

Advancements in the Formulations and Delivery Systems of Antimalarial Drugs: Challenges and Opportunities in Combating Malaria

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ABSTRACT

The global burden of malaria continues to present serious obstacles to public health, particularly in sub-Saharan Africa and parts of Asia. Traditional antimalarial drugs have been instrumental in combating malaria, but issues such as drug resistance, side effects, and suboptimal bioavailability have prompted the development of innovative drug formulations and delivery systems. Recent advancements in nanotechnology, targeted drug delivery, and controlled-release formulations have enhanced the therapeutic efficacy of antimalarial agents. Nano-carrier systems, such as liposomes, micelles, and dendrimers, offer improved drug stability, targeted action, and reduced toxicity, addressing limitations of conventional treatment regimens. Additionally, transdermal, inhalable, and medication delivery system that are implanted have been explored to improve patient adherence and optimize dosing. The integration of diagnostic tools with therapeutic delivery systems, as seen in combination therapies, allows for better management of drug-resistant malaria. The most effective method for malaria treatment is Artemisinin-based Combination Therapy (ACT) for uncomplicated cases, as it rapidly eliminates parasites and prevents resistance through dual-drug action. For severe or complicated malaria, intravenous artesunate is the gold standard, providing faster parasite clearance and significantly reducing mortality compared to older drugs like quinine. This review highlights the key advancements in the formulation and delivery systems of antimalarial drugs, focusing on the development of novel technologies and their potential to revolutionize malaria treatment, reduce transmission, and mitigate the challenges of resistance and adverse effects.

Keywords- Malaria, drug delivery system, Antimalarial drug, liposome.

I. INTRODUCTION

Due to its high morbidity and fatality rate, malaria is regarded as a serious public health issue. Malaria still has a terrible effect on people's health and means of subsistence worldwide, even though it is preventable and curable ^[1]. Malaria poses a threat to about half of the world's population, who reside in almost 100 countries and territories. One According to the World Health Organization (WHO), there were an estimated 228 million cases of malaria worldwide in 2024, the WHO Africa Region is responsible for 93% of these cases ^[2]. Additionally, according to WHO estimates, 405 000 people died from malaria worldwide

in 2024, with 67% of those fatalities taking place in youngsters younger than of five. According to research, youngsters younger five were more likely than older children and adults to contract severe malaria, an infection linked to major organ damage, in malaria-endemic nations. This has a noteworthy effect on the development of local children ^[3]. Malaria has detrimental effects on national economies in addition to its health burden on individuals and populations. For example, during the 2000–22 period, a 10% decrease in the incidence of malaria cases was linked to a nearly 0.3% increase in global per capita income, highlighting the significance of malaria control in the agenda for sustainable development ^[4]. According to earlier

research, the incidence of malaria decreased by 27.9% between 2005 and 2022, indicating a sharp drop in the disease's burden. However, because visitors from non-endemic areas lack developed immunity against malaria, the decline in malaria prevalence in some regions of the world does not lessen the significant risk that each person incurs when visiting an area where the disease is still endemic ^[5]. An estimated 125 million tourists annually who travel to endemic nations run the risk of contracting malaria. A world free of malaria is WHO's and the international malaria community's aim to reduce malaria mortality rates and case incidence worldwide by at least 40% by 2024 and 75% by 2025, Malaria's Global Technica Strategy, 2016–2030 (GTS) establishes challenging but attainable global targets for 2030 with benchmarks for gauging progress in 2020 and 2025 as well as 90% by 2030, in contrast to 2015 ^[6]. However, according to WHO, worldwide malaria incidence trends are heading in the wrong direction or progress has stagnated. The world is not on course to fulfill the 2020 milestones that would lead us to cut case 90% reduction in incidence and mortality by 2030 (from 2015 levels), even though 31 nations considerably lowered case incidence between 2000 and 2024 and were on track to reduce incidence by 40% or more by 2020 ^[7]. Even if recent studies have revealed important success in lowering malaria deaths and episodes between 2000 and 2024, they did not describe malaria infection in various age groups and were unable to explain why global progress has stalled in the last five years. Therefore, we need updated information about malaria infection to better understand the global incidence trends of malaria infection ^[8].

