



An Ephemeral Review on Malaria

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ABSTRACT

Malaria, of the genus *Plasmodium*, is caused by the protozoan parasites. Most of the transmission is through the bite of an infected female anopheline mosquito. More than 500 million people are affected with malaria each year, resulting in 1-2 million fatalities. *Falciparum* is responsible for the majority of malaria deaths. Pregnant women, children, and anyone who are immunocompromised have the highest rates of morbidity and mortality. Myalgias or arthralgia, malaise or weakness, headache, and chills are the most common symptoms. Microscopy, antigen detection, and polymerase chain reaction (PCR) are among the procedures used to detect malaria parasites. Malaria in pregnancy is a major cause of severe maternal anemia, low birth weight neonates, preterm delivery, and higher infant and maternal death, with primigravidae experiencing these issues more frequently than multigravidae. Chloroquine is the first-line drug for treating three so-called benign malaria, *Plasmodium vivax*, *Plasmodium malariae*, and *Plasmodium ovale*. Artemisinin and derivatives are now mostly used in various regimens. For chloroquine-resistant *falciparum malaria*-quinine, mefloquine, sulfadoxine-pyrimethamine and for chloroquine-sensitive; chloroquine or combination of chloroquine or primaquine are used. The steady decline in the effectiveness of existing anti-malarial monotherapies, most endemic countries have adopted artemisinin combination therapy (ACT) Primaquine helps to prevent malaria recurrence. Severe malaria is a multi-organ disease - Cerebral malaria, pulmonary oedema, acute renal failure, severe anaemia, acidosis and hypoglycemia.

Keywords: Hemozoin, Malaria In Pregnancy, Primigravidae, Multigravidae, Acidosis, Sesquiterpene Lactones, Arthralgia, Parasitemia, Gametocytogenesis.

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Occurrence of malaria globally

Malaria is considered the most common infectious disease in tropical and subtropical areas, and it is a major worldwide health issue, with over 40 per cent of the world's population living in places where malaria is a danger. More than 500 million people are affected with malaria each year, resulting in 1-2 million fatalities; 90% of them are children in Sub-Saharan Africa¹. According to the World Health Organization's (WHO) most current annual global malaria report, it was estimated as 229 million malaria cases in 2019, with 409,000 fatalities⁶. Despite the fact that malaria cases have been reported in 87 countries around the world, Africa is the one that has been hit the hardest by the disease, accounting for 90% of all cases; 7% of instances occur in Southeast Asia and less than 1% in Central and South America. Approximately 2% of instances are found in the Eastern Mediterranean region^{6,7}. *Falciparum* is responsible for the majority of malaria deaths. Pregnant women, children, and anyone who are immunocompromised have the highest rates of morbidity and mortality²⁰. Malaria, which is responsible for roughly 99 per cent of malaria infections in Africa and 94 per cent of all malaria cases and fatalities worldwide in 2019^{3,6}.

Population at Stake

Malaria infection is linked to people with low socioeconomic status¹⁶. Living near a stream was associated with an increased risk of malaria, but only early

INTRODUCTION

Malaria, of the genus *Plasmodium*, is caused by the protozoan parasites, also called the "King of Diseases". The known Five types of *Plasmodium* species that cause diseases in humans are *P.falciparum*, *P.vivax*, *P.malariae*, *P.ovale*, *P.knowlesi*^{1,3}. Most of the transmission is through the bite of an infected female anopheline mosquito. 'Congenital' (transplacental), iatrogenic (e.g., via blood transfusion) and needle-stick or laboratory accident are other rare routes of transmission². Fever is subjected as the main symptom of malaria; usually, children of age under five years suffer from 2 to 11 episodes of fever per year which are often from another origin. As the onset of malaria episodes is in the house hold environment, making early decisions is the key⁴. Evidence shows that the prevalence of malaria (both infection and clinical disease) is higher in pregnant than in non-pregnant women. Malaria infections can be controlled but not cleared during pregnancy despite the immune tolerance, whereas adults have acquired immunity against malaria.⁵



in the transmission season¹⁷. Malaria poses the greatest risk to children and female household members¹⁶. The rainy season, low gestational age, young age of the mother, and living in a rural region were all found to be substantially linked with malaria infection in univariate analysis. Rather than parity, earlier gestation age and young age are key risk factors for malaria infection in pregnant women¹⁸. We discovered that women were more infected during the first trimester of pregnancy¹⁹.

