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(REVIEW ARTICLE)

Malaria: A comprehensive review of pathogenesis, clinical manifestations and current control methods

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Abstract

Malaria is caused by protozoan parasites of the genus Plasmodium and is a main cause of mortality and morbidity worldwide. These parasites have a complex life cycle in their mosquito vector and vertebrate hosts. The primary factors contributing to the resurgence of malaria are the appearance of drug-resistant strains of the parasite, the spread of insecticide-resistant strains of the mosquito and the lack of licensed malaria vaccines of proven efficacy. This minireview includes a summary of the disease, the life cycle of the parasite, information relating to the genome and proteome of the species lethal to humans, *Plasmodium falciparum*, together with other recent developments in the field.

Keyword: Malaria; Pathogenesis; Clinical Manifestations and Control Methods

1. Introduction

Malaria remains one of the most significant infectious diseases in the world, causing substantial morbidity and mortality, particularly in sub-Saharan Africa, Southeast Asia, and parts of Latin America. It is caused by protozoan parasites of the genus Plasmodium and is transmitted to humans primarily through the bite of infected female Anopheles mosquitoes. Despite decades of global health efforts, malaria continues to exert an enormous burden on affected populations, health systems, and economies (Fikadu& Ashenafi,2023)

According to the World Health Organization (WHO) World Malaria Report 2023, there were an estimated 249 million malaria cases and approximately 608,000 deaths globally in 2022. The African Region accounted for about 94% of all cases and 95% of all deaths. Children under five years of age and pregnant women are the most vulnerable groups, accounting for the majority of severe disease and fatalities (WHO, 2022).

Historically, malaria has shaped human civilization, influencing migration patterns, military campaigns, and the genetic makeup of populations living in endemic areas. The selective pressure of malaria has driven the evolution of protective genetic variants such as sickle cell trait (HbAS), glucose-6-phosphate dehydrogenase (G6PD) deficiency, and alpha-thalassemia. These genetic adaptations underscore the deep and longstanding relationship between humans and Plasmodium parasites (Talapko *et al*.,2019).

The disease has attracted enormous scientific interest, leading to the discovery of the malarial parasite by Alphonse Laveran in 1880 and the demonstration of its mosquito transmission by Ronald Ross in 1897 — both achievements recognized with Nobel Prizes. In recent decades, the development of artemisinin-based combination therapies (ACTs), insecticide-treated bed nets (ITNs), indoor residual spraying (IRS), and, more recently, the WHO-approved RTS, S/AS01 and R21/Matrix-M vaccines have transformed the malaria control landscape (White *et al.,*2014).

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This review aims to offer a comprehensive and up-to-date overview of malaria, covering its etiology, epidemiology, life cycle, pathogenesis, clinical manifestations, diagnosis, treatment, drug resistance, prevention, and future directions in research and control.

2. Plasmodium Species

Malaria in humans is caused by five Plasmodium species, each with distinct biological characteristics, geographic distribution, and clinical relevance:

Table 1 A comparison of the five species of Plasmodium that cause human malaria, with respect to their geographical distribution, clinical severity, their recurrence patterns and key biological characteristics

Species	Distribution	Severity	Recurrence	Key Feature
P. falciparum	Africa, SE Asia, Americas	Most severe	No relapses	Cytoadherence, severe malaria
P. vivax	Asia, Americas, some Africa	Moderate	Relapses (hypnozoites)	Schuffner's dots, dormancy
P. malariae	Worldwide (sparse)	Mild	Recrudescence	Quartan fever, nephropathy
P. ovale	West Africa	Mild	Relapses (hypnozoites)	Fimbriated RBCs
P. knowlesi	SE Asia (Borneo)	Moderate-severe	No relapses	Zoonotic from macaques

2.1. *Plasmodium falciparum*

Plasmodium falciparum is the most virulent of the human malaria parasites and is responsible for nearly all malaria-associated deaths. Its unique ability to cause infected erythrocytes to adhere to vascular endothelium via the *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) underlies the pathophysiology of severe disease, including cerebral malaria, severe anemia, and acute respiratory distress syndrome (ARDS). *P. falciparum* also undergoes high-density parasitemia due to its ability to invade erythrocytes of all ages(Dondorp *et al*.,2010) .

