1. INTRODUCTION

Parasite borne diseases are considered as most devastating diseases running from decades. One of such disease known to be the deadliest form of parasite disease is malaria, caused by the genus *Plasmodium*. It is acknowledged as one of the oldest diseases to mankind, known since the period of civilization. This disease history can be easily found in the ancient manuscripts of India, Chinese and Egyptian[1]. In the 5th century malaria was identified as a disease associated with marshes and swamps along with periodic fever[2]. Malaria is known to be the major cause of morbidity and mortality, and had affected a wide range of civilization since ages. It is growing drastically in tropical and subtropical regions of world and re-emerging as the king of all diseases[3].

There were reportedly 156 species of *plasmodium* exist that spread different infections but the most prominent amongst them are five species named *P. falciparum, P. malariae, P. vivax, P. knowlesi* and *P. ovale*[4-6]. These four species infect humans individually but out of these five, two species *Plasmodium falciparum* and *P.Vivax* were mainly responsible for 80% of malaria cases worldwide and 90% overall deaths. ***P. falciparum*** is most known parasite species majorly found in tropical and subtropical areas in Africa, South America and Southeast Asia. This species is most virulent among all as it is the only which can cause pernicious and fatal malaria. ***P. vivax*** is known to be distributed worldwide and one of the most prevalent species in Latin America, Africa and Southeast Asia. This species is responsible for 60% malaria infection in India and causes major life-threatening symptoms. Whereas ***P. ovale*** is not as prevalent as other two species and it is majorly known to be found in the regions of Ghana, Liberia, Nigeria and west African region. ***P. malariae*** known to have irregular geographical distribution around the globe. It is known to be located in Central America, Southeast Asia and Africa. It does not cause any lethal infection, but if left untreated can cause severe and long-lasting damage such as chronic infection and nephrotic syndrome. ***P. knowlesi*** is not similar to the discussed parasites. It belongs to old world Monkeys (macques, *Macaca fascicularis*) and mainly found in Southeast Asia[7].

1.1 Epidemiology

As per the world malaria report 2023, published by WHO, 249 million cases were reported by far in 85 countries till 2022[8]. The majorly affected countries are Pakistan, Ethiopia, Nigeria, Uganda and Papua New Guines. The malaria cases have

shown an incidence since 2000, in 2000 the incidence declined from 81 per 1000 population at risk to 57 in 2019, similarly the incidence was 58 per 1000 population at risk in malaria. Also the malaria cases triggered by species *Plasmodium vivax* were decreased to 6.9 million in 2022 from 20.5million in 2000. The most accountable region for malaria disease is African region where 233million cases were estimated in 2022 which accounts for 94% worldwide malaria cases **(Fig 1.1)**[8]**.**

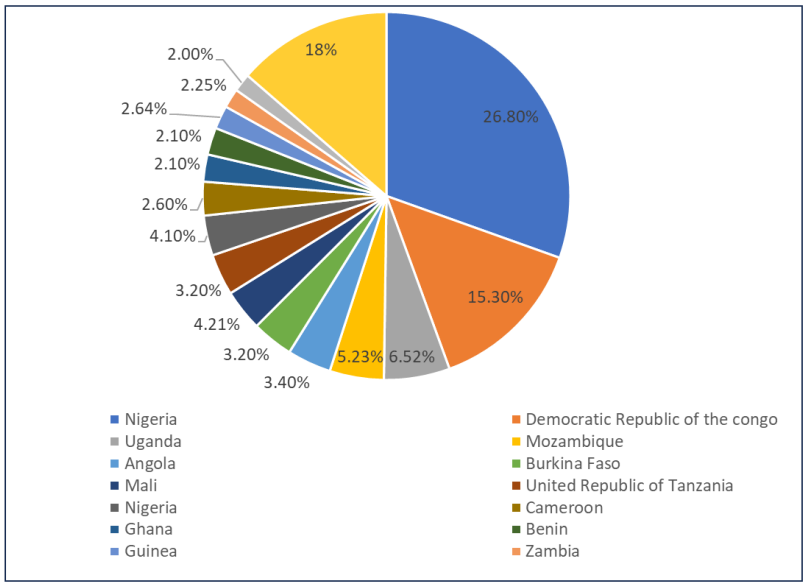


Fig 1.1 Malaria cases reported in various countries

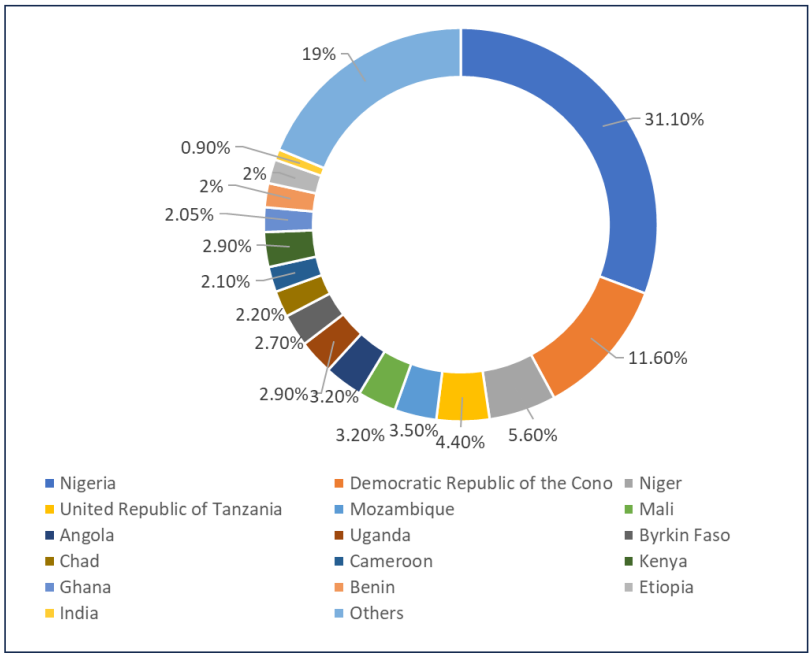


Fig 1.2 Malaria deaths reported in various countries

In Indian region 46% cases were reported due to *P. vivax* and accounted for total 66% malaria cases in the region. Total deaths reported in 2022 were 608000 which was less than accounted in 2019, 631000 (**Fig 1.2**). The most affected age group of malaria was children belonging to age group 5 years or less and pregnant women. In 2022 36% pregnant women get infected with malaria from African region which results in low birthweight in 914000 neonates[8].

