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REVIEW

Malaria: An Overview

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Abstract: Malaria is a global public health burden with an estimated 229 million cases reported worldwide in 2019. About 94% of the reported cases were recorded in the African region. 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. The life cycle of the malaria parasite is a complex process comprising an *Anopheles* mosquito and a vertebrate host. Its pathophysiology 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). Malaria can be diagnosed through clinical observation of the signs and symptoms of the disease. Other diagnostic techniques used to diagnose malaria are the microscopic detection of parasites from blood smears and antigen-based rapid diagnostic tests. The management of malaria involves preventive and/or curative approaches. Since untreated uncomplicated malaria can progress to severe malaria. To prevent or delay the spread of antimalarial drug resistance, WHO recommends the use of combination therapy for all episodes of malaria with at least two effective antimalarial agents having a different mechanism of action. The Centers for Disease Control (CDC) emphasizes that there is no prophylactic agent that can prevent malaria 100%. Therefore, prophylaxis shall be augmented with the use of personal protective measures.

Keywords: malaria, resistance

Introduction

Malaria is named after the Italian term "mal'aria", which means "bad air" to represent the association of the disease with marshy areas.[1] It is an endemic vector-borne parasitic disease caused by protozoan parasites of the genus *Plasmodium* in tropical and subtropical regions worldwide.[2] *Plasmodium* consists of over 200 species, infecting mammals, birds, and reptiles, and malaria parasites generally tend to be host-specific.[3] *Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, Plasmodium ovale*, and *Plasmodium knowlesi* are the five known species of the genus *Plasmodium* that causes malaria in humans.[4,5] Of the five *Plasmodium* species that cause malaria in humans, *P. falciparum* causes severe malaria.[6]

The life cycle of the parasites is a complex process occurring in both vertebrate hosts and a mosquito vector. Besides, it undergoes both sexual and asexual reproduction mechanisms. This makes the development of drugs and vaccines challenging.[7]

The first trial to treat malaria dates back to the 2nd century before Christ (168 BC) when China used Qinghai (Latin *Artemisia annua*) for the treatment of fever and chills.[8] The next documented trial was in the 16th century when the Spanish invaders in Peru discovered the *Cinchona* medications against malaria from the bark of the *Cinchona* tree (Latin *Cinchona succirubra*). The active ingredient of *Cinchona succirubra* which had been used for many years in chemoprophylaxis and treatment of malaria was isolated in 1820 by the French chemists Pierre Joseph, Pelletie, and Joseph Bienaimé Caventou. In 1970, a group of Chinese scientists led by Dr Youyou Tu isolated an active substance Artemisinin, a compound that has proven activity against malaria, from the plant *Artemisia annua*.[9]

Although artemisinin and its derivatives are potent treatments for malaria and are being widely used in combination therapies worldwide, resistance is emerging in some parts of the world. This calls for the need to discover new antimalarial agents possessing high therapeutic value with minimal toxicity, and lower cost.[10]

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Tackling malaria transmission by interrupting parasite transmission or by tackling the insect vector was started in the late 1800s after Laveran in Algeria discovered the cause of malaria and the Plasmodium parasite around 1880–1882. In the early 1900s, numerous effective local initiatives were reported in different parts of the world where malaria was common.[11] Later on, DDT (dichloro-diphenyl-trichloroethane), came to the picture. Even though it was synthesized in 1874, it was only in 1939 that its insecticide properties were discovered. It was used extensively during and after World War II. Due to its high efficacy on malaria vectors, it became the main tool of the malaria eradication campaign launched in 1955 under the auspices of the League of Nations. But due to failure to meet expectations, it was officially abandoned in 1978.[12] Afterwards, other and costlier insecticides were developed (pyrethroids) for use in the impregnation of bed nets. However, the impact of long-lasting impregnated nets (LLINs) has been compromised in recent years by several factors: the emergence of resistance to the insecticide in the mosquito populations, the diversity and changes in the behavior of *Anopheles* since some of the species are (or have become) exophagic/exophilic and early biters.[12]

