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Current and future directions in the prevention and treatment of Malaria

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Abstract The Plasmodium parasite, which is what causes malaria, is spread by the Anopheles mosquito. The two most frequent human Plasmodium infections are caused by Plasmodium vivax and Plasmodium falciparum, respectively. Infected insects spread the illness by biting humans, and the disease then proceeds to infiltrate and kill human cells at every stage of development. Malaria is responsible for the deaths of millions of people every year, the vast majority of whom are residents of developing nations in Africa and Asia. In order to reduce malaria transmission, it is necessary to take preventative measures, such as controlling vectors, using insecticide-treated mosquito nets, engaging in seasonal malaria chemoprevention, and providing intermittent preventive medication to babies and pregnant women. Vaccines like RTS,S/AS01 and PfSPZ, among many others, are available thanks to the work of the World Health Organization and other researchers. Many anti-malarial medications are now showing signs of resistance, yet treatment standards have not altered in a long time. Symptoms such as fever, difficulty breathing, and a sudden onset of headache are shared by both COVID-19 and malaria, which may lead to incorrect diagnosis. This article summarizes the progress made toward a global decrease in malaria incidence and provides context for upcoming clinical trials.

Keywords: malaria, prevention, treatment, vaccines, plasmodium,resistance

Introduction

Malaria is a devastating illness that affects many people. Roughly 228 million cases were reported in 2018, with 85 percent concentrated in only 19 nations. From 2005-2015, the number of reported cases decreased from 585,000 to 405,000, with the sharpest fall occurring in Africa. Children under the age of five account for over 67% of all deaths globally. There was an increase in the number of cases in Africa, Ghana, and Nigeria in 2018 compared to the previous year. However, over this time span, the number of cases fell in places like India and Uganda. Tabulated in Table 1 [1] are the Nations where indigenous cases have not been reported during the last three years. Because of the risk of anemia and the resulting low birth weight in the infant, malaria is a major health risk for pregnant women [1]. Global occurrences might reach 1 billion by 2030 if the WHO does not continue to push efforts ahead and encourage via its goal. Therefore, malaria is a difficult infectious illness, especially in Africa, because of the difficulties involved in preventing and treating the condition

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Table 1: List of countries that have eliminated malaria from 2000 andonward.
These countries have had zero indigenous malaria cases for three yearsconsecutively.

Year	Countries
2000	Egypt
	United Arab Emirates
2004	Kazakhstan
2007	*Morocco*
	Syrian Arab Republic
	Turkmenistan
2008	*Armenia*
2011	Iraq
2012	Georgia
	Turkey
2013	*Argentina*
	Kyrgyzstan
	Oman
	Uzbekistan
2014	*Paraguay*
2015	Azerbaijan
	Sri Lanka
2016	*Algeria*
2017	Tajikistan

WHO awards a certification of elimination for countries that have achieved complete malaria transmission cessation and prevention.

Anopheles mosquitoes are responsible for about 100% of malaria transmission. Warm, humid regions with standing bodies of water are ideal for its survival and reproduction [2]. Plasmodium is a microscopic parasite transmitted to humans by the bite of an infected mosquito (sources: [2, 3]). Plasmodium vivax, Plasmodium malaria, Plasmodium ovale, and Plasmodium falciparum are all species of the genus Plasmodium that may infect humans. P. falciparum is significantly more lethal and is responsible for the great majority of malaria-related fatalities [2, 3], whereas P. vivax is responsible for roughly 40% of malaria infections. Countries in Sub-Saharan Africa have high rates of Plasmodium falciparum transmission. Malaria is caused by the fast-spreading plasmodium parasite, which is spread by the Anopheles mosquito.

