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Global trends in the burden of malaria: Contemporary diagnostic approaches, and treatment strategies

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Abstract

Malaria continues to pose a significant global health challenge, with 247 million cases reported in 2021, primarily concentrated in African countries. Despite substantial progress in reducing malaria cases and deaths over the past two decades, the COVID-19 pandemic disrupted healthcare systems, resulting in a temporary increase in cases and deaths in 2020. Nevertheless, between 2000 and 2021, an estimated 2 billion malaria cases and 11.7 million deaths were averted, with the majority occurring in the WHO African Region.

Accurate diagnosis remains pivotal for effective malaria treatment, and various diagnostic methods have been employed, each with its own limitations. The effectiveness of these methods varies across different populations and environments. To combat the resurgence of malaria and the limitations of current interventions, there is a growing need for new technologies and integrated diagnosis and treatment. This paper reviews global trends in the burden of malaria; contemporary diagnostic approaches, and treatment strategies.

Keywords: Malaria; Diagnosis; Microscopy; Global

1. Introduction

Malaria is not just a health problem; it's a socioeconomic burden that affects millions of lives each year. According to the World Health Organization (WHO), there were an estimated 229 million malaria cases and approximately 409,000 deaths in 2019 [1]. Many of these deaths were preventable with timely interventions, making malaria a tragic disease of missed opportunities. Malaria disproportionately affects vulnerable populations, including children under five, pregnant women and immunocompromised individuals [2, 3].

There are five known Plasmodium parasites responsible for causing malaria in humans, namely *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi* [4]. The prevalence of these Plasmodium species varies across different geographical regions. In tropical Africa, *P. falciparum* is the predominant species, where it inflicts a substantial toll on human health. In South America, *P. vivax* is more prevalent than *P. falciparum*. In the western Pacific and southeast Asia, both *P. falciparum* and *P. vivax* are common culprits behind malaria infections. Studies show that, *P. malariae*, although found

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in various regions, tends to have a lower prevalence [5,6]. In tropical Africa, there are instances of co-infection involving *P. falciparum*, *P. ovale*, and *P. malariae*, highlighting the complexity of malaria transmission and the potential for multiple parasite species to afflict individuals [7, 8]. However, *P. knowlesi* infection, on the other hand, is relatively rare and limited to a few specific forested areas in South-East Asia [9].

Eradicating malaria is an ambitious goal, but it's within reach with the right diagnosis, treatment and control resources. Achieving this goal would not only save countless lives but also yield economic benefits by reducing healthcare costs and boosting productivity. Additionally, it would alleviate the suffering of millions of families and communities burdened by this disease [10, 11]. The fight against malaria requires collective action and sustained investment. With increased funding and a united global effort, we can overcome this relentless health threat and bring an end to the suffering caused by malaria. This article explores the changing dynamics of the malaria landscape, focusing on worldwide trends in the disease's prevalence, the most recent advances in diagnostic methods, and groundbreaking approaches to treatment.

2. Global trends in the burden of malaria

Globally, there were an expected 247 million cases of malaria in 84 countries in 2021, up from 245 million in 2020, with most of this increase coming from African countries [12]. In 2015, the baseline year of the Global technical strategy for malaria 2016–2030 (GTS), there were an estimated 230 million malaria cases. Malaria case incidence decreased from 82 in 2000 to 59 in 2020 (cases per 1000 at-risk population) [12, 13]. There was no change in case incidence between 2020 and 2021. The increase in 2020 was related to the COVID-19 pandemic's impact on healthcare [14] About 96% cases of malaria worldwide were found in 29 countries, and four countries in Africa: Nigeria (27%), the Democratic Republic of the Congo (12%), Uganda (5%) and Mozambique (4%) accounted for almost half of all cases globally [12].

