A background overview on Malaria disease and some perspectives on pharmacological approach. Millions of suffering people still waiting for the cure - are we close enough?

Jaime Alex M. Silva Filho[1], Vitor Francisco Ferreira[2], Wilson C. Santos.[2,3]

[1] Universidade Federal Fluminense, Faculdade de Farmácia.

[2] Programa de Pós-Graduação em Ciências Aplicadas a Produtos Para a Saúde, Laboratório de Inovação Química e Tecnologia Farmacêutica, Niterói, RJ, Brasil.

[3] Instituto Teófilo Hernando, Departamento de Farmacología y Terapéutica, Facultad de Medicina, Universidad Autónoma de Madrid, España.

Casi la mitad de la población mundial está en riesgo de contraer malaria, según los informes de la Organización Mundial de la Salud. Además, en zonas con alta transmisión de malaria, los niños pequeños y las mujeres embarazadas son particularmente vulnerables a la infección y la muerte por malaria. La enfermedad se puede prevenir y tratar, y la prioridad mundial es reducir la carga y muerte, y, a largo plazo, la erradicación de la malaria, ampliando el acceso a medicamentos eficaces y seguros para curar y proteger a las poblaciones vulnerables y desatendidas.

Jaime Alex M. Silva Filho

ORCID: https://orcid.org/0000-0003-3658-3423

E-mail: jaimealex@id.uff.br

Vitor Francisco Ferreira

ORCID: https://orcid.org/0000-0002-2166-766X

E-MAIL: vitorferreira@id.uff.br

Wilson C. Santos

ORCID: https://orcid.org/0000-0001-9971-094X

E-mail: wsantos@id.uff.br

RESUMEN

La malaria es causada en los seres humanos por cinco especies de parásitos eucariotas unicelulares del género *Plasmodium* que se transmiten por la picadura de mosquitos *Anopheles*. Muchos factores contribuyen a la elección del tratamiento de la malaria, dependiendo de la gravedad clínica, la prevalencia local de *Plasmodium spp.*, la genética del paciente, el uso histórico de quimioprofilaxis contra la malaria por parte del paciente, el conocimiento de la resistencia local a los medicamentos antipalúdicos y el estado de embarazo de la paciente.

ABSTRACT

Malaria is caused in humans by five species of single-cell, eukaryotic *Plasmodium* parasites that are transmitted by the bite of *Anopheles* mosquitoes. Many factors contribute to the choice of treatment of malaria depending on clinical severity, local *Plasmodium spp.* prevalence, patient genetics, historical use of malaria chemoprophylaxis by the patient, knowledge of local anti-malarial drug resistance, and the patient's pregnancy status.

1. Introduction and background

Malaria is a disease that has accompanied humanity for millennia and has spread to most of the planet Bruce-Chwatt (1988).

Malaria is caused by a parasite that spreads to humans through the bites of infected female Anopheles mosquitoes. *The Plasmodium* parasites that infect people with malaria cannot survive outside of their hosts: humans and *Anopheles* mosquitoes. Five species of malaria parasites cause significant disease in humans:

Plasmodium falciparum – the most prevalent, causes the majority of severe malaria cases and deaths.

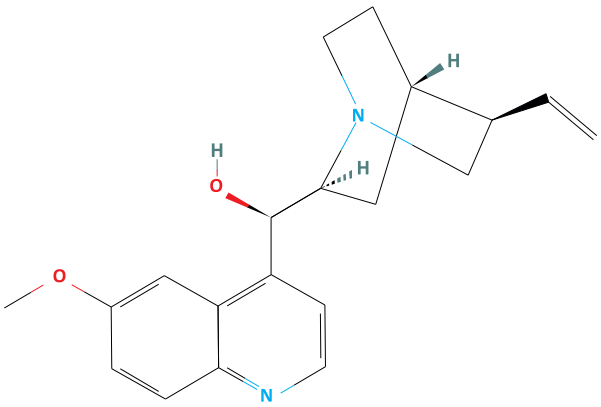
Plasmodium vivax – the main cause of relapsing malaria, with a blood and a liver infection causing acute and ongoing symptoms.

Less prevalent: *Plasmodium ovale, Plasmodium malariae* and *Plasmodium knowlesi.*

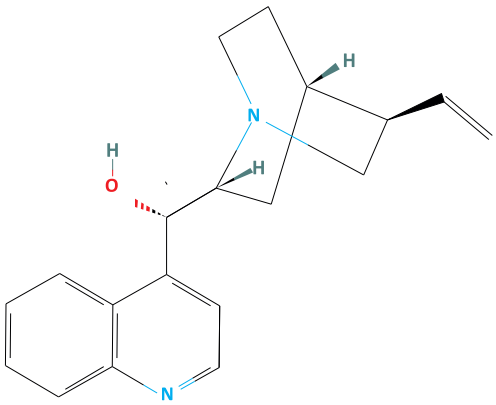
In the early days, treatment for malaria consisted of using the bark of a South American tree known to the indigenous people. The Peruvian Incas were the first people to use quinine as a drug in the form of bark powder from the plant Quina ou Chinchona and which cured an immense number of people who contracted malaria. This treatment was enthroned in Europe by Jesuit missionaries who obtained ethnobotanical and ethnopharmacological knowledge from the native peoples. As soon as they returned from America, the Europeans spread the knowledge of how the native Incas of Peru treated their malaria patients using the bark of this tree. It wasn't long before the remedy was popularly known as “Jesuit powder” (Bruce-Chwatt,1988; Mates, *et al*., 2007). A major challenge and opportunity for the time, therefore, was to discover which compound or compounds were in the bark of the cinchona tree, which had been used for hundreds of years to cure malaria, a disease that was the oldest and deadliest human infectious disease, and yet which remains modern and endemic in many countries, causing many deaths. The use of quinine bark (genus *Cinchona*) was the first successful chemotherapy treatment for malaria and dates back approximately 400 years. However, it was not until 1820 that the antimalarial effect was attributed to alkaloid quinine.