Malaria still has a significant health burden on the world especially in the tropical and subtropical areas where the *Plasmodium falciparum* strains that are resistant to drugs prevail. Although the current treatments, including artemisinin-based combination therapies (ACTs), have already reduced morbidity and mortality, issues of low bioavailability, regular dosing, toxicity, non-adherence of patients to particular interventions, and emergent parasites resistance are daunting ^[9]. The pharmaceutical research community has reacted by increasing its focus on re-developing the antimalarial agents and developing new-generation drug delivery platforms. It is hoped to enhance pharmacokinetics, deliver to the infected cells, minimize off-target side-effects and avoid resistance mechanisms all without incurring the cost and time effort to develop completely novel chemical entities. Conventionally, antimalarial preparations have been based on conventional oral tablets or injectable preparations. Notable drawbacks of such modes, however, include; variable absorption in varying patient groups, high clearance, and high dosages needed to sustain therapeutic levels ^[10]. Moreover, patients in endemic

areas might also experience some logistical challenges in visiting clinics to receive parenteral therapies or undergo multi-day oral treatment, contributing to the increased chances of ineffective treatment and the emergence of resistance. Reformulation therefore aims at increasing the solubility of lipophilic antimalarial agents, increasing their systemic exposure, reducing their release, and preferably targeting them at cells that harbor the parasite (e.g. hepatocytes or red blood cells). In this regard, the sophisticated drug delivery systems have come out as promising tools. Potential has been noted with nanoparticle carriers, such as liposomes, polymeric nanoparticles, lipid-based self-emulsifying systems, dendrimers and solid lipid nanoparticles ^[11]. As an example, antimalarials delivery by liposomes has been shown to have better encapsulation, better bioavailability and more controlled release, and has allowed the opportunity of targeted delivery by ligand modification. Another important innovation is lipid-based self-emulsifying drug delivery systems, which is of use when the antimalarial agent is poorly-soluble since it helps to form fine emulsions in the gastrointestinal tract and consequently enhance absorption ^[12]. Furthermore, injectable and transdermal nano- or micro-carrier are being studied in order to decrease the dose frequency, enhance compliance and address the gastrointestinal challenges. However, with such promising prospects, there are several challenges to translating novel delivery systems into daily antimalarial therapy ^[13-15]. Complexity and cost of manufacturing can be prohibitive in low resources environments where malaria is endemic. Nanocarrier safety and biocompatibility should be thoroughly tested, and stability of scaling up is also a continuous challenge. Moreover, it is challenging to deliver to parasite-infected cells in vivo specifically - parasites can be located in red blood or hepatocytes, and bypassing them via blood or tissue reservoirs is a problem ^[16]. Additionally, the regulatory routes of new delivery systems might require a longer time compared with small-molecule generics, which could slow down access in the area. Resistance is a constantly changing goal: even more efficient delivery systems should expect the effects of parasite evolution, pharmacokinetic differences and patient behaviours in real conditions ^[17-20]. However, the opportunities are attractive. Individualized delivery systems can increase the usability of currently available antimalarial molecules by increasing drug exposure profiles, decreasing toxicity, and enhancing adherence ^[21]. They can also permit reduced doses, combination regimes with synchronized release kinetics, and even re-use of older agents whose limitations (poor solubility, short half-life) were hitherto inaccessible. Also, with targeted delivery, prophylactic or transmission blocking interventions, rather than the treatment of symptomatic infection, may be possible ^[22,23].

