Malaria: Biology, Disease and Control-A Comprehensive Overview

Abstract

Malaria is an infectious disease caused by *Plasmodium* parasites, which are spread to humans through the bites of infected female *Anopheles* mosquitoes. Despite ongoing control efforts, it remains a severe public health threat-particularly in sub-Saharan Africa, where children under five face the highest risk of infection and mortality due to limited access to healthcare. Once in the human host, parasites undergo liver-stage development followed by asexual replication in RBCs, leading to symptoms such as fever, chills, and anaemia. Severe *Plasmodium falciparum* infection can result in cytoadhesion of infected RBCs to endothelial cells, causing microvascular obstruction, organ damage, and cerebral malaria. The increasing resistance to antimalarial drugs and insecticides has substantially hindered eradication efforts. Current research focuses on understanding parasite biology, immune evasion, host-pathogen interactions, and transmission mechanisms. This review provides a concise overview of malaria's etiology, life cycle, transmission, and pathogenesis, emphasizing the need for innovative therapeutic and preventive strategies to overcome ongoing challenges and reduce the global burden of malaria.

Keywords: Malaria, *Plasmodium*, RBCs, Host-pathogen interactions.

Introduction

Malaria remains a major global health concern, affecting over 200 million people annually, with around 619,000 deaths, primarily among young children in sub-Saharan Africa (WHO, 2021). The disease is caused by protozoan parasites *Plasmodium* spp, transmitted through bites of infected female *Anopheles* mosquitoes. Among the six species infecting humans, *P. falciparum* is responsible for the most severe cases and mortality, especially in Africa, while *Plasmodium vivax* significantly contributes to illness in Asia and Latin America (Naing et al. 2014). Other species also cause disease although but less common and generally less virulent (Ahmed & Cox-Singh, 2015). The lifecycle of *Plasmodium* is complex, involving multiple stages within both the mosquito vector and human host. When an infected mosquito bites, it injects sporozoites, which migrate to the liver and multiply before entering the bloodstream. Here, sporozoites invade RBCs, leading to cycles of replication that cause cell rupture, producing the characteristic fever and chills of malaria. In severe cases, malaria can

lead to life-threatening complications such as severe cerebral malaria and anaemia, often due to the blockage of small blood vessels by infected cells (Idro et al. 2010).

Control efforts have made significant progress in reducing malaria transmission through insecticide-treated bed nets, and rapid diagnostic testing. However, the resilience and adaptability of *Plasmodium* species, along with the emergence of drug-resistant strains, underscore the need for novel strategies and continued research. Understanding the biology and transmission patterns of malaria parasites remains critical for developing interventions to reduce and eventually eliminate the disease (Koepfli et al. 2021).

Epidemiology of Malaria

Malaria remains a major global health issue, affecting 97 countries, especially in Africa and Asia. In 2019, the WHO estimated 229 million malaria cases worldwide, with 94% occurring in Africa. Vulnerable populations, particularly children under five, face the highest risk due to underdeveloped immunity, leading to significant morbidity and mortality in this age group.

Malaria transmission is dependent on the Anopheles mosquito, with environmental factors like temperature influencing vector survival and parasite development (WHO 2023). In areas with low and sporadic transmission, immunity is limited, making the entire population susceptible. However, in regions with consistent transmission, partial immunity can develop over time. In recent years, malaria control has faced setbacks, notably during the COVID-19 pandemic, which disrupted prevention and treatment efforts. From 2019 to 2021, pandemic-related interruptions contributed to an estimated 63,000 additional malaria deaths. While preventative measures like insecticide-treated bed nets remain effective, maintaining consistent control efforts is critical to mitigating malaria's global burden (WHO, 2022).

Etiology of Malaria

Among the over 200 identified species of *Plasmodium*, five are responsible causing human malaria: *P. falciparum, P. vivax, P. malariae, P. ovale* and *P. knowlesi*. In Africa, *P. falciparum* is the most prevalent and pathogenic species, accounting for the majority of malaria-related morbidity and mortality (Nureye et al. 2020). Moreover, co-infections with multiple *Plasmodium* species are common, particularly between *P. falciparum* and *P. malariae* in endemic regions (Gnémé et al. 2013).

