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A REVIEW ON MALARIA: BIOLOGY NATURE

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ABSTRACT

Malaria is one of the leading causes of death worldwide. According to the World Health Organization's (WHO's) world malaria report for 2018, there were 228 million cases and 405,000 deaths worldwide. Malaria, caused by Apicomplexan parasite, is an old disease and continues to be a major public health threat in many countries. Six *Plasmodium* species are recognized as the etiology of human malaria, of which Plasmodium falciparum is popular in East and Southern Africa. Malaria is transmitted mainly through *Anopheles gambiae* and *Anopheles funestus*, the two most effective malaria vectors in the world. Antimalarial drugs are key tools for the control and elimination of malaria. Recent decreases in the global malaria burden are likely due to the deployment of artemisinin-based combination therapies. Antimalarial drugs used in the treatment of malaria caused by species other than Plasmodium falciparum also have adverse effects. The objective of this review is to identify the different molecules used in the treatment of these forms of malaria and the adverse effects they cause in humans. Malaria parasite has a complex life cycle that takes place both inside the mosquito and human beings. Generally, diagnosis of malaria is classified into clinical and parasitological diagnoses. Various diagnostic techniques were adopted rapid diagnostic testing (RDT), loop-mediated isothermal amplification (LAMP), and polymerase chain reaction (PCR) the Polymerase Chain Reaction (PCR) is not routinely used because equipment and reagents are expensive and requires highly skilled personnel. Loop-mediated isothermal amplification (LAMP) is a

relatively new molecular diagnostic tool for malaria with all the advantages of PCR (sensitive and specific) without the mentioned disadvantages.

KEYWORD: Malaria, antimalarial drugs, Diagnosis, rapid diagnostic tests, Plasmodium Falciparum, Plasmodium vivax.

INTRODUCTION

Despite important gains in some areas, malaria remains a major problem in most of the tropical world, and it continues to cause hundreds of millions of illnesses and hundreds of thousands of deaths each year.[1] Malaria is caused by infection with a single-cell parasite, Plasmodium. Four Plasmodium spp. cause malaria in human beings: Plasmodium falciparum, P. vivax, P.ovale, and P. malariae.[2] Most serious illnesses and deaths from malaria and also most drug-resistant infections are due to infection with Plasmodium falciparum.[14] The most virulent human malaria parasite.[1] Malaria is transmitted by the bite of a female Anopheles mosquito Malaria is endemic in 104 tropical and subtropical countrie.[3] More than half of the world's population **lives** in areas where malaria transmission occurs.[15] The disease exacts a heavy public health burden on communities in parts of Africa, Asia, and Central and South America.[3] *P. vivax* and *P. ovale* have dormant liver stages that can cause relapses months to years. after an infection is cleared, so they need to be treated with an additional agent that can clear this stage.[16] Malaria symptoms are highly variable and may include chills, sweating, headache, lethargy, myalgia, and cough. Gastrointestinal symptoms can be severe, such as nausea, vomiting, diarrhea, and abdominal pain Physical signs such as pallor, tachycardia, hepatosplenomegaly, jaundice, and increased respiratory rate may also be present in a malaria infection.[17] In cases of cerebral malaria, altered mental status is observed. Single-molecule approaches to malaria treatment have been shown to significantly contribute to drug resistance and are not recommended.[18] For example, at present, treatment of uncomplicated malaria is not recommended for any plasmodial species, is effectively treated in 3 days with an artemisinin-based combination therapy (ArtemisininbaseCombination Therapy" ACT ") that combines a fast-acting artemisinin derivative with a longer-acting antimalarial drug (artemether + lumefantrine, artesunate + amodiaquine, artesunate + mefloquine, artesunate + SP, dihydroartemisinin + piperaquine) Single-molecule approaches to malaria treatment have been shown to significantly contribute to drug resistance and are not recommended.[19] For example, at present, treatment of uncomplicated malaria is not recommended for any plasmodial species, is effectively treated in 3 days with an artemisinin-based combination

therapy (Artemisininbase Combination Chloroquine (CQ) is still the standard drug for *P. vivax*, *P. malariae*, and *P. ovale* in most countries , but *P. vivax* resistance to CQ is emerging in parts of sub-Saharan Africa and Southeast Asia Therapy" ACT ") that combines a fast-acting artemisinin derivative with a longer-acting antimalarial drug (artemether + lumefantrine, artesunate + amodiaquine, artesunate + mefloquine, artesunate + SP, dihydroartemisinin + piperaquine) The World Health Organization (WHO) also recommends the use of ACTs for the treatment of *P. vivax* in affected areas. The use of CQ is avoided in many African countries because of frequently experienced side effects. Artemisinin derivatives are generally well-tolerated.[3]