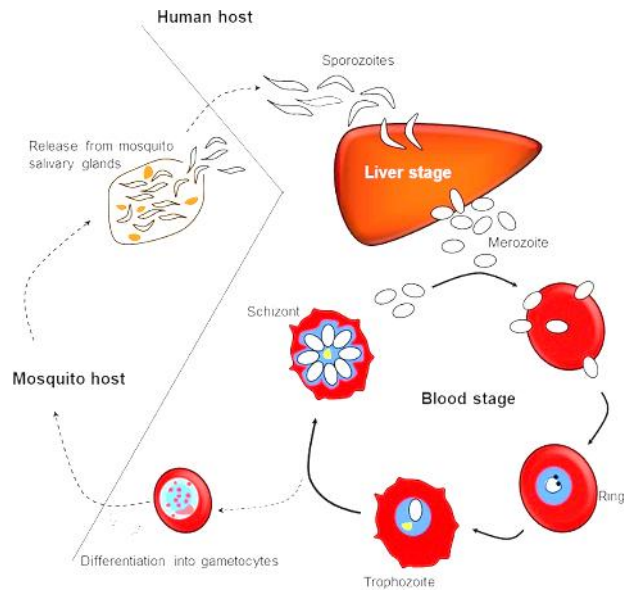


Fig:1 Life cycle of Plasmodium malaria in human vector and mosquito host

Table 1: Clinical trial data of vaccines of malaria

Study title	NCT no.	Drug	Sponsor	Status
A study to assess the experimental malaria vaccines RH5.2-VLP and R21	NCT05357560	RH5.2-VLP and R21	University of oxford	Phase I
Study of the Plasmodium Vivax Transmission-blocking Vaccine Pvs230D1-EPA/Matrix-M to Assess Safety, Immunogenicity, and Transmission-blocking Activity in Healthy Malaria-naïve Adults	NCT05913973	Pvs230D1-EPA/Matrix-M	National Institute of Allergy and Infectious Diseases (NIAID)	Phase I
A clinical trial to evaluate the safety, efficacy and immune responses after vaccination with an investigational rna-based vaccine against malaria	NCT06069544	BNT165e	BioNTech SE	Phase I and II
Open-Label Study to Assess Meplazumab in Adult Patients Diagnosed with Plasmodium Falciparum	NCT06040346	Meplazumab for Injection	Jiangsu Pacific Meinuo Bio Pharmaceutical Co Ltd	Phase II
First-in-Human PfSPZ-LARC2 Vaccination/CHMI	NCT06735209	PfSPZ Vaccine, PfSPZ (7G8) Challenge, Sodium Chloride, 0.9%	National Institute of Allergy and Infectious Diseases (NIAID)	Phase I
Vivax Elimination With Tafenoquine (VET) Study (VET)	NCT06575647	Tafenoquine	Shoklo Malaria Research Unit	Phase IV
R21/Matrix-M in African Children Against Clinical Malaria	NCT04704830	R21/Matrix-M, Biological: Rabies vaccine, Hepatitis A vaccine or Meningococcal vaccine	University of Oxford	Phase III
Targeted Antimalarial Drug Administration for Seasonal Migrant Populations in Amhara	NCT06516042	Dihydroartemisinin-piperaquine	PATH	Phase III

Region, Ethiopia				
Modifying Immunity in Children With Dihydroartemisinin-Piperaquine (MIC-DroP) (MIC-DroP)	NCT04978272	Dihydroartemisinin-piperaquine (DP), DP Placebo	Grant Dorsey, M.D, Ph.D.	Phase III

II. CONVENTIONAL ANTIMALARIAL DRUG FORMULATIONS

The recommended dosage of chloroquine phosphate for the treatment of chloroquine-sensitive *Plasmodium falciparum* is 1000 mg orally once every 12 hours, followed by 500 mg orally every 6, 24, and 48 hours [24]. When treating chloroquine-responsive infections, hydroxychloroquine is best taken orally in 800 mg doses starting at 6 hours, followed by 400 mg doses at 24, and 48 hours. Because of their similarities, *P. malariae* and *P. knowlesi*, two other types of malaria infections, would also be treated in a similar manner [25]. For infections caused by *P. vivax* or *P. ovale* that are resistant to chloroquine, the recommended treatment is 26.3 mg of primaquine phosphate taken orally once day for a duration of fourteen days [26]. Two tablets per day is the recommended dose. It is recommended to take primaquine with food to lessen the chances of experiencing adverse gastrointestinal symptoms such as nausea, vomiting, cramps, and stomach pain. It is important to give the patient another dose if they throw up within 30 minutes of the first one [27]. The recommended dosage of atovaquone-proguanil is 250 mg just once every three days, with each tablet containing 100 mg. The recommended administration schedule for mefloquine involves two oral doses, the first of 750 mg and the second of 500 mg, spaced six to twelve hours apart. To get the most out of mefloquine, it's best to take it with food and eight ounces of water [28-30]. An extra full dose must be administered if vomiting happens within 30 minutes of administration; an extra half-dose must be administered if vomiting happens between 30 and 60 minutes [31]. In cases when *P. falciparum* malaria is resistant to chloroquine, this medicine could be applied as a third-line option, while in simple cases of *P. vivax* malaria, it could be applied as a first-line therapy [32]. In cases of severe malaria, the only intravenous treatment option is quinine gluconate. An intravenous loading dose of 10 mg/kg is given over one to two hours. After that, a continuous infusion of 0.02 mg/kg/minute is maintained for at least twenty-four hours. After a four-hour loading dosage of 24 mg/kg, patients may take 12 mg/kg every eight hours for maintenance for the same amount of time. Injecting quinidine intravenously is necessary until the parasite load falls below 1% and oral therapies are tolerable for the patient. Until the patient is able to tolerate oral medicines, this needs to be done [33]. After quinine intravenous therapy is finished, the patient should start taking quinine orally for the rest of their treatment [34].

When calculating intravenous quinidine gluconate loading doses, renal adjustments are not required. A 25% reduction in the maintenance dosage is required in patients with creatinine clearances of 1 mL/min or below. For seven days in a row, patients will be given quinidine intravenously along with doxycycline, tetracycline, or clindamycin. Both the novel and old parenteral formulations of AS were shown to be generally safe and well-tolerated when administered intramuscularly or intravenously to healthy volunteers in this four-sequence crossover trial [35]. A single subject reported very intense injection-site pain after receiving the intramuscular reference formulation, but all further negative effects that have been reported were mild and short-lived [36]. The subject withdrew from the trial without experiencing any known side consequences. The most common side effect, a disagreeable taste, was reported by both intravenous groups at the same proportion (18.9% vs 17.6%). Through bitter taste receptor-mediated calcium signaling, artesunate has been shown in animal models to reduce airway resistance [37]. Salivary artesunate and dihydroartemisinin concentrations patients with metastatic breast cancer are directly correlated with plasma concentrations, according to previous research [38]. No instances of QT-prolongation ($\Delta QTcF > 60$ ms) were detected in the 293 dosage events. The concentration of the medicine did not correspond with QT-prolongation either [39]. There were no reports of fatalities or other serious adverse effects associated with either AS formulation. Shortly after the inquiry, which included the prescription of medication, concluded, all adverse effects noted during vital sign evaluations and laboratory tests returned to baseline. When compared to the currently used parenteral formulation of AS, the new one did not show any additional safety indication [40].