Epidemiology of Malaria

Following the second world war, incredible success was achieved with the discoveries of DDT and chloroquine, lowering the global extents of both *P. vivax* and *P. falciparum*, and benefiting enormous parts of the Americas, Europe, and Asia.[13] These tremendous gains in malaria control continued until the first decade of the 21st century, but the second decade appears to be a bit harder. Malaria incidence has been on the rise in several places since 2014.[14] In 2019, an estimated 229 million cases were reported worldwide (from 87 malaria-endemic countries). About 94% of the reported cases (215 million cases) were recorded in the African region. The Southeast Asia region accounted for about 3% of the burden of malaria cases globally. In the same year, an estimated 409,000 deaths from malaria occurred worldwide of which 94% happened in Africa.[15]

Malaria affects majorly children under the age of 5 years; with 67% death from the total death in 2019. Underdeveloped immunity is thought to be the major reason that makes children under 5 years of age vulnerable to malaria. Aftereffects of fever and illness like reduced appetite, limited social life, and restricted play contribute to meager growth.[16]

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.[17] 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.[18]

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.[19] *P. malariae* is the species most commonly found in sympatry with *P. falciparum* in malaria-endemic regions of Africa.[20]

In each endemic area, malaria is transmitted by a specific set of *Anopheles* species.[21] 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.[22]

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.[21]

The Life Cycle of Malaria Parasite

The life cycle of the malaria parasite is a complex process involving an *Anopheles* mosquito and a vertebrate host.[23] 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.[24] During this phase (hepatic or pre-erythrocytic phase) the rupture of infected hepatocytes results in the release of thousands of merozoites.[25] 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.[26]

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.[27] 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.[24] 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.[27]

The sexual reproduction cycle of malaria starts when a portion of trophozoites matures to male and female sexual progeny or gametocytes.[28] 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.[29] 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.[30] 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.[31]

Pathophysiology of Malaria

The pathophysiology of uncomplicated malaria is characterized by fever[25] 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).[32] 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.[25]

The binding of matured infected RBC to host endothelial cells (cytoadherence) is the major player in the pathogenesis of severe malaria.[33] 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.[34] 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.[35]

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.[36]

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.[37] 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.[38] 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.[39]

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.[37]

Parasite-derived molecules called toxins are also implicated in the pathogenesis of severe malaria.[40] Glycolipids named glycosylphosphatidylinositol (GPI), coupled with protein or free form, induce the overproduction of cytokines: TNF and interleukin I (ILI) by macrophages.[41] Although cytokines have a physiological role in defending

microorganisms including the malaria parasite when produced in lower amounts,[42] 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.[37]

Diagnosis of Malaria

Diagnosis of malaria can be done through clinical observation of the signs and symptoms of the disease. However, clinical diagnosis of malaria has poor accuracy due to the resemblance of the clinical symptoms with other tropical diseases and the possibility of incidence of coinfection.[43] Other diagnostic techniques used to diagnose malaria are the microscopic detection of parasites from blood smears and antigen-based rapid diagnostic tests. The latter is based on immunologically detecting different malaria antigens such as lactate dehydrogenase (LDH), aldolase, and histidine-rich protein-2 (HRP-2) in a small amount of blood.[44]

Although microscopy and rapid diagnostic test (RDTs) are being used widely, they are less sensitive and less specific to malaria parasites. The shortcomings of the conventional techniques necessitate the development of molecular and biosensing-based methods which are more accurate, easy to quantify, and allow point-of-care (POC) application. Thus, newly developed techniques like dielectrophoretic and magnetophoretic detection are emerging.[45] However, polymerase chain reaction (PCR)-based nucleic acid detection methods that are highly sensitive are applicable only in research laboratories because of their high running and maintenance costs.[44]

Management of Malaria

The management of malaria involves preventive and/or curative approaches. Since untreated uncomplicated malaria can progress to severe malaria, early diagnosis and effective rational treatment are the first core principles in the management of malaria. To prevent or delay the spread of antimalarial drug resistance, WHO recommends the use of combination therapy for all episodes of malaria with at least two effective antimalarial agents having a different mechanism of action.[46]

