International Research Journal of Education and Technology

Peer Reviewed Journal, ISSN 2581-7795

# A COMPREHENSIVE REVIEW ON MALARIA

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## Abstract

Malaria is a serious parasitic disease caused by Plasmodium species and transmitted to humans via the bite of infected female Anopheles mosquitoes. Despite advances in prevention and treatment, malaria continues to pose a major public health challenge, particularly in tropical and subtropical regions, with high morbidity and mortality rates. This review summarizes the epidemiology, life cycle, and pathophysiology of malaria, along with its clinical manifestations and diagnostic approaches. Special attention is given to current antimalarial therapies, including artemisinin-based combination therapies, chemoprophylaxis, and emerging drug resistance. Additionally, recent developments in malaria vaccines, vector control strategies, and novel therapeutic targets are discussed. The socioeconomic impact of malaria, including reduced workforce productivity, increased healthcare costs, and adverse outcomes in children and pregnant women, is also highlighted. Understanding the complex interactions between the parasite, host, and vector is critical for effective disease management and long-term control. This review aims to provide a comprehensive update on malaria, emphasizing recent advancements and challenges in prevention, treatment, and eradication efforts.

## Key words

Malaria, Plasmodium species,Anopheles mosquito,Antimalarial therapy,Drug resistance,Vector control,Epidemiology,Pathophysiology,Clinical manifestations

## Introduction

Malaria is a life-threatening parasitic disease caused by Plasmodium species and transmitted to humans through the bite of infected female Anopheles mosquitoes. Despite significant advances in prevention and treatment, malaria remains a major global public health concern, particularly in tropical and subtropical regions, with high morbidity and mortality rates. This review provides a comprehensive overview of malaria, focusing on its epidemiology, life cycle of the parasite, pathophysiology, clinical manifestations, and diagnostic approaches. [1]Special emphasis is placed on current antimalarial therapies, including artemisinin-

based combination therapies, chemoprophylaxis, and emerging drug resistance. Additionally, recent developments in malaria vaccines, vector control strategies, and novel therapeutic targets are discussed. Challenges such as antimalarial drug resistance, insecticide resistance, and socioeconomic factors affecting disease control are also highlighted. Understanding the complex interactions between the parasite, host, and vector is essential for improving disease management and achieving long-term malaria elimination. This review aims to summarize current knowledge and recent advancements in malaria research, providing valuable insights for healthcare professionals and researchers involved in malaria control and treatment.

Furthermore, malaria exerts a substantial economic and social burden on endemic countries by reducing workforce productivity, increasing healthcare expenditures, and hindering overall development. Recurrent infections can lead to chronic anemia, impaired cognitive development in children, and adverse pregnancy outcomes, including low birth weight and maternal mortality. These long-term consequences emphasize that malaria is not only an acute infectious disease but also a condition with lasting public health implications.[2].

Fig: 1.Female Anopheles mosquito

## 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). Of the 93 countries that were malaria endemic in 2015, 26% (including those that are now certified malaria free) met the GTS morbidity milestone for 2023, 34% made progress in reducing malaria case incidence but by less than the expected target, 15% had similar incidence to 2015 and 26% experienced an increase in case incidence. Despite some progress in malaria control, several factors, including funding gaps, poverty, and climate change, have contributed to setbacks in global efforts to reduce malaria transmission.[3].