Globally, malaria deaths decreased from 577 000 in 2015 and to 568 000 in 2019 [15]. In 2020, malaria deaths increased by 10% compared with 2019, to a total of 625 000 [16]. Estimated deaths declined slightly in 2021 to 619 000 [17]. Due to inefficiencies in the delivery of malaria prevention, diagnosis, and treatment during the pandemic, there were 63 000 deaths between 2019 and 2021 [18]. In the African Region malaria deaths reduced from 841 000 in 2000 to 541 000 in 2018, before increasing to 599 000 in 2020. Estimated deaths decreased again to 593 000 in 2021. Globally, an estimated 2 billion malaria cases and 11.7 million malaria deaths were averted in the period 2000–2021. Most of the cases (82%) and deaths (95%) averted were in the WHO African Region, followed by the WHO South-East Asia Region (cases 10% and deaths 3%) [12].

**Table 1** Malaria cases and death by geographical region in 2021 [12]

WHO region	Malaria cases (%)	Malaria deaths (%)
African Region	95	95.7
Eastern Mediterranean Region	2.2	2.1
South East Asia	2	1.4
Others	< 1	<1

It can be difficult to estimate the burden of malaria, especially in low-income countries where data collection and reporting standards are inadequate [5]. Incomplete and discontinuous reports from single health facilities may alter final global malaria prevalence. Malaria cases are frequently over diagnosed, underdiagnosed, and not all reported cases of malaria are verified by microscopy or rapid diagnostic tests (RDTs) in hyperendemic regions, where mild symptoms of chronic malaria may result in misinterpretation [19].

Studies show that certain socio-demographic characteristics, including sex and occupation exposes individuals to a high risk of malaria infection. Ramdzan *et al.,* [20] conducted a study in Sabah, Malaysia and reported that, majority of males were more susceptible to malaria infection, as a result of their role as breadwinners and their types of occupation. They mainly belonged to the agricultural groups, including farmers, forestry site workers, and loggers, who have a higher risk of exposure to the Anopheles species mosquitoes. This study was consistent with what was earlier reported by Yusof *et al.,* [21] and Das *et al.,* [22] in India. Studies had shown that homes in the low-altitude in Bata district of Equatorial Guinea were more susceptible to malaria. Temperature is one of the most significant parameters impacted by altitude, since it has an impact on the growth and survival of the vector as well as the development of Plasmodium within the vector [23].

Several studies have linked the prevalence of malaria with similar environmental factors in other sub-Saharan countries including Ashanti Region of Ghana [24], northern Sudan [25], western Kenya [26] and Malawi [27]. In the Asia Pacific, there are three main groups of people who are more likely to contract malaria: those who work in malaria-prone areas, those who commute between non-malarious and malarious areas, and those who are at increased risk due to demographic factors including low socioeconomic class [28].