III. INNOVATIVE DRUG DELIVERY SYSTEMS IN ANTIMALARIAL THERAPY

There are particular requirements for the erythrocytic and hepatic phases of medicine distribution when treating malaria, which is why this method is so crucial [41]. Erythrocytic infiltration can only be accomplished by administering a medication that is both present in the serum and ready to infiltrate the erythrocytes. On the other hand, the drug needs to be stable enough to accumulate in the hepatocytes after administration and remain stable throughout the hepatic phase [42]. The distribution of antimalarial medications is complicated since different administration has pros and

cons of its own ^[43]. It is strongly recommended to use the oral method to treat malaria when it is not difficult. In contrast, cerebral malaria prevention via the parenteral route may be necessary in extreme or difficult cases ^[44]. Oral administration of liposomes is challenging since these small particles are vulnerable to the harmful effects of the GIT's gastric acid, bile salts, and pancreatic lipase. As a result of leakage, the medication concentration within the liposomes decreases ^[45]. Commercial use of liposomes for the oral delivery of antimalarial medications has not occurred because of the speed at which they are removed from the gut. The reason liposomes don't have enough time to stay in the body to help with medicine absorption is because the gastrointestinal system experiences dynamic and repeated peristaltic motions. To increase the amount of time that liposomes stay in the GI tract, numerous methods have been developed. One of these is to modify the surfaces of liposomes with mucoadhesive polymers, like cationic chitosan or low-molecular-weight polyethylene glycol (MW 2000) high-density liposomes ^[46]. Although parenteral approaches are effective, they come with a number of drawbacks, such as being intrusive and requiring long-term release monitoring. It is crucial to take precautions to avoid malaria in order to make sure treatment works, as symptoms don't usually show up for a while. Although parenteral models may make delayed release difficult to implement, other delivery methods including intramuscular, transdermal, or implant distribution can open up new possibilities for design. This becomes much more apparent when taking into account the limited dosage. More work goes into the design because of the limited drug load and the need for regulated release. Hence, novel approaches to dosage are necessary, such as burst release for both the starting and maintenance doses, to preserve the therapeutic efficacy ^[47]. Researchers are currently exploring several ways to provide antimalarial liposome formulations, including as through transdermal, oral, and parenteral methods. Clinical trials on liposomes have mostly focused on sterile solutions or lyophilized powders designed for intravenous or intramuscular administration ^[48]. In severe cases of malaria, when the parasite density is enhanced during the erythrocytic phase, it is necessary to administer antimalarial drugs through intravenous injection. When it's not possible to treat the patient orally, this becomes much more important. Liposomes have been studied for their possible application as adjuvants in malaria immunisations when given intravenously ^[49]. The elimination of malaria remains an unreachable objective, despite the use of traditional therapeutic procedures (pharmaceuticals) for a century. Malaria is a burden on society's clinical, social, and economic aspects. The physico-chemical properties, pharmacokinetics, pharmacodynamics, and toxicological features of both established and new pharmaceuticals, as well as drug solubility and stability, absorption, and biodistribution, are problems in the present malaria state