2.2. Plasmodium vivax

P. vivax is the most geographically widespread Plasmodium species and the dominant cause of malaria in Asia and the Americas. A defining feature is its ability to form dormant liver-stage parasites called hypnozoites, which can reactivate weeks to months after the initial infection, causing relapsing malaria. *P. vivax* preferentially invades reticulocytes (immature red blood cells) and uses the Duffy antigen receptor for chemokines (DARC) for invasion, which explains why Duffy-negative individuals — common in West Africa — are largely resistant(Adams& Mueller,2017).

2.3. Plasmodium malariae

P. malariae causes a milder, chronic form of malaria with a 72-hour erythrocytic cycle (quartan fever). It can persist in the bloodstream for decades without causing symptoms, and is associated with nephrotic syndrome (malarial nephropathy) in some patients, particularly children. Unlike *P. vivax* and *P. ovale*, *P. malariae* does not produce hypnozoites; recurrences occur by recrudescence of low-level blood-stage parasitemia.

2.4. Plasmodium Ovale

Plasmodium ovale was the last of the malaria parasites of humans to be described. The pronounced stippling of the infected erythrocyte and its tertian periodicity led early investigators to consider it a variant form of *Plasmodium vivax*. In 1900, Craig (32) described a malaria parasite in the blood of American soldiers returning from the Philippines that had peculiar morphological characteristics and a tertian fever pattern. It is possible that he was describing infections with *P. ovale*(Collins& Jeffery,2005).

2.5. Plasmodium knowlesi

P. knowlesi is a zoonotic species that naturally infects long-tailed and pig-tailed macaques in Southeast Asia but can infect humans, particularly in the rainforests of Malaysian Borneo. It has a 24-hour replication cycle and can cause

rapidly progressing high-density parasitemia, occasionally leading to severe and fatal disease. *P. knowlesi* is now recognized as the most common cause of malaria in Malaysia (Cox-Singh *et al*.,2008)

3. Life Cycle of the Malarial Parasite

The life cycle of Plasmodium is complex, involving two hosts: the Anopheles mosquito (definitive host, where sexual reproduction occurs) and the human (intermediate host, where asexual reproduction occurs). Understanding this cycle is crucial for targeting interventions at multiple stages.

3.1. Mosquito Stage (Sporogony)

When a female Anopheles mosquito feeds on a malaria-infected human, it ingests male and female gametocytes. In the mosquito midgut, gametocytes differentiate into gametes. Fertilization produces a zygote, which develops into a motile ookinete. The ookinete penetrates the midgut wall and forms an oocyst. Inside the oocyst, thousands of sporozoites develop through sporogony. Mature sporozoites migrate to the mosquito's salivary glands, ready to be transmitted during the next blood meal. This extrinsic incubation period lasts approximately 10–21 days, depending on ambient temperature and Plasmodium species(Cowman *et al*.,2016).

3.2. Liver Stage (Exo-Erythrocytic Schizogony)

When an infected mosquito bites a human, sporozoites are injected into the skin with saliva. Within minutes, they enter the bloodstream and travel to the liver, where they invade hepatocytes via interaction with heparan sulfate proteoglycans and the CD81 receptor (for *P. falciparum*) or the DARC receptor indirectly (*P. vivax*). Inside hepatocytes, each sporozoite develops into a liver schizont containing thousands of merozoites — a process called exo-erythrocytic schizogony lasting 5–16 days depending on the species. For *P. vivax* and *P. ovale*, some sporozoites may remain dormant as hypnozoites for weeks to years before reactivating(Dondorp *et al*.,2010).

3.3. Blood Stage (Erythrocytic Schizogony)

Merozoites released from ruptured hepatocytes invade red blood cells (RBCs). Inside the RBC, the parasite progresses through the ring (early trophozoite), trophozoite, and schizont stages. Mature schizonts rupture, releasing 8–32 merozoites (species-dependent) that invade new RBCs. This 48-hour (*P. falciparum*, *P. vivax*, *P. ovale*) or 72-hour (*P. malariae*) cycle is synchronized and corresponds to the periodic fever seen clinically. The rupture of schizonts releases parasite products (including hemozoin, glycosylphosphatidylinositol (GPI) anchors, and DNA) that trigger the immune response and fever(Bhatt *et al*.,2015).