WHO is trying hard to combat the spread of malaria disease across the globe therefore making intensified efforts to provide more effective, affordable and safe antimalarial treatment worldwide. Despite various efforts made by WHO there is an alarming situation due to resistance development against various medications available including artemisinin in parasite[9].

1.2 Life cycle of malaria

Plasmodium parasite life cycle is known to have multifaceted biological phenomena as it encompasses two host mediums i.e., sexual cycle (female Anopheles mosquito) and the asexual cycle (humans). The life cycle of malaria occurs in multiple stages that makes it complex. From different studies it was visualized that to study the existence and growth of parasite in both the hosts i.e., humans and mosquito around 5000 genes and their proteins were utilized which involves in the development of parasite in multiple cells as discussed in **Fig 1.3**[10].

Malaria life cycle was divided into two stages based on the two hosts involved[11]

- **Sporogony within the mosquitoes**

When the female mosquito Anopheles bites human it releases its larvae which reaches into blood of human and results in to the formation of female and male gametocytes of parasites, which further finds its way to enter into the gut of mosquito. The male and female gametocytes undergo a sexual cycle in the parasite which makes the mosquito a host cell. In this host cell zygotes were produced from the combination of female and male gametocytes. These zygotes further convert into the ookinetes which actively moves in to the mosquito gut, these ookinetes converts into oocysts by lairing on the wall of midgut. Oocysts on further development and division produces thousands of sporozoites. Formation of sporozoites take place within 8-15 days, this phase is known as sporogonic phase. After this sporogonic phase oocysts erupt and

release sporozoites in the mosquito body cavity which further transferred to salivary glands of mosquito. When the mosquito again takes any blood meal from human these sporozoites get transferred to human and asexual cycle continued in humans.

- **Schizogony in the human host**

The asexual cycle occurs in human when female Anopheles mosquito inject on human body and releases sporozoites in to the human body. These sporozoites attacks on liver cells and continues later in red blood cells. The asexual cycle is divided into two stages such as (i) Exoerythrocytic schizogony in liver and (ii) Erythrocytic schizogony in red blood cells.

- **Exoerythrocytic schizogony in liver**

When female anopheles mosquito bite human skin to ingest blood meal, it releases ten to hundred sporozoites into human skin. Some of the sporozoites were killed within few minutes by the host cell macrophages and others reaches to liver through blood vessels. In liver these sporozoites invade hepatocytes or some become dormant as hypnozoites and develop into parasitophorous vacuoles also known as tyrophozoites. Sporozoites developed into trophozoites form schizont (comprises 10,000-30,000 merozoites). by asexual multiplication also known as mitosis in a time period of 5-16 days. The schizonts releases merozoites when get ruptured which starts erythrocytic stage. This complete process occurs in a single cycle where merozoites released from schizonts become protected with merosomes which protect merozoites from phagocytosis.

- **Erythrocytic stage**

Merozoites release in blood stream at lung capillaries directs its way into RBCs within minutes and attacks on RBCs through discrete ligands on merozoite and host receptor available on erythrocyte membrane by following molecular interaction phenomena. This attack on RBCs occurs in continuous cycles and increases number of parasites in cells which elevates with each cycle up to 10^{13} per host with growth. Some of the asexual parasites undergoes sexual stage gametocytes without undergoing schizogony and form male and female gametocytes which are extracellular and non-pathogenic and remains inactive in the blood stream of host.

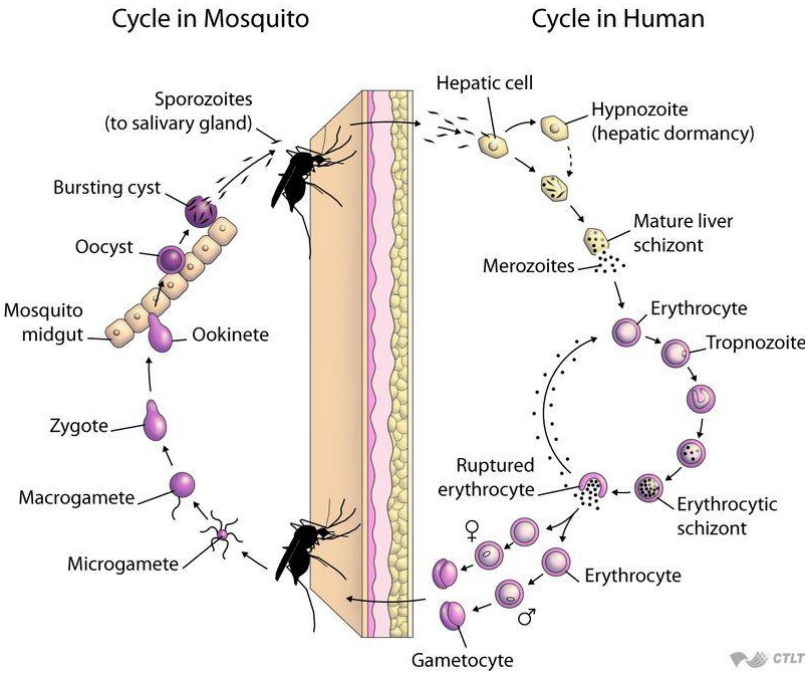


Fig 1.3 Lifecycle of malaria[12]

1.3 Therapeutic targets for antimalarial drugs

With an aim to develop new inhibiting agents different and vital pathways were followed to identify different drug targets[13].

1.4 Pathophysiology of malaria

Malaria infection caused by female anopheles mosquito bite starts spreading in human host but the symptoms of malaria such as ample sweating, fever and chills start appearing after incubation period of 9-14days. This incubation period varies for different plasmodium species such as for *P. falciparum* incubation period is 5 to 7 days, for *P. vivax* 6 to 8 days, for *P. ovale* up to 9 days and for *P. malariae* it is 12-16 days[14].

Malaria infection spread in the human body in different time periods. When schizonts rupture to release merozoites from liver cells in to blood stream this time interval is known as pre-patent period and this phase is known as pre-erythrocytic phase. During this period no symptoms appear in the host body and the host remain asymptomatic. Symptoms starts appearing when pre-patent period is over and this is called as primary attack. In some plasmodium species there exist a relapsing phase in which sporozoites undergo hibernation condition i.e. remains inactive and non-dividing in liver for months and years and on reactivation it can cause clinical relapse[15]. This is known as relapsing malaria and it occurs in parasite *P. vivax* and *P. ovale*.