Pharmacological Treatment of Malaria

Antimalarial agents can be grouped as quinoline derivatives, antifolates, and artemisinin derivatives based on their chemical structures and/or mechanism of action.[47] Quinoline derivatives that comprise chloroquine, amodiaquine, quinine, quinidine, mefloquine, primaquine, lumefantrine, and halofantrine are active against the erythrocytic stage of the parasite.[48] Among them, primaquine is active against the hepatic stage of the parasite and gametocytes.[49]

The antimalarial mechanism of quinolone derivatives is proposed to be the result of the following two-step activities; the first step involves retarding deposition of heme onto the crystal surface by capping the growing hemozoin crystals and the second step involves complexing with free heme in the lumen of the digestive vacuole. The overall outcome of both steps is killing the parasite by halting heme crystallization after being released from the hemoglobin.[50]

Antifolate antimalarial agents can be grouped as class I and class II, based on their mode of action. Class I antifolate agents act by inhibiting the production of dihydrofolic acid through inhibition of the enzyme dihydropteroate synthase (DHPS) and hence the synthesis of nucleic acid.[51] Class II antifolate agents block the reduction of dihydrofolate to tetrahydrofolate by inhibiting the enzyme dihydrofolate reductase (DHFR) in the parasite. Tetrahydrofolate is important for the production of nucleic acid and amino acids. Class II agents have schizonticidal activity and they act on the asexual form of the parasite.[52] Sulfadoxine is among the class I antifolate agents while proguanil and pyrimethamine belong to Class II antifolate agents.[51]

Artemisinin and its derivatives like artesunate, artemether, arteether, and dihydro-artemisinin are of natural origin.[53] The generation of free radicals was the first suggested mechanism of action of artemisinin and its derivatives. The malaria parasite is known to be rich in heme since it causes proteolysis of the host cell hemoglobin. Therefore, artemisinin interacts with intraparasitic heme and gets activated into toxic free radicals through the process. A resulting carbon-centered free radical then kills the parasite by alkylating and denaturing one or more essential malarial proteins. The fact that artemisinin is selectively toxic to the parasite is attributed to its selective interaction with intraparasitic heme.[54]

Prevention of Malaria

Malaria Chemoprophylaxis

Casual prophylaxis is administered as a drug active against the pre-erythrocytic (liver stage) malaria parasite. These drugs can be discontinued after leaving the malaria-endemic area. Whereas, suppressive prophylaxis represents administering drugs that act against asexual blood-stage (erythrocytic) parasites. These drugs must be taken for at least 4 weeks after leaving the area to eliminate asexual parasites emerging from the liver weeks after exposure unlike casual prophylaxis.[46] In areas where *P. falciparum* malaria is prevalent, for instance in sub-Saharan Africa, suppressive prophylaxis is indicated. Whereas, in areas where *P. vivax* coexists with *P. falciparum* or alone, causal prophylaxis is recommended.[55]

The Centers for Disease Control emphasizes that there is no antimalarial agent that can prevent malaria 100%. Therefore, prophylaxis shall be augmented with the use of personal protective measures. Currently, there are four drugs approved to be taken for chemoprophylaxis against malaria, namely atovaquone/proguanil, chloroquine, doxycycline, and mefloquine. Selection is based on client factors (pregnancy, disease conditions like renal impairment and cardiac conduction abnormalities), cost, preference on the frequency of administration, tolerability, resistance profile of the area, and the like.[56]

Vector Control

Insecticide-treated nets (ITNs) and indoor residual spraying (IRS) are the two currently applicable malaria vector control methods recommended by WHO.[57] Whether treated with insecticide or not, bed nets provide a physical impediment against insects. When treated with insecticide, it provides further protection by killing insects coming in contact with the net. Pyrethroids, like permethrin and deltamethrin, were the only insecticides used to impregnate bed nets.[58]

The emergence of pyrethroid-resistant *anopheles* necessitates the discovery of pyrethroid–piperonyl butoxide (PBO). PBO works in synergy with pyrethroid by inhibiting parasitic metabolic enzymes like mixed-function oxidases that quench insecticide`s action by sequestering and detoxifying.[59]

IRS is employed to prevent the entry of mosquitos by covering the walls and floors of a house with insecticide. The effect of insecticide lasts for several months.[60] According to WHO, five chemical classes that meet the safety and efficacy level stated by the WHO prequalification are advised to be used for IRS: pyrethroids, organochlorines, carbamates, organophosphates, and neonicotinoids. Nevertheless, the organochlorine insecticide, DDT, is not included in the prequalified list.[61]