^[50]. Importantly, well-designed medicine liposomes can get over certain hurdles. The majority of the research on nanocarrier systems for the treatment and prevention of malaria has focused on liposomes ^[51]. This is because of their versatility, simplicity of manufacture, and biodegradability. Furthermore, liposomes can encapsulate either electrostatically bound anti-malarial medications on their surface, hydrophilic drugs within their watery core, or lipophilic drugs within their lipid bilayer ^[52]. Previous research on anti-malarial drug delivery systems has focused on liposomes for intravenous injection only because of liposomes' poor intestinal epithelial absorption and inadequate stability in the GI tract ^[53]. This is a major drawback since oral drug delivery has several advantages and is therefore the recommended method of administration. These include, but are not limited to, the following: ease of use, minimal sterility requirements, minimal cost, reduced pain, optimal patient adherence, adaptability to different types of medicine, and design flexibility in dosage forms. In spite of these evident advantages, the oral administration route is not without its share of challenges. The potential for chemical and enzymatic instability of drugs, limited penetration through intestinal walls, and insufficient water solubility are some of the drawbacks ^[54, 55]. Thus, to develop liposomes (or vesicles that resemble liposomes) for the oral delivery of anti-malarial drugs, very innovative research is required in the future. Several techniques exist for this purpose; some of these include changing the lipid content, covering the surface, making the internal aqueous phases thicker, and creating double liposomes and proliposomes. It is not possible to enhance the liposomes' in vivo stability and membrane rigidity all the way through the gastrointestinal track just by adding cholesterol and saturated fats (like DSPC) to the formulations. However, in extreme cases of malaria or when patients are unable to swallow their medications orally due to vomiting, the parenteral delivery of liposomes may be an effective intervention ^[56]. The anti-malarial medications were given an extra boost against the liver stage of malaria infections by being encapsulated in normal liposomes. A decrease in drug toxicity and a decrease in the dosage needed were outcomes of passive targeting, which was used to achieve this goal in the animals studied. Traditional liposomes encapsulating anti-malarial drugs have lysosomotropism enhanced by virtue of their negative charge and small size (less than 100 nanometers). e and quantity of bilayers also affect the amount of medicine carried within liposomes, which in turn affects their efficacy ^[57]. Conversely, it's crucial to note that typical liposomes delivered intravenously are swiftly removed from the bloodstream by the reticuloendothelial system (RES) after they've been opsonized with serum proteins ^[58, 59]. Classic liposomes often have hydrophilic barriers like polyethylene glycols (PEG) placed on them ^[60]. Doing so will reduce the intensity of the aforementioned

conduct. Liposome surfaces were sterically stabilized and receptor binding was inhibited by these biocompatible hydrophilic polymers, which are inert. Drug release kinetics were controlled, in vivo circulation duration was increased, and liposomal formulation pharmacokinetics were enhanced [61]. Loaded PEGylated liposomes with an amino acid sequence derived from *Proteus mirabilis* were able to enhance their targeting to the liver while avoiding harm to nearby organs like the kidneys, lungs, and heart. The lack of indicators that are specific enough for infected hepatocytes has impeded creation of liposomes that target the liver as away to combating malaria infection.

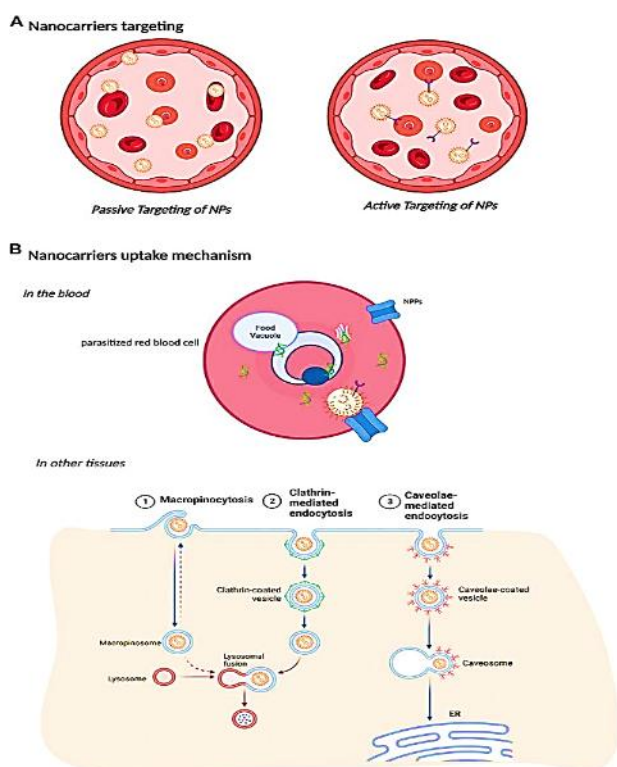


Fig: 2 Both active and passive nanoparticle targeting are depicted schematically here. Red blood cells carry nanoparticles (NPs) throughout the body via the circulatory system in a technique known as passive targeting. To enhance the uptake of nanoparticles (NPs) by both the target site and additional cells, active targeting entails conjugating NPs with affinity ligands on their surface. Molecules on the surface of the target cell population can be interacted with by targeting moieties such as antibodies, integrins, folate, glucose, and transferrin. The process of nanocarrier absorption, or (B). If nanocarriers are already in the blood, they can be trained to identify parasitized RBCs. There is less chance of side effects and the emergence of drug-resistant bacteria and viruses due to the substantially reduced dosage compared to conventional treatments. *Plasmodium* additionally increases the pRBC's permeability by causing the creation of new permeation

pathways (NPPs). To achieve this, we modify the osmotic stability of the pRBC, which opens the parasite up to the entry of nanocarriers. In various organs, the intracellular uptake of nanocarriers is accomplished through distinct endocytosis processes. Nanocarriers are taken up by the cell surface through endocytosis; the specifics of this process are dictated by the nanocarriers' surface area, shape, charge, and size. A method that can lead to endocytosis is macropinocytosis, which is triggered by ruffling of the membrane and protrusions of actin. In order to undergo content breakdown, they combine with lysosomal compartments once consumed. Endocytosis mediated by clathrin is based on clathrin-coated pits on the cell membrane's cytosolic side. Vesicles encased in clathrin undergo vesicular trafficking after their creation in these pits. Similar mechanisms are employed in endocytosis mediated by caveolae. However, lysosome degradation is averted because they fuse to caveosomes.

