GSC Biological and Pharmaceutical Sciences

eISSN: 2581-3250 CODEN (USA): GBPSC2

Cross Ref DOI: 10.30574/gscbps

Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

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Malaria: A comprehensive review of its biology, diagnosis, treatment and prevention

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GSC Biological and Pharmaceutical Sciences, 2025, 31(03), 244-250

Publication history: Received on 07 May 2025; revised on 18 June 2025; accepted on 21 June 2025

Article DOI: https://doi.org/10.30574/gscbps.2025.31.3.0239

Abstract

Malaria remains a significant public health concern globally, particularly in Africa. The disease is caused by Plasmodium genus protozoan parasites, with six species known to infect humans. Despite advances in diagnosis and treatment, malaria continues to cause significant morbidity and mortality, especially among vulnerable populations such as pregnant women and children under five years old. This review aims to provide a comprehensive overview of malaria, including its biology, diagnosis, treatment, and prevention. Here discusses the complex life cycle of Plasmodium parasites, the various diagnostic techniques available, including rapid diagnostic tests, biomarkers, and molecular diagnosis, and the treatment, including artemisinin-based combination therapies. The importance of vector control and prevention strategies, including long-lasting insecticidal nets and indoor residual spraying. Also, the recent advances in malaria vaccine development, including the RTS, S vaccine, which has shown promise in preventing malaria in children. By synthesizing evidence from multiple fields, this review aims to inform future research directions and improve malaria control and prevention efforts.

Keywords: Malaria; Plasmodium Species; Artemisinin-Based Combination Therapies; Loop-Mediated Isothermal Amplification

1. Introduction

Since ancient times, malaria has been acknowledged as a severe health concern. Plasmodium genus protozoan parasites are the cause of this illness [1]. The name malaria is derived from the Italian word "mal'aria," meaning "bad air," to allude to the disease's connection to swampy environments [2]. Human malaria is caused by six species of Plasmodium: Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, Plasmodium ovale curtisi, P. wallikeri and Plasmodium knowlesi. Plasmodium knowlesi is a serious human pathogen in some parts of South East Asia, despite being zoonotic [3]. Malaria, which is more prevalent in Africa, continues to be the most lethal tropical infectious disease. In 2018, malaria was responsible for about 228 million cases and 405,000 fatalities globally, with sub-Saharan Africa generating 93% of these cases.

In 2019, malaria killed 409,000 people, while the total number of cases increased from 228 million to 229 million. In Côte d'Ivoire, malaria continues to be a major public health concern and the most frequent reason for consultations in health facilities. It is responsible for about 43% of morbidity, 11.8% of deaths, 40% of absences from school, 50% of loss of agricultural revenue, and 62% of hospitalizations. All Ivorian inhabitants are vulnerable to malaria, according to the World Malaria Report, with pregnant women and children under five years old being the most vulnerable [4]. The biology of malaria is complex. Model systems utilizing Plasmodium berghei (Pb) and P. yoelii (Py) enhance the awareness of pre-erythrocytic (PE) stage infections; however, knowledge regarding P. falciparum (Pf) remains limited. The PE stage begins when an infected female Anopheles mosquito injects a small number of infectious sporozoites (typically fewer than 100) into the host's epidermis [5].

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2. Plasmodium species diversity and complexity

Numerous Plasmodium species, including Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, Plasmodium ovale, and Plasmodium knowlesi, are responsible for human malaria. The most common species are P. falciparum and P. vivax, but P. falciparum causes the most severe sickness and almost all deaths, whereas P. vivax is usually considered benign [6]. Half of the world's population is expected to be at risk of getting malaria because of P. vivax's remarkable ability to experience long-lasting remission and tolerance of cooler climates than those preferred by strictly tropical Plasmodium species. Evidence suggests that P. vivax may have been a more virulent parasite before the development of modern treatment, even though P. falciparum parasites account for the bulk of malaria-related deaths in the current era. Death records as far north as England suggest that in the nineteenth century, P. vivax probably decreased the average lifespan from 58 to 33 years. More recently, research has revealed that P. vivax can cause severe malaria syndromes that have long been attributed exclusively to P. falciparum. Although P. vivax has considerably affected human health, it remains chronically understudied relative to P. falciparum. The ability to continuously culture P. falciparum in laboratory conditions, compared with the inability to do so for P. vivax, along with the distinct mortality rates of the two species, has resulted in major differences in our comprehension of nearly all aspects of their biology [7].