Malaria Vaccine

Resistance of the parasite to antimalarial agents and toxicity associated with chemoprophylaxis arose the need for the development of an effective vaccine against malaria. Recently, researchers are focusing on designing vaccines and so far, one candidate has emerged to reach a large Phase III trial. In addition, other promising candidates are also under investigation. In general, malaria vaccines can be grouped as pre-erythrocytic, erythrocytic, and transmission-blocking vaccines based on their target on the malaria parasite lifecycle.[62]

RTS, S/AS01 is a monovalent recombinant protein vaccine that successfully passed to advanced clinical trials and studied well in the blockage of *P. falciparum* sporozoite. It initiates an immune response against a protein covering the surface of sporozoite named circumsporozoite protein (PfCSP).[63] Thus, it promotes immunoglobulin G (IgG) antibody response towards the region of the citrate synthase (CS) protein and potent T-cell (CD4+) response.[62]

RTS, S/AS01 is currently recommended by WHO for use on children in sub-Saharan Africa and other regions of the world with moderate-to-high transmission of *P. falciparum*. It should be administered in a schedule of 4 doses in children starting from the age of 5 months. This decision is made based on the result observed on the ongoing pilot program in Ghana, Kenya, and Malawi, which covered 800,000 children since 2019. The pilot program in these three countries will continue to uncover the advantage of administering the 4th dose and the long-term outcome on child deaths.[64] Similarly, PAMAVAC is a promising blood-stage malaria vaccine among vaccines in the pipeline.[65]

Resistance to Anti-Malaria Agents

Though artemisinin and its derivatives are potent treatments for malaria and are being widely used in combination therapies worldwide, resistance is emerging in some parts of the world. This calls for the need to discover new anti-malarial agents possessing high therapeutic value, minimal toxicity, and low cost.[66]

Antimalarial drug resistance has been defined as

> the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within the limits of tolerance of the subject, given that the drug in question got access to the parasite or the infected red blood cell for the duration of the time necessary for its normal action.[67]

In 1978 and 1995 the first case of chloroquine resistance by *P. falciparum* was observed in Africa and Ethiopia, respectively. Similarly, chloroquine treatment failure against *P. vivax* has been reported in Debre Zeit, Ethiopia in 1995.[68] The mechanism of resistance to quinolones is primarily associated with an elevated level of drug efflux. Overexpression of p-glycoprotein transporter, *P. falciparum* multidrug resistance 1 (Pfmdr1) has been implicated in reduced responsiveness of the parasite to chloroquine and other quinolone antimalarial agents.[69]

Resistance to antifolate antimalarial agents is found to be a result of a mutation in the target enzyme DHFR. A study conducted by Sirawaraporn and Yuthavong,[70] using a partially purified DHFR obtained from a cloned strain of pyrimethamine-sensitive *P. chabaudi* and its derived drug-resistant strain, showed a significant decrease in the affinity of binding of pyrimethamine to the enzyme from the resistant clone. Likewise, alterations in kinetic and other properties were also observed. This supports the claim that resistance is a result of a genetic change that further leads to a structurally different enzyme.

Artemisinin-resistant strains of malaria were first reported in 2008 and then spread in South East Asia (Greater Mekong) but not significantly in Africa so far.[71] In Africa, due to the high prevalence of *p. falciparum*, there is repeated exposure of the host to malaria resulting in a higher degree of acquired immunity which in turn enables the host to defend against artemisinin-resistant infections. *P. falciparum* Kelch 13 (PfKelch13) is a molecular marker used to map the geographical distribution of artemisinin resistance. It is a substrate adapter for cullin E3 ligase, with a putative substrate of *P. falciparum* phosphatidylinositol 3-kinase (PfPI3K) and a redox sensor. Mutant K13 results in lowered artemisinin interactions with PfPI3K.[72]

The emergence of resistant strains of malaria and the spread of the disease urges a relentless search for antimalarial agents of a new mechanism of action with better safety and efficacy profile. Therefore, studies to develop new antimalarial agents having a distinct target from the conventional agents, with well-characterized safety, efficacy, and toxicity profile have to be one of the priorities of health science.[73]

Conclusion

One of the most prevalent and easily avoidable causes of death worldwide is malaria. Although the incidence of malaria as well as the rate of malaria-related deaths has been declining for decades, the progress appears to be stagnating. Malaria incidence has been on the rise in several places since 2014.

