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Research Article

Malaria's molecular dance: Mechanism, therapies, and emerging insights

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Abstract

Malaria, caused by *Plasmodium* parasites and transmitted through Anopheles mosquitoes, remains a formidable global health challenge. This abstract provides an overview of the intricate molecular mechanisms underlying malaria pathogenesis, explores current therapeutic approaches, and highlights emerging insights that may shape future strategies for malaria control. The intricate dance between *Plasmodium* parasites and their human hosts begins with the mosquito's bite, leading to the invasion of erythrocytes by *Plasmodium* species. We delve into the molecular mechanisms governing parasite entry and subsequent replication within host cells, shedding light on key factors such as erythrocyte surface receptors and parasite-encoded proteins critical to invasion and survival. While malaria treatment has relied heavily on antimalarial drugs, the emergence of drug resistance necessitates ongoing exploration of novel therapeutic strategies. This abstract reviews current antimalarial drug classes, their mechanisms of action, and the challenges posed by drug resistance. We also highlight promising drug candidates and innovative approaches in the pipeline, including the use of advanced molecular techniques and immunotherapies. Emerging insights from genomics, proteomics, and transcriptomics have deepened our understanding of *Plasmodium* biology and host-parasite interactions. We discuss the potential of these omics approaches in identifying new drug targets, understanding drug resistance mechanisms, and developing vaccines. Additionally, we examine the role of human genetics in influencing susceptibility to malaria and response to treatment. Vector control remains a critical component of malaria prevention. We touch upon emerging strategies, such as genetically modified mosquitoes and novel insecticides, in the context of integrated vector management programs. Finally, we emphasize the importance of a multifaceted approach to malaria control, combining advances in molecular biology, drug development, vector control, and public health interventions.

Keywords

Anopheles mosquitoes, malaria, molecular mechanisms, pathogenesis, *Plasmodium* parasites

Introduction

HIV, TB, and malaria are major causes of morbidity and mortality, particularly in children. *Plasmodium* is a protozoan parasite that causes the sickness and is spread by the vector anopheline mosquito. All Humans are affected by the five species of *Plasmodium falciparum*, *Plasmodium ovale*, *Plasmodium malariae*, *Plasmodium vivax*, and *Plasmodium knowlesi*. Producing more than 225 million cases worldwide each year, there are incident infections that cause almost one million fatalities. *P. falciparum* is the most common malaria species among them, causing the most severe form of the disease, mainly in Africa, of the illness and causing more than 90% of total fatalities. The second most prevalent species, known as vivax, is primarily found in Asia and South America, and is capable of bringing on recurrent malaria (Shah and Valecha 2016). Ross and Grassi's 1898 discovery that malaria parasites are spread through mosquito bites was the catalyst for the beginning of the fight against the disease. Initial malaria control methods were based on this discovery, which led to the installation of window and door screens, the reduction of mosquito breeding places through changes in agricultural practices, and the application of pesticides, specifically dichloro-diphenyl- trichloroethane (Shah and Valecha 2016).

Between 1900 and 1946, these initiatives successfully stopped the spread of the disease to more than 10 nations. The "Global Malaria Eradication Programme" was established by the World Health Organization in 1955, and chloroquine treatment was used to supplement the earliest measures for vector control. An additional 27 nations were deemed malaria-free when the program was formally terminated in 1969. Unfortunately, malaria could not be completely eradicated. Accomplished in the majority of developing nations (Sub-Saharan Africa was not included in the initial eradication program), leading to malaria's current primary spread is to sub-tropical include the tropics. Widespread resistance to existing pesticides, conflicts, significant population shifts, challenges securing ongoing finance from donor nations, and other factors all contributed to the eventual end of the eradication attempt. The other factor was the absence of community involvement, and last but not least, malaria was resistant to chloroquine in South America and Southeast Asia in the 1960s. The spread of *P. vivax* that were due to resistance to chloroquine falciparum to Africa and the lack of a practical, economical replacement finally caused the number of malaria-related deaths to rise by 2 to 3 times in the early 1980s. Chloroquine's only practical substitute at that Sulfadoxine-pyrimethamine was used at the time; however, a year after adoption, it also encountered drug-resistant parasites. Several more antimalarial medications have now been used to fight sulfadoxine and chloroquine-resistant parasites including mefloquine, amodiaquine and quinine (Shah and Valecha 2016).

In the past, relying solely on replacement drugs for malaria treatment has resulted in the emergence of drug-resistant parasites in specific global regions. In 1998, efforts were initiated to combat malaria, showing some success by reducing malaria-related deaths by approximately 20% between 2000 and 2009. These achievements are credited to strategies like vector control, such as the use of long-lasting insecticide-treated bed nets and indoor insecticide spraying. Furthermore, improved diagnostics and the use of effective chemotherapy have played pivotal roles in treating infected individuals and curtailing transmission. Presently, the most effective malaria treatment involves artemisinin-based combination therapies (ACTs), which combine an artemisinin derivative with another drug. ACTs address the limitations of artemisinins, enhance treatment effectiveness, and aim to minimize the development of drug-resistant parasites. Unfortunately, there have been recent reports of artemisinin-resistant parasites emerging in Southeast Asia, posing a threat to ongoing malaria elimination efforts and potentially causing a resurgence in cases and deaths.The rise of drug resistance not only results in treatment failures and increased mortality but also increases the economic burden both at the individual and governmental levels. This burden encompasses expenses related to treatment, the acquisition of bed nets, and lost productivity due to illness, as well as government costs for vector control, healthcare facilities, education, and research. In summary, the emergence of drug-resistant malaria parasites poses a significant challenge to control efforts. Addressing this challenge requires a comprehensive understanding of regional drug resistance patterns, insights into the mechanisms of existing drug action, recognition of cross-resistance between drugs, and identification of genetic markers for resistance surveillance. This knowledge is indispensable for crafting effective, customized drug policies in all malaria-affected countries (Shah and Valecha 2016).