3. Malerial parasite life cycle and biology

The intricate life cycle of Plasmodium parasites includes both asexual reproduction in the human host and sexual reproduction in the Anopheles vector. When a human is bitten by an infected Anopheles mosquito, sporozoites are transferred via the skin [8]. By implanting sporozoites in the subcutaneous capillaries, a female Anopheles mosquito carrying the infection initiates the Plasmodium life cycle. It takes the sporozoites 45 minutes to reach the hepatocytes. Preerythrocytic liver stage, which lasts one to two weeks, is hence the initial stage of the disease. As sporozoites multiply in the hepatocytes, schizonts with a high concentration of merozoites are produced.

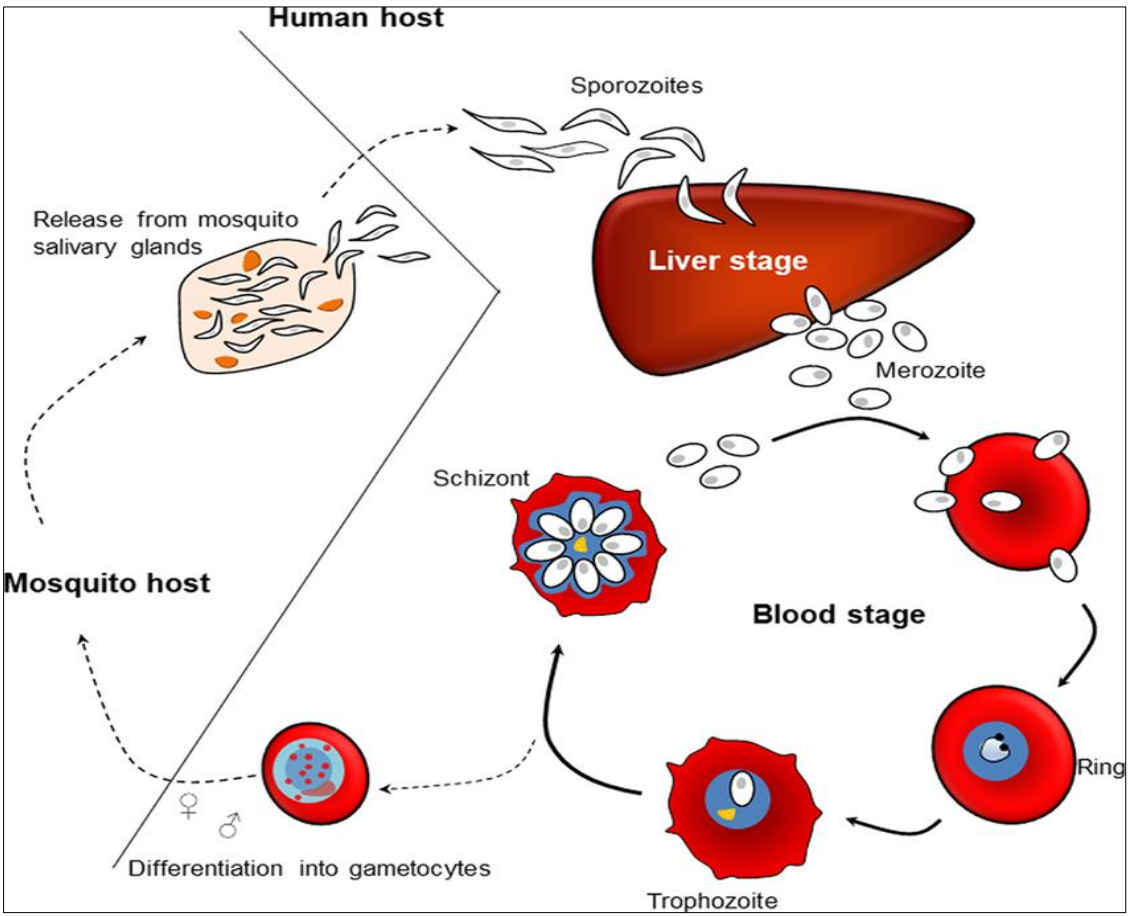

Figure 1 Life cycle of Plasmodium [10]

The merozoites are discharged into the bloodstream following the adult schizonts' breakage, where they parasitise red blood cells and proliferate throughout the body. The erythrocyte cycle is repeated when merozoites develop into trophozoites and schizonts, which then release more merozoites to infect more erythrocytes. The next stage, referred to as the blood stage, is distinguished by a series of cycles of asexual reproduction. Malaria can take anywhere from seven to thirty days to incubate. Plasmodium species infections can cause simple malaria, severe malaria, asymptomatic parasitemia, and even death. The three stages of a normal malaria attack are chilly, heated, and sweating [9].