For over a century after Laveran in Algeria discovered the cause of malaria and the Plasmodium parasite in the late 1800s different approaches have been tried to control and eradicate malaria from the face of the earth with different magnitude of success. Yet even though there have been some tremendous successes in controlling malaria we are not remotely close to eradicating it. With the recent emergence of resistance to current front-line artemisinin-based combination therapy, the need for the discovery of new antimalarials that can act through novel mechanisms of action has been pushed firmly to the top of the development agenda.[74,75] However, more needs to be done, particularly in light of the rising drug and insecticide resistance.

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References

1. Tuteja R. Malaria− an overview. *FEBS J*. 2007;274(18):4670–4679.
2. Escalante AA, Pacheco MA, Riley LW, Blanton RE. Malaria molecular epidemiology: an evolutionary genetics perspective. *Microbiol Spectr*. 2019;7(4):7425. doi:10.1128/microbiolspec.AME-0010-2019
3. Singh B, Daneshvar C. Human infections and detection of Plasmodium knowlesi. *Clin Microbiol Rev*. 2013;26(2):165–184. doi:10.1128/CMR.00079-12
4. Antony HA, Parija SC. Antimalarial drug resistance: an overview. *Trop Parasitol*. 2016;6(1):30. doi:10.4103/2229-5070.175081
5. White N. *Plasmodium Knowlesi: The Fifth Human Malaria Parasite*. The University of Chicago Press; 2008:172–173.
6. Severe malaria. *Trop Med Int Health. World Health Organization;* 2014;19(s1):7–131. doi:10.1111/tmi.12313_2
7. Guttery DS, Holder AA, Tewari R, Laura J. K. Sexual development in Plasmodium: lessons from functional analyses. *PLoS Pathog*. 2012;8(1):e1002404. doi:10.1371/journal.ppat.1002404
8. Premji ZG. Coartem®: the journey to the clinic. *Malar J*. 2009;8(1):1–6. doi:10.1186/1475-2875-8-S1-S3
9. Talapko J, Škrlec I, Alebić T, Jukić M, Včev A. Malaria: the past and the present. *Microorganisms*. 2019;7(6):179. doi:10.3390/microorganisms7060179
10. Sharma C, Awasthi SK. Recent advances in antimalarial drug discovery—challenges and opportunities. In: *An Overview of Tropical Diseases*. IntechOpen; 2015:39.
11. Gachelin G, Garner P, Ferroni E, Verhave JP, Opinel A. Evidence and strategies for malaria prevention and control: a historical analysis. *Malar J*. 2018;17(1):1–18. doi:10.1186/s12936-018-2244-2
12. Nosten F, Richard-Lenoble D, Danis M. A brief history of malaria. *Presse Med*. 2022;51(3):104130. doi:10.1016/j.lpm.2022.104130
13. Snow RW. Global malaria eradication and the importance of Plasmodium falciparum epidemiology in Africa. *BMC Med*. 2015;13(1):1–3. doi:10.1186/s12916-014-0254-7
14. Karema C, Wen S, Sidibe A, et al. History of malaria control in Rwanda: implications for future elimination in Rwanda and other malaria-endemic countries. *Malar J*. 2020;19(1):1–12. doi:10.1186/s12936-020-03407-1
15. World Health Organization. *World Malaria Report 2022*. World Health Organization; 2022.
16. Assefa A. The third Ethiopian Malaria Indicator Survey 2015 (EMIS-2015); 2016.
17. Nureye D, Assefa S. Old and recent advances in life cycle, pathogenesis, diagnosis, prevention, and treatment of malaria including perspectives in Ethiopia. *Sci World J*. 2020;2020:1–17.
18. Lalremruata A, Jeyaraj S, Engleitner T, et al. Species and genotype diversity of Plasmodium in malaria patients from Gabon analysed by next generation sequencing. *Malar J*. 2017;16(1):1–11. doi:10.1186/s12936-017-2044-0