Within the mosquito, the parasite undergoes a complex life cycle. Parasite species and environmental factors determine the length of the cycle, which may range from eight days to more than two weeks [2]. Parasite sporozoites in the mosquito's salivary glands are released after feeding, staying on the skin for many hours before entering the circulation [2-4]. Once inside, the sporozoites infect the liver and spread to the rest of the body.

development of hepatocytes and the onset of the liver stage [2-4]. A single parasite may produce 10,000 to 40,000 merozoites [2, 3] during the course of 5 to 16 days. After this, the infected hepatocytes burst, releasing the merozoites into the circulation [2, 3], where they infect red blood cells and enter the next stage of growth, asexual

erythrocyte development. (Hypnozoites, parasites that lie latent in hepatocytes, may induce a relapse

a later time [3].) After infecting new RBCs, the parasites reproduce rapidly [2, 3]. Malaria is characterized by a high body temperature and chills due to the rupture of infected erythrocytes, which release deadly merozoites [2]. Red blood cells infected with P. falciparum prefer to concentrate in the capillaries of various organs, including the brain, making P. falciparum more virulent than other parasite species [2, 3]. After completing their asexual replication cycle, a certain percentage of parasites will initiate sexual reproduction by forming non-pathogenic female and male gametocytes [2, 3]. Gametocytes may enter an uninfected mosquito at this time, allowing the parasite to multiply and produce more sporozoites [2, 3]. This rapid development—from sporozoites to gametocytes—justifies the development of effective strategies for parasite prevention and therapy.

The World Health Organization (WHO) has a strategy to address and battle malaria, as stated in the 2019 Malaria World Report. It has set a lofty goal, supported by a rigorous and well-thought-out strategy, of reducing worldwide malaria fatality rates and case occurrences by 90% compared to 2015 by 2030. In addition, by the end of that time frame, the WHO hopes to have eradicated malaria

at

from all 35 countries where it is now present. The elimination of malaria forever is the fourth and last primary goal. These four core worldwide initiatives serve as a blueprint for how we should go about advancing prevention measures and therapeutics. In 2018, the commercial sector in the United States increased financing for pharmacological research and development with the goal of creating a single-exposure radical cure [1]. This analysis summarizes the previous decade's worth of progress in preventative and treatment methods and looks forward to the opportunities that lie ahead.

Prevention

When combating infectious disease, an essential initial aspect that lays the foundation for disease control is prevention. There are a few preventative strategies in place that aim at lowering the incidences of malaria. Earlier prevention strategies, such as vector control, are still recommended but cannot be the primary prevention method. Table 2 compiles the prevention strategies outlined by WHO. See figure 1 for current prevention and treatment strategies.

Commodities to help with prevention are being delivered globally and have been for some time. For example, between

Table 2: Summary of the World Health Organization's prevention strategies in its 2019 world malaria report

Prevention Strategy	Description/Standard of Use
Vector Control	Reducing the odds of mosquitoes biting humans
ITNs	Bed nets treated with insecticides to kill mosquitos as they serve as a form of personal protection.
Indoor Residual Sprays (IRS)	Residual insecticide sprayed inside housing structures
Seasonal Malaria Chemoprevention (SMC)	Administered to children 5 to 59 months of age in areas whose malaria transmission rates are seasonally high in the Sahel subregion of Africa.
Intermittent Preventative Treatment in Infants (IPTi)	In areas of moderate to high malaria transmission, WHO recommends IPTi to infants which often corresponds to their routine vaccination schedule.
Intermittent Preventative Treatment in Pregnancy (IPTp)	In areas of moderate to high malaria transmission, WHO recommends IPTp to pregnant women

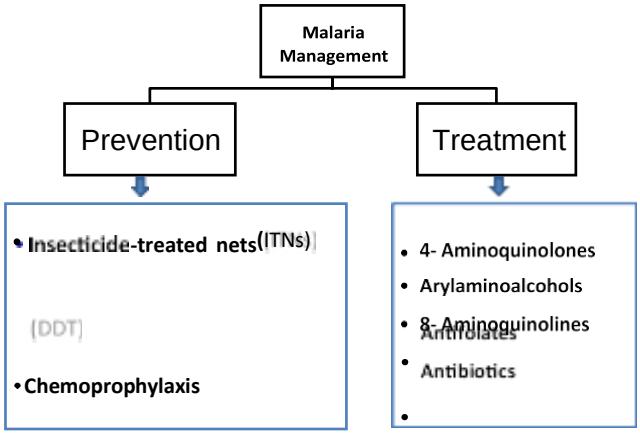

Figure 1: Malaria Management: Current prevention and treatment Strategies

2016 and 2018, over 600 million insecticide-treated mosquito nets (ITNs) reached sub-Saharan Africa, India, Uganda, Ethiopia, and the United Republic of Tanzania. In terms of residual spraying, it used to be that indoor residual spraying showed some protection when used to spray inside homes with insecticides; but their protection declined to only about 2% in 2018. However, some studies have found ways to combine their use with other preventative strategies such as ITNs to maximize protection [1, 5]. Also, in areas where transmission is categorized to be moderate or high risk, the WHO recommends that they receive, mostly women and