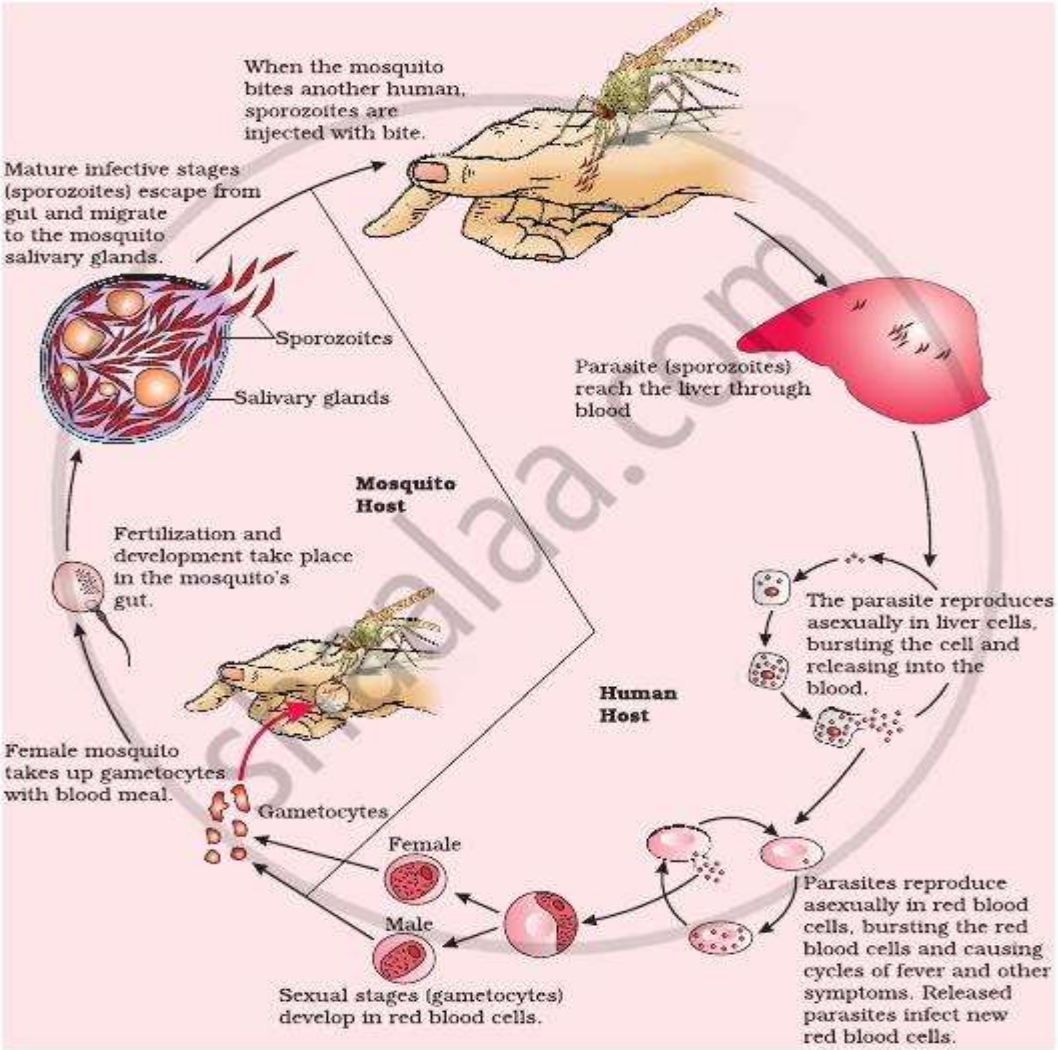
Sub-Saharan Africa remains the region most affected by malaria, accounting for ~94% of global cases in 2023, with the highest burden concentrated in countries such as Nigeria (30.9%), the Democratic Republic of the Congo (11.3%), Niger (5.9%), and United Republic of Tanzania (4.3%). In 2023, the region reported 246 million cases and 569,000 deaths. The overwhelming prevalence of *P. falciparum*, the most virulent malaria species, exacerbates the disease burden, especially among vulnerable groups such as young children58 and pregnant women.59 While adults in endemic areas often develop partial immunity,60 young children continue to face the greatest risk of severe disease.61 The high transmission rates are largely driven by favorable environmental factors, including the tropical climate, which supports year-round breeding of *Anopheles* mosquitoes.62,63,64 Despite this, significant challenges persist in controlling malaria, such as weak health infrastructure, limited access to diagnostic tools, and the high cost of prevention measures (such as insecticide-treated bed nets and antimalarial medications).65 These barriers hinder the effectiveness of malaria control efforts and contribute to the ongoing high burden of the disease. The rapid spread of artemisinin partial resistance (ART-R) in Africa also poses a serious threat to malaria control efforts, with potential economic and health impacts. Urgent regional initiatives are required to address ART-R through coordinated cross-border actions, enhanced surveillance, diversified treatments, and strengthened health systems, similar to the successful approaches in Southeast Asia, to prevent the further spread of resistance and safeguard malaria elimination goals.[4].