Development of Disease

Plasmodium spp. is a global disease with a complicated lifecycle that alternates between female Anopheles mosquitoes and vertebrate hosts and necessitates the production of distinct zoite forms to infiltrate different cell types at different phases¹⁵.

Anopheles mosquitoes inject sporozoites into human hepatocytes to start the infection process (pre-erythrocytic infection takes around 2 weeks). Hepatocytes break, releasing merozoites, which cause erythrocytic infection and cause malaria symptoms⁸. When merozoites leave the liver, they infiltrate erythrocytes and grow into early trophozoites. When the parasite divides, the trophozoites become schizonts, which are made up of multiple daughter merozoites (blood schizogony)³⁹. After being ingested into the mosquito midgut, blood-stage parasites can cycle many times via red blood cells (RBCs) or differentiate into male and female gametocytes ready for sexual reproduction. The resulting ookinete migrates through the midgut wall and begins asexual replication, forming a new brood of sporozoites that will be placed in the mosquito salivary glands and released into another human host⁸. Exponential parasite growth with greater than 10-fold increase every 48 hr means that high total body parasitemia is achieved quickly. Most malaria deaths occur in children and are dominated by three syndromes that can occur separately or in combination: severe anemia, cerebral malaria, and respiratory distress. In a proportion of untreated or partially treated individuals, the initial infection is not controlled and progresses to severe or complicated malaria, which may lead to death¹⁵.

Clinical Manifestations

Clinical diagnoses are made based on the signs and symptoms of the patient as well as physical examination findings. Fever, headache, weakness, myalgia, chills, disorientation, abdominal pain, diarrhoea, nausea, vomiting, anorexia, and pruritus are among the first signs of malaria. Myalgias or arthralgia, malaise or weariness, headache, and chills are the most common symptoms. Following the discovery of parasites in the peripheral blood and the start of treatment, symptom frequency increased dramatically^{1,14}. Fever, pains, and anaemia are the most common malaria symptoms. The typical tertian or quartan fever pattern, in which each paroxysm lasts between 6 and 12 hours and is divided into cold, hot, and sweating stages, is frequently seen in so-called "benign" malaria. Fever is

thought to be a parasite-killing adaptive reaction of the host. The fever in falciparum malaria, on the other hand, is frequently erratic. Water-borne and air-borne infections, for example, frequently produce symptoms that aid in transmission (e.g., diarrhoea and cough)¹⁵.

Diagnosis

Modalities for the diagnosis of malaria¹¹:

(HRP-2) = Histidine-rich protein-2,

(pLDH) = Plasmodium lactose dehydrogenase.¹²

Diagnostic modality	Test principle
Light microscopy of Giemsa - stained blood smears	Direct visualization of parasites
Immunochromatographic assays (rapid diagnostic tests)	Detection of parasite antigens: HRP-2, pLDH or parasite aldolase
PCR	Amplification of 18S rRNA genes or other plasmodium genes
Flow cytometry	Detection of hemozoin within phagocytes by depolarization of laser light.
Laser desorption Mass spectroscopy	Detection of heme from parasite hemozoin by mass spectrometry

Targets of Malaria Diagnosis: iRBCs or leukocytes that have ingested parasites are cellular targets of malaria diagnosis in humans. Nucleic acids, antigens, and hemozoin are examples of detectable analytes (chemical constituents). Human anti-parasite antibodies are among the other analytes⁸.

Laboratory diagnosis of Malaria: Microscopy, antigen detection, and polymerase chain reaction (PCR) are among the procedures used to detect malaria parasites in the peripheral blood¹⁰. Because there are inadequate microscopes and/or skilled microscopists to read and interpret the slides, traditional diagnosis based on the inspection of Giemsa-stained thick and thin blood smears under a microscope is incorrect in many regions. Newer, more powerful malaria diagnostics are now available, and the relative merits of approaches based on fluorescence microscopy or nucleic acid detection (including PCR) both necessitate skills and equipment that are not uniformly available in many malaria-endemic areas. Diagnostic tests based on immuno-assays, which were recently launched, overcome this problem because they are simple to conduct and interpret and do not require complex equipment or expert help. They're also quick (<10 minutes/test) and inexpensive⁹.



