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A Review on : Malerial Pathogenesis

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ABSTRACT

Malaria is a disease caused by repeated cycles of growth of the parasite Plasmodium in the erythrocyte. Various cellular and molecular strategies allow the parasite to evade the human immune response for many cycles of parasite multiplication. Under certain circumstances Plasmodium infection causes severe anemia or cerebral malaria; the expression of disease is influenced by both parasite and host factors, as exemplified by the exacerbation of disease during pregnancy. This article provides an overview of malaria pathogenesis, synthesizing the recent field, laboratory, and epidemiological data that will lead to the development of strategies to reduce mortality and morbidity.

Introduction:

The term Maleria was derived from the Italian word"*malaria*" meaning foul air.It is a protozoal blood infection caused by a mosquito-born eapi complex an parasitewhich is transmitted to humans during the bite of an infected female Anopheles mosquito species.The United States National Institute of Allergy and InfectiousDiseases(NIAID) defines malaria as a disease caused by a parasite that lives part of its life in humans and part in mosquitoes.

This review aims to present all aspects of malaria in a coherent and comprehensive manner.An attempt was made to give introductory concepts regarding history,causative agents prevalence, and incidence of malaria. It also provide sold and new notions about the cell biology, pathophysiologe,diagnosis, and management of malaria in one umbrella including some tips from Ethiopia. In advance, we seek to summarize recent developments in drug, vaccine, and control measures ofmalaria.

Malaria is anancient disease that could be traced back to the very earliest human history. It was accepted as a disease by Hippocrates in the fourth century BC.In the early seventeenth Century, the Peruvian bark of Cinchona tree was known to treat fever.In 1847,Heinrich Meckel identified black-brown pigment granules in the blood and spleen of aninsane person.

OthmerZeidler synthesized Dichloro-Diphenyl-Trichloroethane (DDT) in 1874 for his thesis.Alphonse Laveran noticed parasiteswhich he called *Oscillariamalariae*in the blood of a malaria patient in1880.The genus plasmodium was portrayed by Ettore Marchiafava and Angelo Celli in 1885.The whole transmission cycle of the parasite was elucidated in 1897 by Ronald Ross. In 1898, Camillo Golgi and others demonstrated that human malaria was transmitted by *Anopheles* mosquitoes.

Chloroquine was discovered in 1934 by hens Andersag. He called his compound resochin. In early 1950s, malaria was thought to be eliminated from the USA. Then after, human infection with *Plasmodium knowlesi*was recognized in 1965. Artemisinin was isolated from the plant *Artemisia annua*in 1971.Next, a polymerase chain reaction-(PCR-)based malaria detection was depicted in the early 1990s,and meanwhile malaria rapid diagnostic tests (RDTs) were developed.

The genus *Plasmodium* (the causative agent for malaria) is thought to have originated from Dinoflagellates(photo- synthetic protozoa). From more than 200 Different species of Plasmodium,atleast 13 species are pathogenic to humans. Five of them *falciparum*, *vivax*, *ovale*(2 species),and *malariae*, are well-known etiology of human malaria. Moreover, disease with *knowlesi*occur in people when an Anopheles mosquito infected by a monkey bites humans Of these species, *falciparum* (dominant in East and Southern Africa) is mainly prevalent on the African continent and is responsible for most deaths from malaria. *Plasmodium vivax* has a wider geographic distribution. Although it can occur throughout Africa, the risk of infection with *vivax*isquitelowthere because of the absence of Duffygeneinmany African populations. There is however,a growing evidence that Vivax isbeing transmitted among Duffy blood group-

negative inhabitants in Africa.

Pathophysiology of Maleria:

Malaria is transmitted majorly through bites of the genus *Anopheles* mosquitoes which includes more than 537 recognized species.*A.*gambiae,*A.*funestusandA.pharoensiswere confirmed as the principal vectors in Ethiopia. Due to residence ofthe parasite in RBCs, malaria can also be transmitted through blood transfusion, organ transplant, or shared use of needles or syringes contaminated with blood. A new-born baby may acquire congenital malaria before or during delivery.Furthermoremalaria transmission is largely affected by global weather patterns including *El Nino* and *La Nina.*Around 44% of the world's population is at risk from malaria. According to the latest estimates219,000,000 malaria casesmost (92%) from World Health Organization (WHO) African Regionoccurred globally in 2017 and the disease led to 435,000 deathsmost (93%) of which were also in WHO African Region. Almost all (99.7%) cases due to malaria are resulted from *falciparum*.In 2017.The number of global malaria mortality in children less than five years is estimated to be 266,000 .Pregnant women have increased susceptibility to *falciparum* malaria. In malaria endemic are as*falciparum*contributes to 8–14%of low birth weightwhich in turn decreases the chance of a baby's survival.