IV. CHALLENGES IN ANTIMALARIAL DRUG FORMULATION AND DELIVERY

The aminoquinoline chloroquine has been the go-to antimalarial medicine for decades since it is the most cost-effective, effective, and safe option among the several available drugs. Parasites that were resistant to this drug were initially found in Thailand in 1957, and then again in 1959 at the border of Colombia and Venezuela. Resistance had spread to East Africa by the late 1970s, and by the mid-1980s, it had become a major problem in several parts of the continent [62]. Chloroquine is now only applicable in specific areas of Central America due to the lack of evidence that it is an effective medicine elsewhere [63]. However, new data on the prevalence of chloroquine-resistant genes in these areas presents a highly alarming scenario for public health authorities [64]. Amodiaquine outperforms chloroquine, according to recent research, especially in areas where chloroquine resistance is common. This led some countries to acknowledge amodiaquine and artesunate as the main treatments for the infectious condition. Parasite strains in Tanzania have been found to be highly resistant to amodiaquine, which could make the use of artesunate-amodiaquine in other African nations even more challenging [64]. In order to combat chloroquine-resistant malaria, several countries have turned to the alternative antimalarial drug sulfadoxine-pyrimethamine. However, studies have revealed that this combination has a relatively low treatment failure rate in some South American and Central and Middle Eastern Asian nations, compared to 52.8% in eastern Africa [65]. Where artesunate-mefloquine is used as first-line treatment, mefloquine resistance is still a problem in the Greater Mekong sub-region, especially in Cambodia and Thailand. To address this issue, the most advanced candidate, RTS, S/AS01, was developed by

GlaxoSmithKline (GSK) and the PATH Malaria Vaccine Initiative (MVI) with funding from the Bill & Melinda Gates Foundation. This vaccine has demonstrated protective efficacy in children ranging from 30-50% [66, 67] and is assumed to be the first-generation malaria vaccine (with a World Health Organization recommendation anticipated for 2015). This is why new approaches to developing a vaccine with lasting protective effects must be seriously considered [68]. The reason for this is that Phase III testing have shown that RTS, S, the top candidate for a malaria vaccine, has very moderate effectiveness.

V. TRIPLE ARTEMISININ-BASED COMBINATION THERAPIES (TACTS)

Due to the short half-life of artemisinin in ACTs, parasites may be exposed to the partner drug alone, which raises the likelihood of parasite resistance. Triple artemisinin-containing combination therapies (TACTs) have been the subject of recent debate. An artemisinin component and two medications now utilized as ACT partners would make up TACTs [69]. There are antagonistic resistance mechanisms in combinations such piperazine, mefloquine, lumefantrine, and amodiaquine, thus they are often suggested. An atovaquone-proguanil ACT is another combination that is presently under investigation. Anjouan Island, in the Union of the Comoros, was administered artemisinin-piperazine (AP) in three monthly rounds, with or without low-dose primaquine (LDPMQ) [70-72]. Nearly 97,000 people took part in this latest large-scale study. This study aimed to examine Pfk13 Kelch-propeller gene polymorphisms, parasitemia rates, adverse events, mortality rates, and *P. falciparum* malaria rates.

The Union of the Comoros island of Anjouan saw a significant drop in malaria cases after treating its residents with artemisinin-piperazine (AP) and low-dose pyrethoid (LDPMQ). An excellent degree of coverage was achieved, with 85 to 93% of the population receiving treatment. The AP + LDPMQ group saw a significant drop in malaria hospital rates, from 310.8 to 2.06 per 100,000 people, while the AP-only group saw a decrease from 412.1 to 2.60 per 100,000 people. Hospitalization rates decreased most sharply in the AP-only group. Each regimen was well-tolerated and showed no significant side effects; the combined efficacy of AP and LDPMQ was 99.08%, while AP alone was 99.13%. Malaria samples analyzed following MDA administration did not show any signs of selection for Pfk13 Kelch-propeller mutations. A recent large-scale trial looked at various antimalarial treatments [73]. The treatments that were included in the list were as follows: DHA-PPQ, AS-MQ, AT-L, and AT-L plus amodiaquine. There was a significant improvement in the 42-day PCR-corrected efficacy