Malaria in Pregnancy

Pregnant women are more likely than non-pregnant women to contract malaria, presumably due to immunological, hormonal, or other changes that occur during pregnancy⁵. Malaria in pregnancy is a major cause of severe maternal anaemia, low birth weight neonates, preterm delivery, and higher infant and maternal death, with primigravidae experiencing these issues more frequently than multigravidae^{21,5}. Low maternal age, low parity, and low gestational age are all risk factors for malaria in pregnancy (MiP). It is well known that younger women (primigravidae and multigravidae), particularly adolescents, are more susceptible to malaria infection than older women, regardless of parity⁵. Malaria infection in pregnant women causes more severe symptoms and results, including miscarriage, intrauterine death, premature birth, low-birth-weight neonates, and neonatal death²⁰. Malaria prevalence appears to rise during the second trimester⁵.

Quinine plus clindamycin for 7 days is the first-line treatment for uncomplicated malaria in the first trimester, followed by artesunate plus clindamycin for 7 days. Both artesunate and quinine (parenteral) may be considered in the first trimester⁵. For severe malaria, parenteral artesunate is favoured over quinine in the second and third trimesters, and the first-line treatment is an artemisinin-based combination therapy (ACT) known to be efficacious in the region, or artesunate and clindamycin for 7 days, or quinine and clindamycin for 7 days⁵. During the initial three days of treatment, the short-acting but strong artemisinin component (i.e., artemether, artesunate, or dihydroartemisinin) significantly reduces the number of parasites²². The longer-acting companion medicine (lumefantrine, piperaquine, amodiaquine, or mefloquine) kills the remaining parasites, preventing malaria from returning²². The World Health Organization (WHO) mainly recommends that all pregnant women with uncomplicated *P. falciparum* malaria be treated with artemisinin-based combination therapy during the second or third trimester²². However, treatment should not be postponed and should begin as soon as possible with the most easily available medicine⁵. Regular chemoprophylaxis, intermittent anti-malarial medication, and insecticide-treated bednets are all preventative methods²¹.

Congenital malaria: Where placental malaria was active at the time of delivery, cord blood parasitaemia may be found. Babies born to non-immune women who have untreated or incompletely treated malaria are at risk of developing an infection at birth²¹.

Management

The infecting *Plasmodium* species, the severity of the disease, the patient's age, the degree of background immunity (if any), the treatment susceptibility of the infecting parasites, and the availability of medications and resources must all be considered while treating malaria

^{23,24}. Malaria caused by the *falciparum* parasite is still a major source of morbidity and mortality around the world²⁵. Patients with malaria should be treated right away since *P. falciparum* infections can proceed to severe disease or death in as little as 1 to 2 days. If the species cannot be determined, the patient should be treated as if infected with *P. falciparum* until the infecting species can be determined²⁶.

Cinchona alkaloids (quinine and quinidine), chloroquine, amodiaquine, pyrimethamine, pyrimethamine/sulfadoxine, mefloquine, pyrimethamine/ sulfadoxine/ mefloquine, sesquiterpene lactones (Artemisinin, Artemether, and Sodium Artesunate), primaquine, and other drugs are currently available antimalarials²⁷.

In almost every country of the world, chloroquine is the first-line drug for treating three so-called benign malaria, *Plasmodium vivax*, *Plasmodium malariae*, and *Plasmodium ovale* (World Health Organization 1997), though Artemisinin and derivatives are now used in various regimens and appear to be effective (World Health Organization 1997)^{24,28}. Two particularly effective regimens for chloroquine-resistant *falciparum* malaria include at least four doses of quinine followed by a single dose of mefloquine or a single dose of sulfadoxine-pyrimethamine²⁹. Oral quinine plus clindamycin, or quinine/quinidine plus doxycycline, is a reasonable alternative in older children (>7 years of age)²³.