Malaria infection affected humanity for thousands of years, until science unraveled the transmission and cycle of the *Plasmodium spp.* parasites that affect humans. During this period, scientists have also discovered other substances in forest plants that contribute to mitigating the infection and, furthermore, the need for the transmitting mosquito (the infected female *Anopheles* mosquito). Regarding the mosquito, considered to be humanity's greatest predator, Winegard reported that “The oldest reference to a mosquito-borne disease dates back 3200 years BC in Sumerian tablets, discovered in the ‘cradle of civilization’ between the Tigris and Euphrates rivers in ancient Mesopotamia, which clearly describe evil fevers attributed to Negal, the Babylonian God of the underworld, represented as an insect resembling a mosquito” (Winegard, 2022).

In 1811, the Portuguese physician Bernardo Antonio Gomes (1768-1823) isolated a compound from the gray variety of quina bark and called it cinchonine. In 1920, French chemist and pharmacist Pierre-Joseph Pelletier (1788-1842) and Joseph Bienaim Caventou (1795-1887; Haas and Caventou, 1994), two scientists specialized in the isolation of alkaloids, discovered that Bernardo Antonio Gomes compound was actually a



Quinine in 1811



Cinchonine in 1820

Figure 1: *Chemical structures of quinine and cinchonine*

mixture of two molecules: quinine and cinchonine (Figure 1) and that quinine was the most active substance against the malaria protozoan (Del Pine *et al.*, 1951; Oliveira *et al.*, 2019). He isolated several other alkaloids, such as quinine, cinchonine, strychnine, colchicine and veratrine (Ikan, 1991; Mann *et al.*, 1996).

After the discovery of the alkaloids present in the *Cinchona* genus, the powder was marketed using the bark of the trees, but over time an active compound was isolated, however it wasn't until 1887 that quinine was produced in the form of a quinine sulphate salt. The extraction of the substance was not a quick process, but it continues to be carried out and marketed to these days. Cinchones remain the unique economically practical source of quinine and several pharmaceutical companies manufacture this drug (Hutter *et al.*, 2024).

The search for new antimalarial drugs to replace the natural alkaloid quinine with another more active and less expensive drug began before, during and after the First World War (Gachelin and Opinel, 2011). The war focused on malaria cases, which had become a huge public health problem in Europe (França *et al.*, 2008). The cut in the supply of quinine to allied countries boosted the search for alternatives for the prophylaxis of the disease. In the 1930s, the only promising synthetic antimalarial drug that was Atabrinet or quinacrine was already known, but tis drug was highly toxic and still had its authorized use. The German scientists started during the Second World War a program to discover the antimalarial compound chloroquine whose structure is based on the quinoline ring that is present in the natural antimalarial drug quinine (Ferreira and Ferreira 2021). The drugs were used for many years in the initial treatment and prevention of malaria due to their unique antiparasitic effects. From all antimalarials in the class, chloroquine (Figure 2) was the first drug used and it has stimulated the development of others (Coatney, 1963). Chloroquine is no longer used alone to treat patients with *Plasmodium falciparum* due to the emergence and spread of resistant strains. Chloroquine is also used as an immunomodulator in rheumatic diseases, such as systemic lupus erythematosus (Meinão *et al.*, 1996; Wozniacka *et al.*, 2006) and rheumatoid arthritis (Mota *et al.*, 2012), among other autoimmune diseases.

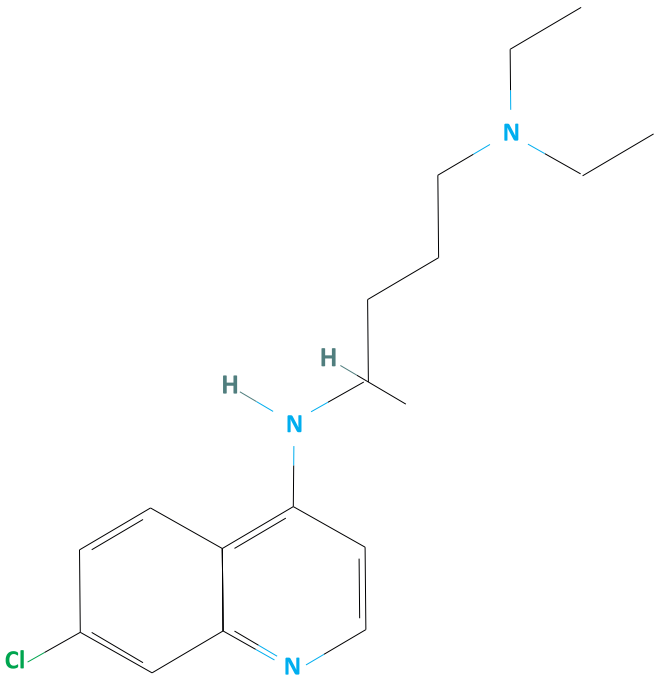


Figure 2: *Chemical structures of chloroquine*

"Nearly half of the world's population is at risk of malaria, according to World Health Organization reports"

2. Malaria transmission and life cycle for the parasites on humans

In essence, human and female *Anopheles* mosquitoes become infected with malaria through cyclical contact that can be explained starting with female mosquitoes that ingest human blood for egg generation. After that, humans contract malaria when bitten by a mosquito carrying the *Plasmodium* parasite. The parasite initially proliferates in the liver cells before moving onto the red blood cells to infect them and leading to rupture. To complete the cycle, parasites that grow inside red blood cells create more parasites that infect other red blood cells. The blood-stage parasites that cause malaria in humans are responsible for the disease's symptoms. The female *Anopheles* mosquito consumes these parasites while blood-feeding, and a parasite form known as a sporozoite then migrates to the mosquito's salivary glands and initiates a cycle of development and multiplication in the insect. When the *Anopheles* mosquito feeds on the blood of another human the parasites begin a new cycle in the liver. By serving as a vector, the infected mosquito spreads the disease from one person to another (Islam MR *et al.*, 2023).

