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Revisiting Malaria Elimination: Prevention, Diagnosis and Treatment

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Abstract

Malaria is a deadly infectious disease caused by the protozoan parasites of *Plasmodium* genus. Although malaria prevention, diagnostic testing along with treatment programs ensued a sharp global decrease in malaria-related mortality, drug and non-drug interventions such as usage of both untreated- and insecticide-treated mosquito nets played a significant role as well. The intricacies of the physiological pathways and molecular mechanisms of malaria pathogenesis have been extensively studied. Various technologies used in these studies hold promise for the identification of new interventions and adjunctive therapies. In this review, we discuss recent developments in our understanding of malaria biology, and the dynamics of this disease. We will focus on the preclinical and clinical evidence supporting the preventive or potentially harmful effects of anti-malarial medications for both the prevention and treatment of malaria.

Keywords: *Malaria Pharmacology; Prevention; Diagnosis; Treatment*

Abbreviations

ACT: Artemisinin-Based Combination Therapy; CQ: Chloroquine; G6PD: Glucose-6-Phosphate Dehydrogenase Enzyme; IRS: Indoor Residual Spraying; LLINs: Long-Lasting Insecticidal Nets; pfHRP2: Plasmodium falciparum Histidine-Rich Protein 2; pLDH: Plasmodial Lactate Dehydrogenase; RDTs: Rapid Diagnostic Tests; RBC: Red Blood Cells; USFDA: United States Food and Drug Administration; WHO: World Health Organization; WHOPES: World Health Organization Pesticide Evaluation Scheme

Introduction

Malaria is an infectious disease, which can affect people of all ages. It is a major global health challenge because its signs and symptoms range from mild to severe. An estimated 40% world population continue to be at increased risk of malaria. Though malaria among children has declined, severe malaria still continued to be the leading cause of mortality among children and nonimmune adults in developing countries [1]. There is a positive correlation between all-cause mortality and the levels of malaria endemicity and transmission intensity [2,3]. Although we have a greater understanding of the molecular basis of vector-human and host-parasite interactions, 438,000 people died by malaria globally in 2016 according to a recent report by the World Health Organization (WHO) [4,5]. The vast majority of these deaths appear to be in children [5].

Treating healthy individuals with moderate to severe malaria has reduced malaria incidence during 2000 - 2015 [4]. The decrease in malaria-related mortality rates during the same time period was 60%. The report also described 65% fewer deaths of children under five, a high risk population with infection, illness, and death [4]. These significant achievements in the global malaria response during this period are attributed to pharmacological advancements and therapeutic interventions in malaria prevention, diagnosis, as well as treatment. Many novel antimalarial drugs have been developed over the last several decades that decreased morbidity and mortality and increased patients quality of life, but the resistance development in malaria parasites against most of the antimalarial drugs further worsen the scenario of malaria public impact.

To eradicate malaria, the WHO heightened partnerships with developing and developed countries as well as private sectors to create a global platform to communicate and share the research on malaria in order to enhance the development of effective approaches to eliminate malaria in regions where the prevalence of malaria is high [6-8]. One of the recommended prevention strategies was a combination of drug and the use of nets. The aim was to abolish the spread of disease from person to person by restricting the vector mosquitos' contacts with the human body. Malaria, a vector-borne disease, has a night-time feeding behavior. As results, non-drug interventions played a significant role in protection against new malaria infections in many areas of the world due to limited access to care and treatment. The usage of non-treated and insecticide - pretreated bed nets have provided strong protection against the malaria-transmitting vector, but they have not been highly effective in eradicating malaria infections. Insect repellent creams and solutions have also been helpful in reducing mosquito bite. Moreover, several preventative medications (e.g. chemoprophylaxis) have been used that were highly effective in preventing malaria acquisition.

This review summarizes the current state-of-the-art in malaria prevention, diagnosis, treatment, and insecticide resistance, and their effects in the research, public health, and on malaria vector control interventions.

Malaria parasites

Malaria is a parasite infection caused by parasitic protozoans that belong to the genus *Plasmodium*. There are four species of malaria parasite that are passed on by the bite of infected female *Anopheles* mosquitos. The parasites that infect humans include *P. falciparum, P. vivax, P. ovale* and *P. malariae*. It appears that the transmission intensity of these species varies mainly by the landscape, climate, and seasonal migrant populations [9]. Interestingly, *Anopheles* mosquitoes are attracted to bovine blood meals than humans, highlighting the zoophagic features of malaria vector [10].