Malaria is transmitted through the bite of infected female *Anopheles* mosquitoes. Approximately 400 identified species of *Anopheles*, around 30 serve as malaria vectors,

exhibiting nocturnal feeding habits between dusk and dawn (Pimenta et al. 2015). These vectors tend to have stable distribution areas, where local mosquito species rarely disappear and often develop resistance to eradication efforts. The introduction of non-native vector species into these regions can lead to severe outbreaks, as these species may carry *Plasmodium*.

Once a mosquito transmits the parasite to a human host, *Plasmodium* travels through the bloodstream to infect liver cells, marking the onset of the asymptomatic liver stage. Within the liver, the parasites mature and multiply, eventually releasing merozoites back into the bloodstream, where parasites invade RBCs and initiate the symptomatic blood stage. During this stage, the cyclical fevers associated with malaria, known as malarial paroxysms, arise due to the synchronized rupture of infected RBCs. The periodicity of the fever varies by species; for instance, *P. vivax* typically causes fever every 48 hours if left untreated.

Life Cycle of the Malaria Parasite

The malaria parasite undergoes a complex life cycle that requires both a human host and an *Anopheles* mosquito to complete (**Figure 1**). The infection begins when sporozoites are introduced into the skin and bloodstream of a human host through the saliva of an infected mosquito. Once in the bloodstream, the sporozoites invade hepatocytes to undergo a phase of asexual replication known as the hepatic or pre-erythrocytic phase. During this phase, the rupture of infected hepatocytes releases thousands of merozoites into the bloodstream (Siciliano et al. 2015). In infections caused by *P. vivax* and *P. ovale*, some merozoites develop into dormant forms called hypnozoites, which can stay hidden in liver cells for several months to even four years before reactivating and starting a new cycle of red blood cell infection (Ryan et al. 2019). The erythrocytic phase involves the interaction of merozoites with RBCs.

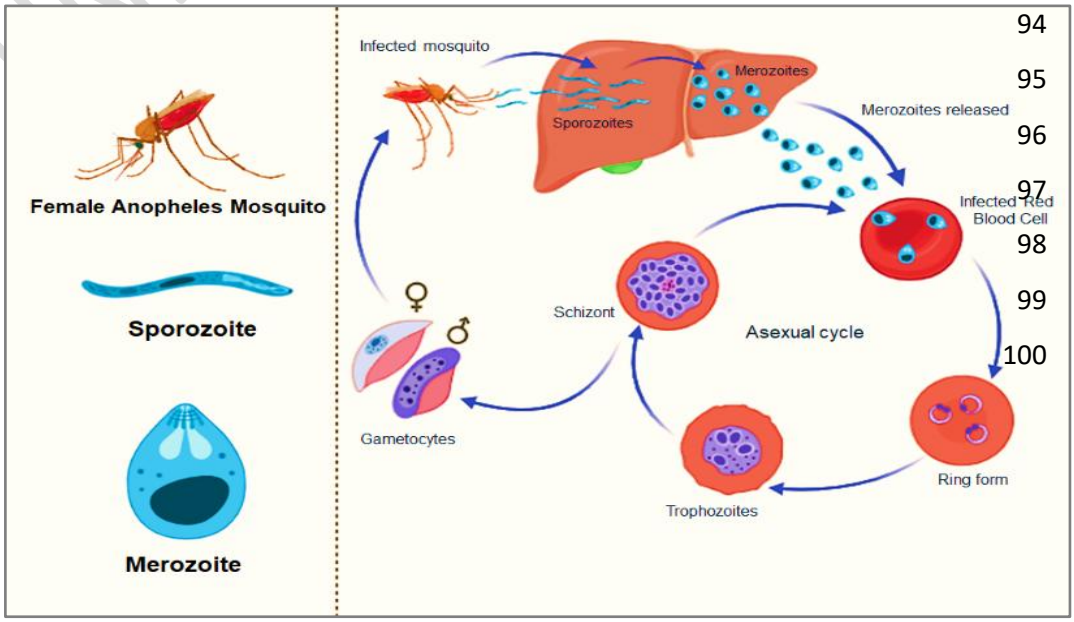

Figure 1: Life cycle of *Plasmodium* Spp.