Malaria has a long and significant history, plaguing humanity for centuries. It has afflicted people from various civilizations, spanning from ancient Neolithic communities to early Chinese and Greeks, impacting both the wealthy and the less fortunate. In the 20th century alone, malaria led to the tragic deaths of an astounding 150 million to 300 million individuals and accounted for 2 to 5 percent of all global fatalities.While malaria primarily affects impoverished populations in sub-Saharan Africa, Asia, the Amazon basin, and tropical regions today, it's important to note that 40 percent of the world's population still resides in areas where malaria transmission remains a persistent threat (Kenneth et al. 2004). The likely introduction of malaria to Rome during the first century AD marked a pivotal moment in European history. It is believed that the disease spread from the African rainforest, traveling up the Nile to the Mediterranean, eastward to the Fertile Crescent, and northward to Greece. Greek traders and settlers likely brought it to Italy, and subsequently, Roman soldiers and merchants transport-

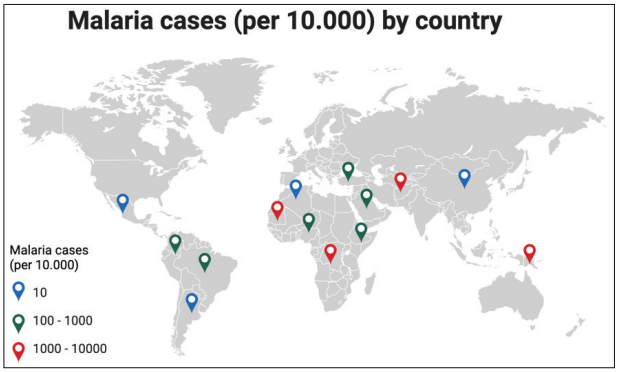


Figure 1. Malaria cases in the world.

ed it further north to countries like Britain and Denmark (Kenneth et al. 2004). The data of malaria cases around the world can be seen in Fig. 1.

The parasitic choreography: Malaria's mechanistic intricacies

Life cycle of the malaria parasite

In general, the life cycle of *P. knowlesi* is no different from other plasmodium, except that this plasmodium has the shortest erythrocyte cycle, which is every 24 hours. The incubation period of *P. knowlesi* in Anopheles mosquito vectors is about 10 days, so it requires a relatively long-lived vector or the same as the *P. malariae* vector. Once inside the mosquito body, sporogony formation lasts for 9–10 days at 25 °C. When a mosquito bites a human, approximately 100 sporozoites are injected through the bite. The exoerythrocyte cycle takes approximately 5 days for maturation of *P. knowlesi* but the parasite does not form hypnozoites in liver cells. In the life cycle of *P. knowlesi*, gametocyte formation occurs later after several asexual cycles, usually 3–5 times. The formation of *P. knowlesi* gametocytes is relatively slow, taking about 48 hours (Asmara 2018).

Sporozites are discharged from the salivary glands of female anoples mosquitoes, which carry malaria parasites, into the mosquito's blood and liver tissue upon biting a human. The malaria parasite uses exo-erythrocytic stage (also known as the sizon stage) of liver cells to produce tissue. Merozoites and cryptozoites produced by the ruptured liver cells penetrate the erythrocytes and create the sizon stage (erythrocytic stage). From immature trophocytes to old/mature sizon, it begins to form there. Merozoites occur when erythrocytes rupture. In female Anopheles mosquitoes, the majority of the merozoites return to the erythrocytes, and a tiny percentage become male gametocytes. The sporogony stage of the mosquito's life cycle is when females are ready to be sucked in by male malaria mosquitoes and continue its life cycle. Male gamete cells, or micro gametes, mate with female gamete cells, or macro gametes, which are referred to as zygotes, inside the stomach of a mosquito. After developing into an ookinete, the zygote passes through the stomach wall of the mosquito and matures into an oocyst. Sporozites are released when the oocyst grows and bursts; these sporozoites travel to the salivary glands of the mosquito and become ready to transmit to people. Specifically, *P. vivax* and *P. ovale* can transmit to humans as part of their parasitic cycle in liver tissue (tissue sizon). Embedded in liver tissue, dubbed hypno parasites, do not carry on their life cycle to erythrocyte cells. Sabic and Fitriany (2018).

The life cycle of malaria can be seen in the Fig. 2.

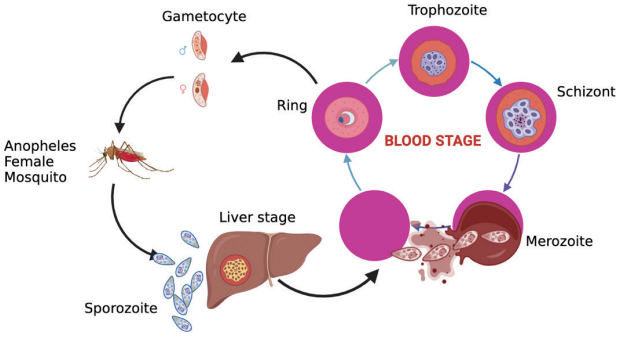


Figure 2. Life cycle of Malaria.

Host-parasite interactions

Anopheles mosquito. In humans, the only mosquitoes that can transmit malaria are mosquitoes female Anopheles. When biting an infected host (a human infected with malaria), Anopheles mosquitoes will suck in malaria parasites (plasmodium) along with blood, because in the blood of humans who have been infected with malaria there are many malaria parasites. The malaria parasite then reproduces in the body of the Anopheles mosquito, and when you bite another human (who is not infected with malaria), the malaria parasite enters the victim's body along with mosquito saliva. Malaria in humans can only transmitted by female Anopheles mosquitoes (Fitriany and Sabic 2018).

Immune evasion strategies

Immunity to malaria is developed when the body can either prevent *Plasmodium* from entering or inhibit its growth. This condition primarily occurs in regions where individuals carry gametocytes in their blood, which can infect Anopheles mosquitoes. Children often play a crucial role in this process (Fitriany and Sabic 2018). Malaria transmission is common in many tropical and subtropical areas. However, countries like the United States, Canada, Europe, Australia, and Israel have eradicated local malaria. Nonetheless, local outbreaks may still occur due to tourists from endemic areas introducing the disease. While congenital malaria, transmitted through the placenta, is rare, neonatal malaria is relatively common. Neonatal malaria typically occurs due to the mixing of infected maternal blood with the baby's blood during childbirth.

Targeting the dance partners: Current therapeutic strategies

Antimalarial drugs and treatment approaches

In many countries with an endemic form of the disease, artemisinin-based combination therapy (ACT) is the main first- and second-line treatment option for malaria. According to Arya et al.'s work from 2021, ACT is made up of the medications known as partner drugs and artemisinin (or one of its derivatives). In particular, ACT combines a strong but short-acting artemisinin derivative with a more durable companion medication as the main first-line antimalarial therapy. Examples are amodiaquine-artesunate (Coarsucam) and artemether-lumefantrine (CoArtem) (Ecker et al. 2012).