Global malaria case incidence was reduced by 59% in 2017. A reduction in mortality rates (44.1%) was also reported in this year. Not only health related impact but also there is a severe economic burden in terms of lost days of work due to the disease. Of course, malaria is considered to take off 1.3% from the economic growth and 40% of public health expenditure of some African countries. It affected developing countries in many aspects including determent of tourism. A complex story that has many players,settings, &potential outcomes.As with any truly sucessfull parasites the observed outcome of evolutionin malaria is the undisturbed transition from mosquito to human to mosquito with little impact on the vector and host.Althoughimpactof the maleria can be seen at individualcommunitycountryand global levelfrom the parasite's perspectivehealthy host serving as two blood meals with a bit off ever in between is the norm.Infacthuman clinical disease is quite rare relative to the global interaction network of mosquitos and humans. The biology ofplasmodiumfalciparum malaria parasitesas measured invitro is the five species infecting human.

Plasmodium vivaxplasmodium ovule allickeriplasmodium ovalecurtisplasmodium malariaeand plasmodium knowlesiundegoes 10 or more morphological statesreplicate from a single to 10,000 cellsand vary in total population from onetomanymoredixonet.

In additionall of these parasite (with the exception of P.knowles in human)have been exposed four thounsands of milenniato the physicalimmunologicaland more recently chemotherapeutic barries in mosquito and humanswhich place tremendous selection pressure across the species.It is clear a finely tunedwellrehearsedand deftly exeucatedprogram.A similarselection pressure has beenplacedon humans and resulted in suchfascinating evaluationary outcomes as sinkle cell diseasehemoglobinopathiescytokines mutationsand enzyme deficiencywhich confeas a conceptual groupthe ability to survive to maturity andreproduction(Ban~ulsetal.2013;Perry 2014).Death from maleria at an age less than 6 year (the current most common demographic)cannot be a goal of the parasite (speaking teleologically) and thusitsoccurrence should be causes for conern or 0.2% leaves the unfortunate mortality as anaberrant foot note in the overall biology of the species as a whole (WHO2015).We should nothoweveracceptevenonedeathfromapreventableandtreatabledisease.

Life Cycle of Malaria:

ParasiteThe human malaria parasite has a complex life cycle as shown in Figure. The motile infectious formPlasmodium sporozoiteis passed to individuals when the insect bites the skin probes for a blood vessel from which to feed releases various vasodilators to increase its chance of finding a vessel and salivateintothe blood to prevent clotting. Within 30–60 min of inoculationthe thread like sporozoites are carried to the liver by thecirculatorysystem.Over a period of 7–12 days, the sporozoites growinto schizonts and can develop up to30,000 merozoiteswhich rupture the hepatocytes. On the other handsome *vivax* and *ovale*sporozoites turn into hypnozoitesa form that can remain latentintheliverfor months or years and cause relapses in infected people. Interestingly, recurrence of falciparummalaria was reported in patients some years after leaving an endemic area.

Ittells that atleastoccasionallyfalciparumhas adormant stage.Then the asexual cycle begins with the merozoites invading RBC to grow by consuming hemoglobin. Within the host RBCthe parasite undergoes development from the early ring stage to late trophozoite and then after mitotic divisions to the schizont stagewhich contains 6 tomerozoites depending on the parasite species.When the erythrocyticschizont ruptures the released merozoites continue the life cycle by invading other RBCs. Cyclical fevers are typically happening shortly before or at the timeof RBC lysis as schizonts rupture to release new infectious merozoites. This occurs every 48 h in tertian malaria and every 72 h in quart an malariainfection.