3.4. Sexual Stage (Gametocytogenesis)

Some merozoites differentiate into male and female gametocytes rather than proceeding with asexual replication. Gametocytes circulate in the bloodstream and are taken up by feeding mosquitoes, completing the transmission cycle. Gametocyte development takes approximately 10–12 days for *P. falciparum*. Antimalarial drugs that target gametocytes are important tools for interrupting transmission(Dondorp *et al*.,2010).

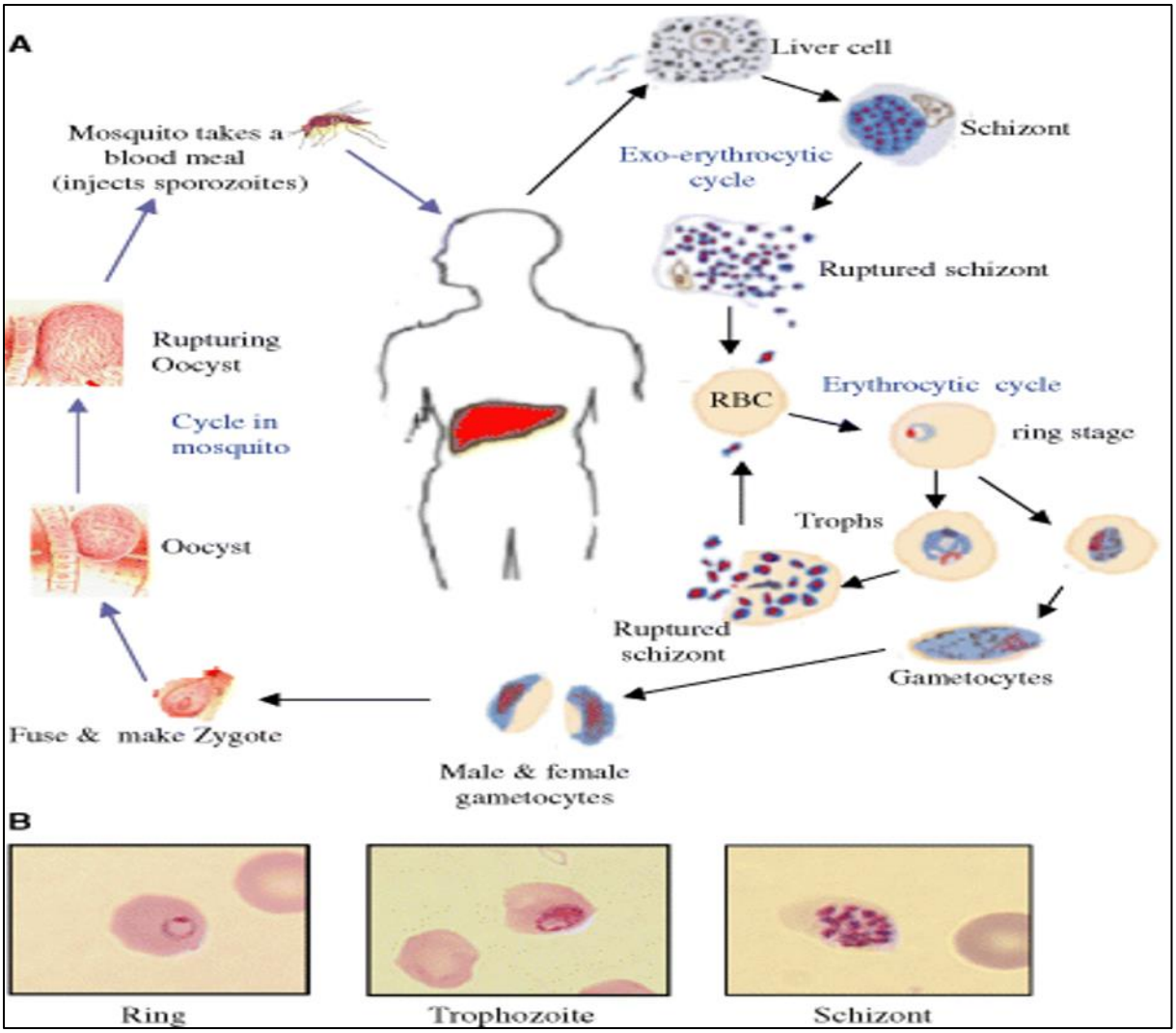

Figure 1 (A) Life cycle of the malaria parasite *P. falciparum*. (B) Different intra erythrocytic stages of development of *P. falciparum* in culture(Tuteja, 2007)