4. Advancement in malarial diagnostic treatment

4.1. Rapid diagnostic techniques

Rapid diagnostic tests (RDTs) and microscopy remain the primary means for confirming clinical malaria diagnosis in most endemic nations. Additionally, they are frequently employed in prevalence surveys. In other situations, such as active and reactive case detection and screening pregnant women, they are similarly less useful. Clinical Plasmodium falciparum infections are more sensitive to RDTs because they are usually linked to higher parasite densities and, consequently, higher anti-genemia levels. Sensitivity is significantly decreased though, when asymptomatic infections are discovered [11]. One of the biggest benefits has been the use of malaria RDTs in places that are typically underserved by traditional medical care. Malaria is now routinely tested for using RDTs, and patients are treated according to the test results by CHWs (community health workers), who are often volunteers trained to provide certain basic health services. The only major infectious disease that CHWs now routinely check for as part of integrated community case management is malaria. CHWs can enhance access to healthcare by offering a level of differentiated management of febrile illness by distributing oral rehydration salts, zinc, antimalarial drugs, and malaria testing to the general people [12].

4.2. Biomarkers

Chemicals that may be subjectively analyzed and assessed as indicators of biological processes, pathogenic stress, or therapeutic response are known as biomarkers [13]. Biomarkers are now crucial for improving the accuracy and effectiveness of malaria diagnosis. Certain chemicals, proteins or other quantifiable signs found in a patient's bodily fluids or tissues are known as biomarkers. When it comes to malaria, biomarkers can indicate the type of Plasmodium species that is causing the infection, whether the parasite is present and even the disease's stage [14]. The three types of biomarkers are imaging, cellular, and molecular. Chemicals that may be subjectively analyzed and assessed as indicators of biological processes, pathogenic stress or therapeutic response are known as biomarkers [13].

4.3. Molecular Diagnosis

Finding submicroscopic infections of the two main species, P. falciparum and P. vivax, which serve as disease reservoirs and can only be found using extremely sensitive techniques, is a crucial part in diagnosing and curing malaria. The most promising techniques for identifying submicroscopic Plasmodium infections and differentiating between mixed infections are molecular diagnostic techniques. Several PCR-based techniques, such as PCR-restriction fragment length polymorphism, multiplex PCR, nested PCR, loop-mediated isothermal amplification, quantitative real-time PCR (qPCR) and more recently, droplet digital PCR (ddPCR), have been developed for the diagnosis of malaria to achieve this [15]. These molecular assays, which are based on real-time quantitative PCR, contain closed systems and quantitative features that lower labour costs, time, reagents, and contamination risk in comparison to traditional PCR. With a detection limit of less than two parasites per millilitre and the ability to detect multiple targets simultaneously in a single run to boost the test's sensitivity and specificity, multiplex real-time PCR has improved the ability to detect mixed Plasmodium infections and Plasmodium species in cases of low parasitaemia [16].

4.4. Microscopy

The gold standard method of diagnosing malaria is to look at blood smears under a microscope to look for malaria parasites. To give the parasites a unique look, the material is typically treated with Giemsa or Leishman staining before analysis. A quick and easy method for identifying the active form of parasites in blood is the Giemsa staining routine for malaria blood films [17]. A drop of blood is placed on a glass plate and combined with Giemsa staining solution to enhance the visibility of parasites within red blood cells under a microscope. This is conducted to determine malaria infection by light microscopy. Additionally, blood smears, both thick and thin, are utilized to diagnose malaria. Whereas a thin smear finds malaria species and parasite stages, a thick smear usually indicates the presence of the parasite in blood. A competent microscopist can identify the quantity of infected cells in a single blood film in 20 to 30 minutes by analyzing the variations in red blood cell size, shape, and colour [18]. Determining parasitemia through microscopic examination has certain drawbacks, including being time-consuming, requiring skilled personnel and heavily relying

on the observer's performance, which might produce inconsistent and variable results. Additionally, the quality of the Giemsa-stained PB smear, which may fluctuate and is a contributing factor to irregular parasite density monitoring [19].

4.5. Loop-Mediated Isothermal Amplification

For the diagnosis of malaria, Loop-Mediated Isothermal Amplification (LAMP) has shown promise, especially in places with inadequate medical facilities. Without the requirement for the heat cycling apparatus required for PCR, LAMP is an isothermal nucleic acid amplification method that enables DNA or RNA to be amplified at a steady temperature. Because of its simplicity and low infrastructure requirements, LAMP is better suited for field use [20]. An empirical analysis indicates that workers with merely three days of training in LAMP processes and no prior experience in molecular diagnostic techniques can achieve results from LAMP within 60 to 90 minutes of initiating sample processing. Therefore, one of the top priorities for the elimination of malaria is the development of field-ready assays that can identify infection early enough to allow for treatment. Evaluating the diagnostic accuracy of LAMP for the identification of uncomplicated malaria in pregnancy was the aim of the current investigation [21].