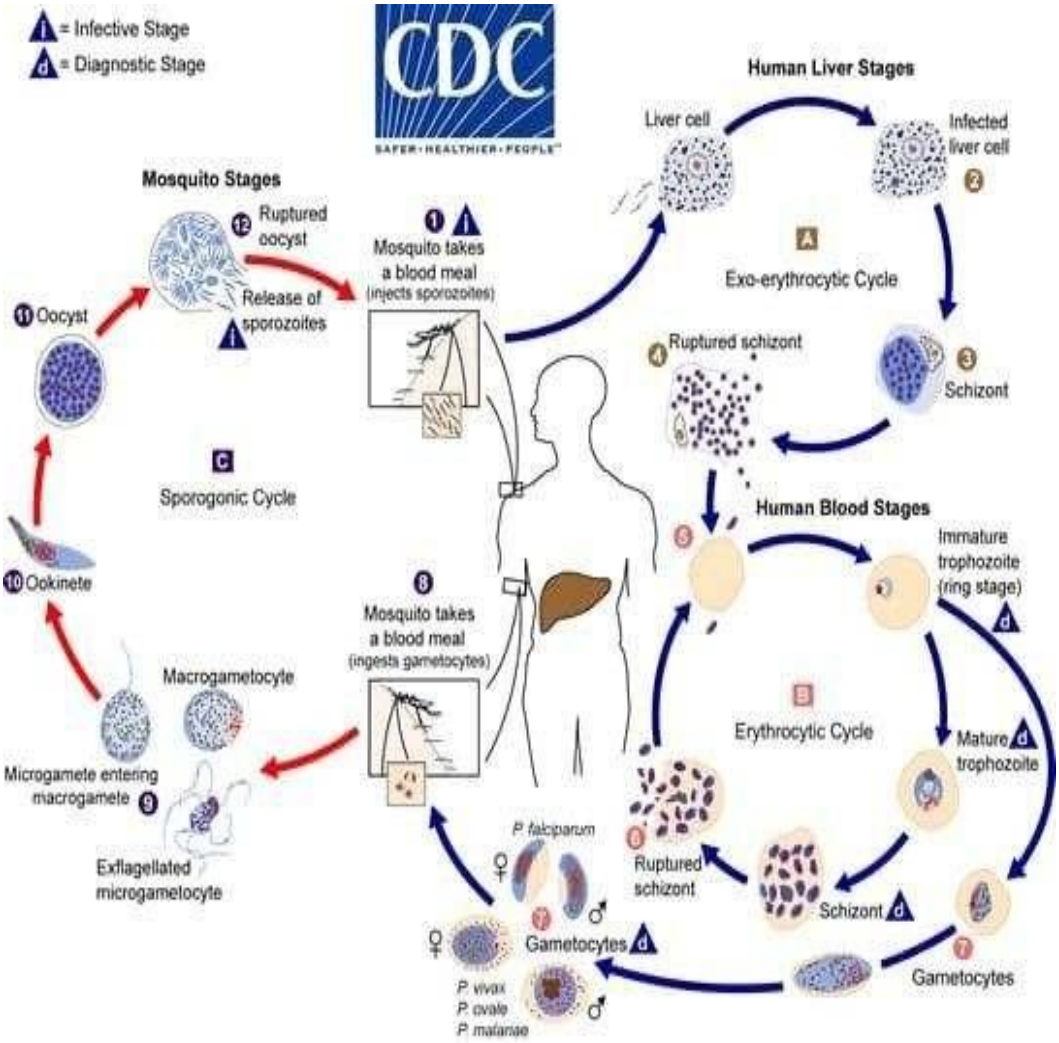

Fig.Life Cycle of Maleria

Uncomplicated Malaria:

The geographic regions where the human population is at risk for malaria infection(2.5 billion), annually 215,000,000 clinical in-fections occur for which patients have symptoms and seek medical attention. Patient illness representshowever, a subset of all individuals who have been bitten by infected mosquitoes and a much larger portion of the "at-risk" population would show a positive malaria smear or other diagnostic test if they were screened. The exact malaria parasite biology within these two groups is probably very similar with the essential differences being due to the human immune responsenumber of prior infections and exposure profile.

The symptoms of malaria infection can only begin in any ill patient with the first liver schizont rupture and release of merozoites into the peripheral circulation this event is silent for the vast majority of patients who will become clinically ill. As the parasites continue through their asexual life cycle of merozoite reinvasion trophozoite developmentand schizont rupture over 24 to 48 hoursthe level of parasitemia parallels the level of human response (i.e. fever C- reactive protein [CRP]and tumor necrosis factor a [TNF-a] until the patient crosses a threshold of awareness and "feels ill" (Oakley et al. 2011). Uncomplicated malaria is defined as symptoms present (fever) but no clinical or laboratory signs to indi-cate severity or vital organ dysfunction (WHO 2015).

