. Molecular aspects of severe malaria. Clin. Microbiol. Rev. 13, 439–450 (2000).
74. Wang, Y. et al. Neurons upregulate PD-L1 via IFN/STAT1/IRF1 to alleviate damage by CD8+ T cells in cerebral malaria. J. Neuroinflamm. 21, 119 (2024).
75. Chen, Q. et al. The Semiconserved Head Structure of Plasmodium falciparum Erythrocyte Membrane Protein 1 Mediates Binding to Multiple Independent Host Receptors. J. Exp. Med. 192, 1–10 (2000).
76. Smith, J. D. et al. Identification of a Plasmodium falciparum intercellular adhesion molecule-1 binding domain: a parasite adhesion trait implicated in cerebral malaria. Proc. Natl. Acad. Sci. USA 97, 1766–1771 (2000).
77. Wassmer, S. C. et al. Investigating the pathogenesis of severe malaria: a multidisciplinary and cross-geographical approach. Am. J. Trop. Med. Hyg. 93, 42–56 (2015).
78. Jensen, A. R., Adams, Y. & Hviid, L. Cerebral Plasmodium falciparum malaria: the role of PfEMP1 in its pathogenesis and immunity, and PfEMP1-based vaccines to prevent it. Immunol. Rev. 293, 230–252 (2020).
79. Miller, L. H., Baruch, D. I., Marsh, K. & Doumbo, O. K. The pathogenic basis of malaria. Nature 415, 673–679 (2002).
80. Albrecht, L. et al. Var gene transcription and PfEMP1 expression in the resetting and cytoadhesive Plasmodium falciparum clone FCR3S1. 2. Malar. J. 10, 1–9 (2011).
81. Joergensen, L. M. et al. The kinetics of antibody binding to Plasmodium falciparum VAR2CSA PfEMP1 antigen and modelling of PfEMP1 antigen packing on the membrane knobs. Malar. J. 9, 1–12 (2010).
82. Chen, Q. et al. Developmental selection of var gene expression in Plasmodium falciparum. Nature 394, 392–395 (1998).
83. Pasternak, N. D. & Dzikowski, R. PfEMP1: an antigen that plays a key role in the pathogenicity and immune evasion of the malaria parasite Plasmodium falciparum.Int. J. Biochem. Cell Biol. 41, 1463–1466 (2009).
84. Kraemer, S. M. & Smith, J. D. J. C. o. i. m. A family affair: var genes, PfEMP1 binding, and malaria disease. Curr. Opin. Microbiol. 9, 374–380 (2006).
85. Lavstsen, T., Salanti, A., Jensen, A. T., Arnot, D. E. & Theander, T. Sub-grouping of Plasmodium falciparum 3D7 var genes based on sequence analysis of coding and non-coding regions. Malar. J. 2, 1–14 (2003).
86. Jensen, A. T. et al. Plasmodium falciparum associated with severe childhood malaria preferentially expresses PfEMP1 encoded by group A var genes. J. Exp. Med. 199, 1179–1190 (2004).
87. Rottmann, M. et al. Differential expression of var gene groups is associated with morbidity caused by Plasmodium falciparum infection in Tanzanian children.Infect. Immun. 74, 3904–3911 (2006).
88. Smith, J. D. et al. Analysis of adhesive domains from the A4VAR Plasmodium falciparum erythrocyte membrane protein-1 identifies a CD36 binding domain.Mol. Biochem. Parasitol. 97, 133–148 (1998).
89. Baruch, D. I. et al. Identification of a region of PfEMP1 that mediates adherence of Plasmodium falciparum infected erythrocytes to CD36: conserved function with variant sequence. Blood 90, 3766–3775 (1997).
90. Ockenhouse, C. F. et al. Molecular basis of sequestration in severe and uncomplicated Plasmodium falciparum malaria: differential adhesion of infected erythrocytes to CD36 and ICAM-l. J. Infect. Dis. 164, 163–169 (1991).
91. Quintana, M. D. P., Angeletti, D., Moll, K., Chen, Q. & Wahlgren, M. Phagocytosisinducing
antibodies to Plasmodium falciparum upon immunization with a recombinant PfEMP1 NTS-DBL1α domain. Malar. J. 15, 416 (2016).
92. Stucke, E. M. et al. Serologic responses to the PfEMP1 DBL-CIDR head structure may be a better indicator of malaria exposure than those to the DBL-α tag. Malar. J. 18, 273 (2019).
93. Hviid, L. & Lopez-Perez, M. Analysis by flow cytometry of α(2)-macroglobulin and nonimmune IgM-binding to Plasmodium falciparum-infected erythrocytes.Methods Mol. Biol. 2470, 435–444 (2022).
94. Harmsen, C. et al. Immunization with virus-like particles conjugated to CIDRα1domain of Plasmodium falciparum erythrocyte membrane protein 1 induces inhibitory antibodies. Malar. J. 19, 132 (2020).
95. Kinyua, A. W. et al. Antibodies to PfEMP1 and variant surface antigens: protection after controlled human malaria infection in semi-immune Kenyan adults.J. Infect. 106252 (2024).