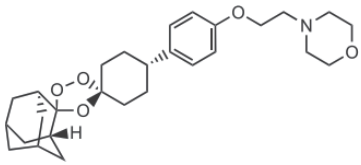
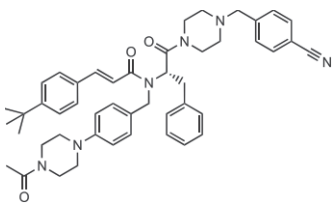
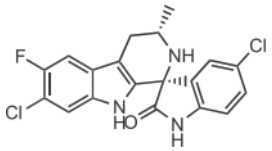
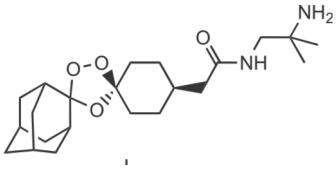
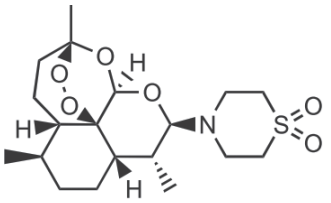
For the treatment of uncomplicated malaria, it has historically been common in Africa to administer a single basic therapy or medicine. As levels of drug resistance rise, the standard strategy has been to switch out the existing medication with a cutting- edge alternative that has not yet been impacted by resistance, as seen by the situation in Kenya. For instance, the principal therapy strategy was changed from chloroquine to sulfadoxine-pyrimethamine in 1998. In the years from 2004 to 2006, the artemisinin-based combination treatment (ACT), artemether-lumefantrine, replaced sulfadoxine- pyrimethamine. The aforementioned strategy, often known as the "wait-and-switch" tactic, places a significant burden on monitoring networks and public health systems in underdeveloped nations. It has been shown through a study conducted by Boni et al. in 2008 that this particular strategy yields subpar outcomes in terms of both morbidity and mortality. In order to reduce mortality and morbidity, delay the establishment of resistance, and prevent treatment failures, a more sustainable approach would involve the proactive use of antimalarial drugs that are already on the market. For the treatment of malaria cases worldwide, the World Health Organization (WHO) presently suggests six different Artemisinin-based Combination Therapies (ACTs). These include: a) combining artesunate with amodiaquine; b) combining artemether with lumefantrine; c) combining artesunate with sulfadoxine-pyrimethamine; d) combining artesunate with mefloquine; e) combining artesunate with pyronaridine; and f) combining dihydroartemisinin with piperaquine. These various ACTs are crucial elements of the treatment plans implemented by numerous nations fighting malaria endemicity (Arya et al. 2021). Notably, Indonesia has adopted ACTs containing the drugs artesunate and amodiaquine as a first-line therapy strategy (Mutabingwa 2005).

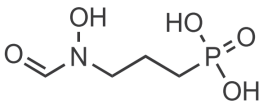
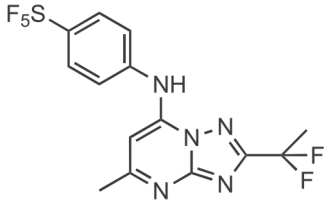
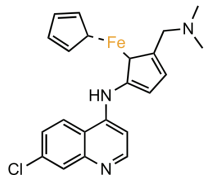
Using mosquito nets is a practical method to prevent and minimize the interaction between Anopheles spp. mosquitoes and individuals who are healthy while sleeping at night. Additionally, using mosquito repellent is also advisable. Since Anopheles mosquitoes tend to seek blood during nighttime, consistently sleeping under intact and undamaged mosquito nets can effectively guard against Anopheles spp. mosquito bites (Harijanto 2010). The most effective way to prevent and control malaria is to break the chain of transmission with 3M Plus method (cover, drain, hoarding). In addition, a simple preventive measure that can be adopted by everyone in the community is to avoid or reduce malaria mosquito bites. Avoiding outdoor activities at night, sleeping inside mosquito nets, coating your body with anti-mosquito bite material, installing screens on vents, cleaning mosquito nesting sites, and clearing bushes or shady or shady trees around the house, are just some of the additional ways to tackle this problem. In dealing with clinical problems, medication can be used to prevent and stop clinical attacks (Avichena and Anggriyani 2023). Antimalaria drugs are listed in Table 1.

Challenges in drug resistance

The importance of follow-up to determine the prevalence of susceptible strains circulating in malaria patients is highlighted by the second-line treatment of drug-resistant malaria in the ACT. All polymorphisms chosen and/or implicated in the transcription factor (TF) were connected to the artemether derivative's companion medicine, according to the current review. Furthermore, compared to lumefantrine, the usage of artesunate and sulfadoxine-pyrimethamine was linked to a greater risk of the establishment of drug resistance, according to a meta-analysis done by Arya et al. in 2021. Contrarily, compared to lumefantrine, the risk was found to be decreased when utilizing dihydroartemisinin and piperaquine. The various combinations of lumefantrine with artesunate and mefloquine, artesunate and amodiaquine, and artesunate and sulfadoxine-pyrimethamine, did not significantly differ from one another. Because dihydroartemisinin and piperaquine show the lowest likelihood of resistance forming to artemisinin-based therapies, they could be used as a potential strategy in countries where the use of the artemisinin-based combination therapy (ACT) is not implemented to mitigate the development of ACT resistance. In areas where the efficacy of ACT has been shown to be reduced, another strategy to maintain the effectiveness of artemisinin-based combination therapy (ACT) would involve the intermittent use of alternate antimalarial medications, such as chloroquine. A few years after the antimalarial medicine chloroquine was discontinued in Malawi, some writers reported a restoration of plasmodial sensitivity to it, suggesting that reintroducing it as first-line therapy in these regions in conjunction with other medications, like with ACT, would be an interesting strategy. It is also important to note that the use of several partner drug Artemisinin- based Combination Therapies (ACTs), often known as "triple ACTs," has aroused debate. This alternate tactic has recently been researched and supported in a study by Arya et al. (2021). According to research done in Papua by Rahmalia et al. (2023), the vast majority of study participants expressed a general belief in the effectiveness of biomedical interventions for the treatment of malaria, whereas the use of traditional or herbal remedies

Table 1. Antimalaria drug classification and mechanism of action.