The most common species is *P. falciparum*, which also accounts for the most malaria-related deaths. Notably, the expected total lifetime transmission of this parasite is significantly high in young children [3]. Moreover, Ethiopia has a high prevalence of mutations in both chloroquine- and sulfadoxine-pyrimethamine - binding sites in *P. falciparum*, which is presumably acquired through interhuman transmission [9]. Thus, this parasite is capable of altering human susceptibility to malaria. However, no evidence of mutation in codons -mediated artemisinin resistance is detected, suggesting the presence of a yet uncharacterized biochemical pathway(s) in *P. falciparum*. Alternative strategies should be considered for both malaria non-endemic and endemic regions. These strategies can potentially be the development of new antimalarial drugs, identifications of the new biochemical pathway, characterization of drug-based combination therapies to a polymorphic site, and characterization of the relationship between multilocus geneotypes and antimalarial drugs.

P. vivax has a broad geographic distribution. While high altitudes and cold climates can be debilitating to many malaria species, *P. vivax* can grow at low temperature in female *Anopheles* mosquito vector. [11]. In certain African and southern Vietnam [12] malaria-endemic areas, *P. vivax*/*P. falciparum and P. vivax*/*P. knowlesi* are commonly found, this may lead to a co-infection. Additionally, *P. vivax* and *P. ovale* forms a dormant liver stage called hypnozoites, increases its survival, acts as a potential inventory of infection, can be activated months after primary infection when the conditions are optimum and cause relapse [13].

P. Ovale is clinically a relevant parasite species, which can cause disease in humans. Estimates of malaria show that *P. Ovale* is present at a very low prevalence in many geographical regions [14,15]. However, the study also indicates that this species is under-reported [16]. Unlike *P. vivax and P. falciparum,* evidence suggests that *P. ovale* tend to cluster in the Southern region rather than other regions of the Bioko Island in Equatorial Guinea (West Central-Africa) [17], describing not only *P. ovale* species' distribution but also a selective geographical explanation and the relation between populations of such parasites. An association of *P. falciparum* and *P. ovale* is known to occur in humans [18]. *P. ovale* reduction likely involves drug resistance, prevention, *P. ovale* control interventions on *P. ovale* outcome and *P. falciparum* or other species co-infection.

P. malariae, a human parasite species with a quartan cycle, is present at a low prevalence. It is capable of causing a long-lasting, chronic infection. *P. malariae* has a wide geographic distribution. Although *P. malariae* is considered to have a benign course, individuals with anemia infected by *P. malariae* tend to exhibit significantly high morbidity prevalence[19]. It becomes imperative to monitor *P. malariae* coinfected person and initiate treatment on an individual basis.

Biology of malaria

Understanding of the life cycle of the malaria parasite in relation to its epidemiology is briefly reviewed here in order to navigate the intricacies of the complex parasite-vector-host triad; that are aligned with the need to improve therapeutics and improve patients' lives. Malaria is caused by protozoal parasites of the genus *Plasmodium*. Five species of *Plasmodium* cause malaria disease in humans, and they follow a similar life-cycle (Table 1). When the female *Anopheles* mosquito bites a human host, it injects sporozoites into the bloodstream. These sporozoites then rapidly penetrate the liver parenchymal cells, where they propagate to liver-stage schizont (mother cell). Then, schizonts rupture and release the parasites as merozoites. Merozoites are capable of penetrating into red blood cells where the asexual reproduction occurs. In RBCs, merozoites reproduce and eventually rupture the cells and producing more merozoites which in turn going to infect other RBCs leading to massive destruction of RBCs. A small percentage of merozoites differentiate into gametocytes, which are taken up by the mosquito during another subsequent blood feeding. In mosquito, these gametocytes convert to sporozoites. *Plasmodium vivax* and *Plasmodium ovale* malaria transform to hypnozoites, a dormant stage, in the liver. These parasites lie dormant in liver cells and cause a relapse of malaria, often after months to years. However, the dogma that hypnozoites give rise to relapses in human malaria infections has been challenged[20].