4. Epidemiology

Malaria is endemic in over 90 countries, predominantly within the tropical belt between 35 degrees north and 35 degrees south latitude. According to the WHO World Malaria Report 2023, there were approximately 249 million cases of malaria in 2022, compared to 247 million in 2021. The African Region bears the greatest burden, accounting for 94% of global cases. Nigeria, the Democratic Republic of the Congo, Uganda, Mozambique, and Niger together account for approximately 51% of all malaria deaths globally(Cowman *et al*.,2016).

Children under five years of age are the most affected demographic, accounting for approximately 80% of all malaria deaths in the African Region. Pregnant women are another high-risk group, as malaria during pregnancy is associated with maternal anemia, premature birth, low birth weight, and increased infant mortality — a syndrome known as placental malaria (or pregnancy-associated malaria, PAM). Non-immune travelers from malaria-free countries who visit endemic regions are at very high risk of severe disease due to lack of acquired immunity(Desai *et al*.,2007).

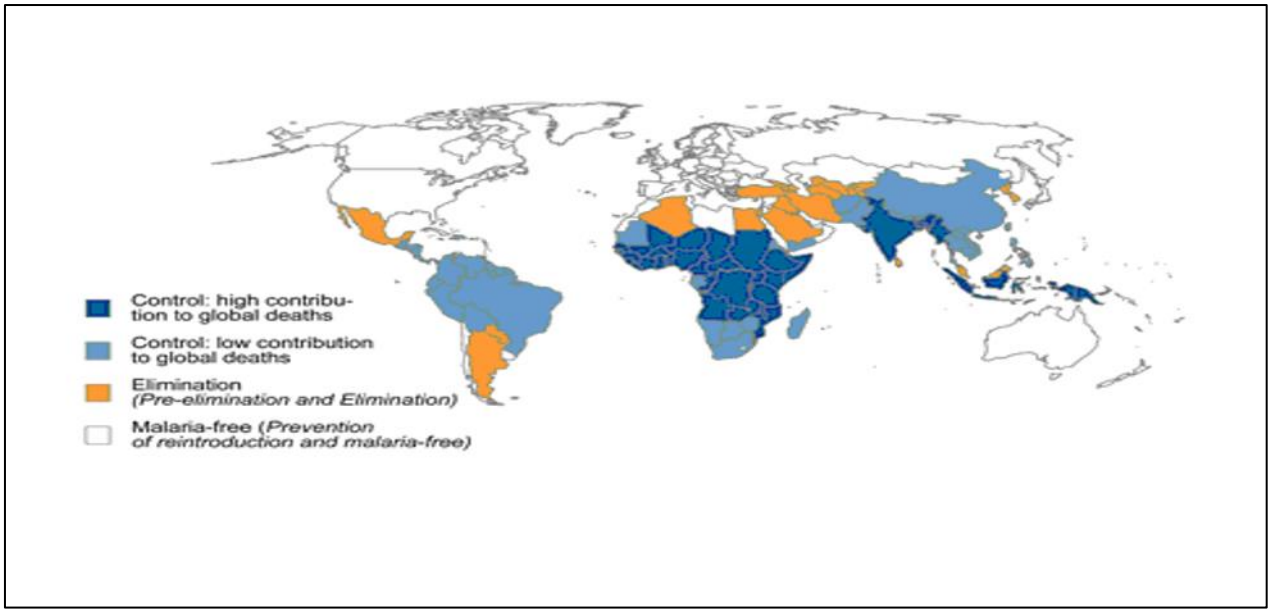

Figure 2 Malaria endemic countries around the world (WHO, 2022)

5. Transmission Determinants

Malaria transmission depends on a complex interplay of environmental, biological, and socioeconomic factors. Key determinants include: the density of Anopheles mosquito vectors; temperature (optimal between 20–30 degrees Celsius, affecting both mosquito survival and parasite development); rainfall and humidity ,altitude; human behavior , housing quality; and access to healthcare. Climate change poses a significant threat, as warming temperatures and altered rainfall patterns may expand the geographic range of Anopheles mosquitoes and extend transmission seasons in currently endemic areas(Sollelis *et al.,*2024).