The impact of malaria burden on health is difficult to define and measure, and it is therefore as a result difficult to determine its relative cost. The past years have witnessed unprecedented efforts to monitor and control malaria, including renewed political and financial commitment and increased availability of both old and new strategies and tools [29]. However, malaria still maintain a major health issue, particularly in Africa. Important issues such as the fragility of many health systems, the rise of insecticide and drug resistance, and particularly the expected decline both in funding and in the coverage of key interventions if they are not replaced as needed, urgently need to be addressed [30].
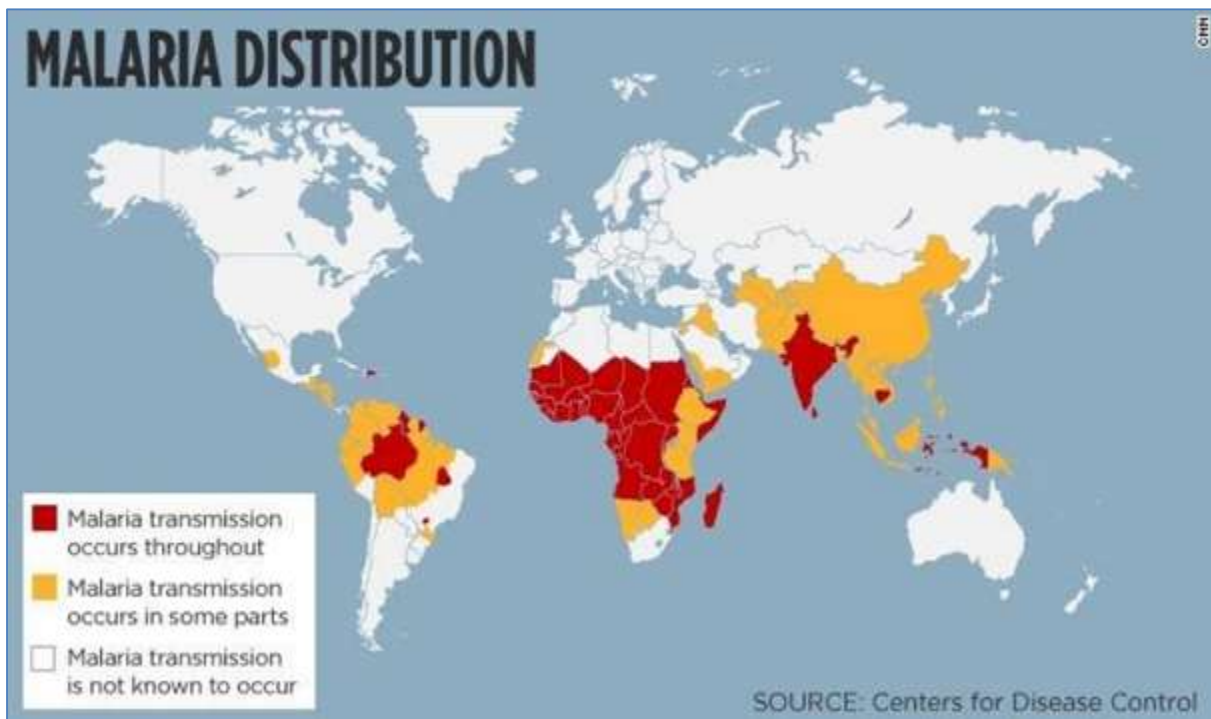
Source: Extracted from google.

Figure 1 Distribution of areas at risk of malaria transmission

3. Current malaria diagnosis methods

Accurate diagnosis is essential for malaria treatment to be successful. The need to create effective diagnosis methods has increased due to the rising prevalence of malaria worldwide, both for developed countries and developing countries where there is commonly a lack of diagnostic tools and the disease is a major social burden [31, 32]. The current diagnostic methods for identifying Plasmodium species include light and fluorescence microscopy, RDTs like immunochromatographic lateral flow assays [33], serology, Quantitative Buffy-Coat (QBC) concentration, and nucleic acid amplification techniques such as Polymerase Chain Reaction (PCR) and isothermal amplification [34]. However, the effectiveness of these methods in identifying malaria parasites varies in different population and environments [35]. Some shortcomings of these techniques have been identified, related to sensitivity, specificity, accuracy, precision, time consumed, cost-effectiveness, labor intensiveness, the need for skilled microscopists, and the issue of inexperienced technicians [36, 37].

3.1. Microscopic diagnosis of malaria

Microscopic examination of blood has been one of the most reliable ways to detect malaria ever since French scientist Laveran made the significant discovery of the plasmodium parasite [38]. Malaria is usually diagnosed microscopically

by staining thick and thin blood films with Giemsa, Wright's, or Field's stains on a glass slide, to identify malaria parasites [39].

A glass slide is covered with two drops of the patient's blood. A blood spot is stirred in a circle with the corner of the slide to prepare a thick blood film. The preparation should not be very thick, and it is then allowed to dry without fixative. After drying, the area is stained for 20 minutes with diluted Giemsa (1:20 vol/vol), and the film is then washed for 3 minutes in buffered water. The slide is allowed to vertically air-dry before being examined under a light microscope. A thin blood film is prepared by placing the smooth edge of a spreader slide in a drop of blood at an angle of 45°, the blood is then spread throughout the surface with a quick, steady sweep [40]. After that, the film is completely fixed with methanol, and air dried. After the sample has dried, it is stained for 20 minutes with diluted Giemsa (1:20, vol/vol), and any remaining stain is immediately removed by washing the slide in a jar of buffered water. The slide is then viewed with a light microscope after being allowed to air-dry [41]. This method has been widely adopted by laboratories around the world due to its ease of use, low cost, and ability to identify infected species and assess parasite density, which enables optimal malaria management [42]. However, it might be difficult to establish and maintain high-quality microscopy.