The merozoites orient themselves and attach to the RBC membrane, warping the surface of the host cell. The merozoite actively invades the erythrocyte by manipulating and reorganizing its cytoskeleton, allowing it to continue asexual reproduction inside the host cell. Different *Plasmodium* species show preferences for erythrocytes at various stages of maturity. *P. vivax* and *P. ovale* mainly target young red blood cells, whereas *P. falciparum* and *P. knowlesi* are capable of invading erythrocytes regardless of their age. In contrast, *P. malariae* tends to infect older red blood cells (Baron et al. 1996). Once inside the host cell, the merozoite matures into a trophozoite, then transforms into a schizont. Upon rupture of the schizont, newly formed merozoites are released into the bloodstream, where they invade fresh red blood cells, perpetuating the asexual replication cycle (Jong et al. 2021).

The sexual reproduction phase of the malaria life cycle initiates when some trophozoites mature into male and female sexual gametocytes. These gametocytes are responsible for transmitting the malaria parasite from the mammalian host to the mosquito during feeding. When an Anopheles mosquito takes a blood meal, the mature gametocytes are transferred to the mosquito's midgut. Inside the midgut, the gametocytes convert into fertile gametes, marking the next stage where these gametes fuse to form zygotes. The zygotes further develop into motile and invasive ookinetes (Venugopal et al. 2020). These ookinetes then transform into oocysts within the basal lamina of the midgut. The mature oocysts eventually release sporozoites, which migrate to the salivary glands of the mosquito.

Mechanisms/Pathophysiology

The invasion of host cells by *Plasmodium* parasites is a complex process that begins in the mosquito vector and is completed in the human host. During a blood meal, a female *Anopheles* mosquito ingests gametocytes from an infected human. These gametocytes develop into sporozoites within the mosquito’s gut and then migrate to the salivary glands, ready to be transmitted in a subsequent bite. Upon entering the human bloodstream, *Plasmodium* sporozoites quickly migrate to the liver and invade hepatocytes. Within these liver cells, the sporozoites multiply, forming merozoites that are eventually released back into the bloodstream (Venugopal et al. 2020). In the blood, merozoites target RBCs and initiate the erythrocytic stage of the life cycle. This stage is marked by the parasites’ unique ability to enter and replicate within RBCs through specific ligand-receptor interactions. *Plasmodium*

surface proteins bind to receptors on host erythrocytes or reticulocytes, facilitating entry (CDC Malaria, 2019). Different *Plasmodium* species show preferences for certain types of blood cells; for example, *P. falciparum* can invade both mature erythrocytes and immature reticulocytes, while *P. vivax* predominantly invades reticulocytes, which are less common than erythrocytes (Lim et al. 2016). After entry, the parasite undergoes development from a ring-stage trophozoite into either a mature trophozoite or a gametocyte. The mature trophozoites consume hemoglobin and progress to form schizonts, which replicate and rupture the RBCs, releasing new merozoites into circulation. This cell rupture leads to symptoms associated with malaria, such as fever and anemia. *P. falciparum*, in particular, expresses erythrocyte-binding proteins that interact with essential RBC receptors like basigin and CD55 (complement decay-accelerating factor), ensuring a high efficiency of invasion and survival within the human host.

The pathogenesis of malaria is driven by the secretion of IFN-gamma and TNF-alpha in response to parasite-derived toxins (Bedu-Addo et al. 2014). The innate immune response is primarily marked by monocytes and macrophages phagocytosing infected cells within the splenic red pulp. IFN-gamma and TNF-alpha stimulate CD4-positive lymphocytes to undergo class switching, supporting the development of adaptive immunity (Bedu-Addo et al. 2014). TNF-alpha also inhibits hematopoiesis, contributing to malaria-associated anemia. Splenomegaly and hepatomegaly are common as the spleen and liver enlarge. In uncomplicated malaria, fever arises due to the rupture of red blood cells, the engulfment of merozoites by macrophages, and the presence of trophozoites that present antigens, all of which stimulate the release of TNF-alpha (Baron et al. 1996). The pattern of fever varies by species: *P. vivax* and *P. ovale* typically cause tertian fever with a 48-hour cycle, *P. malariae* induces quartan fever every 72 hours, while *P. falciparum* often triggers fever approximately every 48 hours, but its timing can be irregular (Baron et al. 1996).

In severe malaria, the binding of infected RBCs to the endothelial cells of blood vessels, known as cytoadherence, plays a critical role in pathogenesis. This process is more pronounced in *P. falciparum*, due to its unique gene expression of proteins that aid in cytoadherence and immune evasion, which contributes to its high virulence compared to other malaria species. Key proteins involved include *P. falciparum* erythrocyte membrane protein 1 (PfEMP1), stevor, and rifin encoded by the stevor, rif and var, gene families, respectively. Among these, PfEMP1 is particularly well-studied, known for its ability to bind endothelial receptors via its expression on the surface of infected erythrocytes (Lavstsen et al. 2005).