Drug names	Chemical structure	Mechanism and dose
Artefenomel		N Next-generation synthetic ozonide artefenomel (or OZ439) has demonstrated improved antimalarial effectiveness against the *P. berghei* murine model of malaria in comparison to the currently available antimalarials arterolane (or OZ277), chloroquine, artesunate, pyrimethamine, sulfadoxine, and mefloquine. Although the exact mechanism of artefenomel's action is unknown, it is widely accepted that it involves reactive species that are produced when the ozonide, Fe (II), and heme react and are released when the parasite digests hemoglobin. A more recent study contends that the radicals then interfere with hemoglobin digestion, depriving the parasite of its primary source of amino acids and exposing it to ozonide for an extended period of time, further interfering with other critical biochemical pathways like nucleotide, vitamin, cofactor, protein, and lipid metabolism. When compared to arterolane, artefenomel has stronger in vitro antiplasmodial action, which is likely because its heme-mediated activation and degradation are more evenly balanced (Umumararungu et al. 2023). Ato According to reports, artefenomel was safe and well-tolerated in healthy humans at doses as high as 800 mg/day either all at once or in several daily doses for up to three days. Artefenomel can cause a number of serious adverse medication reactions, such as dyspepsia, vasovagal syncope, flushing, headache, nausea, gastrointestinal hypermotility, and diarrhea. Contrary to artemisinins, which are contraindicated in the first trimester of pregnancy because they have been shown to be hazardous to developing animals' embryos, artefenomel has a lesser propensity for doing so (Umumararungu et al. 2023).
ACT-451840		An antimalarial drug known as ACT-451840, synthesized from phenylalanine, has been found to have strong antimalarial effects. By killing male gametocytes (IC50 = 5.89 nM), ACT-451840 has also been shown to prevent the transmission of *P. falciparum* to mosquitoes, which is a highly desired characteristic for novel antimalarial medicines. However, the compound is inactive against female gametocytes at concentrations below 20 M. ACT-451840 also has an IC50 of 30 nM and prevents the growth of oocysts in mosquitoes. According to modeling, six consecutive daily doses of 300 mg of the medicine ACT-451840 are required to obtain a 90% cure rate in human subjects. This would result in a sustained plasma concentration of the medication of 10-15 ng/ml (Umumararungu et al. 2023).
Cipargamin		A synthetic spiroindolone antimalarial drug called cipargamin (KAE609/NITD609) was developed by the Norvartis Institute for Tropical Diseases. Cipargamin reportedly works by preventing mosquito transmission and inhibiting *P. falciparum* ATPase ATP4 (PfATP4), according to reports from docking studies and functional assessments. Cipargamin increases the pH of the parasites' cytosol, which causes the parasites to die. It also causes the intact parasitized erythrocyte and the isolated blood stage of *P. falciparum* to expand. According to clinical investigations, cipargamin is well tolerated in healthy volunteers at both single high doses (300 mg/kg) and numerous low doses (150 mg/kg) for roughly 3 days. Furthermore, following a single dose of 150–300 mg/kg of cipargamin, both fever and parasite clearance occurred within eight hours (Umumararungu et al. 2023).
Arterolane		The potential synthetic trioxolane peroxide medicine Arterolane (also known as RB×11160 or OZ277) was created by Medicines for Malaria Venture and Ranbaxy Laboratories Limited as an antimalarial medication. It is currently undergoing phase 3 clinical studies. In contrast to semi-synthetic artemisinins, arterolane has a lower efficacy (apparent Ki = 7700 nM) and acts by blocking the detoxification of *P. falciparum* encoded PfATP6 and the haem sarcoplasmic endoplasmic reticulum calcium ATPase. The peroxide bond of arterolane is reduced by Fe (II) in this process, which happens in the parasite's feeding vacuole. Following this, free radicals are produced, which alkylate a variety of parasite proteins, including endoplasmic reticulum membrane-associated PfATP6, which inhibits the ATP-dependent Ca2+ pump, a homolog of mammalian sarcoplasmic/endoplasmic reticulum Ca2+ ATPase. It is also thought that by reacting with ferriprotoporphyrin IX, a compound linked to iron, the reactive species created inhibit the detoxification of the hemoglobin. Numerous more intracellular enzymes also experience dysfunction. Arterolane was shown to be well tolerated in single dosages of 600 mg and multiple doses of 200 mg for up to 7 days. Additionally, it has been discovered that the 200 mg dose is ideal because it may eliminate 90% of the parasites in just 24 hours (Umumararungu et al. 2023).
Artemisone		A synthetic artemisinin derivative called Artemisone (also known as BAY 44-9585) was initially created by the University of Science and Technology of Hong Kong in partnership with a German business, Bayer Healthcare Pharmaceuticals. High cell permeability and moderate lipophilicity defined artemisone. Artemisone works by preventing the plasmodium parasites' asexual stage. Additionally, in vitro tests showed that artemisone is not neurotoxic and is ten times more effective than artesunate against *P. falciparum*. Artemisone and its three main metabolites cannot be found in the body after three days, according to human tolerance experiments, indicating that they do not accumulate in the body.

Drug names	Chemical structure	Mechanism and dose
Fosmidomycin		The antimicrobial compound fosmidomycin works by preventing 1-deoxy-d-xylulose 5-phosphate reductoisomerase (DXR), which is in charge of the non-mevalonate pathway of soprenoid synthesis. It is primarily removed by the urine and has an oral bioavailability of between 10 and 30 percent with a plasma half-life of about 1.9 hours. It was determined that fosmidomycin has additional uses, and phase II trials are currently being conducted on the medication for the treatment of malaria. According to reports, the selective toxicity track of fosmidomycin, which involves the creation of isoprenoids, is what gives it its antimalarial properties.
DSM265		In a clinical experiment, the triazolopyrimidine class of drug DSM265 was used to prevent and treat malaria brought on by *P. falciparum*, *P. vivax*, and *P. cynomolgi*. It is a new generation of antimalarial medication. DSM265 can partially stop the parasites' transmission stage and is effective against all stages of the malaria parasite, including the liver and blood stages. DSM265 disrupts the plasmodium life cycle by specifically inhibiting the enzyme dihydroorotate dehydrogenase, which catalyzes the production of pyrimidine nucleotides necessary for DNA and RNA synthesis. It halts growth before the development of schizonts in both circumstances and prevents the development of liver and blood stage parasites.
Ferroquine		Ferroquine, a chloroquine derivative or compound created by Sanofi-Aventis, has the ability to control the *P. falciparum* strain that causes the majority of resistant malaria and is chloroquine resistant. Due to its strong internal hydrogen bonds to the 4-amino group and the terminal nitrogen atom, as well as its organometallic characteristics that make it more rigid than chloroquine and cause a net change in its shape, this drug was thought to be a better antimalarial drug than chloroquine. Due to its capacity to target lipids, prevent the formation of hemozoin, and produce reactive oxygen species, ferroquine has a multifaceted mechanism of action.