The human host duringan initial infection, macrophage ingestion of merozoites, ruptured schizonts, or antigen-presenting tro-phozoites in the circulation or spleen leads to release of TNFA. The molecule, along with others in a cascadeis responsible for fever during infection. Other important molecules found during active infection include interleukin 10 (IL-10) and interferon g (IFN-g) among maleria pathogenesis others. In subsequent infectionssome degree of antibody production produced by the prior macrophageT-cell B-cell axis of the immune system confers additional macrophage activity leading to a more efficient clearance of parasites and production of new antibodies.

P.Falciparum:

P.falciparum (Pf) modifies the surface of the infected red blood cell and creates an adhesive phenotype, which removes the parasite from cir-culation for nearly half of the asexual life cycle a unique time frame among the malaria parasites (Grau and Craig 2012). The binding of the in-fected erythrocytes can occur with endotheliumplateletsor uninfected red blood cells (Fair-hurst and Wellems 2006; Kraemer and Smith 2006; Smith et al. 2013). The parasite accomplishes this cytoadherant ("sticky cell") state through the P.falciparum erythrocyte membrane protein 1 (PfEMP1), which is the product of var gene transcription (Smith et al.(2013).Within a given Pf parasitethere are 60 copies of the vargeneeach highly variable and different from the others. These genes represent some of the most diverse within the parasite's genome and within the total parasite population. Their expression is driven by several mechanisms in-cluding immune selection pressure and epigenetics. This aspect of the parasites's biology (var gene expression) occurs in all infections includ-ing asymptomatic and uncomplicated malaria. The potential of this humanparasite interaction to cause disease in humans has a definite spectrum discussed below (Smith et al. 2013). Regardless of the disease variabilitythe sequestration (temporary removal of the parasite from circulation through red cell surface binding) of Pf occurs during every human infection for half of the asexual life cycle.

P.vivax:

P.vivax (Pv) is the most common malaria par-asite causing clinical disease outside of Africa (WHO 2015). Unlike Pf but like all other human malaria parasitesPv does not show a prolongedperiod of sequestration during infection (Costa et al. 2011). The parasite isthusprobably more frequently exposed to clearance by the spleen and more commonly seen on a peripheral blood smear during an infection. One of the unique features of Pv is the red cell preference for reticulocytes and the use of predominantly the Duffy antigen for invasion although not absolutely.This leads to a clinical infection with a lower level of parasitemia than is seen in Pf.Because reticulocytes are larger than mature red cells the infected cells appear larger than the cells around them on peripheral blood smear. Characteristic Schuffner's dots which are caveola vesicle structures are seen in both Pv and P. ovale (Udagama et al. 1988).

P.ovale:

P. ovale (Po) was shown to be two distinct species (P. ovalecurtisi and P. ovalewallikeri), which only differ by a shorter latency period in P. ovalewallikeri and genetic sequence differ-ences (Oguike et al. 2011). Thus, these two sym-patric organisms are impossible to distinguish, present with the same clinical syndrome, and respond to the same therapy. Although their behavior is similar to the Duffy blood group antigen for invasion of red blood cells. On peripheral blood smearthe diagnostic forms are the comet form of the trophozoite as well as the oval appearance of infected red blood cells cells and the presence of fimbria or finger-like projects of the red cell membrane.

P.malariae:

P. malariae (Pm) is the most benign form of malaria infection with several distinct clinical features. Patients have fever every 72hours during an infection due to the longer parasites life cylce.the number of merozoitesproducted with each schizont ruptured us lower and thus parasite are lower overall in these patient compared with other typeofmaleria .this long life cycle and lower level of infected leads to a more robust immune response. Thus is often considered to cause a chronic maleria they may last decades.

Diagnosis ofMalaria :

Malaria must be diagnosed early and accurately to end up with an effectivemanagement of patients. Broadly one can classify it into clinical and parasitological diagnoses.Clinical diagnosis is based on the patient's symptoms and on signs at physical examination.All of the suspected malaria should be confirmed with a parasitological diagnosis in all settings.Light microscopy and RDTs are routinely employed methods for para sitological diagnosis of malaria.Detection of the parasite songiemsastained peripheral blood smears by light microscopy is used as the gold standard fordiagnosisofmalaria. As malariae have almost similar morphologymicroscopy alone is insufcient to diagnose.In case of vivax, ovaleand development stages sub sequent to the liver cycle can be seen in the peripheral blood.However infalciparumonlyringforms and bananalike gametocytes are usually present in the peripheral blood since mature parasites become sequestered.