"in areas with high malaria transmission, young children and pregnant women are particularly vulnerable to malaria infection and death"

Infected female *Anopheles* mosquitoes are a major source of mosquito bites that transmit malaria. Only *Anopheles* mosquitoes can spread malaria, therefore, only after ingesting blood from a sick person (Islam MR *et al.*, 2023). Besides, due to the malaria parasite presence in an infected person's red blood cells, malaria can also be transmitted via other means, such as sharing contaminated needles or syringes or receiving blood transfusions. Congenital malaria is another possibility (CDC, Malaria).

3. Clinical Presentation

The clinical presentation of malaria ranges from asymptomatic parasitemia or uncomplicated disease to severe disease or death and depends on *Plasmodium* species, parasitemia, duration of illness, human immune response, exposure profile and number of prior infections (Doolan and Martinez Alier 2006; Krzych *et al.* 2014; Shahbodaghi SD, Rathjen NA., 2022). In the human body during an initial infection, macrophage ingestion of merozoites, ruptured schizonts, or antigen-presenting trophozoites in the circulation or spleen leads to the release of TNF-a (Chakravorty *et al.* 2008; Randall and Engwerda 2010). This molecule, along with others in a cascade, is responsible for the fever during infection. Other important molecules found during active infection are for instance interleukin-10 (IL-10) and interferon-gamma (IFN-g) (Clark *et al.* 2008; McCall and Sauerwein 2010; Freitas do Rosario and Langhorne 2012; Hunt *et al.* 2014).

In addition, during subsequent infections, some antibody production by the previous B-cell axis of the immune system provides additional macrophage activity, leading to more efficient parasite clearance and the production of new antibodies. (Wykes and Good 2006; Freitas do Rosario and Langhorne 2012; Krzych *et al.* 2014; Hviid *et al.* 2015). As the parasite continually presents its protein repertoire during infection, the human host's immune system develops additional antibodies that provide greater protection. (Milner DA Jr, 2018).

The asymptomatic parasitemia is related to the symptoms of malaria infection that can only begin in any infected patient with the first liver schizont rupture and the release of merozoites into the peripheral circulation; however this event is silent for the vast majority of patients who will become clinically ill (Milner DA Jr, 2018). So, as the parasites continue through their asexual life cycle of merozoite reinvasion, trophozoite development, and schizont rupture over 24 to 48 hours, the level of parasitemia parallels the level of human immune response until the patient crosses a threshold of awareness and starts "feeling ill" (Oakley et al, 2011). On other hand, uncomplicated malaria is defined as the presence of symptoms present, such as fever, but no clinical or laboratory signs to

indicate severity or vital organ dysfunction (Milner DA Jr, 2018).

The incubation period for malaria varies according to the species of plasmodium. For *P. falciparum,* it ranges from 8 to 12 days; for *P. vivax*, it ranges from 13 to 17 days and for *P. malariae*, it is from 18 to 30 days (Brazil, Ministério da Saúde, 2021). The acute malaria crisis is characterized by episodes of chills, high fever and sweating. It lasts from 6 to 12 hours and can display temperatures of 40 °C or higher (Brazil, Ministério da Saúde, 2021). Nevertheless, the classic pattern of fever every two days is not regularly observed, and it will depend on the infecting species (Brazil, Ministério da Saúde, 2021).

In general, the paroxysms are recurrent febrile episodes which coincide with the rupture of schizont-infected erythrocytes in the host circulation (Karunaweera, N. et al, 2007). For example, in established infections of *P. vivax* temperature spikes occur at 48 hours intervals (Karunaweera ND, *et al.* 2003). They are usually accompanied by headache, myalgia, nausea and vomiting. After the first paroxysms, the fever may become intermittent (Brazil, Ministério da Saúde, 2021). Because of the nonspecific symptoms, malaria is commonly confused with other acute febrile illnesses, such as dengue, zika and chikungunya, which makes early diagnosis more difficult (Brazil, Ministério da Saúde, 2021).

At advanced stages, severe disease manifestations may include severe anemia, lactic acidosis, hypoxia, splenomegaly, liver and kidney disease, visual defects, cerebral malaria with neuronal damage and other dysfunctions. Besides, malaria may lead to coma before death (Fairhust RM, Wellems TE, 2010; Zaki SA, Shanbag P., 2011; Plewes K, Turner GDH, Dondorp AM, 2018). According to Giha *et al*., anemia was the predominant symptom of malaria in 45% of cases, followed by convulsions (21%), cerebral malaria (16.4%) and hypotension (11.8%). However, Mohanty et al reported cerebral malaria (52%) as the leading cause of death in *P. falciparum* infection.

4. Malaria pharmacology

Malaria treatment aims to target the parasite at key points in its evolutionary cycle, which can be didactically summarized as follows: interruption of blood schizogony, which is responsible for the pathogenesis and clinical manifestations of infection; destruction of latent forms of the parasite in the tissue cycle (hypnozoites) of the species *P. vivax* and *P. ovale*, thus preventing relapses; interruption of parasite transmission through the use of drugs that prevent the development of sexual forms of the parasites (gametocytes) (Brazil, Ministério da Saúde, 2021). The choice of malaria treatment can be influenced by several facts, including the identification of the infecting malaria parasite, the severity of symptoms, age of patient and whether the patient is pregnant or breastfeeding.

Currently, the major advance in antimalarial therapeutics is the use of drugs derived from artemisinin (qinghaosu) (Ma N *et al*., 2020). This unusual compound (a sesquiterpene lactone peroxide) is derived from the leaves of the plant *Artemesia annua*, and its derivatives, artemisinin, dihydroartemisinin (DHA), artesunate and artemether, form the cornerstone of current antimalarial treatment (Hanboonkunupakarn B and White NJ, 2022).