Life cycle of malaria parasite

The human malaria parasite has a complex life cycle as shown in Figure. Motile infectious form, Plasmodium sporozoite, is passed to individuals when the insect bites the skin, the thread-like sporozoites are carried to the liver by the circulatory system.[18] Over a period of 7–12 days, the sporozoites grow into schizonts and can develop up to 30,000 merozoites, which rupture hepatocytes.[29] On the other hand, some *vivax* and *ovale* sporozoites turn into hypnozoites, a form that can remain latent in the liver for months or years and cause relapses in infected people. Interestingly, recurrence of *falciparum* malaria was reported in patients some years after leaving an endemic area.[20] It tells that, at least occasionally, *falciparum* has a dormant stage. The asexual cycle begins, with the merozoites invading RBC to grow by consuming hemoglobin. Within the host RBC, the parasite undergoes development from the early ring stage to late trophozoite and then after mitotic divisions to the schizont stage, which contains 6 to 32 merozoites, depending on the parasite species.[21] When the erythrocytic schizont ruptures, the released merozoites continue the life cycle by invading other RBCs. Cyclical fevers are typically happening shortly before or at the time of RBC lysis as schizonts rupture to release new infectious merozoites. it occurs every 48 h in tertian malaria and every 72 h in quartan malaria infection.[24] During this repeated cycle, some merozoites differentiate into male and female sexual forms known as erythrocytic gametocytes with one nucleus and then awaiting the arrival of a bloodseeking female *Anopheles* mosquito. Intake of gametocytes by the mosquito induces gametogenesis. flagellated forms of microgametes, formed by exflagellation, penetrate or fertilize the macrogametes generating zygotes. Zygotes change into ookinetes and then become a round oocyst. Inside the oocyst, the nucleus divides repeatedly, with the formation of a large number of sporozoites and enlargement of the oocyst .When the sporozoites are fully formed,

the oocyst bursts, releasing the sporozoites into the haemocoel (The mosquito's body cavity). sporozoites migrate to the salivary glands, thus completing the life cycle Entrance of the sporozoites from the mosquito's salivary glands into a new human host perpetuates the malaria life cycle.[4]