In are as where microscopy is not readily availableRDTs can be used and are based on thedetectionof antigens or enzymatic activities associated with the parasites. Themost common antigens for RDT sareP.falciparum histidine rich protein2(PfHRP2) specific for falciparum malariaand two enzymes of the parasite glycolytic pathwaysnamelyplasmodial lactate dehydrogenase (pLDH) and aldolase.LDH can bespecific forfalciparumorvivax malaria.. ButsomeislatesfromtheAmazon regionAfricaand India

havebeen found lacking the PfHRP2 probably HRP2 gene deletonwhich threatens the ability to diagnose and appropriately treat people infected with falciparum malaria.In 2005,single-species RDTs were introduced. Years after multispecies RDTs are being supplied by FMoHto healthposts.

PCR-based methods, another parasitological diagnostic means, are the most sensitive test able to identify low levels of parasitemia, parasite species, or mixed infections, but not a suitable method for routine use. A species-specific loop- mediated is other mal amplification (LAMP) method has become widely accepted for identifying knowlesi infections. Besides, PCR is helpful as a research tool in epidermiological studies, clinical trials, and for detection of molecular markers of drug resistance to antimalarial agents.

Malaria Vaccine:

The emergence and spread of drug and insecticide resistance has been limiting the current malaria control measuresthus safe and effective vaccine is required to achieve the world malaria eradication programmeobjectives.The justification for a malaria vaccine development is the observation that people living in endemic areas develop clinical protective immunity despite the morphological changes and antigenic variations during the parasite life cycle allows them to escape the protective immune responses of the host.So far three types of vaccine candidates have been intensively investigatedpreerythrocytic vaccines to prevent bloodstage infection bloodstage vaccines to clear parasitaemia and prevent clinical diseaseandtransmissionblocking vaccines to prevent infection of mosquitoes and interrupt malaria transmission in populations.

Several asexual blood stage vaccinesmost target merozoiteantigensare in clinicalresearches. Candidates for erythrocyte stage vaccine are None has resulted in clearclinicalprotectionprobably due to the highly polymorphic nature of the vaccine structures . But eforts to enhance the efcacyeither with an ovel adjuvants using viral vector primeboost strategies or by combining AMA1 and MSP1have been increasing even though new nonpolymorphic falciparum ligandsCX3CL1- binding protein.

Treatment of Malaria:

Traditional Medicine:

This use varies among countries depending on a number of factors. In Singapore and the Republic of Korea where the conventional health-care system is quite well established76% and 86% of the respective populations still commonly use TMs. About 90% of general hospitals provide TM services for both outpatients and inpatients in China. Over 100 million Europeans are TM users .In developing countries80%ofthepeoplealmostexclusivelyuse TMs. Virtually80% of the population living in Ethiopia is de-pendent on traditional medicine which essentially involves the use of plants .More than 1,200 plants thatpossessantimalarial activities are reported worldwide . For exampleAmpelo-zyziphusamazonicus and Strychnopsisthouarsii were commonly used in malariaendemic areas of Brazil and Madagascarand their antisporozoite activities have been demonstrated.It is probable that some of antimalarial plants contain as yet un discovered active constituents.

Ethiopia is rich in a wide range of tropical habitats remarkable biodiversityand use of traditional remedies for the treatment of various ailments.Studies conducted on numerous traditionally claimed Ethiopian medicinal plants confirmed their antimalarial activities including PhytolaccadodecandraJusticiaschimperiana ,Artemisia abyssinica, Vernoniaamygdalina,BuddlejaPolystachya, Strychnos mitis, Echinopskebericho Aloe trichosantha, Cadabarotundifolia, Adhatodaschimperiana, Piper capense and Gardenia ternifolia.