***Plasmodium* species**	**Geographical distribution**	**Manifestation**
Plasmodium falciparum	Distributed widespread in tropical areas	Severe disease Most fatal
Plasmodium vivax	Distributed widespread in all tropical areas	Can transform to hypnozoite dormant stage and causes relapse of malaria
Plasmodium ovale	Mainly in west African countries	Can transform to hypnozoite dormant stage and causes relapse of malaria
Plasmodium malariae	Mainly in African countries	Cause nephrotic syndrome
Plasmodium knowlesi	Mainly in Malaysia, Thailand, Myanmar	Zoonosis, Microscopically similar to *P. malariae* Severe disease/fatalities

Table 1: *Plasmodium species for malaria.*

Prevention of malaria

The malaria parasite life cycle is consist of three main life-cycle stages: asexual-stage parasite, sexual-stage parasite, and gametocytes. Gametocytes infect invertebrate vectors (female *Anopheles* mosquitoes); whereas asexual stage parasite, sporozoites, parasitize definitive hosts, those in which sexual development occurs. Although our understanding of the pathogenoproteomics of malaria is incomplete[21]; our current knowledge has enabled us to understand malaria infections, and the interplay between host and the development of malaria parasites in humans. The ecological relationship between human and various malaria parasites has quantitatively been evaluated. It has been well-demonstrated that in the majority of human malaria parasites (*P. vivax, P. Ovale*, *P. malariae*) infection the majority of individuals harbor few quiescent parasites. However, individuals harbor *P. falciparum* tend to have heavy parasite burdens that the infection can be lethal. The prevention of malaria infections is unique.

To prevent malaria infection, the earth topography has been divided into non-endemic and endemic localities. In non-endemic areas, the preventive strategy is the usage of antimalarial drugs to prevent the transmission of infection from infective human to travelers going to the countries where malaria is endemic. Currently, several chemo-prophylactic drugs are available, which are effective in preventing the development of malaria parasites in blood even after mosquito bites [22]. It is not possible to eradicate female *Anopheles* mosquitoes in endemic areas because further parasite infection is almost inevitable. Integrated control methods have been recommended on the basis of new knowledge of the ecology of parasite interaction with the host, recent advances in malaria epigenetics, epidemiology of the malaria infection, and the use of new drugs. Integrated control methods have been effective for simultaneously suppressing the contact between mosquitos and the human body, the transmission from infected human host to another human body, control of *Anopheles* mosquito populations of predefined areas through appropriate pesticides, drug-resistant malaria, and insecticide-resistant mosquitoes. The methodologies of preventing infection (net, long-lasting insecticidal nets, and spray), which have been established for malaria parasites, currently appears to be the logical means of preventing transmission of all human malaria infection. Several indoor residual spraying (IRS) are also available that kill the malaria vector. The WHO recommends IRS as one of three primary means of malaria control. Finally, targeting treatment toward the population with the greatest risk of malaria, pregnant women and children, also seem to be the strategy of choice for the most prevalent infection, *P. falciparum*.

Long-lasting insecticidal nets (LLINs)

LLINs are designed by either coating or by incorporating the insecticides in the material of nets. World Health Organization Pesticide Evaluation Scheme (WHOPES) is the body that promotes and coordinates the testing and evaluation of pesticides for public health [23]. WHOPES has an evaluation and testing program that include studying the safety, efficacy and operational acceptability of public health pesticides and developing specifications for quality control and international trade. Most of the LLINs are based on Alpha-cypermethrin, Permethrin, Deltamethrin and Piperonyl butoxide (PBO) incorporation into the polyethylene or polyester material of the net [23]. All WHOPES approved LLINs are given in table 2 [24].