19. Gnémé A, Guelbéogo WM, Riehle MM, et al. Plasmodium species occurrence, temporal distribution and interaction in a child-aged population in rural Burkina Faso. *Malar J*. 2013;12(1):1–9. doi:10.1186/1475-2875-12-67
20. Bruce MC, Macheso A, McConnachie A, Molyneux ME. Comparative population structure of Plasmodium malariae and Plasmodium falciparum under different transmission settings in Malawi. *Malar J*. 2011;10(1):1–12. doi:10.1186/1475-2875-10-38
21. Carpenter CC, Pearson GW, Mitchell VS, Oaks SC Jr. *Malaria: Obstacles and Opportunities*. National Academies Press; 1991.
22. Pimenta PF, Orfano AS, Bahia AC, et al. An overview of malaria transmission from the perspective of amazon anopheles vectors. *Mem Inst Oswaldo Cruz*. 2015;110:23–47. doi:10.1590/0074-02760140266
23. Siciliano G, Alano P. Enlightening the malaria parasite life cycle: bioluminescent Plasmodium in fundamental and applied research. *Front Microbiol*. 2015;6:391. doi:10.3389/fmicb.2015.00391
24. Ryan ET, Hill DR, Solomon T, Aronson N, Endy TP. *Hunter's Tropical Medicine and Emerging Infectious Diseases*. Elsevier Health Sciences; 2019.
25. Baron S. *Medical Microbiology*. Galveston (TX): University of Texas Medical Branch at Galveston; 1996.
26. Jong EC, Stevens DL. *Netter's Infectious Diseases-E-Book*. Elsevier Health Sciences; 2021.
27. Zuccala ES, Baum J. Cytoskeletal and membrane remodelling during malaria parasite invasion of the human erythrocyte. *Br J Haematol*. 2011;154(6):680–689. doi:10.1111/j.1365-2141.2011.08766.x
28. Venugopal K, Hentzschel F, Valkiūnas G, Marti M. Plasmodium asexual growth and sexual development in the haematopoietic niche of the host. *Nat Rev Microbiol*. 2020;18(3):177–189. doi:10.1038/s41579-019-0306-2
29. Ngwa CJ, Rosa T, Pradel G. *The Biology of Malaria Gametocytes*. Rijeka, Croatia: IntechOpen; 2016.
30. Bennink S, Kiesow MJ, Pradel G. The development of malaria parasites in the mosquito midgut. *Cell Microbiol*. 2016;18(7):905–918. doi:10.1111/cmi.12604
31. Smith RC, Barillas-Mury C. Plasmodium oocysts: overlooked targets of mosquito immunity. *Trends Parasitol*. 2016;32(12):979–990. doi:10.1016/j.pt.2016.08.012
32. Milner DA. Malaria pathogenesis. *Cold Spring Harb Perspect Med*. 2018;8(1):a025569. doi:10.1101/cshperspect.a025569
33. Craig AG, Khairul MFM, Patil PR. Cytoadherence and severe malaria. *Malays J Med Sci*. 2012;19(2):5–18.
34. Crabb BS, Cowman AF. Plasmodium falciparum virulence determinants unveiled. *Genome Biol*. 2002;3(11):1–4. doi:10.1186/gb-2002-3-11-reviews1031
35. Lavstsen T, Magistrado P, Hermsen CC, et al. Expression of Plasmodium falciparum erythrocyte membrane protein 1 in experimentally infected humans. *Malar J*. 2005;4(1):1–9. doi:10.1186/1475-2875-4-21
36. Roberts DJ, Pain A, Chitnis CE. Molecular pathogenesis of malaria. *Mol Hematol*. 2019;2019:193–206.
37. Chen Q, Schlichtherle M, Wahlgren M. Molecular aspects of severe malaria. *Clin Microbiol Rev*. 2000;13(3):439–450. doi:10.1128/CMR.13.3.439
38. Hermand P, Cicéron L, Pionneau C, Vaquero C, Combadière C, Deterre P. Plasmodium falciparum proteins involved in cytoadherence of infected erythrocytes to chemokine CX3CL1. *Sci Rep*. 2016;6(1):1–12. doi:10.1038/srep33786
39. Wah ST, Hananantachai H, Kerdpin U, Plabplueng C, Prachayasittikul V, Nuchnoi P. Molecular basis of human cerebral malaria development. *Trop Med Health*. 2016;44(1):1–7. doi:10.1186/s41182-016-0033-6