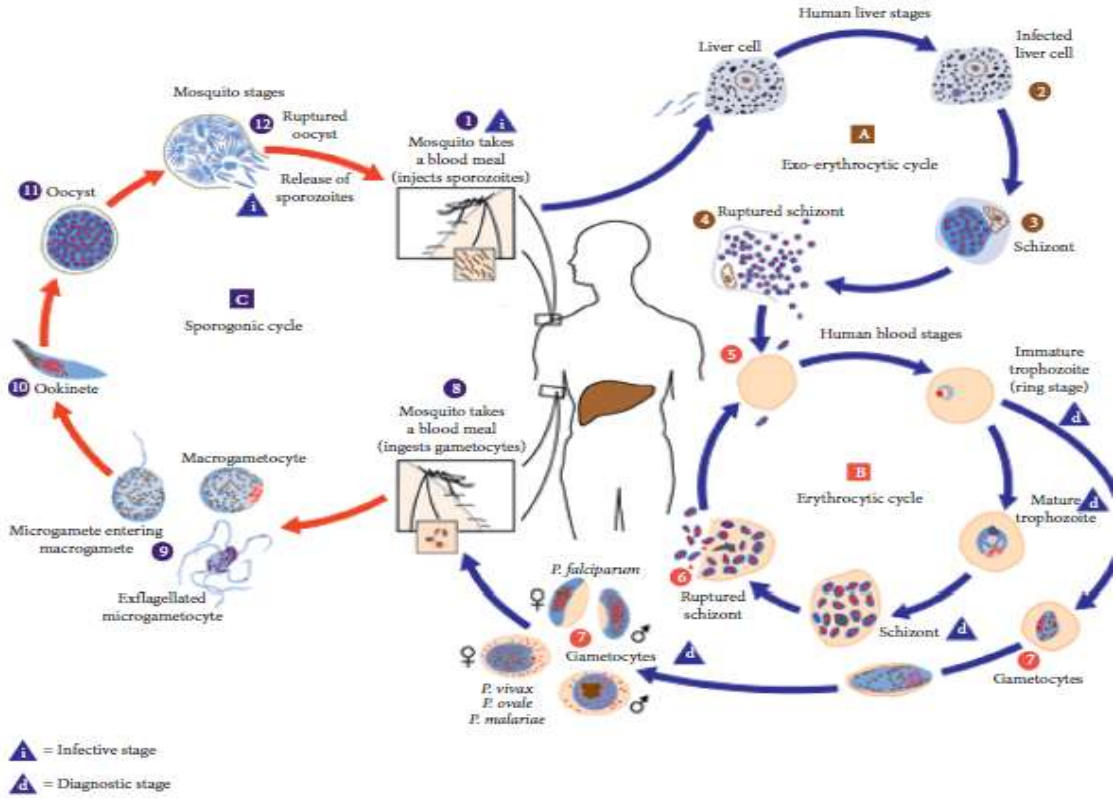


Figure Life cycle of malaria parasites.

Antimalarial drugs

Antimalarial drugs act principally to eliminate the erythrocytic stages of malaria parasites that are responsible for human illness. Drug regimens for treatment of the two most prevalent malaria parasites, P. falciparum and P. vivax, are different. artemisinin-based combination therapy (ACT) is now recommended for the treatment of uncomplicated falciparum malaria in nearly all areas. Chloroquine plus primaquine remains the first-line regimen for radical cure of vivax malaria in most regions. ACT consists of a potent artemisinin component, which rapidly clears most parasites, plus a longer acting partner drug, which eliminates remaining parasites and limits selection of artemisinin resistance.[19] The ACTs recommended by the World Health Organization (WHO) are artemether/lumefantrine, artesunate/ amodiaquine, artesunate/mefloquine, dihydroartemisinin/piperaquine artesunate/pyronaridine, and artesunate/sulfadoxine– pyrimethamine.[26] Multiple drugs are used to prevent malaria.[(1).] Antimalarial drugs could be classified as either single or combined therapies, as shown in the

Table 1 below.[5] Available antimalarial drugs can be divided into multiple classes (Table 1). The 4 aminoquinoline, chloroquine, was the gold standard for the treatment of uncomplicated malaria for many years, but it is no longer appropriate for the treatment of falciparum malaria in nearly all areas because of drug resistance.[13] P. vivax prompted a policy change to ACTs for vivax malaria. Amodiaquine appears to be subject to the same resistance mechanisms as chloroquine, but due to improved potency it provides adequate efficacy against many chloroquine-resistant parasites, and it is a component of the widely used ACT artesunate/ amodiaquine.[22]

Classification of antimalarial drugs

	Drug Name	Mechanism of Action	Use
1.	Chloroquine	Accumulate in the digestive vacuole of parasite inhibition of heme detoxification	Treatment in falciparaum infections where chloroquine remain senstive
2.	Amodiaquine	Accumulate in the digestive vacuole of parasite inhibition of heme detoxification	Treatment of non-severe falciparum infections where chloroquine resistance has emerged
3.	Quinine	Accumulate in the digestive vacuole of parasite inhibition of heme detoxification	Treatment of severe malaria and multidrug resistance falciparaum infections ,Treatment of malaria during pregnancy in the first trimester
4.	Mefloquine	Accumulate in the digestive vacuole of parasite inhibition of heme detoxification	Treatment of non-sever falciparum where chlorquine resistance has emereged Chemoprophylaxis in region where chlorquine resistance
5.	Atovaquone	Targets the cytochrome, located in the inner mitrochondrial membrane of the parasite, inhibition of the respiratory reaction of parasite	Treatment of multidrug resistance falciparaum infections
6.	Sulfadoxine, Sulfene	Inhibit the dihydropteorate synthetase enzyme, inhibition of folate biosynthesis	Treatment of non-sever falciparum in combination with pyrimethamine
7.	Artimisinin	Inhibition of protein synthesis pathway	Combination with qunine increase efficacy of treatment where qunine resistance has emerged

Antimalarial drug resistance

The efficacies of many antimalarial drugs are limited by drug resistance, and recent evidence suggests that parasites are becoming resistant to the newest agents. ICEMR surveillance sites

is highly valuable.[23] Resistance can be assessed by clinical trials comparing antimalarial efficacies of different agents.