Optical microscopy has been used in several research projects since it is the gold standard for determining sensitivity and specificity in diverse demographics and epidemiological conditions [43, 44]. The sensitivity and specificity for this method is 95% and 98%, respectively. It is worth to know that, at low levels of malaria parasites, optical microscopy's sensitivity is not 100% accurate and might vary significantly, depending on the technician [45].

In a study conducted in the central Oromia Region of Ethiopia, sensitivity and specificity of microscopy were found to be 77.63% and 96.41%, respectively, in the detection of malaria parasites [46]. This finding was similar in the studies conducted in Hawassa [47] and Bahir Dar city [48] in which sensitivity and specificity were 82% and 96.2%, 83% and 97%, and 88% and 97%, respectively. Higher specificity and sensitivity were also found in Tanzania, with 84.3% and 90.8%, respectively [46]. The limit of detection for this method is approximately 50-200 parasites per μL of blood, a major limitation to this method [49].

3.2. Rapid diagnostic tests (RDTs)

In order to overcome the limitations of microscopy, a number of innovative malaria-diagnostic procedures have been created after the World Health Organization (WHO) realized the urgent need for new, easy, quick, accurate, and cost-effective diagnostic tests for determining the presence of malaria parasites [49]. Because they are quick, simple, and don't need energy or specialized equipment to perform, RDTs for malaria have become more popular [50]. For the management of malaria cases, rapid diagnostic tests (RDTs) are crucial, especially in rural areas where the disease is endemic and where it is not always possible to acquire high-quality microscopy. This has contributed to a significant increase in number of malaria RDT products since they first appeared on the market in the early 1990s [51].

More than 200 RDT product are used globally, and they all use the same three antigens: Plasmodium lactate dehydrogenase (pLDH), Plasmodium lactate-rich protein 2 (PfHRP-2), and Plasmodium aldolase (pALDO) [52]. All RDTs operate under the same fundamental concept, which allows them to identify malaria antigen in blood flowing over a membrane containing specific anti-malarial antibodies [53]. The blood is dropped into one end of an immunochromatographic strip, which is used in RDTs to identify antigens. The results are shown as lines on the strip surface. Even though the majority of RDT products can be used to diagnose P. falciparum malaria, a new RDT method has been developed to identify *P. vivax* and *P. knowlesi* malaria [54].

Excellent RDT performance has been observed for the diagnosis of malaria [55]. The sensitivity and specificity of RDT have been shown to vary significantly among reports from malaria-endemic areas [49]. Although RDTs are a highly effective and rapid method of diagnosing malaria in patients, they are now requiring to be used in combination with other methods in order to validate the results, identify the infection, and monitor the course of the disease for treatment [56].

The sensitivity of RDTs ranges from 85% to 94.8% and the specificity ranges from 95.2% to 99% [57]. RDTs have been made easier to employ in rural malaria-endemic areas because of their reliability and simplicity. RDT diagnosis in non-endemic areas is becoming more practical, which could shorten the time it takes to treat cases of imported malaria [58]. The detection limit of an ultra-sensitive rapid diagnostic test under development could be up to ten times higher than that of RDTs already in use [59].

3.3. Polymerase Chain Reaction (PCR)

One of the most accurate and sensitive diagnostic tests for malaria, particularly for cases with low parasitemia or mixed infection, has recently emerged in the field of PCR-based techniques [60]. Target genes for malaria are found in blood samples using PCR-based techniques. There are several variations of this test, including nested conventional PCR, multiplex real-time PCR, and reverse transcriptase PCR [61].

Most of these techniques focus on the 18S rRNA gene of the malaria parasite [62]. Although microscopy is frequently employed to measure parasitemia, PCR-based techniques can be used to assess suspected malaria cases and parasite species in the early stages of the disease [63]. PCR-based tests are uniquely useful to identify asymptomatic and submicroscopic patients that microscopy and RDTs miss [64].