was perceived as complementary in nature, serving primarily to alleviate symptoms rather than being regarded as a curative approach. In order to reduce joint pain and general body aches, a wide variety of nettles were topically applied to the skin, causing it to feel heated or pruritic. Notably, some people grew these nettles in their own gardens, and a particular kind of nettle, Laportea decumana, was frequently sold at neighborhood markets, usually by merchants from highland Papuan tribes. Additionally, it was discovered that bloodletting was a common technique among highland cultures. This practice was used to treat localized pain, such as migraines by drawing blood from the forehead. Resistance to antimalarial medications is the main barrier to controlling malaria successfully. Chloroquine resistance began to manifest itself during the malaria control campaign in the late 1950s. Thereafter, concerns about the emergence of resistance to mefloquine and sulfadoxine-pyrimethamine therapy surfaced. Artemisinin has since been used as a strategy to lower the frequency of illness and death linked to malaria on a global scale. However, the development of artemisinin-resistant *Plasmodium falciparum* has seriously jeopardized efforts to control and eradicate malaria.

The World Health Organization (WHO) introduced artemisinin-based combination therapy (ACT) as an alternative approach to combat the issue of antimalarial drug resistance. However, there has been a continuous increase in the number of parasites that have developed resistance to these drugs. The spread of drug- resistant parasites has been attributed to gaps in malaria coverage and the use of suboptimal therapies. According to Azmi et al. (2023), the emergence of artemisinin resistance is associated with a decrease in the drug's effectiveness in eliminating the parasite. Artemisinin, a fast-acting antimalarial medication, has shown its efficacy against virtually all stages of parasite development in the blood phase. As a result of their effectiveness in treating both severe and uncomplicated *P. falciparum* malaria, artemisinin-based combination therapies (ACTs) have become the most widely used antimalarial drugs.

The emergence of *P. falciparum* due to the utilisation of artemisinin as a pharmaceutical intervention for malaria treatment. The expression of artemisinin resistance in a clinical setting is characterised by a reduction in the effectiveness of treatment and an extended period of time required for the elimination of parasites from the body after administering artemisinin or its derivatives, also known as ACT. Treatment failure often occurs in conjunction with gametocytemia and a parasite clearance time exceeding 5 hours. Apart from inherent sensitivity to parasites, other factors including acquired immunity of the patient, initial parasite biomass, adherence to therapy, dosage, medication quality, and pharmacokinetics all influence the results of treatment (World Health Organisation 2020; Azmi et al. 2023) the introduction of *P. falciparum* as a result of the use of artemisinin as a medication to treat malaria. When artemisinin or its derivatives, commonly known as ACT, are administered to a patient, artemisinin resistance manifests as a decrease in therapeutic efficacy and an increase in the amount of time needed for parasites to be removed from the body. Gametocytemia and a parasite clearance time of more than five hours are two conditions that frequently accompany treatment failure. The effectiveness of treatment is influenced by a number of variables in addition to the patient's intrinsic sensitivity to parasites, such as acquired immunity, the initial parasite biomass, adherence to therapy, dosage, pharmaceutical quality, and pharmacokinetics (World Health Organization 2020; Azmi et al. 2023). According to data from the 2013 Riskesdas survey, it is observed that patients residing

in urban areas, where Artemisinin-based Combination Therapy (ACT) is readily accessible, exhibit slightly higher treatment rates compared to those residing in rural areas, as documented by Kinansi et al. in 2021. Furthermore, a study conducted by Rahmalia et al. in 2023, conducted in the Papua region, indicates that the accessibility of malaria treatment has been enhanced by a mining corporation. This enhancement is manifested through the provision of free healthcare access to the Kamoro and Amungme communities, in addition to five other highland ethnic groups, namely, the Damal, Dani, Mee, Moni, and Nduga peoples, who are considered to be directly impacted by mining activities. Pros and Cons of Various Malaria Prophylactic Medications can be seen in the Table 2.

Table 2. Pros and cons of various malaria prophylactic medications.

Medication	Pros	Cons
Chloroquine	Effective against *Plasmodium vivax*	Ineffective in regions with drug resistance
	Generally affordable and accessible	Developing drug resistance
Mefloquine	Effective in regions with drug-resistant *Plasmodium falciparum*	Psychotic side effects
	Weekly dosing	Not recommended for individuals with a history of mental illness
Atovaquone-Proguanil	Effective against *Plasmodium falciparum* and *vivax*	Expensive
(Malarone)	Does not require long-term use	Potential gastrointestinal side effects
Doxycycline	Effective against various *Plasmodium* species	Not suitable for children under 8 years old
	Suitable for long-term prevention	Increased risk of sunburn due to sun exposure
	Affordable	Gastrointestinal side effects

Shining a spotlight on molevular mechanism

Genetic and molecular insights

In malaria-endemic regions, various genetic factors play a crucial role in determining a child's likelihood of surviving the disease. These genes have been identified and their impact on malaria susceptibility provides valuable insights into the host-parasite relationship. One group of well-known gene polymorphisms related to malaria involves human red blood cells (erythrocytes), which play a pivotal role in the malaria life cycle, especially in the pathogenic aspects related to the interaction between infected red blood cells (iRBCs), uninfected red blood cells, and different organs and tissues. Several important events occur during the process of merozoite invasion, such as the attachment of merozoites to the surface of red blood cells, their reorientation within these cells in the case of *P. falciparum* malaria, and the sequestration of parasitized red blood cells (PRBCs) on the endothelium of microvessels, contributing to the development of cerebral malaria. Notably, malaria patients exhibit elevated levels of von Willebrand factor (VWF) compared to non-malaria patients. VWF is released following the activation of endothelial cells in *P. falciparum* malaria patients, and PRBCs have been observed adhering to platelet-covered ultra-large VWF (ULVWF) structures. Plasma proteases, specifically a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, are responsible for cleaving these platelet-coated strings (Wahyuni 2018).