(98%) of DHA-PPQ with mefloquine over DHA-PPQ alone (48%), according to the research examination conducted in piperazine-resistant regions of Cambodia, Thailand, and Vietnam. However, there is a high probability that parasites resistant to both mefloquine and piperazine may spread, given the extensive resistance to piperazine and the identification of such parasites. Perhaps this explains why mefloquine and DHA-PPQ work so well together in the GMS in regions where piperazine-resistant parasites are also vulnerable to mefloquine. Therefore, the possible advantages for resistance prevention may be diminished when transitioning to TACTs following the development of resistance to the component drugs [74]. Furthermore, while research has shown that TACTs are safe and well-tolerated, there has to be further research on tolerance, toxicity, and drug interactions before adding this medication to current treatment strategies. An effective treatment in Africa is artesunate-lactam (AT-L) or artesunate-amodiaquine (AS-AQ). Instead of enhancing patient outcomes, the goal of combining these medications in a TACT or prolonging treatment is to decrease the danger of lumefantrine and amodiaquine being spread to additional patients [75].

Pre-Erythrocytic-Stage Vaccines

These vaccines target the sporozoite and liver stages of the *Plasmodium* parasite, aiming to prevent the parasite from reaching the blood stage, where it causes symptomatic illness.

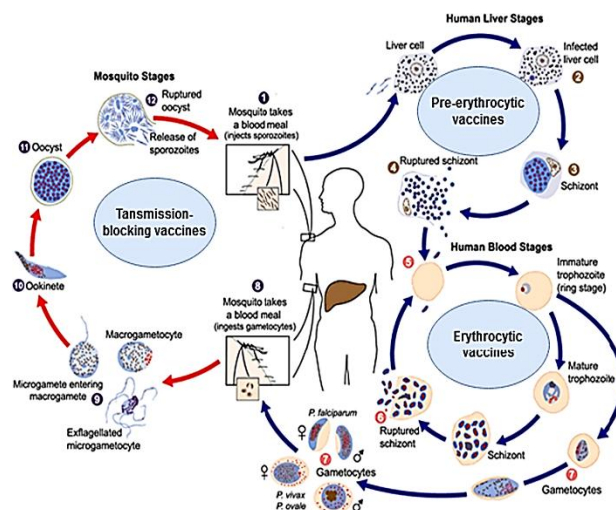


Fig: 3 Preclinical and Clinical Studies Pre-Erythrocytic-Stage Vaccines malaria

VI. WHOLE SPOROZOITE VACCINES (WSVS)

Vaccines against radiation-attenuated sporozoites (RASs) show promise as a tool in the fight against malaria. These immunizations work by interfering with the parasite at its earliest stages of development. These immunizations employ sporozoites

that have been moderately gamma-irradiated to decrease their immune response. The sporozoites are able to infiltrate the liver cells in this way, but they are unable to reach the blood stage, where the symptoms of malaria are produced^[76]. Once sporozoites infect liver cells, they are unable to continue developing due to DNA damage caused by this attenuation process. In turn, this causes the host immune system to become active without actually causing illness^[77].

The Sanaria PfSPZ vaccine is a great example of a vaccine that prevents RAS. This malaria vaccine is made using attenuated sporozoites of *Plasmodium falciparum*, the most deadly malaria parasite species. Clinical trials have shown promising results; the study found that the vaccine protected over 90% of those who received it, suggesting a high incidence of efficacy^[78]. The report suggest that RAS vaccinations, if administered broadly, might have significantly reduced the spread of malaria. Among the many benefits of RAS vaccines is a more thorough presentation of antigens, in contrast to subunit immunizations that exclusively target one antigen. This procedure is costly and technically challenging. Also, there are a lot of logistical problems with administering the PfSPZ vaccination intravenously, especially in low-resource areas. Furthermore, to enhance the overall efficacy of RAS vaccines and to offer broader protection, researchers are looking into combination tactics.

These tactics comprise combining RAS vaccines with other malaria therapies like chemoprophylaxis or alternative vaccination platforms^[79]. One novel approach to combating malaria is the use of vaccines containing genetically attenuated parasites (GAP). The sporozoites utilized in these immunizations have been genetically modified to impede the *Plasmodium* parasite throughout its liver lifecycle phase. This stops the parasites in their tracks before they may cause illness by entering the blood phase^[80]. An example of a GAP vaccine that is now in clinical trials is GAP3KO, which is being developed by Sanaria. The immunization eliminates three crucial genes from the *Plasmodium falciparum* genome, rendering the parasite unable to complete its lifecycle in humans^[81]. Several clear benefits characterize the GAP method as compared to alternative vaccination approaches^[82].

A strong and protective immune response is one of the aims of GAP vaccinations, which aim to stop the parasite from reaching the liver stage. When these modified sporozoites infect liver cells, they unleash a barrage of immune-system-triggering antigens. Because of this, the immune system reacts by boosting the liver's CD8+ and CD4+ T-cell populations. Parasite eradication during the hepatic stage and prevention of bloodstream entry depends on these immune responses^[83]. Clinical trials of GAP vaccinations, including GAP3KO, have shown promising outcomes. Preliminary studies have demonstrated that the vaccine is safe and produces an immunogenic response, with participants developing

strong cellular and humoral immunity as a consequence of the shot.