mosquitoes feed indoors and at night, sleeping under an ITN can drastically reduce contracting it [8]. In 2018, compared with 2010, 24% more people had access to ITNs [1]. However, it is essential to overcome the limitations of ITNs. The nets usually do not work well in low and unstable transmission areas where mosquitoes bite in the early eveningand morning, and some insects have changed their feeding habits in response to the ITNs [8]. Besides, it is vital to educate oneself on the proper use and maintenance of ITNs; the nets have the potential to be a vital tool in the fight against malaria, but their efficacy diminishes by incorrect use [9, 10]. Given this prevention strategy that has been around for some time, their metabolic resistance mechanisms have been *detected* through molecular assays, thus illustrating limited overall efficacy. Fortunately, researchers are investigating new insecticide alternatives such as neonicotinoid and pyrrole at different dosages determine if they can be incorporated in ITNs [1]. Overall, the use of ITNs effectively can drastically help the odds of controlling the disease, especially for the overnight protection it provides.

Intermittent Preventative Treatment for Infants

Following a westernized model, infants living in areas with malaria transmission classified as moderate to high risk receive routine immunization. It is scheduled intermittently at three different intervals of 10 weeks, 14 weeks, and nine months but varies depending on the geographic location.

children, intermittent preventative therapy (IPTp/IPTi). Furthermore, one of the most significant advances in malaria prevention is vaccinations such as RTS, S/AS01 that came about in 2015, and PfSPZ that came about in 2016, as discussed later. Having these preventative strategies backed with strong clinical evidence suggests that there is hope in combating malaria.

Insecticide-treated mosquito nets

In malaria-infected regions, ITNs are an essential public health service that aids in vector control. ITNs appropriately assembled provide almost complete protection from mosquito bites [6, 7]. The insecticides commonly used include pyrethroids, carbamates, and occasionally organochlorine dichlorodiphenyltrichloroethane (DDT) [1]. As most infected

Infants will receive this regardless of being

infected withthe parasite or not to reduce their risk of contracting it. The coverage data is not yet reported for IPTi because, as of 2018, no country has officially adopted it. One of the first countries that began to upscale its adoption of IPTi in 2019 is Sierra Leone [1]. Table 3 lists the combination therapy options paired with IPTi for infants. Pairing these intermittentpreventative treatments with their immunization schedules will make it an easy and quick additional vital to ensuring their protection.

Intermittent Preventative Treatment for Pregnant Women

More than 30 million pregnant women in Africa becomeexposed to malaria. Therefore, a four-dose scheduled regimen

of IPTp1, IPTp2, IPTp3, and IPTp4, each given one month apart, has been adopted by thirty-nine African countries. The data from 2018 currently shows that less and less pregnant women follow through with all four doses. The coverage rates for the first three doses were 60%, 49%, and 31%, respectively [1]. Therefore, follow through for the entire four-dose series is relatively low and is an area for potential adherence education. However, the data from 2018 show better adherence than in 2017 by at least 10%.

Further data shows that pairing IPTp with at least two low doses of sulphadoxine-pyrimethamine (SP) reduces the concerns associated with contracting malaria, including maternal anemia, low birth weight, and perinatal mortality. IPTp gets provided during antenatal care visits following the first trimester. Therefore, it is imperative to malaria transmission control to administer these intermittent preventative therapies to pregnant women.

Vaccinations

In July of 2015, the first vaccine for malaria, Mosquirix, hit the market. It is a recombinant protein-based vaccine, also referred to as RTS,S/AS01. It was an instrumental discoveryas it is the world's first licensed vaccine for malaria, the firstof its kind to be used against a parasitic disease [1]. The vaccine's efficacy as per conducted clinical trials is listed in the table below [11, 12]. Vaccine efficacy does wane over time. A study conducted a 7-year follow-up and found that its efficacy was 4.4% [13]. Table 4 shows some of the efficacy results associated with vaccine studies.