The artemisinins are the fastest acting antimalarials available and are very well tolerated, but resistance has already emerged in Southeast Asia and it has spread to other countries, and there are worrying early reports *of foci* in other regions. The treatment known as Artemisinins-Based Combined Therapy (ACTs) is used in fixed-dose combinations of artemisinins derivatives with some more slowly eliminated antimalarial drugs, such as mefloquine, lumefantrine, piperaquine and amodiaquine, to treat uncomplicated malaria (Hanboonkunupakarn B and White NJ, 2022; Ward KE, Fidock DA, Bridgford JL, 2022). It is active against the four most common *Plasmodium spp.* and it is a fast-acting blood schizonticide. It kills all stages of asexual parasites and it also kills immature and developing gametocytes, thereby reducing gametocyte carriage and transmission potential (Dondorp AM *et al*., 2010). Despite extensive research and contributions from numerous institutions and scientists over the past 30 years, the exact mechanism of action of artemisinins remains unclear. The hypothesis that the free heme released during hemoglobin digestion was first proposed in 1991 by Meshnick et al, and this led to the viewpoint of alkylation of heme as the trigger and target of artemisinins.

Significant steps towards to the identification of artemisinin target proteins have been taken based on proteomics approaches in the past few years. The identification of multiple protein targets of artemisinin by chemical proteomics was particularly notable (Wang *et al*., 2015; Ismail, Barton, Panchana, *et al*., 2016; Ismail, Barton, Phanchana, *et al*., 2016). Moreover, the multi-targeted nature of artemisinins proposed by chemical proteomics was also consistent with the prevailing drug

resistance theory that artemisinin resistance may be conferred by mutations in the propeller domain of the *P. falciparum* Kelch13 gene (Ariey *et al.*, 2014; Birnbaum *et al.*, 2020; Lozano *et al.*, 2018). This protein plays an important role in the endocytosis of hemoglobin from the host cell and since artemisinin and its derivatives are activated by degradation products of hemoglobin, the inactivation of Kelch13 leads to parasite resistance (Birnbaum *et al.*, 2020).

Primaquine is other very important antimalarial drug that is recommended both as a single-dose gametocytocidal for *P. falciparum* malaria and in multi-dose "radical cure" regimens to prevent relapse in *P. vivax* and *P. ovale* malaria (WHO, 2015). However, primaquine is actually underused because of concerns about hemolytic toxicity in glucose-6-phosphate dehydrogenase (G6PD) deficiency (Recht J, Ashley EA, White NJ, 2014). Furthermore, the recent development of rapid G6PD deficiency screening tests is a significant advance that should allow wider safe use of primaquine for radical cure, making elimination of the parasites a more achievable goal (Ley B *et al.*, 2019).

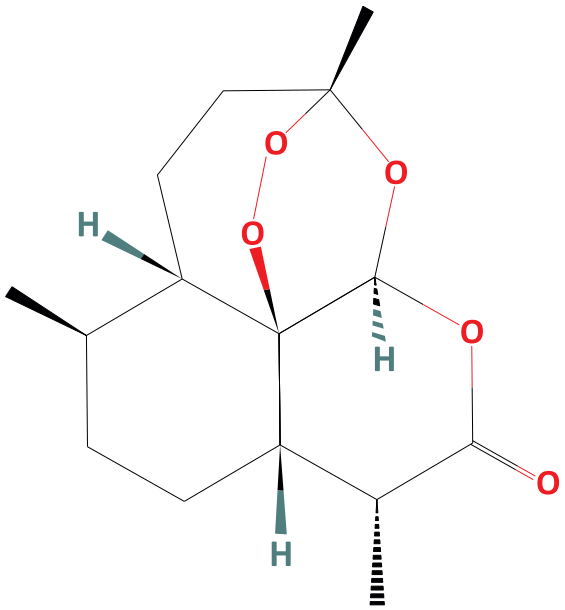


Figure 3: *Structure of artemisinin*

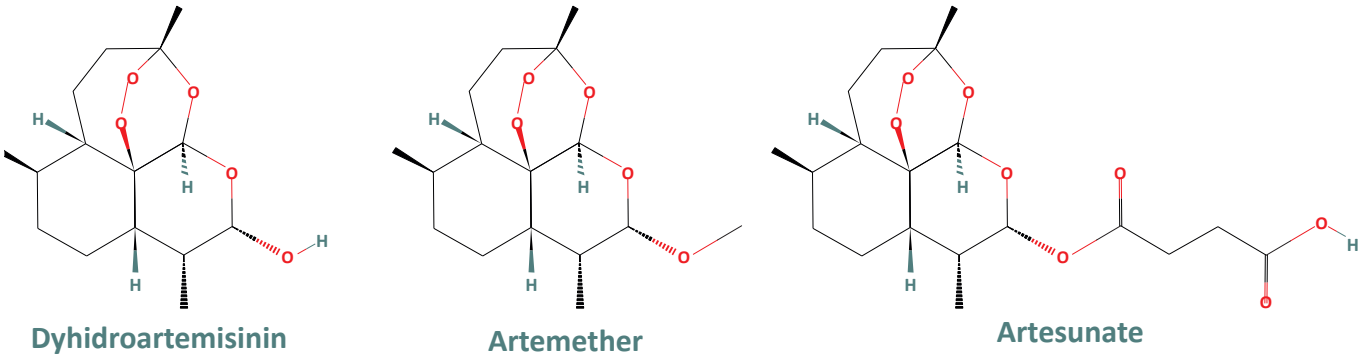


Figure 4: *Chemical structure of primaquine*

In malaria-endemic regions pregnant women were advised to take chloroquine chemoprophylaxis to reduce the adverse effects of *P. falciparum* malaria on the developing fetus associated with low birthweight and neonatal mortality (Garner P, Gulmezoglu A, 2006; Desai M *et al.*, 2007). However, as chloroquine resistance has worsened, the chemoprophylaxis in Africa was replaced by intermittent presumptive treatment with sulfadoxine-pyrimethamine (IPTp-SP; WHO, 2013). The SP combination has shown antibacterial activity that could improve birthweight independent of its antimalarial effect (Desai M *et al.*, 2015). Although the mechanism of these effects remains unclear, a non-malaria-related beneficial effect of SP on birthweight could be due to several mechanisms, including anti-inflammatory effects or changes in the gut or vagina bacterial flora or leading to effects on maternal or infant weight gain, indirect metabolic effects, or a reduction in the effects of genitourinary tract organisms associated with adverse pregnancy outcomes (Dingens A *et al.*, 2016; Gutman J, Slutsker L., 2017).