40. Jakobsen P, Bate C, Taverne J, Playfair J. Malaria: toxins, cytokines and disease. *Parasite Immunol*. 1995;17(5):223–231. doi:10.1111/j.1365-3024.1995.tb01019.x
41. Schofield L, Hackett F. Signal transduction in host cells by a glycosylphosphatidylinositol toxin of malaria parasites. *J Exp Med*. 1993;177(1):145–153. doi:10.1084/jem.177.1.145
42. Dunst J, Kamena F, Matuschewski K. Cytokines and chemokines in cerebral malaria pathogenesis. *Front Cell Infect Microbiol*. 2017;7:324. doi:10.3389/fcimb.2017.00324
43. Murray CK, Bennett JW. Rapid diagnosis of malaria. *Interdiscip Perspect Infect Dis*. 2009;2009:1.
44. Kasetsirikul S, Buranapong J, Srituravanich W, Kaewthamasorn M, Pimpin A. The development of malaria diagnostic techniques: a review of the approaches with focus on dielectrophoretic and magnetophoretic methods. *Malar J*. 2016;15(1):358. doi:10.1186/s12936-016-1400-9
45. Krampa FD, Aniweh Y, Awandare GA, Kanyong P. Recent progress in the development of diagnostic tests for malaria. *Diagnostics*. 2017;7(3):54. doi:10.3390/diagnostics7030054
46. World Health Organization. *WHO Guidelines for Malaria, 3 June 2022*. World Health Organization; 2022.
47. Belete TM. Recent progress in the development of new antimalarial drugs with novel targets. *Drug Des Devel Ther*. 2020;14:3875. doi:10.2147/DDDT.S265602
48. Renslo AR. *Antimalarial Drug Discovery: From Quinine to the Dream of Eradication*. ACS Publications; 2013:1126–1128.
49. Wampfler R, Hofmann NE, Karl S, et al. Effects of liver-stage clearance by primaquine on gametocyte carriage of Plasmodium vivax and P. falciparum. *PLoS Negl Trop Dis*. 2017;11(7):e0005753. doi:10.1371/journal.pntd.0005753
50. Kapishnikov S, Staalsø T, Yang Y, et al. Mode of action of quinoline antimalarial drugs in red blood cells infected by Plasmodium falciparum revealed in vivo. *Proc Natl Acad Sci*. 2019;116(46):22946–22952. doi:10.1073/pnas.1910123116
51. Pinheiro L, Feitosa LM, Silveira FF, Boechat N. Current antimalarial therapies and advances in the development of semi-synthetic artemisinin derivatives. *An Acad Bras Cienc*. 2018;90:1251–1271. doi:10.1590/0001-3765201820170830
52. Nzila A. The past, present and future of antifolates in the treatment of Plasmodium falciparum infection. *J Antimicrob Chemother*. 2006;57(6):1043–1054. doi:10.1093/jac/dkl104
53. Rosenthal PJ. *Antimalarial Chemotherapy: Mechanisms of Action, Resistance, and New Directions in Drug Discovery*. Springer Science & Business Media; 2001.
54. Meshnick SR. Artemisinin: mechanisms of action, resistance and toxicity. *Int J Parasitol*. 2002;32(13):1655–1660. doi:10.1016/S0020-7519(02)00194-7
55. Castelli F, Odolini S, Autino B, Foca E, Russo R. Malaria prophylaxis: a comprehensive review. *Pharmaceuticals*. 2010;3(10):3212–3239. doi:10.3390/ph3103212
56. Control CfD. *Prevention. CDC Yellow Book 2020: Health Information for International Travel*. Oxford University Press; 2019.
57. World Health Organization. *Insecticide-Treated Nets for Malaria Transmission Control in Areas with Insecticide-Resistant Mosquito Populations: Preferred Product Characteristics*. World Health Organization; 2021.
58. Lindsay SW, Thomas MB, Kleinschmidt I. Threats to the effectiveness of insecticide-treated bednets for malaria control: thinking beyond insecticide resistance. *Lancet Glob Health*. 2021;9(9):e1325–e1331. doi:10.1016/S2214-109X(21)00216-3