In the context of natural resistance to malaria infection in humans, variations in the Duffy blood group have been extensively studied. Individuals with different blood group polymorphisms within the Duffy blood group (Fy) exhibit varying levels of resistance to vivax malaria. This resistance stems from the fact that the Duffy protein acts as a receptor for the protozoa responsible for *P. vivax* malaria but not for other human malaria parasites. Consequently, Duffy blood group polymorphisms hold significant importance in regions where *P. vivax* is prevalent. The gene responsible for the Duffy blood group is located on chromosome 1q22–q23 and spans a length of 2,772 bp from the promoter to the ORF. Within the promoter region, a polymorphism involving the T and C bases at nucleotide -46, known as GATA-1, is noteworthy. It's worth noting that even individuals with negative Duffy heterozygotes can still be susceptible to *P. vivax* infection. The Fy gene is located on chromosome 1 and consists of two exons, Fya and Fyb, encoded by the co-dominant alleles FYA and FYB. While the FYA allele is well-documented, a newly discovered FYB allele contains three single nucleotide polymorphisms (SNPs) (Wahyuni 2018).

Pathogenesis and disease progeression

Malaria infection begins with the introduction of the parasite's sporozoite stage, which resides in the salivary glands of mosquitoes, into the host's liver. This transmission occurs when an infected female mosquito bites an uninfected individual, drawing blood and injecting a small amount of saliva into a skin wound. Notably, male mosquitoes do not engage in blood-feeding, so the transmission of the parasite relies entirely on female mosquitoes. The saliva of these mosquitoes contains enzymes that prevent blood clotting and reduce pain sensitivity, serving as anticoagulants and anti-inflammatory agents. Typically, each bite from an infected mosquito can carry anywhere from 5 to 200 sporozoites, which then proceed to infect the human host. These sporozoites can linger in the skin for a considerable period before eventually entering the bloodstream. Only those that manage to evade immune cells can quickly access the human bloodstream through blood vessels, where they briefly circulate before

invading liver cells (Harijanto 2010). As schizonts are released from hepatocytes, they introduce merozoites into the bloodstream, marking the beginning of the blood stages within the malaria life cycle. This phase begins as merozoites invade red blood cells and become enclosed within a parasitophorous vacuole. Over the next 48 hours (or 24 hours in the case of *Plasmodium berghei*), *Plasmodium falciparum* parasites undergo maturation within this vacuole, transitioning from ring-shaped trophozoites to schizonts through a process of asexual reproduction. This reproductive process yields 12–16 daughter merozoites. The rupture of both the red blood cell membrane and the parasitophorous vacuole releases these merozoites, initiating a new cycle of red blood cell invasion and multiplication. Without treatment, this proliferation of parasites in the bloodstream leads to symptomatic disease. Within red blood cells, certain parasites differentiate into male or female gametocytes, which are the sexual forms of the parasite. When mosquitoes ingest these sexual stages during blood feeding, the fusion of male and female gametocytes results in the formation of a zygote. This zygote, known as an ookinete, penetrates the mosquito's abdominal wall and matures into oocysts. As these oocysts mature, they rupture, releasing sporozoites that migrate to the mosquito's salivary glands. From there, these sporozoites can infect new hosts, continuing the malaria life cycle. It's important to note that, except for the zygotic form, *Plasmodium* spp. remain haploid throughout their life cycle. Currently, only the asexual blood stages have been used for transfection, as they can be easily cultured in vitro or collected from the blood of infected animals (Shah and Valecha 2016).

Emerging insights and breakthroughs

Recent discoveries in malaria research

Malaria remains a significant global public health challenge, impacting nearly half of the world's population. It's essential to recognize that malaria is not a uniform disease; it can be caused by various parasite species within the *Plasmodium* genus. These different species can lead to a variety of symptoms and health issues, posing unique challenges for control efforts (Prugnolle et al. 2011). Recent advancements in the field have created opportunities for in-depth investigations into the evolution of *Plasmodium* species and their genomes. The recent discovery of *P. falciparum* in bonobos, chimpanzees, and gorillas, as well as the presence of *P. ovale*, *P. malariae*, and *P. vivax* in these primates, highlights the potential for *Plasmodium* species to transfer between humans and primates, and vice versa. It is crucial to identify the genetic and ecological factors that facilitate the adaptation of these pathogens to different host species. This is particularly concerning for the wildlife conservation community, as the recurrent transmission of human infectious diseases to great apes could hasten their endangerment. Similarly, it is imperative to conduct systematic research into the presence of primate *Plasmodium* species in human populations, especially those living in close proximity to primates, such as forest-dwelling communities. This research will help evaluate whether great apes could act as reservoirs of *Plasmodium* for humans and the associated risk of disease emergence (Prugnolle et al. 2011).

Advancements in diagnostic

Molecular methods like PCR and LAMP have greatly improved the research and diagnosis of malaria. They allow for more sensitive and specific detection of the parasite's DNA, making it easier to identify and manage the disease. Real-time PCR, nested PCR, and multiplex PCR offer various advantages in terms of sensitivity and specificity, while LAMP is known for its simplicity and rapid results in isothermal conditions. These methods have revolutionized malaria diagnosis and monitoring (Fitri et al. 2022). That's a fascinating insight into the importance of biomarkers in malaria diagnosis. The use of various types of biomarkers, including genomic, transcriptomic, proteomic, and metabolomic markers, can provide valuable information for determining parasite species, estimating parasitemia, assessing the immune response, and offering prognostic information. Expanding research into alternative body fluids like saliva and urine for disease-related markers is an exciting development in this field, potentially leading to more accessible and less invasive diagnostic methods (Krampa et al. 2017). The development of self-contained biosensors for malaria detection is a promising advancement in diagnostics. One notable example is the cell-based label-free electrochemical biosensor created by Kumar et al., which immobilizes a monoclonal antibody onto a gold nanoparticle-modified electrode to detect parasitized red blood cells. This approach has shown good sensitivity and a wide linear range, potentially addressing the challenge of limited known biomarkers in malaria (Krampa et al. 2017). Additionally, the use of Surface Enhanced Raman Spectroscopy (SERS) for probing hemozoin content in red blood cells is another innovative technique. It allows for ultrasensitive detection of hemozoin even at low parasitemia levels, which is crucial for early diagnosis of malaria. These developments represent significant strides in improving the accuracy and sensitivity of malaria diagnostics (Krampa et al. 2017).