Nevertheless, SP resistance is widespread and other alternatives are already in use. Despite the widespread resistance to sulfadoxine-pyrimethamine (SP), alternative treatments have already been adopted. Increasing evidence suggests that dihydroartemisinin-piperaquine (DP) offers highly effective antimalarial chemoprevention lasting approximately one month. Additionally, DP is well tolerated and appears to be safe for use during pregnancy. (Ahmed R *et al.*, 2019). First, dihydroartemisinin is the major active metabolite of artemisinin derivatives, such as artemether and artesunate, and it reaches high concentrations in red blood cells infected with *P. falciparum*. The endoperoxide bridge of dihydroartemisinin appears to be essential for its antimalarial activity, resulting in free radical damage to parasite membrane systems as previously explained (Keating GM, 2012). Specifically, dihydroartemisinin interferes with mitochondrial electron transport and parasite transport proteins, inhibits plasmodial sarco-endoplasmic reticulum calcium adenosine triphosphatase and disrupts parasite mitochondrial function (Eckstein-Ludwig U, 2003; Keating GM, 2012). Piperaquine is a bisquinolone, and although its exact mechanism of action is unknown, it is thought to be similar to that of chloroquine, a close structural analog of piperaquine, which binds to toxic heme in the acidic lysosome-like parasite digestive vacuole and prevents its detoxification, thus allowing free heme toxicity to the parasite (White NJ *et al.*, 2013; Sugiarto SR, Davis TME, Salman S., 2017; Coban C, 2020).

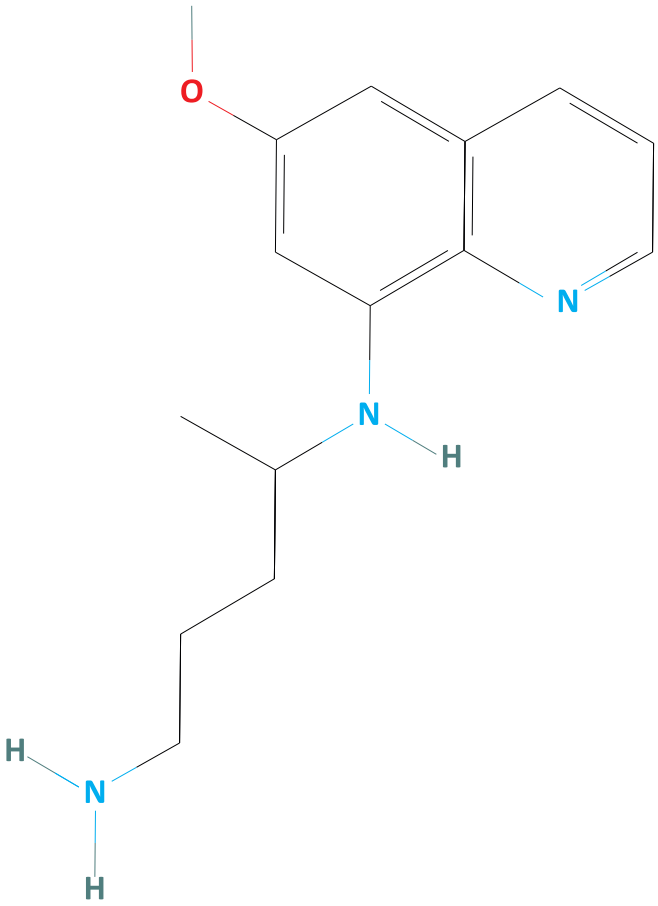


Figure 5: *Chemical structure of primaquine*

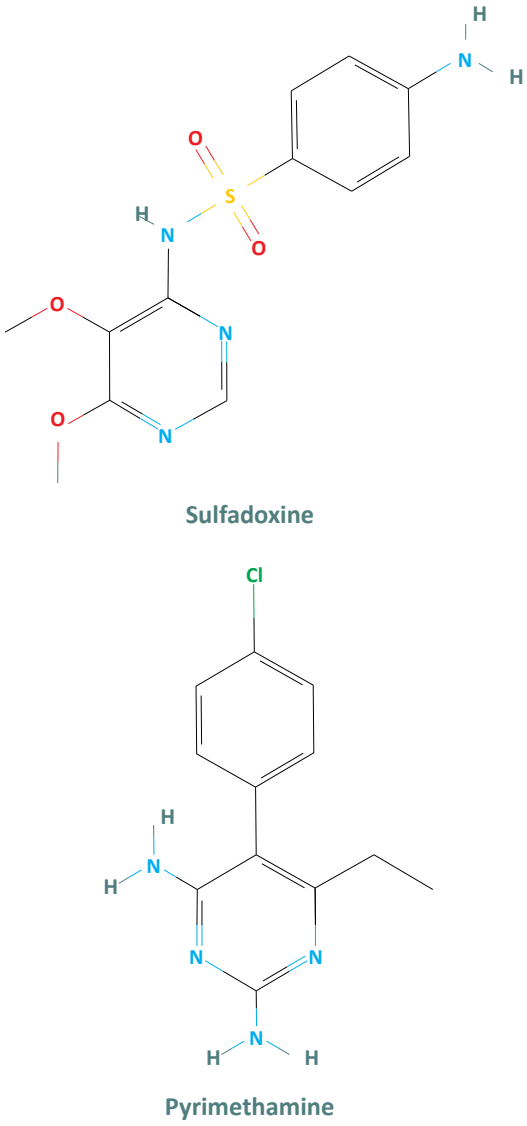


Figure 6: *Chemical structure of SP.*

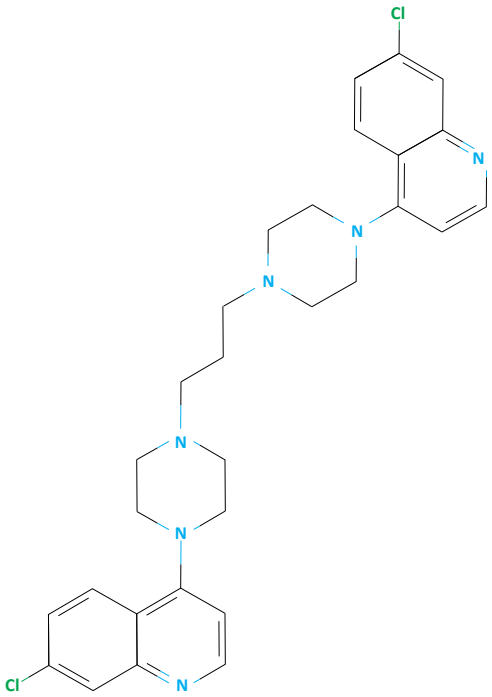


Figure 7:. *Chemical structure of piperaquine.*

"The most common human-infecting Plasmodium species are P. falciparum, P. vivax, P. malariae, and P. ovale, with P. falciparum being the most dangerous"