Product	Product Detail	Status	Manufacturer
Duranet	Alpha-cypermethrin incorporated into polyethylene	Full WHOPES recommendation	Shobikaa Impex Pvt Ltd, India
Interceptor	Alpha-cypermethrin coated on polyester	Full WHOPES recommendation	BASF, Germany
MAGNet	Alpha-cypermethrin incorporated into polyethylene	Full WHOPES recommendation	V.K.A. Polymers
Olyset Net	Permethrin incorporated into polyethylene	Full WHOPES recommendation	Sumitomo Chemical, Japan
PermaNet 2.0	Deltamethrin coated on polyester	Full WHOPES recommendation	Vestergaard Frandsen, Switzerland
Royal Sentry	Alpha-cypermethrin incorporated into polyethylene	Full WHOPES recommendation	Disease Control Technologies, USA
SafeNet	Alpha-cypermethrin coated on polyester	Full WHOPES recommendation	Mainpol GmbH, Germany
Yorkool	Deltamethrin coated on polyester	Full WHOPES recommendation	Yorkool International Limited, China
DawaPlus 2.0	Deltamethrin coated on polyester	Interim WHOPES recommendation	Tana Netting, UAE
LifeNet	Deltamethrin incorporated into polypropylene	Interim WHOPES recommendation	Bayer Crop Science, Germany
MiraNet	Alpha-cypermethrin incorporated into polyethylene	Interim WHOPES recommendation	A to Z Mills, Tanzania
Olyset Plus	Permethrin and PBO incorporated into polyethylene	Interim WHOPES recommendation	Sumitomo Chemical, Japan
Panda Net 2.0	Deltamethrin incorporated into polyethylene	Interim WHOPES recommendation	Vestergaard Frandsen, Switzerland
PermaNet 3.0	Combination of deltamethrin coated on polyester with strengthened border (side panels), and deltamethrin and PBO incorporated into polyethylene (roof)	Interim WHOPES recommendation	Vestergaard Frandsen, Switzerland
Veeralin	Alpha-cypermethrin and PBO incorporated into polyethylene	Interim WHOPES recommendation	Vector Control Innovations Private Limited, India
Yahe	Deltamethrin coated on polyester	Interim WHOPES recommendation	Fujian Yamei Industry & Trade Co. Ltd., China
DawaPlus 3.0	Combination of deltamethrin coated on polyester with strengthened border (side panels) and deltamethrin and PBO incorporated into polyethylene (roof)	Interim WHOPES recommendation	Tana Netting, UAE
DawaPlus 4.0	Deltamethrin and PBO incorporated whole net	Interim WHOPES recommendation	Tana Netting, UAE

Table 2: *Long lasting insecticidal net (LLIN) approved by WHOPES.*

Indoor Residual Spraying (IRS)

IRS is spraying with an insecticide to kill mosquitoes that spread malaria [25]. A dilute solution of insecticide is sprayed on the inside walls of certain types of dwellings particularly those areas with walls made from porous materials such as mud or wood. Total 12 insecticides currently approved by the WHO [25] for use in malaria control (table 3).

Pesticide name	MOA class	Recommended formulations	Manufacturer selected by WHOPES
Alpha-Cypermethrin	Contact	WP 5% and 10%, SC 2.5%, 5%, 6% and 10%	BASF Agro, Megmani Organics Limited, Gharda Chemicals Limited, Heranba Industries Limited, Bharat Rasayan Limited,
Bendiocarb	Contact and airborne	WP (800 g/kg), WP-SB (800 g/kg)	Bayer CropScience
Bifenthrin	Contact	WP	FMC Corporation
Cyfluthrin	Contact	WP (100 g/kg)	Bayer CropScience
Deltamethrin	Contact	WP (50 g/kg), WG (250 g/kg), WG-SB (250 g/kg), SC (10g/kg or g/l), SC-PE (62.5 g/kg or g/l), WP 2.5% and 5%, WG 25%.	Bayer CropScience, Tagros Chemicals India Ltd., Gharda Chemicals Limited, Heranba Industries Limited, Argos South Africa
Etofenprox	Contact	WP 20%	Mitsui Chemicals Agro
Fenitrothion	Contact and airborne	WP 40%	Sumitomo Chemical Company
Lambda-Cyhalothrin	Contact	WP 10%, CS 10%, WP (100g/kg), CS (100g/lit)	Syngenta Crop Protection AG, Tagros Chemicals India Ltd.
Pirimiphos-Methyl	Contact and airborne	WP, EC (500g/lit), CS (300g/lit)	Syngenta Crop Protection AG
DDT	Contact	WP	None
Malathion	Contact	WP	None
Propoxur	Contact and airborne	WP	None

Table 3: *List of indoor residual sprays (IRS) that meet WHOPES specifications for use against Malaria vector.*
**CS: Capsule Suspension; EC: Emulsifiable Concentrate; SC: Suspension Concentrate; SC-PE: Polymer Enhanced Suspension Concentrate; WG: Water Dispersible Granules; WG-SB: Water Dispersible Granules in Sealed Water Soluble Bags; WP: Wettable Powder; WP-SB: Wettable Powder in Sealed Water Soluble Bags.*

Prophylaxis medicines

Preventative medications (chemoprophylaxis) must be taken by persons traveling to an area where malaria is prevalent. When taken properly, it is highly effective in preventing malaria acquisition. However, the degree of protection probably depends on exposure. There are several kinds of chemoprophylaxis medicines are available. All United States food drug administration (USFDA)-approved regimens have been highly effective, when patients are compliant, and very well tolerated. Therefore, the choice of the drug can be customized on the basis of patient preference, side effect profile, and cost (table 4).