VII. METHODS MOST EFFECTIVE FOR MALARIA TREATMENT

Malaria has remained among the most important infectious diseases in the world and it requires quick and efficient treatment measures to avert morbidity, mortality and transmission. The choice of the correct antimalarial regimen is dependent on the species of plasmodium, severity of infection, drug resistance, and factors that may be patient specific like age, pregnancy, and comorbidities. Artemisinin-based combination therapies (ACTs) and parenteral artesunate have become the most effective and globally supported approaches to the management of the uncomplicated and severe malaria, respectively^[84].

In the case of simple malaria especially the one caused by *Plasmodium falciparum*, ACTs are the gold standard of treatment prescribed by the World Health Organization (WHO). These combinations involve a fast-acting artemisinin derivative in combination with a longer-acting partner drug in order to guarantee full parasite clearance and minimize the development of resistance. Artemisinin derivatives including artemether, artesunate and dihydroartemisinin are fast-acting agents against the asexual blood stages of the parasite, causing reactive oxygen radicals to damage parasitic proteins and membranes. Their companion drugs, including lumefantrine, mefloquine or amodiaquine or piperazine, have longer half-lives and have a sustained antimalarial effect after the artemisinin molecule has been cleared, eliminating remnant parasites and suppressing recrudescence^[85].

Artemether-lumefantrine, the most commonly used ACT, is very effective in clearing infections caused by *P. falciparum* and is very safe. It will have a clearance rate of parasites between 48-72 hours and a cure rate of over 95 percent in most of the endemic areas. Other effective oral combinations include dihydroartemisinin-piperazine that provides the benefit of extended post-treatment prophylaxis because piperazine has a long elimination half-life, which assists in suppression of reinfection in areas with high transmission. Artesunate-amodiaquine, artesunate-mefloquine are also to be advised in areas where they have proven effective with minimal resistance. These oral regimens are mostly given across three days keeping the patient adherent with the treatment and at the same time avoids the chances of treatment failure^[86].

When malaria is caused by *Plasmodium vivax* or *Plasmodium ovale*, it needs a radical cure not only clearing the stages of malaria in blood, but also destroying the dormant liver forms (hypnozoites) in order to avoid relapse. The initial regimen is a course of chloroquine on blood-stage parasites in chloroquine-sensitive areas or of ACT in resistant areas followed by a

course of primaquine over 14 days or a single-dose regimen of tafenoquine to cure the infection radically. Both, tafenoquine and primaquine are used to treat the hypnozoite stage, however, glucose-6-phosphate dehydrogenase (G6PD) deficiency must first be tested to prevent hemolytic complications^[87-89].

In case of critical or complex malaria, parenteral therapy is necessary to minimise death. Quinine has been ousted by intravenous artesunate as the treatment of choice due to its better efficacy and safety and quick parasite clearance. Artesunate works by generation of free radicals by cleavage of its endogenous bridge into heme upon exposure to heme in the parasite, resulting in massive destruction of parasite cells and death^[90]. Clinical trials and meta-analyses have continually shown that IV artesunate causes 35 percent less mortality than IV quinine, especially in patients with high parasitemia or organ dysfunction. The normal dose regimen consists of 2.4mg/kg body weight given intravenously at 0, 12 and 24 hours after which oral therapy is then issued once a day until the patient can withstand the oral therapy. Once the improvement in clinical situation is noted, the treatment is to be finished with a complete three-day course of an ACT to make sure that the rest of parasites are completely removed^[91].

VIII. CONCLUSION

Advancements in the formulation and delivery systems of antimalarial drugs have significantly improved the efficacy, safety, and patient compliance in malaria treatment. Innovations such as controlled-release formulations, nanotechnology-based drug delivery systems, and the development of combination therapies have played a crucial role in overcoming challenges like drug resistance, poor bioavailability, and adverse side effects. The incorporation of targeted delivery systems, such as lipid-based nanoparticles, has further enhanced the therapeutic outcomes by ensuring the drugs reach the site of infection more efficiently.

Additionally, the advent of novel medication delivery techniques, including transdermal patches and inhalable formulations, has the potential to enhance patient compliance, especially in regions with high malaria burden. These approaches aim to reduce the frequency of dosing and enhance the convenience of treatment, which is critical in ensuring adherence to therapy in endemic areas. Despite these advancements, challenges such as high costs, complex manufacturing processes, and regulatory hurdles remain. However, the continuous development of novel drug delivery systems holds great potential for optimizing treatment of malaria, reducing transmission, and ultimately contributing to the global goal of malaria eradication. Future research should focus on addressing these barriers while continuing to explore innovative solutions to improve treatment outcomes.

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