Another ACT that remains effective is the artesunate-amodiaquine (van der Pluijm RW *et al.*, 2020). Artesunate is a semisynthetic derivative of artemisinin and following oral administration, it is rapidly converted to dihydroartemisinin (DHA), which is the principal active metabolite (Luo X.D. and Shen C.C., 1987; Bethell D.B. *et al.*, 1997). Amodiaquine is a 4-aminoquinoline structurally similar to chloroquine. It is used in several African countries as monotherapy and in combination for the treatment of uncomplicated *P. falciparum* malaria. When administered orally, amodiaquine is rapidly metabolized to desethylamodiaquine, the main active metabolite (Krishna S. and White N.J., 1996). The mechanism of action of amodiaquine and its active metabolite is probably similar to that of chloroquine, leading to accumulation of heme which is toxic for the parasite (KROGSTAD DJ *et al.*, 1987).

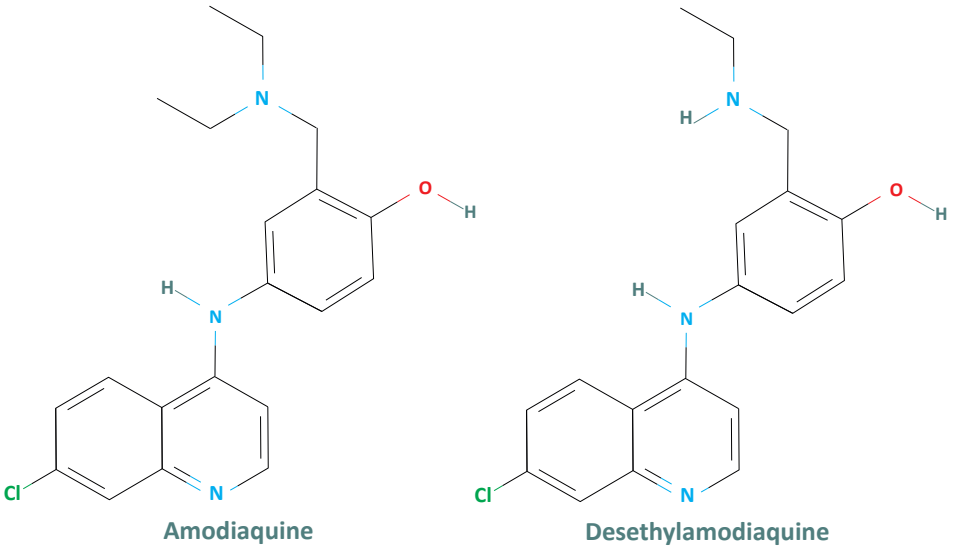


Figure 8: *Chemical structure of amodiaquine and its active metabolite.*

"Prompt malaria treatment is essential, with hospitalization and monitoring for severe cases"

The artemether-lumefantrine combination is another ACT used to treat uncomplicated malaria in both adults and children (Omari AA, Gamble C, Garner P., 2005; WHO, 2013). Artemether is readily demethylated to DHA and after oral administration its plasma concentrations exceed those of the parent compound and thus contribute a similar or greater proportion of the antimalarial activity (Grace JM *et al.*, 1998). Lumefantrine is structurally, physicochemical, and also in the mechanism of action similar to the aryl amino alcohol group of antimalarials, including quinine and mefloquine (Wernsdorfer WH *et al.*, 1998). By analogy with chloroquine and related compounds, lumefantrine is thought to have the same mechanism of action (White NJ, van Vugt M, Ezzet F, 1999). Following that, mefloquine is used in combination with artesunate and it has a similar mechanism of action to lumefantrine. The drug has a slower elimination half-life, resulting in a post-treatment prophylactic effect that provides additional benefit in highly endemic settings (Eziefula AC, 2016). However, extensive use of artesunate-mefloquine and mefloquine monotherapy, primarily in Southeast Asia, has shown that notable drug-related adverse effects are early vomiting during treatment and self-limiting neuropsychiatric effects, most commonly dizziness and insomnia (Luxemburger C *et al.*, 1996; Frey SG *et al.*, 2010; Schlagenhauf *et al.*, 2011).