PCR appears to be the most accurate method for diagnosing malaria, having demonstrated higher sensitivity and specificity than traditional microscopic analysis of stained blood smears [60]. However, PCR-based approaches require the purchase of a thermocycler, which may be too expensive for places with limited resources to apply the approach [65]. Additionally, it is not practical for usage in field situations and requires specialists to conduct the test. The sensitivity and specificity for the various PCR types varied from 98% to 100% and 88% to 94%, respectively, when microscopy was used as the gold standard [65]. Malaria diagnostic methods like microscopy and RDTs are frequently used and aid in malaria control efforts. But to completely eradicate malaria, more accurate detection methods are needed for preventing transmission [66].

In comparison to microscopy, multiplex real-time PCR was shown to have outstanding sensitivity of 100% (95% CI 93-100) and superior specificity of 83.2% (95% CI 77.57-87.87), according to a study by Belachew *et al.*, [67]. Similarly, in Toronto, Canada, a study conducted using multiplex real-time PCR reported comparable sensitivity of 99.4% [68]. However, the specificity reported in this study was lower than microscopy (100%) and RDT (98.5%).

3.4. Serological tests

Serological diagnosis of malaria requires the identification of antibodies of asexual blood stage malaria parasites. In recent years, immunofluorescence antibody testing (IFA) has proved to be an accurate serologic test for malaria [69]. Although IFA is time-consuming, it is highly sensitive and specific and usually regarded as the gold standard for malarial serology testing [70]. IFA can occasionally be used to provide proof of recent infection in epidemiological surveys and blood donor screening [71].

The fundamental idea behind IFA is that, after infection with any Plasmodium species, specific antibodies develop within two weeks after initial infection and continue to exist for three to six months after parasite elimination. IFA counts both IgG and IgM antibodies in patient serum samples using a particular antigen or crude antigen that has been produced on a slide, coated, and stored at -30°C until used. Titers > 1: 20 are often considered positive, and 1: 20 are considered unconfirmed. Recent infections can be categorized as those with titers > 1: 200 [72]. IFA is delicate and simple, but it takes time. Because it cannot be automated, there is a limit to the number of sera that can be examined each day. Additionally, it needs fluorescence microscopy and qualified personnel; readings might be affected by the technician's degree of expertise, especially for serum samples with low antibody titers [73].

4. Novel Approaches for Diagnosing Malaria:

Traditional Rapid Diagnostic Tests (RDTs) have been instrumental in the rapid and cost-effective diagnosis of malaria, particularly in resource-limited settings. However, a new generation of RDTs is now making strides in the field, offering enhanced sensitivity and specificity. These next-generation tests have the capacity to detect even minute quantities of Plasmodium parasites, thus significantly diminishing the likelihood of false-negative outcomes [74]. Furthermore, they exhibit the remarkable ability to differentiate between various Plasmodium species, facilitating more precise and tailored treatment approaches. Next-generation RDTs are finely tuned to detect exceedingly low levels of Plasmodium parasites, making them exceptionally sensitive [75]. This heightened sensitivity ensures that even early or low-level infections are reliably identified.

These advanced RDTs are designed to provide highly specific results, reducing the occurrence of false-positive readings [74]. This specificity is crucial in regions where multiple diseases with similar symptoms coexist. One of the distinguishing features of next-generation RDTs is their ability to differentiate between various Plasmodium species [76]. This capacity is of paramount importance, as different species may necessitate distinct treatment approaches due to variations in drug susceptibility [77]. These RDTs retain the advantages of simplicity and accessibility associated with

traditional RDTs, making them suitable for point-of-care testing [78]. They can be administered quickly and easily by healthcare workers in diverse clinical settings [77].

It is important to note that while next-generation RDTs offer tremendous promise in malaria diagnosis, they must be deployed alongside other critical components of malaria control and management, including vector control, access to effective treatment, and surveillance [79]. Additionally, continued research and development efforts are essential to further enhance the performance and accessibility of these advanced diagnostic tools [80].