6. Pathogenesis

The pathogenesis of malaria is multifactorial and involves both direct parasite-mediated injury and immune-mediated tissue damage. The blood stage of infection is responsible for virtually all clinical manifestations.

The episodic fever characteristic of malaria is triggered by the synchronous rupture of erythrocytic schizonts. Released parasite products particularly glycosylphosphatidylinositol (GPI) anchors, hemozoin (malaria pigment), and Plasmodium-derived nucleic acids — activate pattern recognition receptors (TLRs 2, 4, 7, 8, and 9) on immune cells, triggering the release of pro-inflammatory cytokines including TNF-alpha, IL-1, IL-6, and IL-12. These cytokines reset the hypothalamic thermostat, producing fever, rigors, and systemic inflammation(Miller *et al*.,1994).

Malarial anemia results from multiple mechanisms: direct destruction of parasitized RBCs during schizont rupture; phagocytosis of both parasitized and non-parasitized RBCs by activated macrophages ; dyserythropoiesis and in some patients, rosetting and sequestration of RBCs(Moxon *et al*.,2020).

A unique and critical feature of *P. falciparum* pathogenesis is the ability of infected erythrocytes to adhere to the microvascular endothelium. PfEMP1 proteins exported to the surface of infected RBCs bind to host endothelial receptors including ICAM-1, CD36, VCAM-1, E-selectin, and thrombospondin. This cytoadherence leads to the sequestration of parasitized RBCs in the deep microvasculature of vital organs, including the brain, lungs, kidneys, and placenta. Sequestration obstructs microcirculation, induces endothelial activation and inflammation, and leads to tissue hypoxia(Dondorp *et al*.,2010).

Cerebral malaria (CM) is the most severe neurological complication, defined by the WHO as unarousable coma not attributable to other causes in a patient with *P. falciparum* infection. The pathogenesis involves sequestration of parasitized RBCs in cerebral microvasculature, disruption of the blood-brain barrier, cerebral edema, neuroinflammation, and excitotoxicity. Brain swelling demonstrated by MRI is an important predictor of death and

neurological sequelae. Approximately 25% of children who survive cerebral malaria suffer long-term neurocognitive deficits(Moxon *et al*.,2020)..

During pregnancy, the placenta expresses high levels of chondroitin sulfate A , a ligand that preferentially binds to *P. falciparum*-infected erythrocytes expressing VAR2CSA a specific PfEMP1 variant. This leads to massive accumulation of parasites in the intervillous spaces of the placenta, causing local inflammation, impaired nutrient transfer, placental dysfunction, intrauterine growth restriction (IUGR), and adverse pregnancy outcomes. Multigravid women in endemic areas acquire protective antibodies against VAR2CSA, reducing susceptibility with successive pregnancies(Dondorp *et al*.,2010)..

7. Clinical Manifestations

The classic presentation of uncomplicated malaria involves a prodrome of malaise, headache, fatigue, myalgia, and anorexia, followed by the paroxysm — the characteristic febrile episode consisting of three stages: the cold stage (intense chills and rigors, lasting 15–60 minutes), the hot stage (high fever up to 40–41 degrees Celsius with flushing and dry skin, lasting 2–6 hours), and the sweating stage (profuse diaphoresis and defervescence, lasting 2–4 hours). These paroxysms occur every 48 hours for *P. falciparum*, *P. vivax*, and *P. ovale* (tertian fever) and every 72 hours for *P. malariae* (quartan fever). Additional features include splenomegaly, hepatomegaly, and pallor from anemia(Moxon *et al*.,2020)..

Severe malaria, caused almost exclusively by *P. falciparum* (though *P. vivax* and *P. knowlesi* can occasionally cause severe disease), is defined by the presence of one or more of the following criteria: impaired consciousness/coma (cerebral malaria), severe anemia (Hb < 7 g/dL in children), respiratory distress, multiple convulsions, circulatory collapse, pulmonary edema, abnormal bleeding, jaundice, hemoglobinuria, hyperparasitemia (>5% parasitized RBCs), hypoglycemia (blood glucose < 2.2 mmol/L), and acute kidney injury (Olotu *et al*.,2016).