1.4.1 Processes in digestive vacuole

1.4.1.1 Haemoglobin digestion and heme polymerization

Heme targets were broadly explored as they serve as the first choice of antimalarial drugs. These targets were studied for the asexual phase of malaria cycle. In erythrocytic phase 80% haemoglobin were digested by the parasite and degraded into heme and globin part[16]. These heme and globin part serves various functions for the parasite. The heme part (α-hematin or ferriprotoporphyrin IX) work as a pre-oxidant is converted into hematin (β-hematin, ferroprotoporphyrin) as the free heme part is toxic to parasite[17]. Whereas the globin part involves in the synthesis of crucial amino acids. The heme and globin part are considered as potential targets to develop potent antimalarials drugs. There are already some heme targeting drugs known in the market such as artemisinin, artesunate and artemether which act by forming radical adducts with heme which stops heme conversion into hemezoin and other drugs like chloroquine, amodiaquine, mefloquine and piperquine act by inhibiting conversion of α-hematin into β-hematin which will kill parasite[18]. Enzymes associated with these targets are plasmepsin I, II (aspartic protease) and Falcipain II (cysteine protease).

1.4.1.2 Redox cycle (oxidative stress)

During the process of hemezoin formation from heme, reactive oxygen species (ROS) were generated which were neutralize by the parasite's antioxidant system. The antioxidant enzymes work to counterbalance these ROS are superoxide dismutase (SOD), lutathione peroxidase (GPx) and catalase therefore these enzymes can serve as potential targets for antimalarial drugs[19,20]. Enzymes associated with redox cycle are Glutathione reductase and Thioredoxin reductase.

1.4.2 Processes in nucleic acid metabolism

1.4.2.1 Folate pathway

This is the most common target explored and studied for designing new compounds having antimalarial activity. There is a quantity of enzymes intricated in folate metabolism such as methylenetetrahydrofolate reductase (MTHFR), methionine synthase (MS), dihydrofolate reductase (DHFR) and serine hydroxymethyltransferase (SHMT). Folate synthesis is essential for parasite as it further synthesize thymidylate and parasite DNA, therefore inhibition of folate synthesis due to the inhibition of enzymes involved in folate metabolism results into thymidylate and parasite DNA

deficiency. Antimalarials drugs reported to act on folate metabolism and enzymes are sulfadoxime (blocks DHPS enzyme activity), pyrimethamine, trimethoprim and proguanil (blocks DHFR activity)[21].

1.4.2.2 Pyrimidine metabolism and electron transport chain target

Pyrimidine metabolism takes plus in the mitochondria that is significant for the existence of parasite. It mainly known for protein synthesis and electron transport chain. In mitochondria most explored target is electron transport chain which regenerates mitochondrial coenzymes Q i.e., ubiquinone and cytochrome bc1. Antimalarial drugs acting on this target are atovaquone which is known to be effective against the resistant strain of parasite[21]. This highlights the importance of this target in developing new antimalarial drugs.

1.4.2.3 Proteases

Proteases inhibitors were known through ages as these are massively used in antiviral chemotherapy such as saquinavir, lopinavir and ritonavir drugs[22]. Therefore, this has been explored in malaria and from research it was found that proteases were involved in degradation of haemoglobin as mentioned in **Fig 1.4**[23]. Main proteases involved in the malaria life cycle are cysteine proteases (falcipains, FP-1,2 and 3) and aspartic proteases (plasmepsins, PM-I-V)[24].

1.4.3 Membrane processes and signalling targets

Membrane targets have been widely explored due to their importance in parasite survival in human host. Parasites are consists of numerous membranes such food vacuole membrane, parasite plasma membrane (PPM) and parasitiphorous vacuole membrane[25]. To build protective layer around its parasitophorous vacuole, cytoplasm and other cellular machinery parasite initiate synthesis of phospholipids. The most common phospholipid is phophatidylecholine (PC), combined from plasma unsaturated fat. Phospholipids were synthesized from fatty acids and targeting inhibition of fatty acid synthesis can be proved as an effective target[26]. Some of molecules designed targeting membrane processes has shown activity in nanomolar such as quaternary ammonium and bis-ammonium quaternary salts linked with elongated lipophilic alkyl chain and another bis-ammonium salts with lengthy alkyl chain[27,28].

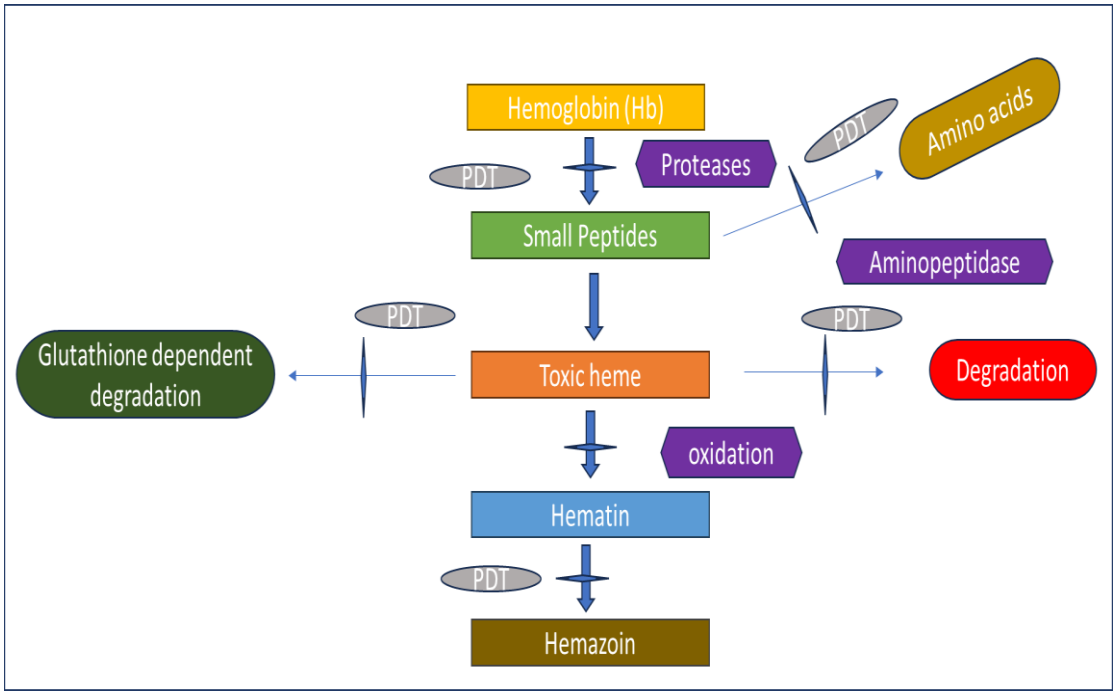


Fig 1.4 Targeting proteases for designing antimalarial agents[23]

1.4.3.1 Parasite transporters

In erythrocytes of human host, the transport pathway alters once the parasite invades, which results into changes in nature of solutes permeation and its intensities. These changes in NPPs (new permeability pathway) induces the permeability of pantothenate which is essential for survival of parasite[29]. This pathway also passes the waste of parasite out of RBCs[30].