## Etiology of Malaria

protozoan parasites of the genus *Plasmodium* originate from photosynthetic protozoa named *Dinoflagellates*. About 200 different species of protozoa have been identified so far and among them, at least 13 species are known to be pathogenic to humans. Five of the parasites namely *P. falciparum, P. vivax, P. malariae, P. ovale* (*P. ovale curtisi* and *P. ovale wallikeri*), and *P. knowlesi* are well-known etiologies of malaria in humans. In Africa, the most prevalent and pathogenic species is *P. falciparum*. However, malaria infection from most malaria-endemic regions of Africa shows the presence of multiple sympatric species and co-infection within an individual human host or mosquito vector. [5].*P. malariae* is the species most commonly found in sympatry with *P. falciparum* in malaria-endemic regions of Africa. In each endemic area, malaria is transmitted by a specific set of *Anopheles* species. So far, more than 400 different species of *Anopheles* mosquitoes have been identified. But only 30 of them are known to transmit malaria. All vectors of malaria undergo the bite between dusk and dawn. Stability is observed in the distribution pattern of the mosquito species in malaria-endemic regions of the African continent. The complete disappearance of a given vector species from a region is unusual and when the non-indigenous vector is introduced to the area, it is a serious public health concern since it is known to result in devastating epidemics. Indigenous vectors are hard to eradicate with known vector eradication activities.

**The Life Cycle of Malaria Parasite**

Fig:2.Life cycle of parasite




The life cycle of the malaria parasite is a complex process involving an *Anopheles* mosquito and a vertebrate host. The first stage of the infection is the entrance of the sporozoites in mosquito saliva into the skin and bloodstream of the human host and then, it invades hepatocytes to undergo asexual replication.[6]. During this phase (hepatic or pre-erythrocytic phase) the rupture of infected hepatocytes results in the release of thousands of merozoites. In the case of *P. vivax* and *P. ovale* infections, some form dormant hypnozoites which remain within hepatocytes for periods of several months, and even as long as 4 years, before developing and multiplying to initiate a new episode of erythrocytic infection. [7].

The erythrocytic infection involves the interaction of the merozoites with the red blood cells (RBC). The merozoites head orients and adjoin with the erythrocytes membrane by deforming the surface host cell. Then, through parasite-induced reorganization of the erythrocyte cytoskeleton, the parasite enters the erythrocyte to undergo the second asexual reproduction. While younger erythrocytes are targeted favorably by *P. vivax* and *P. ovale*, erythrocytes of any age are invaded by *P. falciparum* and *P. knowlesi*. In contrast, *P. malariae* prefers senescent erythrocytes. [8].After invading RBC, merozoites reproduce into trophozoites and then into schizonts which erupt from the erythrocytes to release merozoites and reinvade new RBCs and continue the asexual replication cycle.

The sexual reproduction cycle of malaria starts when a portion of trophozoites matures to male and female sexual progeny or gametocytes. The transmission of the malaria parasite from the mammalian host to the mosquito is mediated by these gametocytes. During the bite of an anopheles mosquito, the matured gametocytes will be taken to the midgut of the mosquito. Inside the midgut, gametocytes get converted into fertile gametes and the next stage involves the conversion of zygotes into ookinetes which are motile and invasive. [9].The ookinetes in turn get converted into oocysts in the midgut basal lamina. The oocyst then matures releasing sporozoites, which migrate to the salivary gland of the mosquito. The parasite is transmitted to another mammalian host through an infected mosquito bite.[10].

## Pathophysiology of Malaria

The pathophysiology of uncomplicated malaria is characterized by fever secondary to the rupture of erythrocytes, macrophage ingestion of merozoites, and/or the presence of antigen-presenting trophozoites in the circulation or spleen which mediates the release of tumor necrosis factor α (TNF-α). Fever associated with malaria infection is known by its periodicity which differs among different species of the parasite. Tertian fever ("tertian malaria") is expected in *P. vivax* and *P. ovale* malaria as a progeny of schizonts matures every 48 hours in these species. In contrast, *P. malariae* is attributed to quartan fever ("quartan malaria") which occurs every 72 hours. However, the fever in falciparum malaria may occur every 48 hours, but is usually irregular, showing no distinct periodicity.

The binding of matured infected RBC to host endothelial cells (cytoadherence) is the major player in the pathogenesis of severe malaria. The expression of genes that encode proteins involved in cytoadherence and immune evasion explains the virulence of *P. falciparum* when compared with other species. The *P. falciparum* erythrocyte membrane protein 1 (PfEMP1), rifin, and stevor proteins are encoded by members of the var, rif, and stevor gene families, respectively. Var gene-encoded PfEMP1 is the best-characterized variant surface antigen which is expressed on the surface of infected erythrocytes where it mediates binding to endothelial receptors. [11].