Digital microscopy, when coupled with Artificial Intelligence (AI) algorithms, is revolutionizing the field of malaria diagnosis, offering numerous benefits that extend beyond conventional methods. This transformative approach enhances the accuracy of blood smear examination by automating the detection and quantification of malaria parasites in blood samples [81]. Automated digital microscopy significantly accelerates the diagnostic process. Tasks that traditionally consumed hours or even days of painstaking manual work can now be accomplished in a fraction of the time. This accelerated turnaround time is particularly invaluable in cases where swift diagnosis is paramount for effective treatment [82]. Human error is an inherent risk in manual microscopy. Factors such as fatigue, variations in expertise, and subjectivity can introduce inconsistencies in results. Digital microscopy, guided by AI, minimizes the likelihood of such errors, ensuring more consistent and dependable diagnostic outcomes [81].

Digital microscopy enables the storage of digital images of blood smears, creating archives for retrospective analysis and long-term data retention [82]. These archives serve as valuable resources for research, quality control, and the monitoring of disease trends over time. By diminishing the dependency on highly specialized microscopists and reducing labor costs, digital microscopy with AI algorithms can prove to be a cost-effective solution for malaria diagnosis, particularly in settings with limited resources [83]. However, it's important to note that the successful implementation of digital microscopy with AI algorithms requires investment in equipment, training, and quality assurance measures. Additionally, ensuring access to reliable power sources and maintaining equipment in resource-limited settings can be challenges that need to be addressed [84].

The exploration of specific biomarkers, including antigens and antibodies, represents a promising frontier in the realm of malaria diagnosis [85]. Researchers are actively developing immunoassays and serological tests that target these biomarkers, with the aim of offering rapid and dependable diagnostic solutions [86]. Biomarker-based immunoassays and serological tests are designed for speed and accuracy. They can swiftly detect the presence of malaria-specific antigens or antibodies in patient samples, facilitating rapid and reliable diagnoses [87]. This is particularly crucial in regions where timely treatment can make a significant difference in patient outcomes. Some biomarkers can differentiate between various Plasmodium species responsible for malaria [88]. This capability aids in tailoring treatment regimens to the specific species, as different species may respond differently to antimalarial drugs [89]. Certain biomarkers provide insights into the severity of the infection by quantifying the parasite load in the patient's bloodstream [90]. This information assists healthcare providers in assessing the stage and progression of the disease, enabling them to make informed decisions regarding treatment and patient care [91].

While biomarker-based diagnostics show immense promise, challenges such as test sensitivity and specificity, as well as the potential for cross-reactivity with related pathogens, need to be carefully addressed [92]. Additionally, the choice of biomarkers and the adaptation of tests to different malaria-endemic regions are critical factors in the success of these diagnostic approaches [93].

Nanotechnology has ushered in a new era in the field of malaria diagnosis by enabling the creation of highly sensitive biosensors [94]. These miniature devices are engineered to detect malaria-specific biomolecules swiftly and with remarkable precision, rendering them ideal for point-of-care testing [95].

Nanoscale materials and structures possess unique properties that enhance the sensitivity of biosensors [96]. They can detect even trace amounts of malaria-specific biomolecules, making early and accurate diagnosis possible [97]. Nanotechnology-based biosensors operate quickly, providing rapid test results. This speed is crucial in clinical settings where immediate diagnosis can lead to prompt treatment and improved patient outcomes [98]. The compact nature of nano-sensors makes them highly portable and suitable for point-of-care testing [99].

Healthcare workers in remote or underserved areas can easily carry and use these devices, bringing diagnostics closer to those in need. Some nano sensors offer the capability for real-time monitoring of disease progression. This continuous data collection can aid in treatment monitoring and decision-making. Many nano sensors are engineered to detect multiple biomarkers simultaneously, providing a comprehensive assessment of a patient's condition. This is beneficial for diagnosing co-infections or monitoring disease severity [99].

5. Treatment of malaria

Reducing the burden of malaria globally has seen significant progress, but in recent years, that progress appears to have declined. This could be a result of a number of issues, including financial goals not being met, mosquitoes becoming resistant to pesticides that are commonly used, or health system failures in specific areas [1]. Currently, the only methods of managing and preventing malaria are the widespread use of insecticide-treated nets (ITNs), the spraying of insecticide indoors or in places where larvae are found, and the use of drugs [100]. Although more can be achieved by increasing the use of these current interventions, they probably won't be enough to completely eradicate the disease from all places [101].