1.4.3.2. Apicoplast

Apicoplast serves as major target for the study of antimalarial drugs as it serves as a hub of various functions occur in parasite such as synthesis of heme, isoprenoids, fatty acids and iron-sulfur clusters biogenesis. The most effective targets in apicoplast for antimalarial drugs development is synthesis of fatty acids and isoprenoid precursor[31].

1.5 Currently available antimalarial drugs in the market

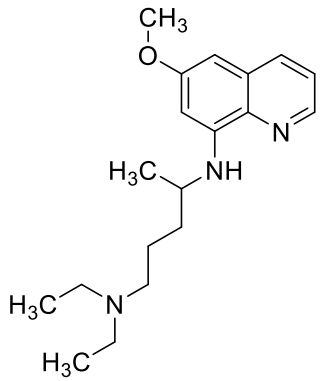
In 1880, after discovery of malaria parasite a number of malaria control programmes were started and to successfully control the disease therapeutic and chemoprophylactic approaches were used[32]. Various efforts were made to eliminate this disease but due to the development of resistance by the parasite against already existing antimalarial drugs limited the exertions to complete abolish this disease. Antimalarial

drugs available in market were designed to target various stages of parasite life cycle and due to the emergence of resistance targeting more than a single target has become prime importance. Antimalarial drugs have been categorize on the basis of chemical structures and targets.

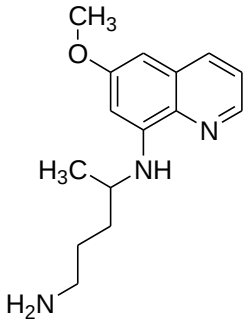
1.5.1 Quinoline and its derivatives

8-Aminoquinolines

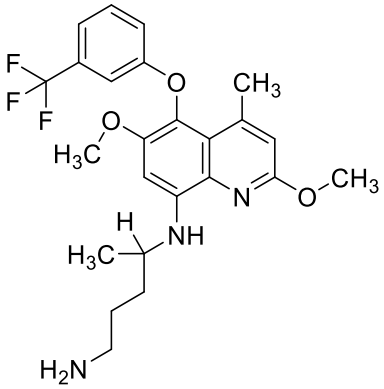
Pamaquine **(1)** second antimalarial drug discovered after methylene blue to treat malaria which acts on the hypnozoite form of parasite. This drug was discontinued from the market due to its severe toxicity[33]. Primaquine **(2)** was synthesized to overcome the toxicity of pamaquine detected due to the presence of terminal diethyl amino group. Primaquine was synthesized having unsubstituted primary amine which acts against the exo-erythrocytic and sexual blood stage of parasite[9].



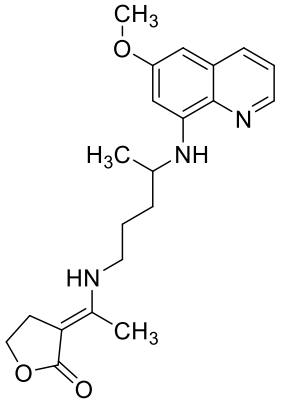
Pamaquine **(1)**



Primaquine **(2)**



Tafenoquine **(3)**



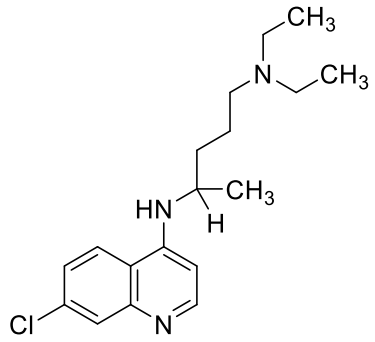
Elubaquine **(4)**

Tafenoquine **(3)** is recognized to have higher efficiency in contrast to blood and liver stage of parasite. Tafenoquine is more lipophilic due to the presence of

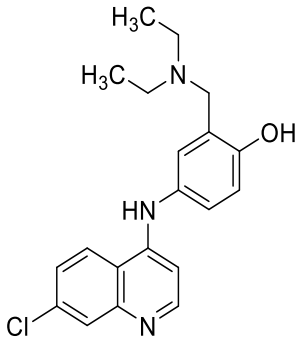
trifluoromethyl phenoxy substituent[34]. From the series of 8-aminoquinoline only primaquine and tafenoquine is in clinical use. Elubaquine **(4)** drug is known to be used against *p-cynomolgi* in rhesus monkey. In humans also it has come under clinical trials especially in the areas of Thailand and found to show comparable activity along with the tolerability and safety as primaquine[35].

1.5.2 4-Aminoquinoline

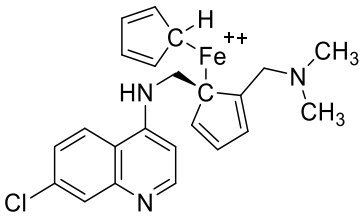
Chloroquine **(5)** is known to be one of the utmost efficient medications for the treatment of malaria introduced in 1632. Chloroquine was known to be most reliable and affordable drug before emergence of resistance in 1957. Chloroquine was known to invade food vacuole of parasite via simple diffusion process. Chloroquine used to form a complex with heme by getting protonated due to the acidic nature of food vacuole. This compound is extremely noxious for parasite and results in to cell lysis that results into cell death. This drug can be safely used for the pregnant women and can be used as a prophylactic agent[32]. Amodiaquine **(6)** is structurally modified form of chloroquine resulted from the enhance lipophilicity of side chain. This drug has established as most efficient than chloroquine in the case of chloroquine resistant *Plasmodium falciparum* malaria at the initial stage. On further development amodiaquine was observed to be decreased due to the biotransformation of amodiaquine analogue p-aminophenol to quinonimine[32].