Promising vaccine development

In October 2021, the World Health Organization (WHO) provided a recommendation for the extensive deployment of the RTS,S/AS01 (RTS,S) malaria vaccine, commercially known as "Mosquirix." This recommendation was primarily targeted at children at risk in sub-Saharan Africa and other regions where malaria transmission, caused by *Plasmodium falciparum*, is prevalent. The approval of this groundbreaking vaccine was grounded in the outcomes of a pilot program conducted in Ghana, Kenya, and Malawi. It's noteworthy that the RTS,S vaccine represents a significant achievement as the first vaccine sanctioned by the WHO for the combat against malaria, with its development

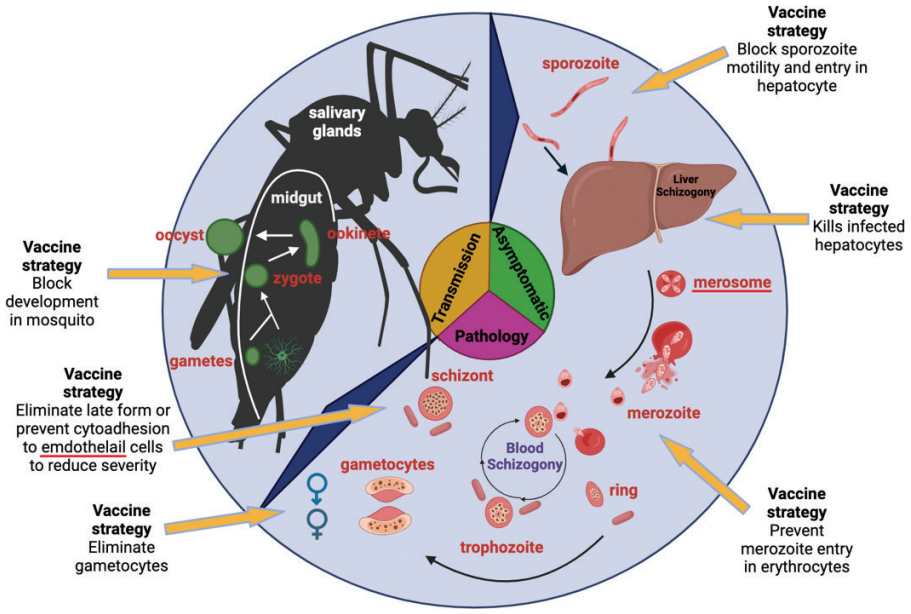


Figure 3. Vaccine develop stargety.

having origins dating back to the 20th century. The development journey of the RTS,S malaria vaccine, also known as "Mosquirix," is a remarkable one that spanned roughly three decades. It began in the early 1980s with its conceptualization and design and culminated in its approval and recommendation by the WHO in 2021. This vaccine has navigated significant challenges and deviated from conventional vaccine development norms. It was a collaborative effort between the PATH Malaria Vaccine Initiative (MVI) and GlaxoSmithKline (GSK), with support from a network of African research centers and the Bill and Melinda Gates Foundation. The initial concept for RTS,S was formulated based on the scientific knowledge available at that time. The first successful human trial, demonstrating protection against *Plasmodium falciparum* sporozoite infection, was conducted in 1996 at the Walter Reed Army Institute of Research (WRAIR) using the RTS,S vaccine developed by GSK. Nonetheless, as the implementation of the RTS,S vaccine in sub-Saharan Africa has not yet begun, there is apprehension that numerous countries with limited resources and healthcare infrastructure may struggle to satisfy the vaccination needs of their citizens. Consequently, strategies must be formulated to facilitate international organizations and agencies, including the Global Alliance for Vaccines and Immunization (GAVI) and the United Nations Children's Fund (UNICEF), in providing funding for vaccine procurement. In summary, as emphasized by WHO Director-General Dr. Tedros Adhanom Ghebreyesus, the introduction of the malaria vaccine for children signifies a major scientific achievement and a significant step forward in child healthcare and malaria control efforts. This remarkable vaccine brings hope to individuals, communities, and nations that have long struggled with the burden of malaria, and it holds great promise for the global community as a whole. The journey of the RTS,S vaccine, from its inception to WHO endorsement, resembles a story of unwavering dedication to advancing scientific knowledge and improving global health. The WHO's recommendation signifies the beginning of a new era in malaria treatment, offering a positive and effective approach to reducing and eventually eradicating malaria infections (Egbewande 2022) (Fig. 3).

Towards a new rhythm: Future prospects in malaria control

Strategies for malaria eradication

In this Viewpoint, we present an updated global malaria strategy that consists of two key elements. First, control efforts would be stepped up in the holoendemic and hyperendemic regions of tropical Africa, Asia, and Latin America, which are the epicentre of the malaria endemic (Feachem and Sabot 2018) Second, and as of right now, nations on the periphery of the endemic zone would make simultaneous efforts to totally stop disease transmission. As each nation eventually ends malaria transmission, one or more of its neighbours would start to work towards eradication using the newly malaria-free region as a model, taking advantage of the decreases in transmission brought on by the intensified control effort. Until malaria is eliminated or new technology allows a change in strategy, this process will continue (Feachem and Sabot 2018). The following three worldwide activities are suggested based on training experience for the elimination of malaria and the training gaps mentioned above. To begin, it is advisable to establish a collaborative effort involving organizations such as the Roll Back Malaria Partnership, the Global Fund to Fight AIDS, Tuberculosis, and Malaria, as well as bilateral aid agencies. This collective effort should focus on conducting a comprehensive assessment of the training deficiencies within various sectors, including front-line workers, entomologists, individuals engaged in basic and applied research, and malaria-sensitive managers and leaders within healthcare systems. The objective

of this initiative would be to provide accurate assessments of the training needs and to evaluate the existing human resources available for the purpose of malaria eradication (Wirth et al. 2018). As a second step, following the evaluation conducted by the expert committee, it is advisable to augment financial support allocated to malaria eradication training. This increased funding can be accomplished through collaboration with governmental organizations, such as the Fogarty International Centre at the National Institutes of Health, private foundations like the Wellcome Trust and the Bill & Melinda Gates Foundation, as well as multilateral organizations such as the Special Programme for Research and Training in Tropical Diseases (TDR) (Wirth et al. 2018). Third, using the most up-to-date electronic training techniques and adult-oriented pedagogy, establish new networks for training for the elimination of malaria that include universities and research institutions in malaria-endemic nations along with the implementing government agencies. To develop the theory and experience of eliminating malaria, the training networks would link new information to field practise (Wirth 2018)

The role of global collaboration

Malaria remains a significant public health challenge, with approximately 240 million reported cases and more than 600,000 fatalities reported globally. In recent decades, coordinated international efforts to combat malaria have resulted in substantial reductions in its prevalence and mortality rates (WHO 2020). The burden of malaria is still disproportionately concentrated in Africa and Asia. Effective initiatives related to vector control, malaria treatment, and diagnostics have played a pivotal role in reducing the impact of malaria, with notable programs including the Global Malaria Eradication Program during the 1950s and 1960s, the Roll Back Malaria campaign, and the Global Fund for Combating Malaria, HIV, and TB. These efforts collectively contributed to the significant decline in malaria cases and deaths observed over the past two decades (Poore et al. 2004).