The side effects that accompany vaccines sometimes occur immediately after the vaccine and some in a few days. According to Ofori-Anyinam et al., in RTS,S/AS01, patients experienced generalized convulsive seizures. These febrile convulsions' incidences occurred within 7-days of vaccine administration, and its likelihood increased with each subsequent dose administration. Furthermore, there were increased cases of meningitis and cerebral malaria cases. However, this study had analysis limitations as these effects may be due to other vaccines that the patients receivedsimultaneously with the RTS,S/AS01 [14]. Therefore, Mosquirix brought a vaccine to malaria where none existed before. Even though efficacy results have not shown a high efficacy level, they are a step forward in the right direction. At the same time, researchers studied another vaccine for its efficacy and safety profile in adults against *Plasmodium falciparum*, the Plasmodium falciparum (Pf) sporozoite (SPZ) or PfSPZ vaccine. It is a radiation-attenuated malaria vaccine that, when used against the same strain as in the vaccine, can result in 100% protection against that strain for three weeks after five IV doses, as studies have shown [15, 16]. Table 5 outlines the data for the PfSPZ vaccine. Researchers use controlled human malaria infection (CHMI) to test the vaccine's efficacy to examine its physiological and

immunological response to malaria parasites.
PfSPZ is safe,
well-tolerated, and easy to administer.

The percentage of efficacy obtained with PfSPZ warrants further clinical trials to study different doses to achieve greater efficacy against heterologous CHMI. Therefore, the safety and efficacy profile of PfSPZ shows great promise in providing prevention against *Plasmodium falciparum* andother potential strains.

Testing and Diagnosis

The diagnosis of malaria is a challenge in countries with the highest number of cases. The challenge presents itself due to the nature of symptomology and their classification. For example, it is common for patients to present with a fever. Before diagnostic testing was made available, it led physicians to prescribe antimalarial

drugs unnecessarily whenthe patient's fever could have otherwise been due to other febrile illnesses [1]. The lack of hindrance in prescribing antimalarials resulted in resistance to medications used inthe early treatment of malaria years ago, which is a problem we are combating today. Other symptoms associated with malaria are minor and include chills, sweats, and headache. As a result, medical personnel that grew accustomed to

Table 3: Summary of the regimens used for infants and their efficacy in the prevention of malaria

Regimen	Standard of Use/Efficacy
IPTi + SP	Dual action against anemia and clinical malaria
SMC + AQ + SP	Specifically, for children aged 3 to 59 months, this combination has 75% efficacy against clinical attacks and severe malaria averting thousands of deaths and many more cases.

Table 4: Summary of RTS,S/AS01 efficacy results.

Author	Months after first dose of vaccine	Incidences of first episode (episodes per person-year)	Average Efficacy (%)
Penny et al.	14	0.32	45
Agnandji et al.	14	0.31	30

Table 5: Summary of the percentage of protection achieved and thus the efficacy of PfSPZ [15, 17-19]

Author	# Doses	PfSPZ Dose	Type of CHMI	% Protection against CHMI after 3 weeks
Epstein et al.	5	2.7×10^5	Heterologous	92.33
	3	4.5×10^5	Homologous	86.7
Lyke et al.	3	9.0×10^5	Homologous	64
Olotu el al.	5	2.7×10^5	Heterologous	70
Bastiaens et al.	3	7.5×10^4	Heterologous	60

seeing thousands of malaria cases might skip the testing and immediately administer an antimalarial drug where further testing could have indicated a different diagnosis. The goal is to have medical personnel perform a test right after identifying symptomology to ensure the correct action course. This reflex of testing upon specific symptomology has risen approximately 50% from 2010 [1]. Therefore, malaria diagnosis through parasitological testing, rapid diagnostic tests, or microscopy addresses the challenge of malaria diagnosis with its general symptomology profile.