The first synthesized drug to become widely used to treat malaria was chloroquine (CQ). Chloroquine was introduced in the early 1940s, however *P. falciparum* resistant parasites emerged by the early 1960s [102]. After chloroquine resistant spread throughout most of malaria-endemic countries, the drug was replaced by sulfadoxine-pyrimethamine (SP) as first-line therapy [103]. However, rapid development of SP resistance was observed in Southeast Asia, Africa, and Latin America [104]. Following recommendations from the World Health Organization (WHO), artemisinin-based combination therapy (ACT) has now become the standard of care for treating malaria in endemic areas. This is because, despite their short half-life, ACT has shown to cause quick and significant reductions in parasite density [105]. However, parasites with decreased susceptibility to ACT have been reported [106].

Several malaria vaccines targeting a wide range of parasite antigens are currently being developed. Pre-erythrocytic vaccines (PEVs) fight malaria parasites as soon as they infect a person (after being released from a feeding Anopheles mosquito's salivary glands) and before the infection progresses to the harmful "blood-stage" [107]. One vaccine of this type, the RTS, S vaccine, has been evaluated in large clinical trials in sub-Saharan Africa, and has been shown to reduce the incidence of malaria in young children. However, it has relatively short duration of protection [108]. This vaccine is currently being implemented in three countries: Malawi, Ghana, and Kenya as part of an Expanded Program on Immunizations [109]. Transmission-blocking vaccinations (TBVs) are those that stop the spread of the malaria parasite by focusing on the sexual and sporogonic phases [110]. TBVs do not provide direct protection against infection: rather, they seek to prevent an infected human from transmitting malaria parasites to a feeding mosquito, i.e., preventing parasites from successfully infecting the mosquito [110].

Significant increases in funding from domestic governments, bi- and multi-lateral donors, but most notably from the Global Fund to fight malaria, have assisted the control and management of the disease [111]. Disbursements to malaria-endemic countries from bi- and multi-lateral donors increased from US$100 million in 2000 to US$1.84 billion in 2011 [112]. The majority of funding for the fight against malaria has generally come from local governments, a small number of bilateral donors like Australia, and most crucially, from donors who are routed through the Global Fund [113]. Although 41% of all persons currently at risk (PAR) for malaria live in the 34 malaria-eliminating countries, only 7% of total malaria Global Fund grants go to eliminating countries [112].

6. Novel Approaches for Malaria treatment

Efforts to discover and develop novel antimalarial drugs with innovative mechanisms of action remain a critical focus in the fight against malaria. This endeavor encompasses several approaches, including the exploration of natural products, repurposing existing drugs, and leveraging computational techniques to identify promising drug targets [114].

Natural products have long served as a valuable reservoir of potential antimalarial compounds, originating from a variety of biological sources such as plants, microorganisms, and other organisms [115]. Scientists employ a systematic approach to screen these natural substances with the goal of identifying compounds possessing anti-malarial properties [116]. This strategy draws upon the vast diversity of nature and, importantly, honors the traditional medicinal wisdom of malaria-endemic regions [117]. Nature is teeming with an immense variety of organisms, each with its unique biochemical composition [118]. This biodiversity provides a vast pool of chemical compounds that have evolved for various purposes, including defense against pathogens. Many of these natural compounds exhibit potential anti-malarial activity [119].

Indigenous communities in malaria-endemic regions have, for generations, harnessed the healing properties of local plants and natural resources to combat malaria and other illnesses [116]. The systematic screening of natural products respects and builds upon this invaluable traditional knowledge. Natural products may be combined with other antimalarial compounds to create combination therapies, which are effective against drug-resistant strains of the

malaria parasite and can help delay the emergence of resistance [120]. Ethnopharmacological studies involving collaborations with indigenous communities can yield valuable insights into traditional remedies for malaria [119]. These insights can guide the discovery of novel natural products with anti-malarial potential. It's important to note that the process of identifying, isolating, and characterizing active compounds from natural products can be labor-intensive and require specialized expertise [121]. Additionally, rigorous scientific testing, including preclinical and clinical trials, is necessary to determine the safety and efficacy of these compounds as potential antimalarial drugs [118, 121].