The PfEMP1 family forms electron-dense protrusions named knobs on the membrane of parasitized RBC (pRBC) by getting inserted into and protruding from the erythrocyte membrane. Knobs serve as a site by which parasitized erythrocyte binds to other cell surfaces like normal RBC and endothelium.

The adhesion of parasitized erythrocytes to vascular endothelium leads to sequestration, the phenomenon by which infected RBCs translocated from the peripheral circulation by getting bound to the vascular endothelium, in the deep microvasculature of various tissues and organs. Host molecules like cluster of differentiation 36 (CD36), intercellular adhesion molecule-1 (ICAM1), thrombospondin (TSP), P-selectin, chondroitin sulfate A (CSA), and protein C receptor have been identified as receptor binding for pRBC to the endothelium. For instance, when PfEMP1 on infected RBCs binds to host receptors such as ICAM-1 and CD36 on brain endothelial cells, it mediates sequestration to cause cerebral malaria. [12].

On the other hand, pRBCs can bind to uninfected RBCs and impair microcirculation then cause hypoxia. The phenomenon is called rosettes, the spontaneous binding of normal RBCs to malaria-infected RBCs. Blood group antigens A and B, CD36, complement receptor 1 (CR1), and heparan sulfate-like glycosaminoglycans (HS-GAGs) are the five identified receptors on RBCs implicated in the process of rosettes.

Parasite-derived molecules called toxins are also implicated in the pathogenesis of severe malaria. Glycolipids named glycosylphosphatidylinositol (GPI), coupled with protein or free form, induce the overproduction of cytokines: TNF and interleukin I (ILI) by macrophages. Although cytokines have a physiological role in defending microorganisms including the malaria parasite when produced in lower amounts, overproduction causes high-grade fever, upregulation of endothelial receptor expression, and

upregulation of nitric oxide production, this in turn may cause local damage and suppression of erythrocyte production in the bone marrow.

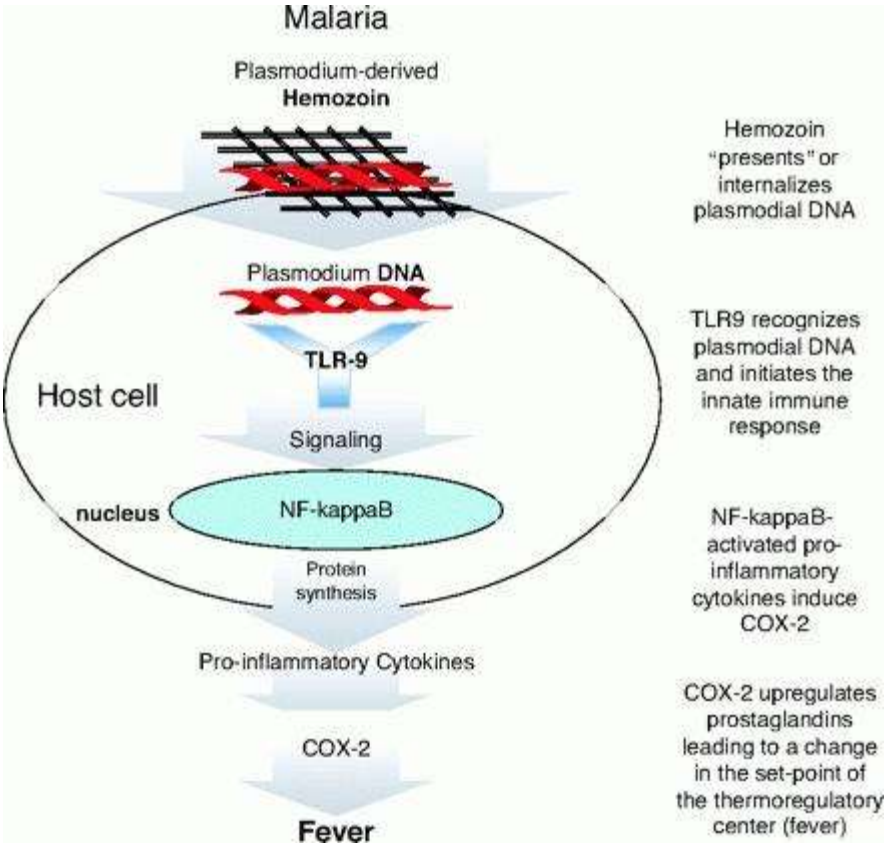



Fig:3. Flowchart of malaria causing fever

## Prevention

Malaria can be prevented by avoiding mosquito bites and by taking medicines. Talk to a doctor about taking medicines such as chemoprophylaxis before travelling to areas where malaria is common.