Drugs	Advantages	Disadvantages
Atovaquone/Proguanil (Malarone) (100 mg of proguanil and 250 mg of atovaquone once daily	treatment starts 1-2 days before traveling, so it is good for last-minute travelers. It is only taken for 7 days after traveling rather than 4 weeks so it is good choice for shorter trips.	Not recommended in women who are pregnant or breastfeeding a child less than 5 kg Not Recommended for people with severe renal impairment.
Chloroquine (300 mg once weekly)	Good choice for long trips because it is taken only weekly.Recommended for all trimesters of pregnancy.	Not effective in chloroquine or mefloquine resistance area.
Doxycycline (100 mg once daily)	Prevent additional infections (e.g. Rickettsiae and leptospirosis). Good for last-minute travelers because the drug is started 1-2 days before traveling. Least expensive.	Not recommended for pregnant women and children < 8 years old Increased risk of sun sensitivity. Upset stomach
Mefloquine (250 mg once weekly)	It is taken only weekly so good for long trip. Recommended for pregnant women.	Drug needs to be started at least 2 weeks prior to travel so it is not a good choice for urgent travelling. Not recommended for persons with cardiac conduction and seizure disorder Parasites may deveoped resistance to mefloquine in some particular area.

Table 4: *Medicines available for malaria prophylaxis.*

Prophylaxis medicines

All malaria diagnostic tests are intended to detect blood-stage disease; there are no reliable tests for dormant malaria in an asymptomatic patient. Different malaria diagnostic methods are summarized in table 5.

Diagnostic method	basics	advantages	disadvantages
Microscopy	Nuclear staining	Highly sensitive	Higher chances of misdiagnosis
Rapid Diagnostic Test	Antigen-Antibody reaction	Highly Sensitive for *P. falciparum*	Less sensitive for species other than falciparum
PCR	Parasite specific DNA detection	Highly sensitivity for all *plasmodium* species including *P. knowlesi*	Costly due to equipment and maintenance

Table 5: *Methods Available for malaria diagnosis.*

Microscopic diagnosis

The traditional method for diagnosing malaria was solely depended on light microscopy of patient blood smears. The microscopic parasitemia method with the help of Giemsa stain was developed in 1904 [26]. Although microscopy techniques have made great contributions to malaria research and remain and will continue to be suitable techniques, these techniques are time-consuming, and tedious method. Moreover, significant misdiagnosis of false positives (7 - 36%), false negatives (5 - 18%), and wrong identification (13 - 15%) have been reported in the diagnosis of malaria in the United Kingdom [27] and Thailand [28,29] due to poor sensitivity and selectivity of microscopy techniques. Despite this, microscopy of thick and thin blood films remains the mainstay of diagnosis.

Microscopy diagnosis is based on preparation of blood smears on glass slides and stain it with Giemsa and observe it under a light microscope. Thick blood smears on slide come with high sensitivity. However, it is difficult to accurately count the parasitemia and confirm the species of *Plasmodium* in such slides. This smear comes with lesser sensitivity than thick smear however this type of slides are good for accurate determination of parasitemia and do a species-specific analysis of malaria [30,31].

Rapid diagnostic tests

Recent advances in pathology and histopathological diagnosis of malaria triggered the development of an easier and significantly accurate malaria diagnostic test. One such test has been rapid diagnostic tests (RDTs). Malaria RDTs kits have been developed. RDTs test that is 99.9% reliable has been a popular technique in the absence of a good quality microscopy service.

RDTs have emerged as a promising alternative to microscopy for the diagnosis of malaria and have been listed as an acceptable means of diagnosis in recent WHO guidelines. Three antigens - *Plasmodium falciparum* histidine-rich protein 2 (PfHRP2), plasmodial aldolase and plasmodial lactate dehydrogenase (pLDH) are currently used for RDTs. Tests targeting HRP2 contribute to more than 90% of the malaria RDTs in current use. RDTs for malaria are now widely available [32]. Table 5 summarizes the strengths and limitations of RDTs along with the alternative diagnostic methods. They are particularly useful as an additional test in laboratories with relatively few cases in a year but do not give information on the parasite density (which has prognostic value). They are a useful adjunct to malaria films for diagnosis in a non-endemic setting, but should not be used as a substitute for microscopic blood smears slides.