Malaria Rapid Diagnostic Tests

In the event that malaria prophylaxis is insufficient, rapid and accurate case tracking requires reliable diagnostic techniques. An early diagnosis may lower transmission risk, save lives, and lessen the severity of malaria in patients. Malaria rapid diagnostic tests (mRDTs) are available, and the vast majority of them can only identify P. falciparum. It's less expensive than techniques like microscopy and simple enough that most clinics can implement it [20]. There was a 47% increase in the number of people who had a malaria test in 2018 compared to

2010 [1]. One 2017 research revealed various issues with mRDTs, including doctors not always prescribing ACTs after a good result and doctors sometimes prescribing them after a negative result. There was general agreement, however, that mRDTs led to less ACT prescriptions being written [21]. These results are worrisome because they point to a possible worldwide problem: the incorrect prescription of anti-malarial and anti-microbial drugs, which may lead to a rise in drug resistance. These results further underscore the need of providing enough formal training to the people who do these tests and subsequently prescribe antimalarials. Therefore, mRDTs are disseminated as one of the diagnostic tools to aid in quicker and more effective diagnosis.

Ensuring sufficient market access is just as important as making sure the right methodology is followed when testing the efficacy of mRDTs. Having mRDTs readily accessible at medication distribution locations may greatly enhance malaria testing and diagnosis, as shown in a randomized experiment of 310 vendors in Tanzania [22]. The results of this one-year test show how advantageous wider market access may be. It may improve conformity between test findings and subsequent action if combined with thorough and appropriate preparation. By making services more easily accessible, patients have a better chance of receiving a timely diagnosis and treatment.

However, mRDTs are not without their drawbacks. mRDTs diagnose by detecting HRP2, a gene expressed by parasites like P. falciparum. Some parasites, however, would still test positive by microscopy despite having stopped expressing the genes that the mRDTs were designed to pick up. Positive blood samples that mRDTs missed in 2010 owing to a lack of pfhrp2/3 were discovered by microscopy.

[1]. In this situation, microscopy would provide the most reliable results. However, doctors cannot give it out until the patient has malaria symptoms and an mRDT test comes back negative.

Current Treatment Guidelines in WHO Regions:

First-line treatments such as AL, AS-AQ, AS-MQ, and DHA-PPQ remain effective with only a 10% failure rate in some WHO regions. However, treatment failure rates tend to be higher in countries like India, ranging from 0% to 24%. Surprisingly, Thailand, which uses DHA-PPQ as its first-line treatment, is experiencing a failure rate of 92.9%, which warranted their first-line treatment to change to AS- PY. Table 6 outlines the diagnosis criteria and medications used by WHO regions for each category [1]. The different drug classes are listed in Table 6 and figure 2 showing the chemical structure of the different classes.

ACT: artemisinin-based combination therapy; AL: artemether-lumefantrine; AM: artemether; AQ: amodiaquine; ART: artemisinin; AS: artesunate; AT: atovaquone; CL: clindamycline; CQ: chloroquine; D: doxycycline; DHA: dihydroartemisinin; MQ: mefloquine; NQ: naphroquine; PG: proguanil; PPQ: piperaquine; PQ: primaquine; PYR: pyronaridine; QN: quinine; SP: sulfadoxine-pyrimethamine;T: tetracycline [25-34].

Table 6: Summary of Treatments Used for each species and diagnosis severity

Species	Diagnosis	Treatments Used
P. falciparum	Uncomplicated Unconfirmed	AL, AS + AQ, DHA-PPQ
		CQ, AS + SP, AL + PQ
	Uncomplicated Confirmed	AL, AS + AQ, DHA-PPQ
		QN + CL, QN + D, CQ + PQ
		AL + PQ, AS + MQ
		AS + MQ + PQ, AS + SP + PQ
		AS + SP, DHA-PPQ + PQ
		AS + MQ, PYR
		AS, QN, AM, QN + AS

	Severe	AS + D, QN + D, QN + T
		QN + CL, AL, AS + MQ
		AS + AL, PYR, AS + AL + PQ
P. vivax		PQ, AS + AQ + PQ, CQ
		CQ + PQ, AL, AL + PQ
		AS + PQ + AQ, DHA-PPQ + PQ
		AS + MQ + PQ, PQ + PPQ
		ACTs + PQ, PYR

ACT: artemisinin-based combination therapy; AL: artemether-lumefantrine; AM: artemether; AQ: amodiaquine; ART: artemisinin; AS: artesunate; AT: atovaquone; CL: clindamycline; CQ: chloroquine; D: doxycycline; DHA: dihydroartemisinin; MQ: mefloquine; NQ: naphroquine; PG: proguanil; PPQ: piperaquine; PQ: primaquine; PYR: pyronaridine; QN: quinine; SP: sulfadoxine-pyrimethamine; T: tetracycline [25-34].