Chloroquine **(5)**



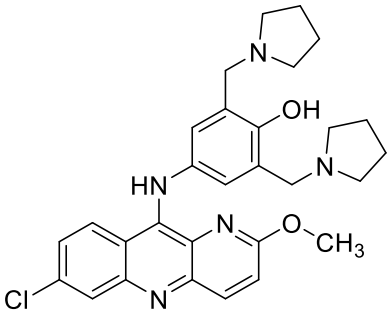
Amodiaquine **(6)**



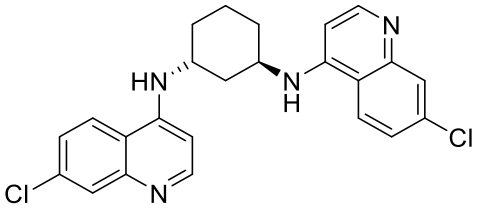
Ferroquine **(7)**

Ferroquine **(7)** was known to be active against CQ-sensitive as well as CQ-resistant strain. This drug is having ferrocenyl moiety in its side chain that increases its lipophilicity[36]. Pyronaridine **(8)** drug has similarity with amodiaquine as it belongs to the class of mannich base schizonticides having aminophenol moiety. Pyronaridine is

having two mannich base side chains[36]. Bisquinolines **(9)** are designed to overcome the resistance of chloroquine as it comprises of two 4-aminoquinoline moieties linked with a variety of linkers of different length. The activity of these bisquinolines depends on the steric bulk against chloroquine resistant strain. One such bisquinoline was piperaquine, that was mostly consumed in china. Piperaquine was reported to have some side effects related to blood pressure but these are well tolerated so piperaquine was marketed[37].



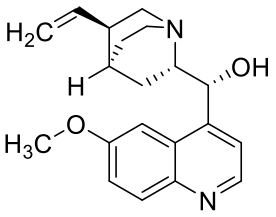
Pyronaridine **(8)**



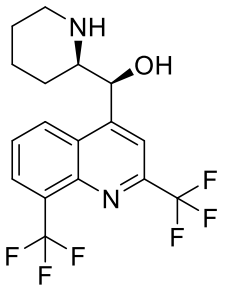
Bisquinoline **(9)**

1.5.3 Aryl amino alcohols

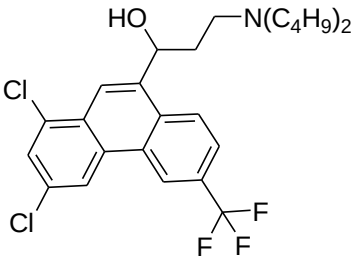
Quinine **(10)** one of the oldest natural drugs introduced in 1632 for malaria treatment. This drug was isolated from cinchona bark and it is having an isomer named quinidine which is also been used to treat uncomplicated malaria[38]. First case of resistance of quinine was found in 1910.



Quinine **(10)**



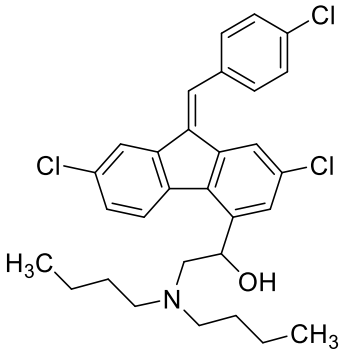
Mefloquine **(11)**



Halofantrine **(12)**

Mefloquine **(11)** was known as a simplified form of quinine which was used some parts of thailand since 1977, its first case of resistance was reported in 1982[39]. Halofantrine **(12)** Halofantrine was known to have high risk of cardiac arrhythmias and it belongs to the series of phenanthrene methanol. Halofantrine were known to shows resemblance with mefloquine due to its high lipophilicity and insolubility in water[40,41].

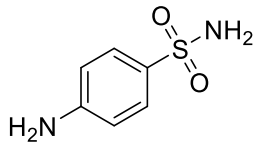
Lumefantrine **(13)** This drug is structurally similar to halofantrine but has less potency as compared to halofantrine. but from studies it was revealed that its oral absorption is enhanced by 16 fold when taken with fatty meal[42].



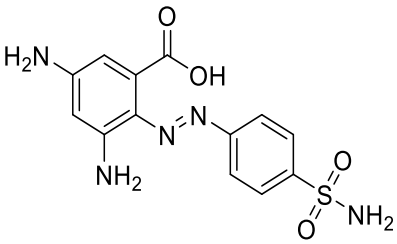
Lumefantrine **(13)**

1.5.4 Antifolates as antimalarial agents

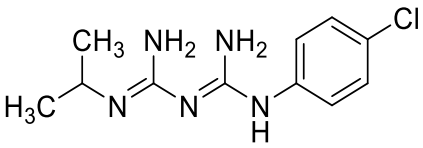
Antifolates were broadly used for dealing with malaria. These drugs act on enzymes dihydrofolate reductase (DHFR) and dihydropteroate synthase (DHPS) and alter the folate biosynthetic pathway by inhibiting the synthesis of DNA/RNA biosynthesis by limiting the translation of folic acid into tetrahydrofolic acid. Some of the marketed antifolate drugs are sulphanilamide **(14),** sulfachrysoidine **(15),** proguanil **(16),** pyrimethamine (**17),** cycloguanil **(18),** trimethoprim **(19)** and methotrexate **(20)**[43]. Pyrimethamine and trimethoprim was declared as safe to be used during pregnancy.