Lower the risk of getting malaria by avoiding mosquito bites:

- Use mosquito nets when sleeping in places where malaria is present.
- Use mosquito repellents (containing DEET, IR3535 or Icaridin) after dusk.
- Use coils and vaporizers.
- Wear protective clothing.
- Use window screens.

**Vector control**

Vector control is a vital component of malaria control and elimination strategies as it is highly effective in preventing infection and reducing disease transmission. The 2 core interventions are insecticide-treated nets (ITNs) and indoor residual spraying (IRS).

Progress in global malaria control is threatened by emerging resistance to insecticides among *Anopheles* mosquitoes. However, new generation nets, which provide better protection against malaria than pyrethroid-only nets, are becoming more widely available and represent an important tool in global efforts to combat malaria.[13].

*Anopheles stephensi* presents an added challenge for malaria control in Africa. Originally native to parts of south Asia and the Arabian Peninsula, the invasive mosquito species has been expanding its range over the last decade, with detections reported to date in eight African countries. *An. stephensi* thrives in urban settings, endures high temperatures and is resistant to many of the insecticides used in public health.

**Chemoprophylaxis**

Travellers to malaria endemic areas should consult their doctor several weeks before departure. The medical professional will determine which chemoprophylaxis drugs are appropriate for the country of destination. In some cases, chemoprophylaxis drugs must be started 2–3 weeks before departure. All prophylactic drugs should be taken on schedule for the duration of the stay in the malaria risk area and should be continued for 4 weeks after the last possible exposure to infection since parasites may still emerge from the liver during this period.[14].

**Preventive chemotherapies**

Preventive chemotherapy is the use of medicines, either alone or in combination, to prevent malaria infections and their consequences. It requires giving a full treatment course of an antimalarial medicine to vulnerable populations at designated time points during the period of greatest malarial risk, regardless of whether the recipients are infected with malaria.

Preventive chemotherapy includes perennial malaria chemoprevention (PMC), seasonal malaria chemoprevention (SMC), intermittent preventive treatment of malaria in pregnancy (IPTp) and school-aged children (IPTsc), post-discharge malaria chemoprevention (PDMC) and mass drug administration (MDA). These safe and cost-effective strategies are intended to complement ongoing malaria control activities, including vector control measures, prompt diagnosis of suspected malaria, and treatment of confirmed cases with antimalarial medicines.

**Vaccine**

Since October 2021, WHO has recommended broad use of the RTS,S/AS01 malaria vaccine among children living in regions with moderate to high *P. falciparum* malaria transmission. The vaccine has been shown to significantly reduce malaria, and deadly severe malaria, among young children. In October 2023, WHO recommended a second safe and effective malaria vaccine, R21/Matrix-M. Vaccines are now being rolled out in routine childhood immunization programmes across Africa. Malaria vaccines in Africa are expected to save tens of thousands of young lives every year. The highest impact will be achieved, however, when the vaccines are introduced alongside a mix of other WHO-recommended malaria interventions such as bed nets and chemoprophylaxis.

**Genetic mutations**

Most rapid diagnostic tests (RDTs) for malaria target one or two specific proteins produced by the *P. falciparum* malaria parasite: HRP2 and HRP3. However, parasites with genetic mutations, that prevent the expression of these proteins, are not detected by these tests. This means that malaria patients may not be diagnosed, allowing these mutated parasites to spread. In 2024, these mutated

parasites were reported in 42 malaria endemic countries; with Viet Nam reporting for the first time in 2024. Although the estimated prevalence is still low in most countries, it exceeds 15% in Brazil, Djibouti, Eritrea, Ethiopia, Nicaragua and Peru.

**Elimination**

Malaria elimination is defined as the interruption of local transmission of a specified malaria parasite species in a defined geographical area as a result of deliberate activities. Continued measures to prevent re-establishment of transmission are required.