Figure 2: Chemical Structure of Anti-Malarial Drugs

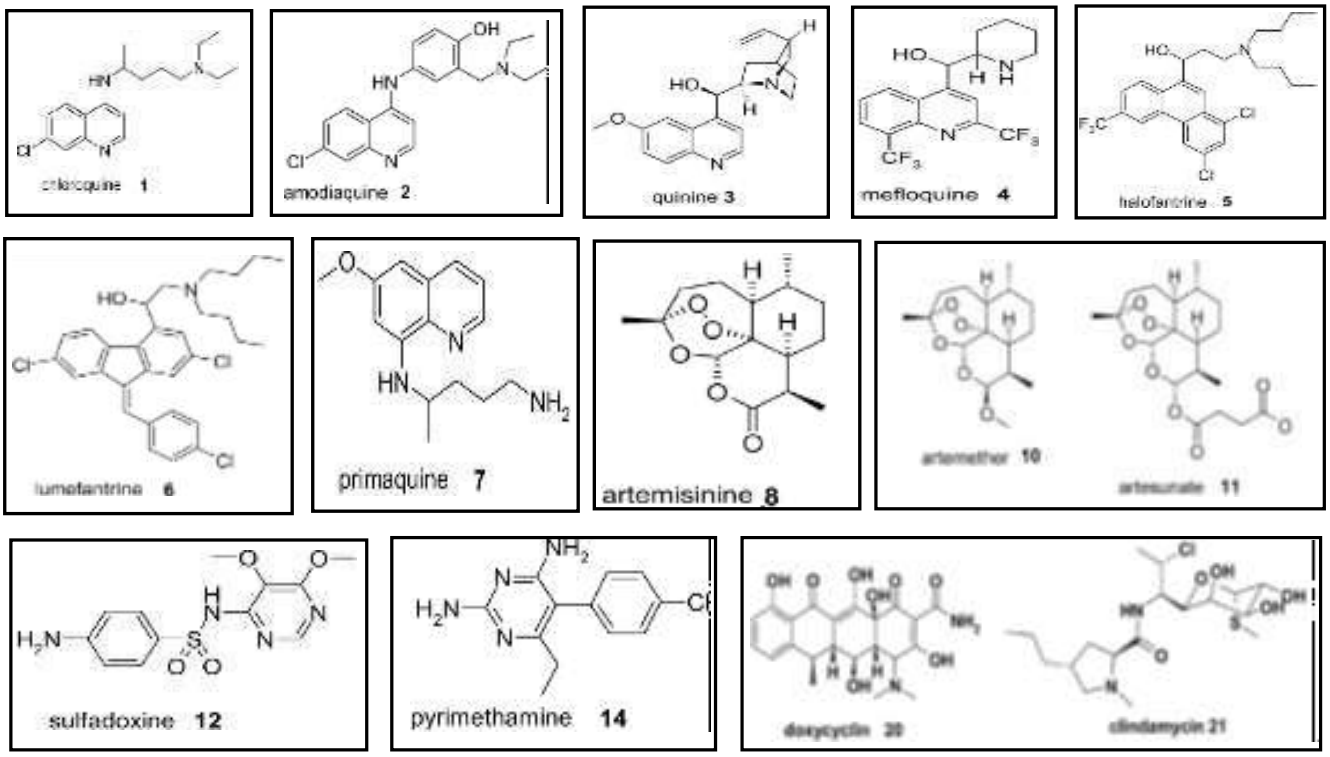

Table 7: Summary of current clinical trials seeking to enhance prevention and treatment of malaria

Area of Focus	Intervention	Subjects	Primary Outcome
Vaccine	SB257049	5 to 17 months old	P. falciparum asexual parasitemia > 5000 parasites/microliters and presence of fever ≥ 37.5℃
Prophylaxis	Artemether-lumefantrine with multivitamins	16 to 65 years old	28-day PCR positivity rate of Plasmodium infections of any species and proportion of participants with confirmed clinical malaria of any species reported between day 0 and 28