Diagnosis of Malaria

Traditional malaria diagnosis relies on clinical observation, but this approach has limited accuracy due to the similarity of malaria symptoms with other tropical diseases and the risk of co-infections (Murray et al. 2009). Consequently, blood smear microscopy and rapid diagnostic tests (RDTs) have become more widely used diagnostic methods. In microscopy, skilled personnel identify *Plasmodium* parasites in blood smears, yet this process is labor-intensive and requires laboratory resources. RDTs offer a quicker alternative, detecting malaria antigens like histidine-rich protein-2 (HRP-2) and aldolase. Although RDTs are easier to administer, it can have reduced sensitivity and specificity, especially when parasite levels are low (Kasetsirikul et al. 2016). To address these challenges, molecular techniques such as polymerase chain reaction (PCR) are increasingly employed due to their high sensitivity and ability to detect low parasite densities (Kasetsirikul et al. 2016). However, PCR's high cost and technical requirements limit its availability to well-equipped laboratories.

Advances in malaria diagnostics are focusing on more accessible, accurate, and point-of-care (POC) methods. Emerging techniques like dielectrophoretic and magnetophoretic detection offer improved accuracy and convenience for POC testing. Non-invasive approaches are also under development, such as detecting malaria antigens in saliva or urine, identifying specific volatile compounds in breath, and measuring haemozoin in skin blood vessels (Singh et al. 2014). Additionally, next-generation sequencing adapted for high-throughput use could enable genetic screening for drug-resistant mutations in *P. falciparum,* helping track and manage resistance patterns effectively (WHO, 2015). These innovations promise to enhance malaria diagnosis, making it faster, more precise, and accessible in diverse healthcare environments.

Prevention of Malaria

Causal prophylaxis, which targets the liver stage of the malaria parasite, has proven effective in preventing infections shortly after exposure to endemic areas. Medications such as atovaquone/proguanil and primaquine exemplify this approach, allowing travelers to discontinue treatment upon exit from malaria-prone zones. This is particularly beneficial in short-term travelers who may only spend limited time in these regions. Studies suggest that causal prophylaxis significantly reduces the incidence of malaria infection among travelers who adhere to prescribed regimens. Conversely, suppressive prophylaxis addresses the

asexual blood-stage parasites that can evade the immune system following initial liver-stage infection. Drugs like doxycycline and mefloquine are employed in areas with a high prevalence of *P. falciparum*, necessitating extended treatment for at least four weeks after leaving the malaria-endemic area. Emerging research indicates that any lapses in medication adherence could heighten the risk of clinical malaria due to the delayed emergence of parasites from liver dormancy. This underscores the importance of patient education regarding the risks associated with non-compliance. The Centers for Disease Control and Prevention (CDC) highlights that no antimalarial medication can offer 100% protection against malaria. Implementing preventive measures like applying insect repellent, covering exposed skin with appropriate attire, and utilizing mosquito nets while sleeping can significantly reduce infection risks. Integrating these strategies can mitigate exposure to mosquito bites, thereby reducing the risk of acquiring malaria even with prophylactic medication.

Moreover, individual patient factors-such as pregnancy, pre-existing health conditions, and local drug resistance patterns-play critical roles in determining the appropriate prophylactic treatment. Research indicates that patient preferences regarding the frequency of administration and tolerability of side effects should also guide drug selection. Surveillance data reflecting regional resistance patterns further inform healthcare providers when recommending prophylactic strategies.

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Dear Editor-in-Chief,

I am writing to respectfully request a waiver of the article processing charges (APCs) for our manuscript titled "Malaria: Biology, Disease and Control-A Comprehensive Overview," which has not been submitted yet.

I am Dr. Tapas Haldar, currently working as a Senior Researcher at the ICMR - National Institute for Research in Bacterial Infections. Unfortunately, we do not have access to institutional or grant funding to support the publication fees. Given our financial constraints and the importance of making this research accessible through your journal, we kindly request your consideration for a full waiver of the APCs.

We deeply value the opportunity to contribute to your journal and hope that you can support us in making our work publicly available despite our limited resources.

Thank you for your time and understanding.

Sincerely,

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