In 2024, 37 countries reported fewer than 1000 indigenous cases of the disease, up from just 13 countries in 2000. Countries that have achieved at least 3 consecutive years of zero indigenous cases of malaria are eligible to apply for the WHO certification of malaria elimination. Since 2017, 14 countries have been certified by the WHO Director-General as malaria-free, including Maldives (2015), Sri Lanka (2016), Kyrgyzstan (2016), Paraguay (2018), Uzbekistan (2018), Argentina (2019), Algeria (2019), China (2021), El Salvador (2021), Azerbaijan (2023), Tajikistan (2023), Belize (2023), Cabo Verde (2024), Egypt (2024), Georgia (2025), Suriname (2025) and Timor-Leste (2025).

## Differential Diagnosis

The differential for undifferentiated fever is extremely broad and varies based on geographic location and age. In a 2017 review of fever in returning travelers, 77% had protozoal malaria, 18% had a bacterial enteric fever (*Salmonella enterica, typhi*, or *paratyphi*), and 5% had another infection. In patients presenting with fever and significant somnolence or seizures, viral or bacterial meningitis or meningoencephalitis must remain on the differential and prompt consideration of lumbar puncture. Viral etiologies include avian influenza, Middle East respiratory syndrome coronavirus, hemorrhagic fever (Ebola virus, Lassa fever, Marburg hemorrhagic fever, Crimean-Congo hemorrhagic fever), yellow fever, dengue, Japanese encephalitis, Rift Valley fever, hepatitis virus (A or B), viral gastroenteritis, and rabies. Bacterial etiologies include anthrax, epidemic typhus, ehrlichiosis, leptospirosis, melioidosis, murine (endemic) typhus, spotted fever group rickettsioses, Q fever, and Yersinia pestis.

The differential in children varies by region, with the most likely etiology being a viral or bacterial infection. In a 2014 study of febrile children in a tropical region, 10.5% were diagnosed with malaria, 62% were diagnosed with a respiratory infection, 13.3% with a systemic bacterial infection (usually *staphylococcus* or *streptococcus* bacteremia), and 10.3% with gastroenteritis (viral or bacterial). Urinary tract infection and typhoid may also be considerations. Meningitis must be ruled out in somnolent children.

## Treatment / Management

Treatment for patients diagnosed with malaria includes schizonticidal medications, supportive care, and hospitalization for high-risk patients. Naïve adult and pediatric patients receiving active antimalarial treatment should remain inpatient for at least 24 hours to ensure adequate and correctly timed medication dosing and to trend parasitemia to evaluate treatment response. Higher initial parasitemia and poor downtrend are associated with fluid imbalance, renal dysfunction, and respiratory distress syndrome. Unstable patients, particularly those with cerebral malaria or significant respiratory sequelae, require intensive care. [15].

Treatment involves combination therapy targeting both the hepatic and erythrocytic forms. The chief antimalarials are chloroquine, hydroxychloroquine, primaquine, artemisinin-based combination therapy (ACT), and atovaquone-proguanil. Chloroquine and hydroxychloroquine are synthetic forms of quinine. They disrupt the erythrocytic stage by interfering with parasitic hemoglobin metabolism and increasing intracellular pH. They generally require two days of treatment, allowing for better tolerance and shorter admissions. However, chloroquine may enhance gametogenesis, contributing to resistance, which is a concern, particularly in South Asia. Primaquine is a hypnozointocidal agent added for P. vivax or P. ovale infection for the eradication of liver parasites and the prevention of dormancy and relapse. [16].

Primaquine is contraindicated in pregnant and G6PD deficient patients due to fetal teratogenicity and hemolytic reaction (will see bite cells and Heinz bodies on blood smear), respectively.[3] Artemisinins are active against all parasite lifecycle stages. Atovaquone targets the cellular electron transport chain inhibiting ATP production; proguanil enhances atovaquone's effect by sensitizing parasitic mitochondria.[21] Atovaquone-proguanil is active against the erythrocytic and extraerythrocytic forms.