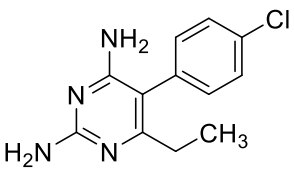
Sulphanilamide **(14)**



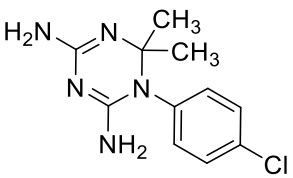
Sulfachrysoidine **(15)**



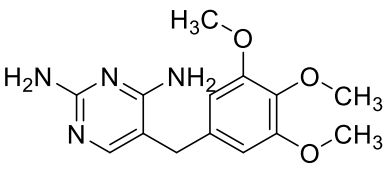
Proguanil **(16)**



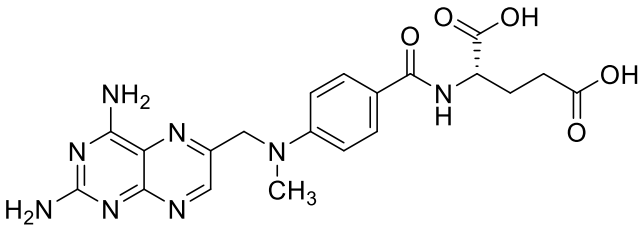
Pyrimethamine **(17)**



Cycloguanil **(18)**



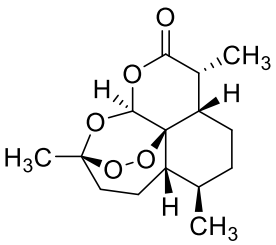
Trimethoprim **(19)**



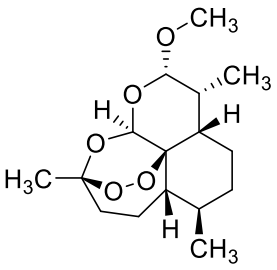
Methotrexate **(20)**

1.5.5 Artemisinin derivatives

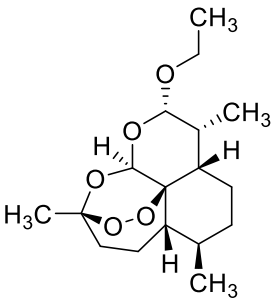
Artemisinin **(21)** was extracted from the leaf of Artemisia annua Chinese traditional herb. It belongs to sesquiterpene lactone 1,2,4-trioxane class which is known to be active against drug-sensitive as well as drug resistant stage of malaria[44]. But artemisinin has shown some limitations such as poor oil and water solubility and high rate of recurrence which resulted in the synthesis of artemisinin derivatives having better oil solubility. Artemether **(22)** and arteether **(23)** are two most effective artemisinin derivatives synthesised from dihydroartemisinin with alcohol in presence of acid catalyst. These artemisinin derivatives were safe to use under emergency treatment for severe multi-drug resistant malaria as these derivatives act on the blood schizonticides[45].



Artemisinin **(21)**



Artemether **(22)**



Arteether **(23)**

1.5.6 Combination therapies

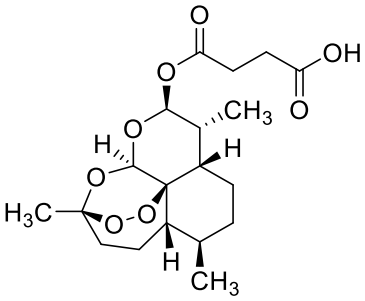
In an attempt to diminish the chance of resistance and to improve the efficacy two or more drugs in combination were used based on their synergistic and additive activity potential. Although the combination drugs have their individual mechanism of showing efficacy along with different biological targets. Combination therapy drugs were classified in two different classes.[46]

1.5.6.1 Artemisinin based combination

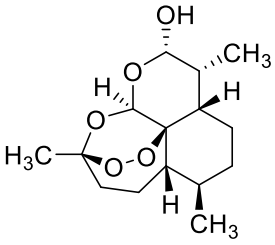
Artemisinin based combinations were proved to be utmost fruitful and effective as an antimalarial agent. Sesquiterpene combinations were developed based on two approaches; (a) Drug having short half-life combined with drug having long half-life, e.g. Artemether with lumefantrine; (b) Combination reducing drug resistant of individual drug[46].

Examples of artemisinin-based combination therapy

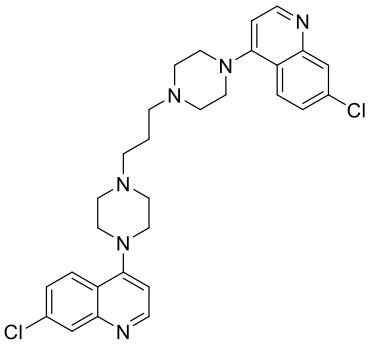
- Combination of amodiaquine (**6**) with artesunate (**24**)
- Combination of mefloquine (**11)** with artesunate (**24**)
- Combination of pyronaridine (**8**) with artesunate (**24**)
- Combination of lumefantrine (**13**) with artemether (**22**)
- Combination of dihydroartemisnin (**25**) with piperaquine (**26**)



Artesunate (**24**)



Dihydroartemisinin (**25**)

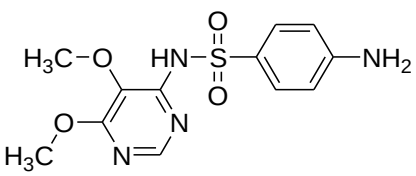


Piperaquine (**26**)

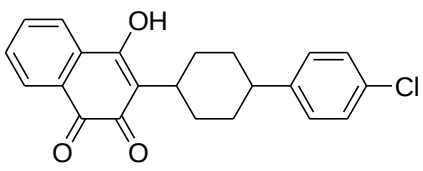
1.5.6.2 Non-artemisinin-based combinations

- **Quinoline based combination**

In this combination, first line and second line drugs used in malaria caused by *P. falciparum* such as chloroquine (CQ), sulfadoxine-pyrimethamine (**27**). Another quinoline based combination used is amodiaquine (AQ), sulfadoxine-pyrimethamine. Both these combinations were reported to show same kind of pharmacokinetic properties although the mode action is different for individual drugs[47],[48].



Sulfadoxine (**27**)



Atovaquone (**28**)

- **Naphthoquinone based combination**

Main drug belongs to this class is atovaquone **(28)** which is a structural analogue of ubiquinone. Atovaquone were known to target electron transport chain and interrupt pyrimidine synthesis. Drugs used in the combination with atovaquone is proguanil which is a pro-drug that converts into cycloguanil on biotransformation. In combination with atovaquone proguanil was reported to reduce resistance caused by atovaquone[49].

Another non-sesquiterpene combination is consist of mefloquine with sulfadoxine-pyrimethamine[50]. This combination was reported to delay drug resistance phenomena. Other than this quinine-tetracycline and quinine-doxycycline combinations were also reported.

1.6 Drug resistance in malaria: A persistent challenge to effective treatment

The World Health Organization (WHO) first defined drug resistance in 1967 as the ability of a parasite to withstand the effects of a drug administered at its recommended or even higher doses. In such cases, the parasite continues to proliferate without displaying sensitivity to the drug. Similarly, *Plasmodium* parasites, particularly *Plasmodium falciparum*, have developed resistance to existing antimalarial treatments. *P. falciparum* is the primary contributor to drug resistance, accounting for over 90% of global malaria cases[51].Although numerous antimalarial drugs have been developed, only a limited number have remained effective for extended periods, as resistance has emerged against most treatments. This growing challenge underscores the urgent need for new antimalarial agents[3]. Studies suggest that multiple factors contribute to the development of resistance, including prolonged drug elimination half-life, weakened host immunity, high transmission rates, and specific biological characteristics of *Plasmodium* species.

1.6.1 Mechanism of antimalarial drug resistant

When *Plasmodium* parasites are exposed to an antimalarial drug, the initial response is often effective. However, over time, the parasite adapts to the drug-induced environment, gradually reducing the drug's impact. Once the parasite fully adapts, the drug loses its effectiveness, allowing the parasite to survive and proliferate despite continued drug exposure. This phenomenon, known as drug resistance, typically develops when the parasite is subjected to prolonged and continuous drug

pressure[23].The mechanisms of resistance vary depending on the drug to which the parasite is exposed. Some common adaptations include delayed parasite clearance, increased transmissibility, reduced gametocyte susceptibility, and resistance at the ring stage. Different antimalarial drugs exhibit resistance through one or more of these mechanisms, as outlined in **Table 1**[52].