A course of chloroquine [10 mg/kg followed either by 10 mg/kg at 24 hr and 5 mg/kg at 48 hr or by 5 mg/kg at 12, 24, and 36 hr (total dose, 25 mg/kg)] can be used to treat *falciparum* malaria that is chloroquine-sensitive. All other kinds of malaria, including *vivax*, should be treated with a combination of chloroquine and primaquine^{29,24}. Because of the steady decline in the effectiveness of existing anti-malarial monotherapies, most endemic countries have adopted artemisinin combination therapy (ACT) as an anti-malarial drug policy because of side effects, poor compliance, and the introduction of newer, better-tolerated therapies like ACT^{30,31}.

All other malarious locations have chloroquine-resistant *P. falciparum* strains, and three treatment alternatives are currently recommended: (a) oral quinine plus tetracycline, doxycycline, or clindamycin; (b) atovaquone-proguanil; or (c) mefloquine [15 mg/kg in a single dose]. The first two alternatives are the best. When mefloquine is taken at therapy levels, a greater rate of moderate to severe neuropsychiatric responses is reported. Atovaquone and proguanil combination was found to be more tolerable than quinine and tetracycline^{26,24}. Artemisinin [Artesunate - In combination with a total of 25 mg of mefloquine/kg, give a total of 10–12 mg/kg in divided doses over 3–5 days, If used alone, the same total dose is given over 7 days (usually 4 mg/kg initially followed by 2 mg/kg on days 2 and 3 and 1 mg/kg on days 4–7); Artemether - Same regimen as for artesunate] has been demonstrated to be effective in vivo in the treatment of CRPF infection in recent research^{32,24}.



There hasn't been any indication of resistance to artemisinin compounds in *P. falciparum* malaria. These medications work quickly to destroy malaria parasites that have become resistant to other treatments³³. *P. falciparum* asexual stage parasites are swiftly killed by ACT, which prevents gametocytogenesis. Artemisinins are active against gametocytes in stages I–IV but not adult infectious gametocytes (stage V)³⁴.

Oral quinine [10 mg salt/kg every 8 hr for 7 days, combined with tetracycline (4 mg/kg four times daily) or doxycycline (3 mg/kg once daily) for 7 days. Clindamycin (10 mg/kg twice daily for 3–7 days) is an alternative to tetracycline] is still being utilized as a treatment for uncomplicated malaria in a number of places, owing to periodic stockouts of the required ACT^{30,24}.

Primaquine helps to prevent malaria recurrence. A single dosage of primaquine is now advised at the end of an artemisinin-based combination treatment in places where transmission reduction is a priority^{35,36}. Although the majority of cases are straightforward, 1% develop severe disease, resulting in more than 400 000 fatalities every year, 60% of which are children under the age of five. Pregnant women are more likely to have a higher risk of severe disease and mortality³⁷.

When appropriate treatment is delayed, severe malaria develops. Severe malaria is a multi-organ disease with cerebral malaria as one of its forms. It is critical to have adequate supportive treatment in order to survive³⁸.

Cerebral malaria, pulmonary oedema, acute renal failure, severe anaemia, and/or bleeding are the most serious sequelae of severe malaria. The most prevalent metabolic problems are acidosis and hypoglycemia. Any of these issues can develop quickly, leading to death in a matter of hours or days³⁹. Quinine is the most effective treatment for severe *falciparum* malaria when given as an intravenous infusion²⁹. According to recent research, intravenous artesunate, rather than quinine, should be used to treat severe *falciparum* malaria in adults and children and is currently recommended as the first-line therapy^{30,37}.

The use of an artesunate suppository containing both artesunate and an antibiotic (ideally one with anti-malarial activity) could be the next logical step, and early research into its feasibility is now underway⁴⁰.

CONCLUSION

Malaria is a mosquito-transmitted parasitic infection caused by the five *Plasmodium* species. It is the main threat in tropical and sub-tropical areas, the treatment for which should be done as quickly as possible. If delayed many other major complications might occur. For the treatment of Malaria, the early diagnosis of the disease is important. There is a need to find new diagnostic tests, the results of which should be quick and accurate. One such tests are the immuno-assays which were recently introduced are simple to conduct, quick and are

inexpensive. Another important point to be considered is the increase in the resistance of drugs by the disease which makes it harder for the treatment to be done. To overcome this, the combination of new anti-malarial drugs is required for better treatment and to halt the transmission. The artesunate suppository might be the new step in the treatment of malaria. Designing Vaccines can also be useful in the early precaution for malaria.

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