Per the 2019 CDC Guidelines below, appropriate treatment depends on the *Plasmodium* species, clinical stability, age of the patient, and regional antimalarial susceptibility:

- Uncomplicated *P. falciparum* infections in chloroquine-resistant or unknown regions are treated with atovaquone-proguanil 250 mg/100 mg 4 tabs (pediatric: varied weight-based dosing, 6.5 mg/25 mg tabs) daily for 4 days; or artemether-lumefantrine 20 mg/120 mg 4 tabs (pediatric: varied weight-based tabs) at initial dose, then 8 hours later, then twice daily for 2 days; or quinine sulfate 542 mg (pediatric: 8.3 mg/kg) three times daily for 3 days (7 days if in Southeast Asia) plus either doxycycline 100 mg daily for 7 days (pediatrics 2.2 mg/kg every 12 hours), or tetracycline 250 mg daily for 7 days (pediatric: 25 mg/kg/day divided four times daily for 7 days), or clindamycin 20 mg/kg/day divided three times daily for 7 days (pediatric: same); or mefloquine 684 mg (pediatric: 13.7 mg/kg) loading dose followed by 456 mg (pediatric: 9.1 mg/kg) every 6 to 12 hours for total of 1250 mg (pediatric total: 25 mg/kg).[17].
- Uncomplicated *P. vivax* or *P. ovale* infections in chloroquine-sensitive regions receive treatment with chloroquine phosphate or hydroxychloroquine as per above, plus either primaquine phosphate 30 mg (pediatric: 0.5 mg/kg) daily for 14 days or tafenoquine 300 mg once (same in children older than 16 years).

- Uncomplicated *P. vivax* infections in chloroquine-resistant regions (Indonesia, Papua New Guinea) get treated with quinine sulfate as per above plus either doxycycline, primaquine, or tafenoquine as per above; or atovaquone-proguanil as per above plus either primaquine or tafenoquine; or mefloquine as per above plus either primaquine or tafenoquine as per above.
- Uncomplicated infections with any species in pregnant women in chloroquine-sensitive regions require treatment with chloroquine or hydroxychloroquine as per above.
- Uncomplicated infections with any species in pregnant women in chloroquine-resistant regions are treated with quinine sulfate as per above plus either clindamycin or mefloquine as per above in the first, second, or third trimesters; or artemether-lumefantrine as per above in only the second and third trimesters.
- Severe malaria infection in unstable, non-pregnant patients in all regions includes IV artesunate 2.4 mg/kg (pediatric: children greater than 20 kg receive 2.4 mg/kg, children less than 20 kg receive 3.0 mg/kg) at 0, 12, 24, and 48 hours and either artemether-lumefantrine, atovaquone-proguanil, doxycycline, or mefloquine as per above.[18].

## Conclusion

Malaria remains a major global public health challenge despite significant advances in its prevention, diagnosis, and treatment. Caused by Plasmodium species and transmitted by female Anopheles mosquitoes, the disease continues to disproportionately affect populations in tropical and subtropical regions, particularly in sub-Saharan Africa. The complex life cycle of the parasite, its ability to evade host immune responses, and the diversity of clinical manifestations contribute to the persistent burden of malaria worldwide.

Considerable progress has been made in understanding the epidemiology, pathophysiology, and clinical features of malaria, which has led to the development of effective diagnostic tools and therapeutic strategies. Artemisinin-based combination therapies remain the cornerstone of malaria treatment, while chemoprophylaxis and preventive chemotherapies play a crucial role in protecting vulnerable populations. However, the emergence and spread of antimalarial drug resistance, insecticide resistance in mosquito vectors, and genetic mutations affecting diagnostic accuracy pose serious threats to current control efforts.

Integrated prevention strategies, including vector control measures such as insecticide-treated nets, indoor residual spraying, and environmental management, remain essential for reducing transmission. The introduction of effective malaria vaccines, including RTS,S/AS01 and R21/Matrix-M, represents a significant milestone and offers renewed hope for reducing severe disease and mortality, particularly among children. Nonetheless, vaccines must be implemented alongside existing interventions to achieve maximum impact.

Beyond its immediate clinical consequences, malaria imposes a substantial socioeconomic burden by reducing productivity, increasing healthcare costs, and adversely affecting maternal and child health. These long-term effects highlight the need for sustained investment, strong health systems, and coordinated global and regional efforts.

In conclusion, achieving malaria elimination and eventual eradication requires a multifaceted and sustained approach that combines effective treatment, robust surveillance, innovative research, vector control, vaccination, and addressing social and economic determinants of health. Continued commitment from governments, international organizations, researchers, and communities is essential to overcome current challenges and to move closer to a malaria-free world.

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