Resistance to quinine

Resistance to quinine, the oldest antimalarial drug, was reported first in Brazil and later in southeast Asia. Quinine resistance is associated with polymorphisms in several transporters.[16] As stated earlier, SNPs in pfmdr1, pfcrt, and pfmrp1 are linked to decreased sensitivity to quinine. pfmdr1 gene amplification can also lead to quinine resistance Recent studies evaluating associations between polymorphisms in a pfnhe1 microsatellite, in vitro parasite sensitivity, and clinical responses to various drugs have been inconsistent, but these polymorphisms appear to have a modest impact on sensitivity of parasites to quinine, and possibly other drugs.[22]

Resistance to malarone

Atovaquone is a potent inhibitor of electron transport, and studies identified the target of this drug as the critical quinone-binding sites of cytochrome.[24,27] When the drug is used alone, resistance develops rapidly and recrudescence after therapy is common. Resistance is conferred by single-point mutations in the cytochrome b (Pfcytb) gene. Pfcytb mutations 268S and 268N were associated with Malarone treatment failure. However, treatment failure has also been reported in the absence of these mutations.[1,27]

Pregnancy

After the development of infection in a pregnant woman who has never had malaria during pregnancy the infecting parasites are unlikely to be picked up by the reaction.[25] Immune response to surface-expressed antigens, and therefore if resistance to mutant occurs, it does not need to be present in a variant subpopulation to ensure its survival.[25] There are even data that suggest that pregnant women are more attractive to mosquitoes.[30,15] Pregnant women are widely recommended for malaria prophylaxis, but the only drugs that are considered safe are chloroquine, which is not effective against P. falciparum almost everywhere, and proguanil, the drug. Prophylaxis for pregnant women has given way to putative intermittent therapy (IPT) with SP, in which a single therapeutic dose is administered two or three times during pregnancy, Antimalarial resistance is selected using drug concentrations sufficient to inhibit the multiplication of susceptible, but not resistant, parasites Some antimalarials (particularly lumefantrine, halofantrine, atovaquone and to a lesser extent mefloquine) are lipophilic, hydrophobic, and quite variable in absorption.[6]

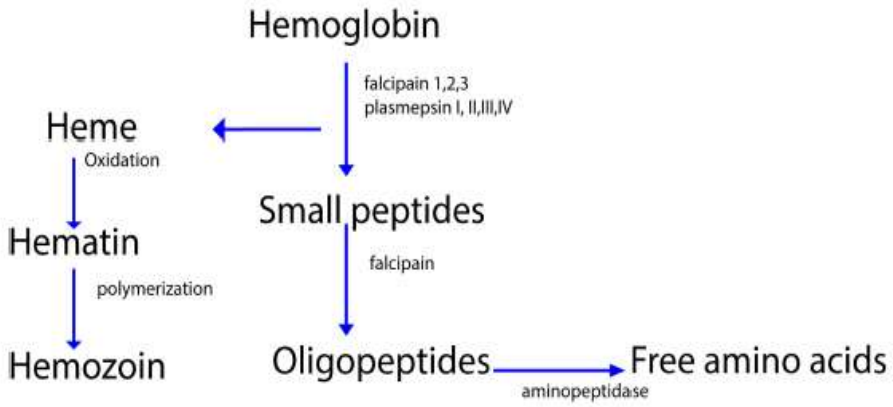


Fig. Degradation of hemoglobin by protease.

Malaria diagnostic methods

The diagnosis of malaria consists of the identification of malaria parasites or antigens in the host's blood Different methods can be used to achieve this, including the use of microscopy, rapid diagnostic tests (RDTs), loop-mediated isothermal amplification (LAMP), and polymerase chain reaction (PCR).[8] Malaria diagnosis involves identifying malaria parasites or antigens/products in patient blood. Malaria is a potential medical emergency and should be treated accordingly. Delays in diagnosis and treatment are leading causes of death in many countries.[9]

Rapid diagnostic tests (RDT)