Table 1: Mechanism of resistance in antimalarial drugs

Antimalarial drugs	Mechanism of Resistance	Site of action
Pyrimethamine and cycloguanil	Dihydrofolate reductase mutation	Cytosol
Sulfadoxine	Dihydropteroate synthetase	Cytosol
Atovaquone	Cytochromeb subunit of bc1 complex single point mutation	Mitochondria
Clindamycin and Doxycycline	Apicoplast encoded rRNA point mutation	Apicoplast
Artemisnin	Mutation in K13	ER, vesicular structures
4-Aminoquinolines (CQ, AQ, PPQ, Mannich base pyronaridine)	PfCRT and PfMDR I transporters Point mutation, increase in haemoglobinase plasmepsin 2 and 3 expression and some mutation in PfCRT.	Digestive vacuole

1.6.2 Measures to tackle antimalarial drug resistance

With continuous development of resistance against already marketed drugs of malaria provoked the necessity for the expansion of new antimalarial agents or to combat the development of resistance adopting different measures[53].

1.7 Combination therapy

Combination therapy was adopted to overcome the resistance develop against individual drug of malaria but with time it has been observed that resistance has developed against existing combination drugs also which further emerges the need for new combinations and discovery of artemisinin given a new hope to the research of antimalarials[12]. Resistance has also been developed against artemisinin but still this drug and its derivatives has been endorsed by WHO to be used in combination with first line antimalarial drugs. Combinations recommended by WHO are as follows: artemether with lumefantrine, dihydroxy artemisinin with piperaquine, artesunate with amodiaquine, artesunate with pyronaridine, artesunate-sulphadoxine-pyrimethamine

and artesunate-mefloquine[12].

1.8 Antimalarial drugs under clinical trials

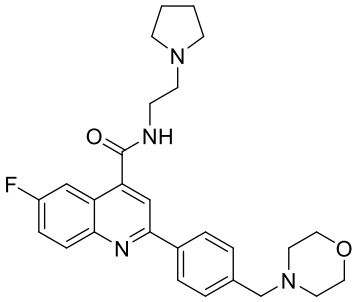
The continuous emergence of resistance to existing antimalarial drugs has created an urgent need for the development of novel therapeutic molecules. Addressing this challenge requires the discovery of compounds that can effectively target drug-resistant strains of *Plasmodium*. Researchers worldwide, in collaboration with pharmaceutical industries, are actively engaged in identifying and developing new antimalarial candidates. Several promising molecular scaffolds are currently undergoing clinical trials[54]. One of the leading organizations in antimalarial drug discovery is Medicines for Malaria Venture (MMV), which collaborates with academic institutions and pharmaceutical companies to accelerate drug development. New antimalarial agents are being designed through various approaches, including target-based drug discovery, rational drug design, the synthesis of peroxides and synthetic peroxides, as well as phenotype-driven screening strategies[55]. As a result of these efforts, approximately 14 drug candidates have entered clinical trials, where they are being evaluated across multiple parameters to ensure efficacy and safety.

Phenotypic screening - In this approach a library containing large number of chemical entities is screened against whole cell parasites. A number of drugs were discovered using this approach which are under clinical trials such as ganaplacide (KAF156), cipragamin (KAE609), cabamiquine (M5717, DDD107498, MMV643121), and ZY-19489[56].

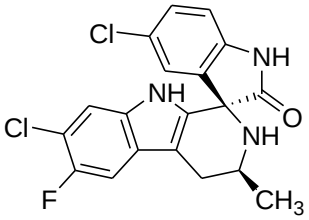
ZY-19489, an antimalarial drug candidate licensed to Zydus, was discovered through high-throughput screening based on a triaminopyrimidine hit. This fast-acting compound primarily targets the asexual blood stage of *Plasmodium* (TCP-1). Preclinical studies have demonstrated its favorable safety profile, pharmacokinetics, low resistance potential, and strong antimalarial activity. Notably, the combination of ZY-19489 with ferroquine—another antimalarial agent also licensed to Zydus—has shown potent efficacy in children with a single-dose regimen, highlighting its potential as an effective treatment option[57].

Cabamiquine **(29),** an antimalarial drug candidate licensed to Merck KGaA, was developed through the optimization of the 4-aminoquinoline scaffold using phenotypic

screening[58]. Resistance mutation analysis has identified its target as eukaryotic elongation factor 2 (eEF2), indicating its mechanism of action in inhibiting protein synthesis. This compound has shown efficacy against both the asexual blood stage and the sexual stage of *Plasmodium*[59]. To enhance its therapeutic potential and minimize resistance, cabamiquine is being co-developed with pyronaridine, a complementary partner drug stage and sexual stage. This molecule is used in combination with pyronaridine which serves as irresistible partner drug.

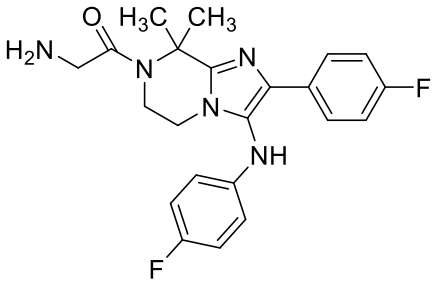


Cabamiquine **(29)**

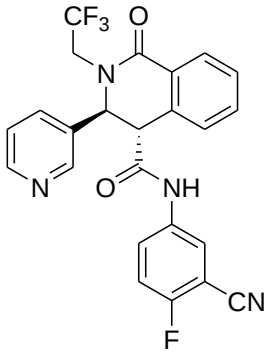


Cipragamin **(30)**

Cipargamin **(30)** was discovered through a collaboration involving the Novartis Institute for Tropical Disease, the Genomics Institute of the Novartis Research Foundation, the Biomedical Primate Research Centre, and the Swiss Tropical and Public Health Institute[60]. Its target, *PfATP4*, has been identified through mutations in the gene encoding this protein. *PfATP4* is a parasite-specific sodium-proton exchanger[61], playing a crucial role in maintaining ionic balance. Cipargamin has demonstrated significant effects on the asexual blood stage of *Plasmodium*, where it increases parasite rigidity and accelerates clearance in *in vivo* models (TCP-1 and TCP-5).