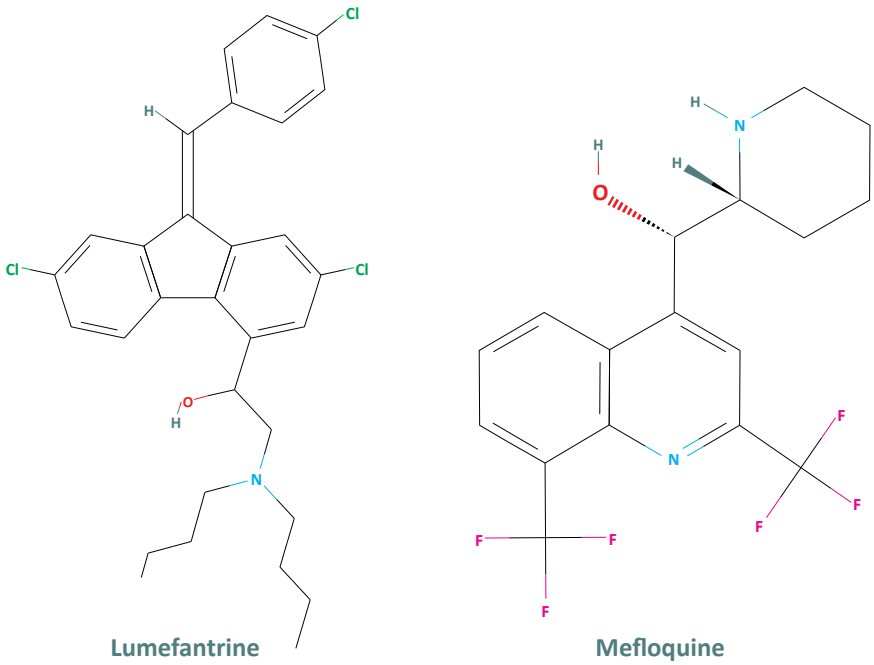


Figure 9: *Chemical structure of lumefantrine and mefloquine.*

Although pyronaridine-artesunate is not new, the recently updated WHO Malaria Guidelines (2022) reaffirmed the use of pyronaridine-artesunate with the highest level of confidence (Chu WY, Dorlo TPC, 2023). Currently, pyronaridine-artesunate is considered a safe and effective ACT for the treatment of uncomplicated malaria in adults and children weighing 5 kg or more in all malaria-endemic areas (WHO, 2023). Pyronaridine is a benzo-naphthyridine derivative with a mepacrine (9-aminoacridine) component and an additional amodiaquine-like side chain (Valdés AF-C, 2011). It is also a blood schizonticide and exerts its antimalarial activity by inhibiting the formation of hemozoin pigment in the parasite digestive vacuole, similar to other quinine-type antimalarials discussed previously (Kumar S *et al.*, 2007). In addition, it is important to note that pyronaridine has recently been shown to intercalate into DNA and inhibit DNA topoisomerase 2 (Topo-2) enzymes (Bailly C., 2021). Based on its metabolism, pyronaridine, as an antimalarial Mannich base, possesses an aminoquinoline moiety that is typically susceptible to metabolism by cytochrome P450 (CYP) enzymes, raising concerns about potential drug–drug interactions (O'Neill PM *et al.*, 2003).

"the hallmark symptom of malaria is its paroxysmal fever that can last up to 10 hours at a time"

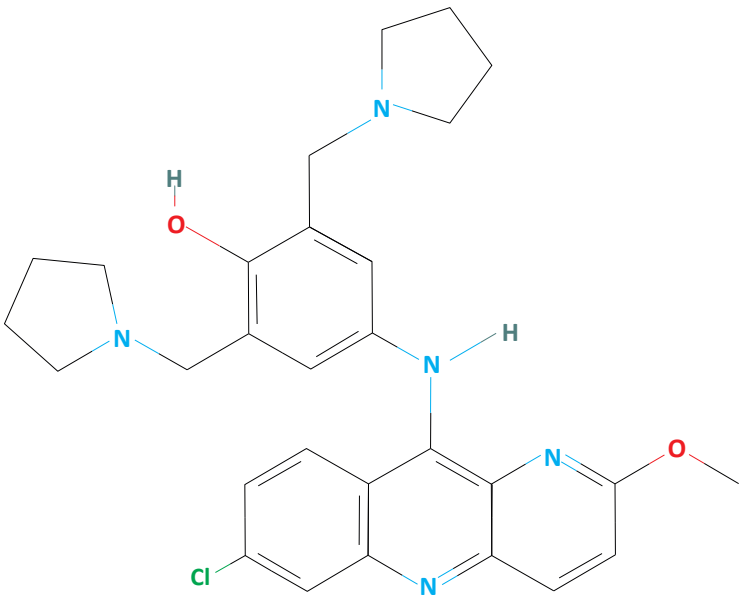


Figure 10: *Chemical structure of pyronaridine.*

"Malaria infection during pregnancy poses significant risks for both the pregnant individual and the fetus"

4.1 Treatments for uncomplicated malaria

World Health Organization (WHO) ACTs as first-line treatment against uncomplicated malaria caused by the *P. falciparum* parasite:

- Artemether-lumefantrine
- Artesunate-amodiaquine
- Artesunate-mefloquine
- Dihydroartemisinin-piperaquine
- Artesunate + sulfadoxine-pyrimethamine
- Pyronaridine-artesunate

As noted above, common symptoms may include fever, moderate to severe chills, shivering, profuse sweating, headache, nausea, vomiting, diarrhea, and anemia, without clinical or laboratory evidence of severe organ dysfunction. If left untreated, uncomplicated malaria can rapidly progress to severe malaria with potentially life-threatening consequences. Timely access to appropriate treatment for uncomplicated malaria is key to preventing progression to severe malaria.

Both major human parasite species *Plasmodium falciparum* and *Plasmodium vivax* can cause uncomplicated malaria. Treatment requires combination therapy with at least two effective antimalarial drugs with different mechanisms of action to prevent drug resistance, and dosing must be weight-based to ensure the necessary drug concentrations (Plewes K *et al.*, 2019). The parasites *P. vivax* and *P. ovale* can also cause relapsing malaria. In relapsing malaria, a form of the parasite remains dormant in the liver, causing symptoms to reappear later. Without proper use of 8-aminoquinolines (primaquine), relapses are very common, affecting about 70% of people. For that, all people diagnosed with *P. vivax* malaria must use this drug unless they have a contraindication (BOULOS, M. *et al.*, 1991; Lacerda MVG *et al.*, 2019).

5. Vaccines

Currently, after decades of research and clinical trials, the World Health Organization (WHO) has recommended the RTS,S malaria vaccine for widespread use in children living in malaria-endemic areas (Zavala F., 2022). This vaccine is a hepatitis B virus-like particle containing a genetically fused portion of the repeat domain and C-terminal region of the *P. falciparum* CSP

(D. M. Gordon *et al.*, 1995). This antigen is the sporozoite-specific molecule recognized by the protective immune responses identified by Ruth S. Nussenzweig *et al.*(1967). It is expressed on the surface of sporozoites of several species of *Plasmodium* and contains a central domain of tandem repeats representing approximately 30% of the total sequence. Experimentally, binding of antibodies to these repeats immobilizes the sporozoites and prevents infection of hepatocytes, an obligatory stage of this infection (D. M. Gordon *et al.*, 1995).