Cerebral malaria is the most feared complication, presenting with altered consciousness, seizures, and coma, with a case fatality rate of 15–25% even with treatment. Malarial hypoglycemia (often exacerbated by quinine-stimulated insulin secretion) requires urgent correction. Acute respiratory distress syndrome (ARDS) and metabolic acidosis are associated with the highest mortality in adult patients(Gething *et al*.,2011).

8. Diagnosis

Prompt and accurate diagnosis is essential for effective malaria management and for preventing unnecessary antimalarial treatment. The WHO recommends that all suspected malaria cases should be confirmed by parasitological testing before treatment.

- Light microscopy of Giemsa-stained thick and thin blood smears remains the gold standard for malaria diagnosis. The thick smear increases sensitivity by concentrating RBCs, allowing detection of parasites at densities as low as 5–10 parasites per microliter. The thin smear allows species identification and estimation of parasitemia. Diagnostic accuracy depends heavily on technician expertise and slide quality. Microscopy can detect all five Plasmodium species and provide quantitative parasitemia data, which is important for monitoring treatment response(Makler *et al.,*1998).

- RDTs detect Plasmodium-specific antigens — most commonly HRP2 (histidine-rich protein 2, specific to *P. falciparum*), pLDH (parasite lactate dehydrogenase, pan-specific or species-specific), and Aldolase — using immunochromatographic lateral flow assays. RDTs provide results within 15–20 minutes without requiring electricity or laboratory equipment, making them ideal for use in resource-limited and remote settings. Current WHO-approved RDTs have sensitivity of approximately 95% for *P. falciparum* at clinically relevant parasite densities. A major limitation is the emergence of pfhrp2/3 gene deletions in *P. falciparum*, causing false-negative HRP2-based RDTs — a growing public health concern in parts of Africa and South America(Tangpukdee *et al*.,2009).

- Molecular Methods (PCR)- Polymerase chain reaction (PCR)-based methods offer the highest sensitivity and specificity for malaria diagnosis, capable of detecting parasitemias as low as 0.5–5 parasites per microliter. PCR is particularly valuable for: species differentiation in mixed infections; detecting low-density submicroscopic parasitemia; confirming Plasmodium knowlesi infection (which morphologically resembles *P. malariae*); and

investigating drug resistance mutations. Quantitative PCR (qPCR) and Loop-mediated Isothermal Amplification (LAMP) offer rapid, field-adaptable alternatives with high sensitivity (Hawkes& Kain,2007).

- Other Diagnostic Approaches- The Quantitative Buffy Coat (QBC) technique uses acridine orange fluorescent staining to detect parasite DNA, offering higher sensitivity than conventional microscopy. Flow cytometry and mass spectrometry-based approaches are emerging research tools. Serology (antibody detection) is not useful for acute diagnosis due to persistence of antibodies long after infection, but has applications in epidemiological surveys(Tangpukdee et al.,2009).

9. Treatment

The WHO currently recommends artemisinin-based combination therapies (ACTs) as the first-line treatment for uncomplicated *P. falciparum* malaria. ACTs combine a fast-acting artemisinin derivative (which rapidly reduces parasitemia) with a longer-acting partner drug (which eliminates remaining parasites and prevents selection of artemisinin-resistant mutants). WHO-recommended ACTs include:

- Artemether-lumefantrine (AL) — most widely used globally
- Artesunate-amodiaquine (ASAQ) — preferred in parts of Africa
- Artesunate-mefloquine (ASMQ) — used in Southeast Asia
- Dihydroartemisinin-piperaquine (DHA-PPQ) — used in Asia and Africa
- Artesunate-pyronaridine — recently approved

A single dose of primaquine (0.25 mg/kg) is recommended to reduce *P. falciparum* gametocyte carriage and interrupt transmission, particularly in low-transmission settings, after testing for G6PD deficiency.

For *P. vivax* and *P. ovale*, chloroquine remains effective in most regions and is combined with a 14-day course of primaquine (0.25–0.5 mg/kg/day) to eliminate hypnozoites and prevent relapse. G6PD testing is mandatory before primaquine use to avoid hemolysis in deficient individuals. Tafenoquine, a recently approved 8-aminoquinoline, offers single-dose radical cure for *P. vivax* but also requires G6PD testing. In areas of chloroquine-resistant *P. vivax* (e.g., Papua New Guinea, parts of Indonesia), ACTs are used. *P. malariae* and *P. knowlesi* are both effectively treated with chloroquine or ACTs(Ashley& Phyo,2018).