Prevention and Treatment	Meplazumab	18 to 55 years old	Presence of anti-bodies in 71 ± 3 days and presence of adverse events
Treatment	KAF156	6 months to < 18 years old	% of participants with PCR-corrected and uncorrected adequate clinical and parasitological response (ACPR) at Day 29
Vaccine	Pfs230D1M-EPA/AS01	1 to 99 years	Safety and reactogenicity of vaccine administration
Treatment	KAF156 + Lumefantrine Solid Dispersion	2 years and older	PCR-corrected adequate clinical and parasitological response (ACPR)
Treatment	New Artemether-lumefantrine dispersible tablet in infants and neonates	Infants and Neonates < 5 kg	ART Cmax concentrations at 1 and 2 hours after the first dose
Prophylaxis and Malnutrition	SMC + Nutrients Supplementation	6 to 59 months	The relative risk of the incidence of clinical malaria, mid-upper arm circumference gain, weight gain and prevalence of anemia
Prevention in Pregnant Women	Azithromycin and Sulphadoxine-pyrimethamine	18 years and older	Number of pregnant women with maternal peripheral blood parasitemia during pregnancy among pregnant women who use sulfadoxine pyrimethamine and azithromycin for malaria prevention in pregnancy,
Vaccine	ChAd63/ MVA PvDBP	18 to 45 years	Efficacy of the two vaccines, assessed by a parasite multiplication rate in vaccinated subjects

Drugs introduced before 2000s

The drug classes quinine, chloroquine, proguanil, sulfadoxine-pyrimethamine, mefloquine, and atovaquone were introduced in 1632, 1945, 1948, 1967, 1977, and 1996, respectively. They have been around for quite some time andstill being used today despite the resistance cases that have emerged, as seen in Table 6. Chloroquine, the first syntheticallydeveloped anti-malarial drug, proved to be an almost magical cure for more than 30 years until the emergence and spread of chloroquine-resistant parasites. However, a study sought to determine whether doubling the chloroquine dose would help combat the resistance. They divided this daily dose into two doses, administrated every day for three days. They were able to show that it was just as efficacious as artemisinin- based combination therapy, so there may still be a place for it in treatment today with slight regimen modification [23]. However, many of the drugs currently used for malaria have been on the market for years. They are not as effective as they need to effectively treat malaria patients.

Current Clinical Trials

We must have more advancement in the prevention and treatment strategies for malaria. A novel drug, SJ733, is an orally bioavailable inhibitor of P. falciparum ATP4. This is the first time this drug has been studied in humans. It recently completed a phase 1a/b trial where pharmacokinetics, safety, tolerability, and antimalarial activity were investigated inhumans. Fasted participants were infected with the blood-stage P. falciparum and then treated with SJ733. They gave them two doses, 150 mg followed by 600 mg with onlyone confirmed side effect, mild bilateral foot paresthesia. The trial results were favorable and have a future of being incorporated in antimalarial therapy [24]. There are many more advancements coming to malaria, and Table 7 identifies the current clinical trials and the interventions studied to further prevention and treatment strategies. These trials holdgreat promise in bringing in new interventions for vaccines, prophylaxis, and treatment. We must move forward in the fight against malaria so that we may reduce transmission cases.

Common links between Malaria and Covid 19

Among the common links reported include the followings:

(a) the low prevalence of COVID-19 in malaria-

endemic countries, (b) the similarity between malaria and COVID-19 symptoms, (c) the role of ACE2 in malaria and COVID-19,
(d) the roles of interferons and the neutralizing antibodies in malaria and COVID-19, and (e) the use of hydroxychloroquine and chloroquine in COVID 19 [25].

Conclusion

Malaria takes millions of lives every year but through the efforts of the World Health Organization, there are strategic plans in place to decrease malaria transmission cases. In

the last decade, diagnostics tests have been developed that are more accurate and provide an avenue of diagnosis for physicians, which aids in the administration of treatments correctly and only when indicated. In addition, funding for research has increased and many clinical trials are underway to bring new vaccines, preventions, and treatments.

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