Drug repurposing, a strategy gaining prominence in the field of drug discovery, involves the exploration of drugs initially developed for different diseases to assess their effectiveness against malaria [122]. This approach offers several advantages, including expedited drug development, bypassing certain early-stage processes such as safety assessments, and a cost-effective means of identifying potential antimalarial candidates [123]. Repurposing existing drugs for new therapeutic purposes can significantly accelerate the drug development timeline. Since these drugs have already undergone rigorous testing for safety and regulatory approval for their original indications, they can progress more swiftly through the drug development pipeline [124]. Drug repurposing can encompass a wide range of drug classes, including antivirals, antibiotics, and immunosuppressants [122]. This diversity increases the chances of identifying compounds with anti-malarial properties.

As drug resistance continues to pose a significant challenge in malaria control, repurposing drugs with different modes of action can be a vital strategy to combat resistant strains of the malaria parasite. However, it also comes with challenges [125]. Not all repurposed drugs will exhibit anti-malarial activity, and rigorous testing and clinical trials are necessary to determine their efficacy and safety for malaria treatment. Additionally, regulatory approval for new indications may be required in some cases [126].

Malaria parasites have demonstrated a remarkable ability to develop resistance to existing antimalarials [127, 128]. By identifying new drug targets and designing drugs that act on them, researchers can address drug-resistant strains more effectively. Investigating the molecular biology of the malaria parasite has not only led to the identification of drug targets but has also provided valuable insights into the parasite's life cycle, growth, and interaction with the host. This knowledge informs the development of novel therapeutic strategies [129]. Targeted therapies can be used in combination with existing antimalarials to create synergistic treatment regimens [130]. Combining drugs that act on different biological processes within the parasite enhances treatment efficacy and reduces the likelihood of resistance [131].

Combination therapies have emerged as a fundamental strategy in the treatment of malaria due to the malaria parasite's propensity to develop resistance to single drugs [132]. Researchers are actively pursuing the development of novel combinations that meet several key criteria, including effectiveness, tolerability, and the ability to delay the emergence of drug resistance [133]. Combining two or more antimalarial drugs with different mechanisms of action increases the likelihood of killing the parasite at multiple stages of its life cycle. This approach ensures a more comprehensive and effective attack on the malaria parasite, leading to higher cure rates. Malaria parasites can develop resistance to individual drugs over time [134]. By using combination therapies, the risk of resistance development is significantly reduced. If resistance emerges against one component of the combination, the other drug(s) can continue to suppress the parasite [132]. Some drug combinations exhibit synergistic effects, meaning that their combined action is greater than the sum of their individual actions [133, 134]. This synergy enhances treatment efficacy and can lead to faster parasite clearance. Some combinations can reduce the risk of recurrent infections (relapses) by targeting different stages of the malaria parasite's life cycle [135]. This is especially relevant for preventing relapses in cases of *P. vivax* and *P. ovale* infections [135].

7. Conclusion

Malaria, a disease that has plagued humanity for centuries, continues to be a global health concern, particularly in African countries where the burden is heaviest. Progress has been made in reducing malaria cases and deaths, but the COVID-19 pandemic posed setbacks due to disruptions in healthcare delivery. Nevertheless, the past two decades have witnessed remarkable achievements, with billions of cases and millions of deaths averted, primarily in the African Region.

Diagnosis remains a critical aspect of malaria control, but the existing diagnostic methods have their shortcomings, including issues related to sensitivity, specificity, cost-effectiveness, and the need for skilled personnel. Addressing these challenges is vital to effectively manage and treat malaria. Looking ahead, the fight against malaria calls for innovative approaches, especially in vector management to combat outdoor transmission. Current interventions such

as insecticide-treated nets and indoor insecticide spraying have limitations, and new strategies are needed to complement these efforts.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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