Since the World Health Organization (WHO) recognized the urgent need for new, simple, quick, accurate, and cost-effective diagnostic tests for determining the presence of malaria parasites, to overcome the deficiencies of light microscopy, numerous new malaria-diagnostic techniques have been developed.[28] This, in turn, has led to an increase in the use of RDTs for malaria, which are fast and easy to perform, and do not require electricity or specific equipment.[9] To address the limitations of microscopy and PCR-based techniques, other methods are being explored.[29] To be validated, these methods must be benchmarked against microscopy or PCR analysis and against reference strains. For example, rapid diagnostic tests (RDTs), according to the WHO (1999), must be able to reliably detect 100 parasites ml 21, equivalent to 0.002 % parasitaemia, and must have a minimum sensitivity of 95 %, compared with microscopy, and a minimum specificity of at least 90 % for all malaria species. Malaria RDTs were developed in the mid-1990s.[10]

Rapid diagnostic tests are immune-chromatographic lateral flow devices that are extensively used for the diagnosis and prevalence estimation of malaria based on the principle of detecting malaria antigens in the blood.[26] The technique involves the application of a blood specimen to the test card (or cassette, depending on the manufacturer) followed by a buffer reagent (3–5 drops).[8] Three types of antigens have been employed in this method, Plasmodium histidine-rich protein (HRP) 2 (pHRP-2), Plasmodium lactate dehydrogenase (pLDH) and Plasmodium aldolase. pHRP-2 is specific to P. falciparum, while pLDH and Plasmodium aldolase are found in all species More than 90% of commercially available RDTs target pHRP-2.[11] Antibodies immobilized on the surface of the test strip detect these parasitic antigens when the blood migrate across it. Each RDT contains a positive control to indicate the validity of the test. Currently available species-specific RDT sare only able to identify P. falciparum and P. vivax species. For other species, the RDT is only able to indicate the presence of the parasite alone without speciation.[11] RDTs remain a useful and widely deployed diagnostic tool for malaria surveillance and control. RDTs remain a useful and widely deployed diagnostic tool for malaria surveillance and control.[12]

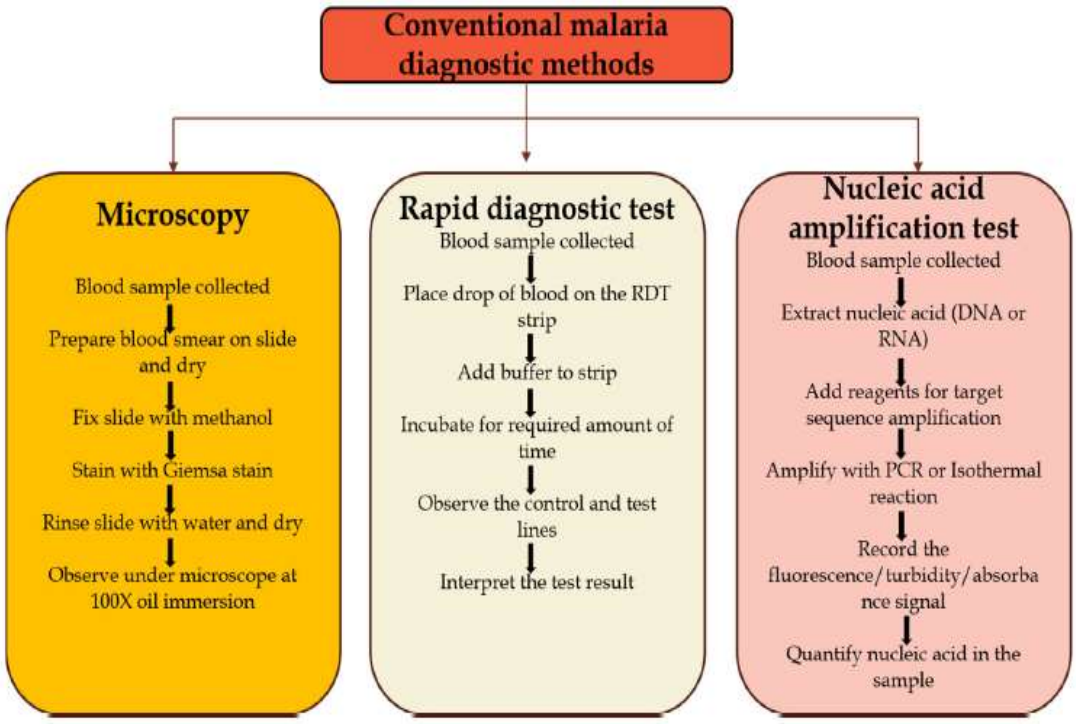
Loop-mediated Isothermal Amplification (LAMP)