59. Martin JL, Mosha FW, Lukole E, et al. Personal protection with PBO-pyrethroid synergist-treated nets after 2 years of household use against pyrethroid-resistant Anopheles in Tanzania. *Parasit Vectors*. 2021;14(1):1–8. doi:10.1186/s13071-021-04641-5
60. World Health Organization. *Indoor Residual Spraying: An Operational Manual for Indoor Residual Spraying (IRS) for Malaria Transmission Control and Elimination*. World Health Organization; 2015.
61. Tangena J-A-A, Hendriks CM, Devine M, et al. Indoor residual spraying for malaria control in sub-Saharan Africa 1997 to 2017: an adjusted retrospective analysis. *Malar J*. 2020;19(1):1–15. doi:10.1186/s12936-020-03216-6
62. Arora N, Anbalagan LC, Pannu AK. Towards eradication of malaria: is the WHO's RTS, S/AS01 vaccination effective enough? *Risk Manag Healthc Policy*. 2021;14:1033. doi:10.2147/RMHP.S219294
63. Draper SJ, Sack BK, King CR, et al. Malaria vaccines: recent advances and new horizons. *Cell Host Microbe*. 2018;24(1):43–56. doi:10.1016/j.chom.2018.06.008
64. World Health Organization. *WHO Recommends Groundbreaking Malaria Vaccine for Children at Risk*. World Health Organization; 2021:1.
65. Bonam SR, Rénia L, Tadepalli G, Bayry J, Kumar HMS. Plasmodium falciparum malaria vaccines and vaccine adjuvants. *Vaccines*. 2021;9(10):1072. doi:10.3390/vaccines9101072
66. Ouji M, Augereau J-M, Paloque L, Benoit-Vical F. Plasmodium falciparum resistance to artemisinin-based combination therapies: a sword of Damocles in the path toward malaria elimination. *Parasite*. 2018;25. doi:10.1051/parasite/2018027
67. World Health Organization. *Nutritional Anaemias: Report of a WHO Scientific Group [Meeting Held in Geneva from 13 to 17 March 1967]*. World Health Organization; 1968.
68. Shibeshi MA, Kifle ZD, Atnafie SA. Antimalarial drug resistance and novel targets for antimalarial drug discovery. *Infect Drug Resist*. 2020;13:4047. doi:10.2147/IDR.S279433
69. Foley M, Tilley L. Quinoline antimalarials: mechanisms of action and resistance and prospects for new agents. *Pharmacol Ther*. 1998;79(1):55–87. doi:10.1016/S0163-7258(98)00012-6
70. Sirawaraporn W, Yuthavong Y. Kinetic and molecular properties of dihydrofolate reductase from pyrimethamine-sensitive and pyrimethamine-resistant Plasmodium chabaudi. *Mol Biochem Parasitol*. 1984;10(3):355–367. doi:10.1016/0166-6851(84)90033-1
71. World Health Organization. Report on antimalarial drug efficacy, resistance and response: 10 years of surveillance (2010–2019); 2020.
72. Blasco B, Leroy D, Fidock DA. Antimalarial drug resistance: linking Plasmodium falciparum parasite biology to the clinic. *Nat Med*. 2017;23(8):917–928. doi:10.1038/nm.4381
73. Tang Y-Q, Ye Q, Huang H, Zheng W-Y. An overview of available antimalarials: discovery, mode of action and drug resistance. *Curr Mol Med*. 2020;20(8):583–592. doi:10.2174/1566524020666200207123253
74. Tse EG, Korsik M, Todd MH. The past, present and future of anti-malarial medicines. *Malar J*. 2019;18(1):1–21.
75. Pereira TB, Rocha e Silva LF, Amorim RC, et al. In vitro and in vivo anti-malarial activity of limonoids isolated from the residual seed biomass from Carapa guianensis (andiroba) oil production. *Malar J*. 2014;13(1):1–8. doi:10.1186/1475-2875-13-317