Treatment of malaria in pregnancy requires special consideration. Quinine plus clindamycin remains the preferred treatment for uncomplicated *P. falciparum* malaria in the first trimester due to limited data on ACT safety in early pregnancy. ACTs (preferably AL) are recommended in the second and third trimesters. Artemisinin derivatives should be avoided in the first trimester unless the risk of malaria is considered to outweigh the theoretical teratogenic risk. For prevention, sulfadoxine-pyrimethamine (SP) is used as intermittent preventive treatment in pregnancy in Africa, administered at each antenatal care visit from the second trimester(Ashley& Phyo,2018).

10. Prevention and Control

Long-lasting insecticidal nets and indoor residual spraying are the two most important vector control interventions. LLINs impregnated with pyrethroids have been credited with a substantial proportion of the malaria burden reduction achieved since 2000. However, the widespread development of pyrethroid resistance in Anopheles mosquitoes has prompted the development of next-generation nets incorporating synergists (piperonyl butoxide, PBO) or alternative insecticides. IRS involves the application of residual insecticides to interior walls and ceilings; it is most effective when achieving >85% coverage in targeted areas(Kakuru *et al*.,2016).

Several chemoprevention strategies have proven highly effective. Seasonal malaria chemoprevention using SP plus amodiaquine during the peak transmission season in the Sahel has been shown to reduce malaria episodes in children under five by up to 75%. IPTp reduces the risk of low birth weight and maternal anemia. Intermittent preventive treatment in infants with SP is recommended in high-burden African settings. Malaria chemoprophylaxis is also recommended for non-immune travelers to endemic regions, using atovaquone-proguanil (Malarone), doxycycline, or mefloquine depending on the region and individual factors(Ashley *et al.*,2014) .

The development of effective malaria vaccines has been a long-standing goal. RTS,S/AS01 (Mosquirix), targeting the circumsporozoite protein (CSP) of *P. falciparum*, was the first malaria vaccine to complete Phase 3 clinical trials and receive WHO recommendation, in October 2021, following the successful Ghana-Kenya-Malawi pilot programme. A 4-

dose schedule in children showed approximately 30–40% efficacy against clinical malaria and 26–30% efficacy against severe malaria over 4 years. R21/Matrix-M, developed by the University of Oxford and manufactured by the Serum Institute of India, demonstrated approximately 75–77% efficacy in Phase 2 trials in West Africa and received WHO recommendation in October 2023, offering a higher-efficacy and higher-volume option. Both vaccines are now being rolled out across endemic African countries as part of routine immunization programs (Moorthy *et al*.,2004).

For travelers and residents in endemic areas, personal protection includes: use of insect repellents containing DEET, picaridin wearing long-sleeved clothing and trousers especially during dusk and dawn; sleeping under LLINs or in air-conditioned, screened rooms; and ensuring windows and doors are properly screened. Travelers should seek pre-travel medical advice regarding chemoprophylaxis and be aware of the need to seek urgent medical attention for febrile illness during or after travel to endemic areas(Kakuru *et al*.,2016).

11. Immunopathology

Immunity to malaria is naturally acquired through repeated exposure and is species- and stage-specific. It is never fully sterilizing individuals in highly endemic areas develop clinical immunity (protection against disease) before they develop anti-parasite immunity (protection against infection). Young children and non-immune adults remain highly susceptible to symptomatic and severe disease (Beeson *et al*.,2016).

The innate immune response is the first line of defense and involves recognition of Plasmodium components by pattern recognition receptors (PRRs) on monocytes, macrophages, dendritic cells, and NK cells. TLR2, TLR4, TLR7, TLR8, and TLR9 recognize GPI anchors, hemozoin, and Plasmodium RNA/DNA, triggering NF-kB-mediated production of TNF-alpha, IL-6, IL-12, and type I interferons. Unconventional T cell populations including NKT cells, gamma-delta T cells, and MAIT cells also contribute to innate responses. While robust innate responses help control parasitemia, excessive cytokine production contributes to immunopathology (Kurup *et al*.,2019).