In addition to the above mentioned diagnostic advantages, polymerase chain reaction (PCR) has been highly improved the detection of various *Plasmodium* species because of the availability of the DNA-based identification approach. PCR is highly sensitive and reliable. This diagnostic test can be used clinically to differentiate between species *Plasmodium vivax, Plasmodium falciparum, Plasmodium malariae, Plasmodium ovale* and *Plasmodium Knowlesi*. This method is however limited by speed, cost, and availability of technology, and is currently not used routinely in clinical practice [33].

Treatment of malaria

Old anti-malarial drug

Many countries have been facing a major ongoing malaria epidemic, especially in the African region. Children, adults, and pregnant women have extracted variant forms of the human malaria parasite. There has been much progress in the development of a treatment strategy that keeps the parasite under control. As mentioned earlier, non-drug treatment strategy has reduced fuelling the cycle of new malaria infections. Although no cure exists for malaria infection, there have been many anti-infective drugs that greatly slowed down the infection. Drugs that have been capable of killing the malaria parasites are briefly described below.

Researchers have been looking for drugs to treat malaria infection for over decades. The first synthetic drug chloroquine (CQ) was discovered in the 1940s [34]. CQ greatly improved the therapeutic outlook for patients with malaria infection throughout the world for a couple of decades [35]. However, the therapeutic efficacy of CQ for malaria parasite was diminished due to the occurrence of CQ resistance [36-38]. Due to the lack of potent alternative drug for treatment of CQ-resistant malaria parasite, the number of deaths increased to 2-3-fold in the 1980s [39]. Thus, a question then arose about where a new drug should intervene in the life cycle of the malaria parasite and the pathology of malaria infection. Since then, several amino quinolones derivatives were initially developed. Several alternative drugs like sulfadoxine, pyrimethamine (SP) [40] and artemisinin [41] emerged later as the first-line of treatment for malaria. These drugs helped million of malaria patients in the last two decades and significantly brought down the malaria mortality rate. However, several cases of parasite resistance were also reported for these new drugs [42,43], suggesting that the malaria parasites are capable of developing multiple mechanisms of drug resistance or as a result of alterations in human cells' epigenetic codes. Resistance to anti-malarial drugs is becoming a major concern in combating malaria parasites affecting a large number of patients with malaria, which could cause an increase in malaria fatalities.

Current Treatment of malaria

Treatment of malaria solely depends on the type of malaria (falciparum or non-falciparum), complication (age, pregnancy, drug resistance, etc.) and severity of malaria. A wide range of new drugs are being developed to prevent new drug resistance and eliminate malaria. There are several antimalarial drugs, which lower parasite infectivity and the level of discomfort caused by the malaria infection via targeting specific life cycle stage of *Plasmodium* species. These drugs represent various classes of drugs with unique chemical structure. Their chemical class, the name of drugs, treatment recommendations, and side effects are summarized in table 6. WHO recommended treatment for malaria in different complications are given in table 7.

Chemical class	Name of drug	Mode of Action	Primary Therapeutic Use	Side effects	Status of resistance
4-Aminoquinolines	Chloroquine, Amodiaquine	Accumulation in digestive vacuole of parasite	Treatment of Non severe falciparum	Blurred vision, nausea, vomiting, abdominal cramps, headache, and diarrhea	Yes
Amino alcohols	Mefloquine, Halofantrine, Lumefantrine	Accumulation in digestive vacuole of parasite	Multidrug resistance falciparum	Mefloquine causes the depression, hallucinations, and anxiety and neurological side effects such as poor balance, seizures, and ringing in the ears. Halofantrine and Lumefantrine cause the abdominal pain, diarrhoea, vomiting, rash, headache, itching and elevated liver enzymes, malaria pigment.	Yes
8-Aminoquinolines	Primaquine	Not precisely known	Infection of vivax and ovale. Prevent relapse. Gametocytocidal agent	Nausea, stomach, pain or upset, vomiting, loss of appetite, Heartburn, and abdominal cramps. Primaquine should not be given to people with glucose-6-phosphate dehydrogenase (G6PD) deficiency due to the risk of high hemo-toxicity.	Yes
Naphthoquinone	Atovaquone	Target cytochrome bc1 complex		Nausea, diarrhea, constipation, headache, weakness, dizziness,muscle pain,mild skinrash,Sweating, and sleep problems (insomnia).	Yes
Artemisinin and derivative	Artesunate Artemether Artemisinin	Not specific	Chloroquine resistance falciparum	Nausea, vomiting, anorexia, dizziness, And Mild blood abnormalities.	Yes