Convention medicine:

Malaria can lead to fatal outcomes in only few daysthus treatment should be started as soon aspossible. The main targets of current antimalarial drugs are asexual blood stages of the parasiteresponsible for the malarial symptoms.Nowadays the available antimalarials can be grouped into five classes according to their chemical structure and biological activity

Chloroquine is a blood schizonticidal agent and the drug of choice for all malarial parasites except for chloroquine- resistant Plasmodium strains.Although almost all strains of malariae are susceptiblefalciparumvivax and even some ovale strains have been reported as

resistant to chloroquine . Chloroquine resistance for falciparum is due topoint mutations in the gene encoding chloroquine resistance transporter (PfCRT) protein resulting in reduced drug accumulation in the food vacuole . Drug resistance to

chloroquine has been reported in Ethiopia.Amodiaquine is effectively against some parasite strains that are resistant to chloroquinealthoughsome cross resistance exists .Piperaquine also has an excellent activity on chloroquine resistantspecies.

Primaquine (tissue schizonticidal agent) is effectively against the hypnozoites of vivax and ovale malaria and can kill gametocytes and consequently block the malaria transmission. Therefore its effect on oocyst and sporozoite formation (and thusonward transmission of treated infection) precedes its ectongametocytescarriage. It has weak activity against the asexual blood stage of vivax malaria. Primaquine is indeed used to achieve complete elimination of relapsing malariadue to vivax or ovale, in combination with a blood schizontocide for the erythrocytic parasites.

Proguanil is a biguanide compound that is active agains tall stages of Plasmodium.SPhas been the drug of choice for IPT in first and second trimester pregnancy and in infants living within malaria-endemic areas.

Classification of Class and Drugs:

Class	Drugs
4-Aminoquinolines	Chloroquine, amodiaquine, hydroxychloroquine
8-Aminoquinoline	Primaquine, pamaquine, pentaquine, isopentaquine
4-quinolinemethanols	Quinine, quinidine,mefloquine
Phenanthrene methanol	Halofantrine
Artemisinin derivatives	Artemisinin,artemether,artesunate,arteether
Antimetabolites	Proguanil, pyrimethamine,atovaquone,dapsone
Antibiotics	Tetracycline, doxycycline, minocycline
Diaminopyridines	Pyrimethamine

Atovaquone is active against all Plasmodium species. It is ubiquinone analogue and acquires resistance related to a single mutation of cytochrome b gene of theparasite.Artemisinin (endoperoxidesesquiterpene lactone) is a potent and fast acting blood schizonticidal killing all parasite stages. Falciparum resistance to them has now been detected in 5 countries in the Greater MekangsubregionCambodia Lao People's Democratic Republic Myanmar Thailandand Vietnam. These resistant strains have the capacity to spread to different parts of the world including Ethiopia and to subsequently become a global threat for malaria control and treatment.

WHO recommends artemisininbased combination therapies (ACT) for the treatment of uncomplicated malaria caused by falciparum parasite or by chloroquineresistant vivaxovalemalariaeand knowlsi. Atovaquone-proguanil may be considered for the treatment of uncomplicated malariaintravelersoutsidemalaria endemic careas.Quinine plus clindamycin is used for uncomplicated malaria treatment in the first trimester of pregnancy.In Ethiopia artemetherlumefantrine (Coartem) is suggested as the firstline drug for uncomplicated falciparum malaria and chloroquine for other species, but oral quinine isconsidered as a second option.

Quinidine plus doxycycline, tetracycline, or clindamycin is the preferred drug in the USA to treat severe malaria.Injectableartesunate is the preferred drug, and intramuscular artemether is an alternative drug. If these two drugs are not available, injectable quinine can be used to manage severe malaria.

Conclusion :

Malaria, an ancient human disease, is still a major source of illness and death in endemic regions, affecting both children and adults. Falciparum and vivax malaria pose a significant threat to community health. Malaria transmission is still dynamic over the world, despite the decline in prevalence and incidence. As a result, malaria control necessitates an integrated approach that includes vector control as well as rapid treatment with potent antimalarial drugs. However, developing resistance to control methods and currently available antimalarial medications makes fighting malaria a difficult task. Despite decades of intensive research, there are currently no licenced malaria vaccines available. Despite the fact that numerous medications are in development, the majority of them are unable to kill both gametocytes and hypnozoites.Resistance to conventional antimalarials will spread across Africa, including Ethiopia, if the past is any indication. Success and resistance are reshaping the malaria landscape, necessitating the development of new instruments and techniques. As a result, the world urgently requires new, safe, and efficient insecticides and medications, as well as vaccinations, to combat the present resistance problem.

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