Adaptive immunity involves both humoral (antibody-mediated) and cellular (T cell-mediated) components. Protective antibodies target merozoite surface proteins (MSP1, MSP2, AMA1), invasion ligands (EBA-175, Rh5), and variant surface antigens (VSAs) on infected RBCs. Antibodies prevent merozoite invasion, inhibit cytoadherence, and facilitate phagocytosis of parasitized cells. CD4+ T helper cells support B cell differentiation and antibody production, while regulatory T cells (Tregs) modulate excessive inflammation (Mohamed *et al*.,2024). The immune evasion strategies of *P. falciparum* particularly the clonal antigenic variation of PfEMP1 — ensure that complete immunity is never achieved, necessitating constant updating of the immune repertoire(Beeson *et al*.,2016).

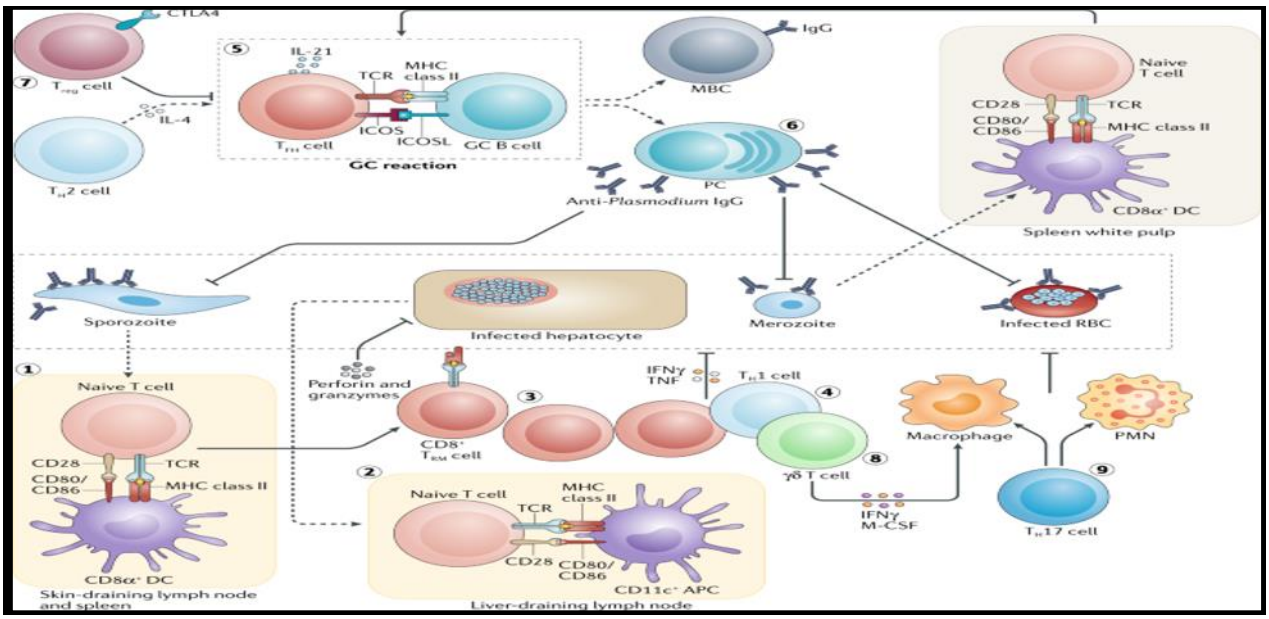

Figure 3 T cell-mediated immunity to malaria (Kurup *et al*.,2019)

12. Conclusion

Malaria remains a formidable public health challenge, particularly in sub-Saharan Africa where it disproportionately affects the most vulnerable populations — young children and pregnant women. The past two decades have seen remarkable progress in malaria control, with global case incidence declining by approximately 27% between 2000 and 2015, driven by the scale-up of LLINs, IRS, ACTs, and diagnostic testing. The approval of the RTS,S and R21 vaccines marks a historic milestone in malaria vaccine development.

However, the threat of artemisinin and partner drug resistance spreading from Southeast Asia to Africa, combined with insecticide resistance in mosquito vectors, raises serious concerns about the durability of current control strategies. Sustained investment in research, new tool development, health system strengthening, and global political commitment will be essential to achieving the ambitious goals of the WHO malaria elimination agenda and, ultimately, eradicating this ancient scourge.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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