KAF156 **(31)**



SJ733 **(32)**

KAF156 **(31),** also known as ganaplacide, is an imidazolopiperazine-derived antimalarial compound identified through the Novartis-Gates Biomedical Science

(NGBS) association. Resistance to this molecule, along with similar compounds such as GNF179, has been linked to mutations in the *Plasmodium falciparum* cyclic amine resistance locus. While its precise molecular target remains unidentified, studies suggest that ganaplacide may interfere with protein processing or secretion. Additionally, it has demonstrated potency against both the pre-erythrocytic and gametocytic stages of the malaria parasite. Its efficacy has been established in both healthy volunteers and malaria patients during Phase I and II clinical trials, supporting its potential as a next-generation antimalarial treatment[62].

The combination of ganaplacide with lumefantrine, a drug also used in artemisinin-based combination therapies (ACTs), has been investigated for its ability to improve solubility and oral bioavailability. This pairing has demonstrated potential in reducing the risk of resistance while maintaining strong antimalarial efficacy[63]. Research on this combination is being conducted by Novartis, which has already advanced the study to Phase III clinical trials. If successful in this phase, the ganaplacide-lumefantrine combination could emerge as a potent non-ACT treatment, comparable to the widely used atovaquone-proguanil (Malarone) [64].

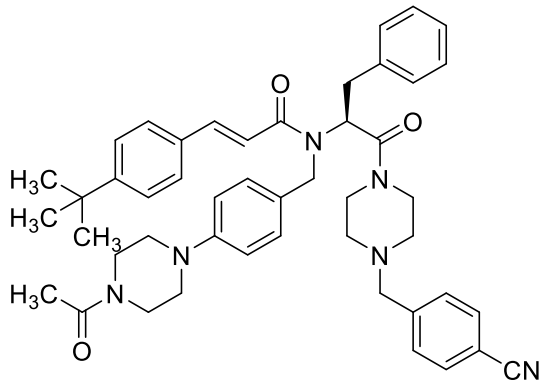
MMV688533, identified in 2017 through an orthology-based screening approach, was initially detected as an impurity during the resynthesis of a key screening hit. Further investigation revealed its potent, fast-acting antimalarial properties, along with a prolonged human half-life. Notably, no resistance to this compound was observed at the laboratory scale. Having successfully completed Phase I clinical trials with acceptable human tolerability, MMV688533 is now progressing to Phase II trials[65].

INE963, discovered through phenotypic screening by the Novartis Institute for Tropical Diseases, is currently undergoing Phase I clinical trials. Plans are in place to advance this compound to Phase II, where it will be evaluated for use in combination therapies to enhance its therapeutic efficacy against malaria[66].

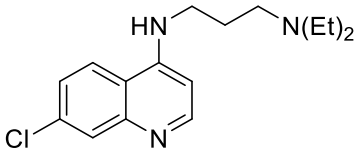
SJ733, a dihydroisoquinolone-derived compound, has exhibited strong activity against *Plasmodium falciparum* and other *Plasmodium* species. Developed through a collaboration between Medicines for Malaria Venture (MMV) and the University of Kentucky, this compound primarily targets blood-stage schizonts and gametocytes. Currently, SJ733 is undergoing Phase I clinical trials to evaluate its safety and

therapeutic potential as a novel antimalarial agent[67].

ACT-451840 known as phenylalanine-derived compound having potent antimalarial activity against *P. falciparum* as well as *P.berghei*[68,69]. AQ-13, a 4-aminoquinoline analogue of chloroquine, has demonstrated strong antimalarial activity against chloroquine-resistant, mefloquine-resistant, and multidrug-resistant strains of *Plasmodium falciparum*. The compound exhibits an IC_{50} range of 5–14 nM, highlighting its potency. Currently, AQ-13 is undergoing Phase II clinical trials to assess its efficacy and safety as a potential treatment for drug-resistant malaria[69].



ACT-451840 **(33)**



AQ-13 **(34)**

1.9 Recent advances to fight against ADR

To fight against ADR and its limitations, few approaches has been given by researchers that can tackle ADR[51]. The approaches are:

- Regional artemisinin-resistance initiative (RAI)
- Nano mimics
- Targeted drug delivery
- Triple artemisinin-based combination therapy and
- Drug development.

Regional artemisinin-resistance initiative (RAI)

To address artemisinin resistance in the Greater Mekong Subregion (GMS), the Global Fund launched the Regional Artemisinin-resistance Initiative (RAI) in 2013. This initiative implemented prophylactic strategies, resulting in an 88% reduction in indigenous malaria cases and a 95% decline in *Plasmodium falciparum* infections. Additionally, the drug-rotation approach has proven effective in mitigating resistance and improving malaria control efforts in the region[51].

Nanomimics

The emergence of resistance to artemisinin-based combination therapies (ACTs) has created an urgent need for alternative antimalarial strategies. In response, nanomimic technology has been developed as an innovative approach to combat drug-resistant malaria. This technology involves the use of polymer vesicles—tiny artificial bubbles-designed to mimic host cell receptors on their surface. By closely resembling natural host cells, these nanomimics can interact with *Plasmodium* parasites, potentially disrupting their lifecycle and offering a new avenue for malaria treatmen[70].

1.10 Development of malaria vaccines

Malaria continues to be one of the deadliest infectious diseases worldwide, despite extensive efforts to control its spread and combat drug resistance. While antimalarial drugs have been the primary treatment approach, researchers have also been striving to develop an effective vaccine since the 1960s[71]. However, malaria vaccine development remains a complex challenge due to the parasite's intricate life cycle, which involves both humoral and cellular immune responses. One significant breakthrough in this field is the RTS,S vaccine, which received approval from the WHO for pilot studies in Ghana, Kenya, and Malawi. This development marks a crucial step toward integrating vaccines into global malaria control strategies[72].

The RTS,S vaccine has been endorsed by the WHO for the short-term prevention of malaria. Developed through a collaboration between GlaxoSmithKline and the PATH Malaria Vaccine Initiative, with funding from the Bill & Melinda Gates Foundation, this vaccine specifically targets the pre-erythrocytic stage of the *Plasmodium* parasite. It has demonstrated the highest efficacy in children aged 5 to 17 months[74]. The vaccine's effectiveness is dose- and time-dependent; when administered in four doses over four years, it achieves approximately 40% efficacy, whereas a three-dose regimen over a shorter period reduces efficacy to 26%. Beyond RTS,S, several other malaria vaccine candidates are undergoing clinical trials[75]. Continued research is focused on optimizing vaccine efficacy by targeting priority areas in malaria immunology and parasite biology[76]. These efforts are crucial for the development of more effective and long-lasting malaria vaccines.

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