The LAMP technique is claimed to be a simple and inexpensive molecular malaria-diagnostic test that detects the conserved 18S ribosome RNA gene of P. falciparum. Other studies have shown high sensitivity and specificity, not only for P. falciparum, but also P. vivax, P. ovale and P. malariae.[9] Molecular methods of malaria diagnosis include polymerase chain reaction (PCR) and loop-mediated isothermal amplification (LAMP) These methods display great potential in areas with a low density of infections which can easily be missed by RDTs.[8] LAMP is a relatively newer method for nucleic-acid amplification first described in 2000, and further modified for ease of visualization of amplified product using a fluorescent or colorimetric dye such as calcein and hydroxy naphthol blue (HNB) respectively.[11] LAMP was performed to amplify Plasmodium DNA to determine if there was Plasmodium DNA (indicator of malaria infection) in the blood samples. LAMP was run on the same 115 DNA samples used for running PCR. A total of 15µl of DNA template was mixed with pan primers (FIP and BIP comprising F1, F2 and B1, B2 priming sites, correspondingly and two "Displacement primers" F3 and B3) and the Bst polymerase (from Bacillus stearothermophilus) that comes dried in the LAMP tube caps. The LAMP tubes were inverted 5 times to mix the DNA template with the reagents in the LAMP tube cap.[29] A thermo-cycler was used to amplify DNA at 65˚C for 45 minutes. Visualization of the results was by

comparing change in turbidity using the negative and positive controls as references by fluorescence under UV light on a table top.[13]

PCR technique

PCR-based techniques are a recent development in the molecular diagnosis of malaria, and have proven to be one of the most specific and sensitive diagnostic methods, particularly for malaria cases with low parasitemia or mixed infection.[9] PCR method amplifies the parasite deoxyribonucleic acid (DNA), thus resulting in high sensitivity (0.004 parasites/µl) When compared with microscopy, PCR-based assays have 100-fold greater sensitivity, especially for low parasitemia infection.[8] PCR-based methods identify the presence of malaria target genes in a blood sample settings.[27] The PCR method also does not provide an easy method of estimating parasite burden that is often used by clinicians.[11] Although PCR appears to have overcome the two major problems of malaria diagnosis-sensitivity and specificity- the utility of PCR is limited by complex methodologies, high cost, and the need for specially trained technicians. PCR, therefore, is not routinely implemented in developing countries because of the complexity of the testing and the lack of resources perform these tests adequately and routinely. Quality control and equipment maintenance are also essential for the PCR technique, so that it may not be suitable for malaria diagnosis in remote rural areas or even in routine clinical diagnostic settings.[9,28]



Flowchart of the currently used malaria diagnostic methods.

CONCLUSION

Malaria, an ancient human disease, remains an important cause of illness and death in children as well as adults in endemic countries. *Falciparum* and *vivax* malaria produce a big challenge in the health of the community. Several products with adverse effects are widely used in the prophylaxis and treatment of malaria caused by species other than P. falciparum. Regardless of the plasmodial species involved, the molecules that can be used are the same Drugs such as chloroquine and proguanil are very rarely associated with serious adverse effects at the recommended doses. Unfortunately, in some parts of the world, these products are no longer effective prophylactic agents. Although current diagnostic methods in use are not all perfect, they continue to play important roles in dealing with the current global malaria situation and to decrease the incidence of malaria. RDTs and PCR are not being utilized to their full capacity due to several barriers and limitations, such as cost, trained personnel, access to equipment, and unreliable electricity. RDTs are a good source of DNA for PCR, LAMP and other molecular techniques. This overuse and over-prescription of drugs is likely contributing to the emergence of anti-malarial resistant Plasmodium parasites. Antimalarial drug resistance poses a very significant threat in the fight against malaria and if not taken care of well in time, could prove to be the undoing of most malaria control programmes . ACT seems to be effective in most of the cases. It will be important to build trust between communities and health workers and to ensure hospitals' and pharmacy retailers' adherence with recommendations based on test results. This will require a multi-sectoral approach and political will to advocate for the implementation of control and elimination strategies.

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