Over the past 15 years, several phase II and phase III vaccine trials have been conducted in endemic areas, and the results have consistently shown that immunization of children from 6 to 12 weeks and from 5 to 7 months old induces protective immunity that neutralizes sporozoite infection or attenuates the clinical severity of infection (Beeson JG *et al.*, 2022). An extensive phase III trial in various endemic areas of Africa showed that efficacy against clinical malaria in children aged 5 to 17 years starts at 74% and declines to 28% and 9% after 1 and 5 years, respectively. In children aged 6 to 12 weeks, efficacy was estimated to start at 63% and decline to 11% and 3% after 1 and 5 years, respectively (RTS,S Clinical Trials Partnership, 2015). The protective effect of this vaccine is temporary and it appears to depend on the intensity of transmission in different endemic areas. This diminished efficacy correlates with reduced levels of anti-CSP antibodies, which suggests that protection depends on sustained high levels of circulating antibodies (White MT *et al.*, 2015). However, there is only limited information about vaccination of adults (Zavala F., 2022). In Gambia, RTS,S immunization of adults resulted in short-lived protection from infection in 34% of vaccines (Bojang KA, 2001).

Although this is a very positive advance and may represent a first step, according to WHO, RTS,S vaccine programs could reduce severe disease in 30% of vaccinated children. Nonetheless, the vaccine does not provide broad sterile immunity. Notably, RTS,S induced immune responses do not affect gametocyte infectivity; therefore, most children and adults will carry parasites that infect mosquitoes and transmission will remain unchanged, ensuring continued endemicity (Zavala F., 2022).

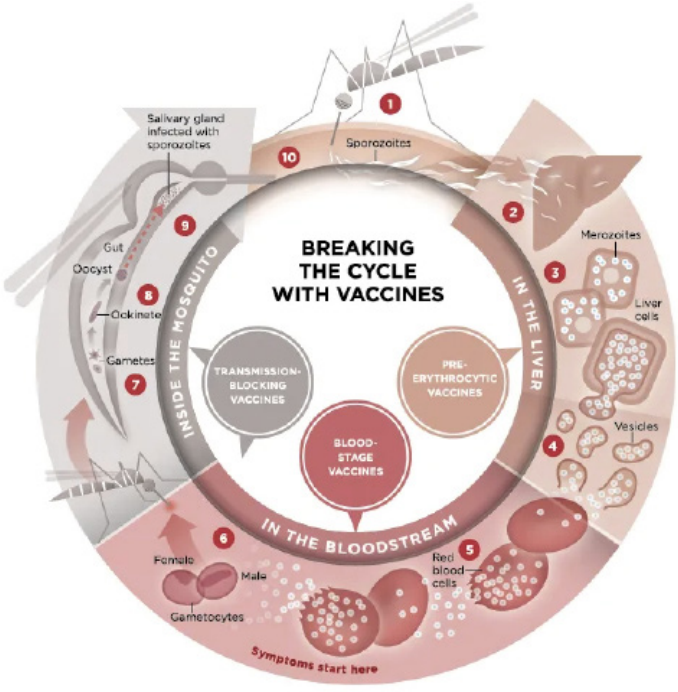


Figure 11: *Malaria parasites life cycle and possible vaccine targets.*

"In children, malaria has a shorter course, often rapidly progressing to severe malaria"

Reproduced from PATH's Malaria Vaccines website at www.malariavaccine.org, 2024, accessed in 12/06/2024.

1. Malaria infection begins when an infected female Anopheles mosquito bites a person, injecting *Plasmodium parasites*, in the form of sporozoites, into the bloodstream.

2. The sporozoites pass quickly into the human liver.

3. The sporozoites multiply asexually in the liver cells over the next 7 to 10 days, causing no symptoms.

4. In an animal model, the parasites, in the form of merozoites, are released from the liver cells in vesicles, journey through the heart, and arrive in the lungs, where they settle within lung capillaries. The vesicles eventually disintegrate, freeing the merozoites to enter the blood phase of their development.*

5. In the bloodstream, the merozoites invade red blood cells (erythrocytes) and multiply again until the cells burst. Then they invade more erythrocytes. This cycle is repeated, causing fever each time parasites break free and invade blood cells.

6. Some of the infected blood cells leave the cycle of asexual multiplication. Instead of replicating, the merozoites in these cells develop into sexual forms of the parasite, called gametocytes, that circulate in the bloodstream.

7. When a mosquito bites an infected human, it ingests the gametocytes, which develop further into mature sex cells called gametes.

8. The fertilized female gametes develop into actively moving ookinetes that burrow through the mosquito's midgut wall and form oocysts on the exterior surface.

9. Inside the oocyst, thousands of active sporozoites develop. The oocyst eventually bursts, releasing sporozoites into the body cavity that travel to the mosquito's salivary glands.

10. The cycle of human infection begins again when the mosquito bites another person.

6. Conclusion

The control, prevention, and potential elimination of malaria continue to require coordinated, multifaceted efforts worldwide, driven by public policies aimed at drastically reducing the number of infections. Despite significant progress over recent decades, the eradication of malaria remains an aspirational goal yet to be achieved. The path to elimination is long and challenging, and in the meantime, millions of people around the world will continue to suffer from this disease. The urgency of the situation cannot be overstated.

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PÍLDORA DE INFORMACIÓN

La secuenciación rápida y económica del ADN está abriendo la puerta a la medicina de precisión o personalizada. Por otra parte, ya existen una docena de tests de genotipación para detectar mutaciones en ciertos citocromos P450 que metabolizan los fármacos; su uso clínico es ya rutina en grandes hospitales; ello permite el ajuste de dosis de los fármacos en pacientes que metabolizan los fármacos con más o menos rapidez.