5. Treatment

5.1. Artemisinin-Based Combination Therapies

Over the past 20 years, millions of lives have been saved by the routine clinical use of artemisinin-based combination treatments (ACTs) for uncomplicated Plasmodium falciparum malaria. These medications continue to be quite effective in the majority of malaria-endemic areas and are the cornerstone of antimalarial treatment. But in a number of malaria-endemic areas, including the Greater Mekong Subregion (GMS) in Southeast Asia, South America, Papua New Guinea, and most recently, Eastern Africa, artemisinin resistance has surfaced [22]. Artesunate-amodiaquine (AS+AQ), artesunate-mefoquine (AS+MQ), artesunate-sulfadoxine–pyrimethamine (AS+SP), artemether–lumefantrine (AL), and dihydroartemisinin–piperaquine (DHA+PQ) are the five artemisinin-based combinations that the WHO now recommends. Artesunate–pyronaridine (AS+Pyr), a more recent ACT, is being explored for usage in situations when existing ACTs are not working [23].

It is hypothesised that artemisinin is a prodrug. It is activated by the erythrocytes cleavage of the endoperoxide moiety by iron of heme, which results in reactive oxygen species that target the nucleophilic groups of parasite proteins and lipids. Only in the blood system, where intraerythrocytic ring-stage parasites are developed and circulated for 24 hours prior to their entry into microvessels, can the stated killing mechanism be observed in P. falciparum-infected patients.

After being exposed to artemisinin, these parasites aggregate to form pyknotic shapes resembling Howell-Jolly body insertions. These parasites are successfully extracted from the bloodstream through a process called "pitting," in which the parasites are expelled from the host's red blood cells (RBCs) as they pass through narrow endothelial slits in the spleen. Consequently, "once-infected" red blood cells return to the peripheral circulation in an unaltered state [24]. Artemisinin is no longer recommended as a monotherapy, except for parenteral treatment of severe malaria. In ACTs, residual partner drug levels destroy the remaining parasites to keep them from coming back, while artemisinin is responsible for getting rid of most of the parasite biomass during the first several days of treatment [25].

6. Control and prevention

Malaria mortality and prevalence can be significantly reduced by controlling the Anopheles vector. Long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) are the two most common traditional vector control strategies, but biological, genetic, and environmental control methods are also being investigated. Vector control has been critical throughout the malaria epidemic, from its inception to its eradication [26]. Environmental management seeks to minimize or reduce vector proliferation and human vector-pathogen contact by destroying, changing, removing, or keeping empty containers that provide a favorable habitat for the mosquito vector's developmental stages eggs, larvae, pupae, and adults [27]. These acts must form the basis of vector control. Mosquitoes can easily enter dwellings due to a variety of factors, including cracks in the walls, exposed eaves, or a lack of ceiling. These parameters were shown to have no effect on the density of interior biting mosquitoes during the intervention period when compared to the baseline period in intervention sites. Furthermore, it was revealed that places where larviciding intervention was utilized provided better protection than non-intervention areas because of features that keep mosquitos out of dwellings, such as window screens or the use of LLINs. Better housing in urban areas has long been regarded to improving mosquito bite protection [28].

7. Vaccines and immunization

On October 6, 2021, the World Health Organisation (WHO) advised that children living in areas with moderate-to-high transmission of Plasmodium falciparum (Pf) malaria get RTS, S, the first vaccine against this fatal disease. This date will be remembered as a watershed moment in malaria control. The RTS, S vaccine is currently undergoing Phase IV implementation studies in three African countries, and it is the first malaria vaccine to successfully complete Phase III clinical trials [29]. The Walter Reed Army Institute of Research (WRAIR) and GlaxoSmithKline (GSK) developed RTS, S, a subunit vaccine based on the Pf circumsporozoite protein (CSP), in 1987 [30]. This vaccine's protective effect is temporary and appears to be impacted by the level of transmission in different endemic areas. Protection necessitates constantly high levels of circulating antibodies, as evidenced by the link between reduced efficacy and lower levels of anti-CSP antibodies [31].

8. Conclusion

Malaria is a complex disease necessitating a comprehensive strategy for control and prevention. By comprehending the biology of Plasmodium parasites, enhancing diagnostic methodologies, and formulating efficient treatments, we can alleviate the burden of malaria. Vector control and preventive measures, such as long-lasting insecticidal nets and indoor residual spraying, are essential for reducing malaria transmission. The advancement of malaria vaccinations, including the RTS, S vaccine, offers potential for malaria prevention in children. Future research should be focused on enhancing diagnostic methods, optimizing treatment outcomes, and assessing the efficacy of malaria control and prevention strategies. Collaboratively, we can diminish the morbidity and mortality linked to malaria and ultimately attain a malaria-free world.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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