Due to this decline, numerous countries have initiated programs aimed at eliminating malaria. The World Health Organization (WHO) has taken the lead in pursuing elimination objectives by implementing the Global Technical Strategy (GTS) for the years 2016 to 2030. The ultimate goal of this strategy is to achieve malaria elimination in at least 35 countries by the year 2030 (WHO 2015).

One of the primary objectives of the GTS is to promote country-to-country and regional collaboration, which has prompted bi-national and multinational efforts to combat border malaria. Inadequate and unregulated interventions in endemic areas along borders have contributed to an increase in malaria control measures and coverage across states. The variations in policies, treatment protocols, and control measures pose challenges to eliminating malaria in border regions (Arisco et al. 2021). The Global Technical Strategy (GTS) has prompted a broader push for increased political commitment to malaria control and country collaborations in managing border malaria (Fambirai et al. 2022).

Malaria control programs present a substantial financial burden for economies, especially in medium- to low-income countries (Njau et al. 2021). Many nations with endemic malaria lack the domestic funding capacity necessary to sustain malaria control and elimination initiatives. As a result, there is an increasing demand for securing financial support for malaria elimination through the establishment of regional and global partnerships. Beyond financial resources, collaborative initiatives should also promote the sharing of health-related data among affected countries. The integration of efforts and collaborative approaches are increasingly acknowledged as effective strategies for advancing malaria elimination. Reflecting on historical experiences, it is evident that a one-size-fits-all approach is not suitable for achieving comprehensive malaria elimination (Putra 2011).

Potential game changers in malaria management

Collaboration and synchronization among policymakers, law enforcement authorities, and the general public play a pivotal role in halting the transmission of zoonotic malaria. It's imperative to plan local socioeconomic activities in a way that avoids outdoor ventures during the peak feeding times of disease-carrying vectors. Equally important is public education, as raising awareness about zoonotic malaria will encourage adherence to preventive measures. For instance, individuals working in tourism, forest resource collection, and logging industries should receive training to align their activities with the knowlesi malaria control program.

Likewise, farmers practicing subsistence cropping near forested areas should be encouraged to transition to more efficient farming practices in relocated farmlands situated farther from the woods. Certain agricultural methods that involve simian primates, like coconut harvesting, should be substituted with simian-free alternatives. Furthermore, proactive measures should be taken to relocate communities from forested regions to non-forested areas equipped with improved building designs that minimize mosquito intrusion, along with enhanced healthcare and sanitation infrastructure layouts. All socioeconomic activities must undergo a thorough review and approval by relevant authorities before implementation. The activity plans should aim to minimize or entirely eliminate exposure to disease-carrying vectors. Clear and informative warnings, as well as preventative measures for knowlesi malaria transmission, should be provided to tourists visiting areas where this disease is endemic. Travelers from foreign countries should receive comprehensive information about this zoonotic illness both before and upon their arrival at these destinations. In the event that tourists fall ill after returning to their home country from a knowlesi malaria endemic area, they should explicitly report their travel history. To assist

in this regard, a health alert card specific to knowlesi malaria could be furnished to travelers arriving in such endemic regions. This card may reduce the likelihood of healthcare workers in the travelers' home countries overlooking a *P. knowlesi* infection if it occurs post-travel (Lee et al. 2022). The emergence of knowlesi malaria has introduced new challenges in our efforts to manage and eliminate malaria from human populations. Recent advancements in *P. knowlesi* research have deepened our understanding of this parasite's pathobiology, genomics, and evolutionary biology, as well as enhanced our ability to detect infections. However, there are several aspects of *P. knowlesi* that warrant further research in the future. Knowlesi malaria adds complexity to malaria eradication programs. Nonetheless, it is possible to develop customized strategies that can effectively interrupt the transmission of knowlesi malaria in humans while minimizing negative impacts on the natural hosts, wildlife biodiversity, and economic development in regions where knowlesi malaria is endemic (Lee et al. 2022).

Conclusion: Navigating the complex world of malaria

Malaria is indeed a vector-borne parasitic disease caused by protozoan parasites belonging to the genus *Plasmodium*. These parasites are transmitted to humans through the bite of infected female Anopheles mosquitoes. These sporozoites are the infective form of the malaria parasite. In uncomplicated malaria, one of the prominent symptoms is fever. The rise in body temperature is a response to the infection. Comparing the risk of death among individuals with malaria in a specific community is not typically how severe malaria is diagnosed or defined. Overall, the stability of mosquito species distribution, the potential introduction of non-indigenous vectors, and the difficulty in eradicating indigenous vectors are all important factors that influence the dynamics of malaria transmission in the malaria endemic. Effective malaria control strategies must take these factors into account to reduce the burden of the disease. It's interesting to hear about the findings from recent systematic reviews on adherence to antimalarial drugs and the different patterns of antimalarial drug use based on the local malaria situation. Antimalarial drug adherence is a crucial factor in effectively treating and preventing malaria, which is a significant public health concern in many regions around the world.

These findings highlight the importance of tailoring malaria treatment and prevention strategies to the specific characteristics of the local malaria situation. It's crucial to consider factors such as the dominant malaria parasite species, drug resistance patterns, and the level of malaria transmission when designing public health interventions. Effective malaria control and elimination efforts involve a combination of strategies, including drug treatment, vector control (e.g., bed nets and indoor residual spraying), and community education to promote adherence to treatment regimens and preventive measures. Public health authorities and healthcare providers must continuously adapt their approaches based on the evolving malaria landscape in different regions.

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