Table 6: *Antimalarial drugs currently available for treatment.*

Malaria Complication	WHO recommended Treatment
Uncomplicated *P. falciparum* malaria in children and adults	Artemether with lumefantrine Artesunate with amodiaquine Artesunate with mefloquine Dihydroartemisinin with piperaquine Artesunate with Sulfadoxine/pyrimethamine
Uncomplicated *P. falciparum* malaria in first trimester of pregnancy	Quinine with clindamycin
Uncomplicated *P. falciparum* malaria in infants with less than 5 kg body weight	Artemisinin-based combination therapy dosed at same mg/kg body weight dose as for children weighing 5 kg
Uncomplicated *P. vivax*, *P. ovale*, *P. malariae*, or *P. knowlesi* during blood-stage infection	ACT as above for *P. falciparum* Chloroquine (if chloroquine-sensitive region) Quinine (pregnant women in first trimester)
Relapse with *P. vivax* or *P. ovale*	Primaquine for 14 days (except pregnant women, breastfeeding women, and G6PD deficiency) Chloroquine for pregnant and breastfeeding women
Severe malaria	24 h of intravenous or intramuscular artesunate and then usual 3-day ACT regimen, if oral medication tolerated Parenteral quinine as an alternative when artesunate is not available
Cerebral malaria	Parenteral artemisinin derivatives or quinine [1]
Resistant malaria	*P. falciparum* malaria in chloroquine resistance artemether-lumefantrine (Coartem) or atovaquone-proguanil (Malarone) are the available treatment choice.

Table 7: *WHO recommended treatment for different complications of Malaria.*

1. Misra UK., et al. "Cerebral malaria and bacterial meningitis". Annals of Indian Academy of Neurology 14.1 (2011): S35-S39.

For children and adults suffering from uncomplicated *P. falciparum* malaria, the artemisinin-based combination therapy (ACT) is recommended for three days. Artemether with lumefantrine, artesunate with amodiaquine, artesunate with mefloquine, dihydroartemisinin with piperaquine and Artesunate with Sulfadoxine/pyrimethamine are the five recommended ACTS for uncomplicated *P. falciparum* malaria. To reduce the transmissibility of treated *P. falciparum* malaria, a single dose of PQ with ACT is given. Though this regimen is not given to pregnant women, an infant aged less than six months, and women breastfeeding the infant aged less than six months. Incomplete dosing and using monotherapy are the wrong approach to treat uncomplicated *P. falciparum* malaria [44].

Treatment in pregnant and lactating women

Malaria can lead to low-birth-weight-infants, severe anemia, pregnancy loss, and death. Quinine with clindamycin for 7-day is the recommended treatment for the pregnant women with uncomplicated *P. falciparum* malaria during the first trimester. To treat second and third-trimester pregnant women with uncomplicated *P. falciparum* malaria, the ACT is recommended. Artemether + lumefantrine, amodiaquine alone, or in combination with SP or artesunate, dihydroartemisinin with piperaquine, and mefloquine with artemisinin derivative are recommended therapies for second and third-trimester pregnant women. Quinine with clindamycin is also an option but only if other effective alternates are not available. Tetracycline and primaquine are not recommended during pregnancy. The quantity of antimalarial enter in breastmilk is considerably small. Tetracycline affect infant bones and teeth and thus is contraindicated in pregnant women [44].

Uncomplicated P. vivax, P. ovale, P. malariae and P. knowlesi malaria

In chloroquine-susceptible infections area, children and adults are treated with either ACT or CQ and in CQ-resistance infections area, children and adults are treated with the ACT. Quinine is used to treat CQ-resistant *P. vivax* malaria in pregnant women (first trimester). To prevent relapse in *P. vivax*, *P. ovale* malaria, children and adults are given primaquine. However, this drug is not recommended during pregnancy, and primaquine is not considered safe in breastfeeding women, infants less than 6-month-old, and glucose-6-phosphate dehydrogenase enzyme deficiency (G6PD) deficient people [44].

Ongoing clinical trials in malaria

Numerous clinical studies have focused on the evaluation of novel drugs' safety, the determination of safe dosage range, side effects, and novel therapeutic(s) against malaria during the past five years. The summary of these ongoing clinical trial has been shown in table 8.

Agents	Class	Target	Clinical Trial	Clinicaltrials.gov Identifier
Phenotypic assay				
KAE609 (cipargamin)	Spiroindolone	PfATP4(Na +-ATPase 4)	Phase II	NCT03334747
MMV390048	PfPI4K	phosphatidylinositol 4-kinase	Phase II	NCT02880241
DSM265	PfDHODH	Dihydroorotate dehydrogenase	Phase II	NCT02123290
KAF156	PfCARL	Cyclic amine resistance locus inhibitor	Phase II	NCT01753323
Synthetic Molecules				
OZ277 + Piperaquine	PfATP6	Pf-encoded sarcoplasmic endoplasmic reticulum calcium ATPase	Phase II and III	NCT02461186
OZ439 + Piperaquine	endoperoxide ozonide	1,2,4-trioxolane	Phase II and III	NCT02083380
Artemisone (BAY-44-9585) + Mefloquine	Artemisin derivative		Withdrawn	NCT00936767
Aminoquinoline scaffolds				
Ferroquine	4-aminoquinolines	Ferrocene – 4-aminoquinoline	Phase II-Terminated	NCT00988507
AQ-13	4-aminoquinolines	Not known	Phase II	NCT01614964
Tafenoquine	8-aminoquinolines	Not known	Phase III	NCT02216123
Antibiotics				
Fosmidomycin	Streptomycin lavenduale	DOXP pathway	Phase II-unknown	NCT02198807
Other agents				
Methylene blue + Primaquine	Phenothiazin dye	Not known	Phase I	NCT01668433

Table 8: *Summary of some of the ongoing clinical trial done in Malaria (clinicaltrial.org).*

The DDD107498, a multiple-stage antimalaria agent, and KAE609, a new Spiroindolone agent, are in Phase I trials and preclinical developmental studies. Both appear to be capable of reducing transmission of the malaria infection with potential for chemoprophylaxis due to non-selectivity against various parasite life cycle stages and late-stage gametocytes. KAF156, an imidazolopiperazine, and DSM265, a dihydroorotate dehydrogenase inhibitor, comprise unique chemical scaffolds new to malaria chemotherapy. KAF156 has potent inhibitory activity not only against asexual stage but sexual blood stage and the pre-erythrocytic liver stages of the malarial parasites [45]. Its mechanism of action is as yet to be determined. DSM265 is a potent inhibitor against both asexual and sexual blood stages, and active against drug-resistant parasite isolates. The safety and efficacy assessments need to be further evaluated for both KAF156 and DSM265, mainly for their use in pregnant women. OZ277, a synthetic non-artemisinin ozonides, activity is weak against high parasitic burdens. Aminoquinoline-contained scaffolds like ferroquine, have promising results but it needs to be combined with appropriate drugs to enhance the efficacy. The electrocardiac events due to AQ-13 leads to prolonged QTC intervals which raises safety concerns for this drug. Tafenoquine, the new anti-relapse drug has safety issues as it causes hemolysis in patients suffering from a G6PD enzyme deficiency. Other drugs, like fosmidomycin (DXP reductoisomerase inhibitor) and methylene blue (potential transmission blocker) showed promising results in clinical trial, however, cannot be used in children [46].

Conclusion

Development of resistance to anti-malarial drugs with the course of time necessitates the discovery of novel therapeutic agents to eradicate malaria. Although groundbreaking approaches have been taken by scientists to discover newer drugs, it is possible that their applications can be limited by lack of efficacy and severe adverse effects in the clinical trials. Therefore, major advancements and investments are required to improve therapeutic efficacy and to adopt different approaches including combination therapy. Moreover, advancement in the methods of prevention has a major role in malaria elimination. There are several WHOPES recommended LLIN and IRSs are available those are helping millions of people to fight against malaria. Effective measures should be taken not only to prevent the transmission of specific malarial parasites but also to interrupt their reestablishment. According to WHO, the success behind malaria treatment depends on several factors, such as structure of the healthcare system, the extent of investment, and several biological elements, including the demographic, environmental, and socio-economic condition of a country. Treatment success also depends on proper and early diagnosis and onset of treatment as early as possible. Therefore, the growing obstacles against the diagnosis of malaria should be overcome to prevent misdiagnosis and to ensure RDTs.

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