International Journal of Pathogen Research

10(3): 29-38, 2022; Article no.IJPR.89600
ISSN: 2582-3876

Global Therapeutic Intervention on Malaria

Augusta Nkiruka Onugha [a], Chukwunonyerem Chika Ogwunga [b*], Mercy Ngozi Madubuike [b] and Okechukwu Charles Josephat [b]

[a] Reddington Hospital, Lagos, Nigeria.
[b] Department of Biotechnology, Federal University of Technology, Owerri, 460114 Imo State, Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. Author ANO wrote the protocol and the first draft of the manuscript. Author CCO worked on the abstract, managed the literature searches while managing formatting and corrections. Author MNM contributed to the literature searches and did the initial proof reading with formatting. Author OCJ contributed to the literature searches, while managing formatting and corrections. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJPR/2022/v10i330252

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/89600

Review Article

Received 19 May 2022
Accepted 26 July 2022
Published 10 August 2022

ABSTRACT

Malaria is a vector-borne infectious disease caused by distinct species of a single-celled parasite called *Plasmodium* sp. However, an infected adult female *Anopheles* sp. mosquito that feeds on blood is responsible for the transmission of malaria. In the year 2020, approximately 241 million malaria cases and 627 thousand malaria deaths were recorded globally. In most tropical and subtropical regions of the world, malaria is one of the leading causes of death. Its transmission cuts across 86 countries with African continent recording approximately 95% deaths in 2020. Africa is mostly affected due to its weather conditions that support the easy spread of *Plasmodium falciparum.* Over time, relevant interventions have been made by researchers in the diagnosis, prevention, and treatment of malaria. Nevertheless, there are still challenges to its treatment and management globally. This review article is focused on the therapeutic intervention on malaria globally. Thus, published primary literatures reporting several relevant and new therapeutic interventions in malaria, as globally attained in the past years were collated and vital information critically reviewed. It is important to note that, the risk of contracting malaria is dependent on the region visited, length of stay, immunity, exposure and compliance with prophylaxis. Hence, to select treatment best suitable as a first-line therapy, combination antimalarial therapy, which

**Corresponding author: Email: Chukwunonyerem.ogwunga@futo.edu.ng;*

consists of two or more antimalarial agents with different mechanisms of action was introduced and has been widely accepted and endorsed to prevent the development of drug resistance. Yet, immunization still remains the best measure for the eradication of malaria.

Keywords: Malaria; immunization; malaria prophylaxis; Plasmodium falciparium; parasite.

1. INTRODUCTION

Malaria is a vector borne infectious disease caused by distinct species of a single-celled parasite called *Plasmodium* sp [1]. There are five species of *Plasmodium* which can infect and cause malaria in humans, they include *Plasmodium falciparum, Plasmodium malariae, Plasmodium vivax, Plasmodium ovale and Plasmodium knowlesi* [2], however, the most fatal and severe cases are caused by *Plasmodium falciparum* which is also the most prevalent specie [3]. An infective female *Anopheles* sp. mosquito is responsible for the transmission of malaria. It is worthy to note that only female mosquitoes feed on blood, while male mosquitoes feed on nectar and do not transmit the disease [4]. Malaria is also a transfusion transmitted disease, as the parasites can be transmitted in a pint of blood donated by an already infected individual [5]. Consequently, malaria can be classified into three: Asymptomatic, Uncomplicated and Severe Malaria [6]. The epidemiology of malaria is dependent on geographical location and the level to which it becomes endemic in these locations though it is mostly found in the tropical region [7]. Over the years, the global impact of malaria cannot be over emphasized as it is one of the leading cause of deaths and diseases in most tropical and subtropical regions of the world. In the year 2020, approximately 241 million malaria cases and 627 thousand malaria deaths were recorded globally [8]. Its transmission cuts across 86 countries with African continent approximately recording 95% deaths in 2020 as reported by World Health Organization (WHO) [9]. From the illustration in Fig. 1, Africa is mostly affected due to its weather conditions, that support the easy spread of *Plasmodium falciparium (*which is a predominant malaria parasite found in this region) and has higher tendency of causing deaths and diseases. Also, the poor economy and inadequate resources of these affected African countries incapacitate their ability to properly control the spread of disease [10].

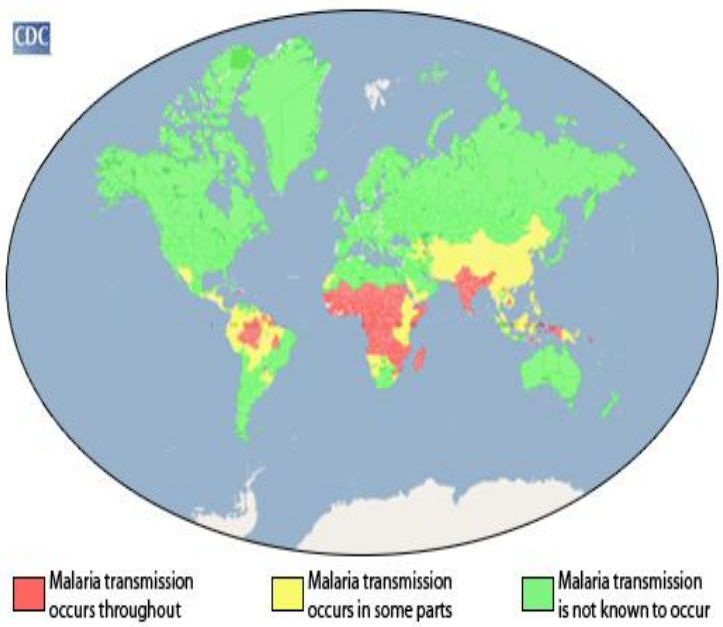

Fig. 1. Global impact of malaria shown by different levels of transmission per continent [10]

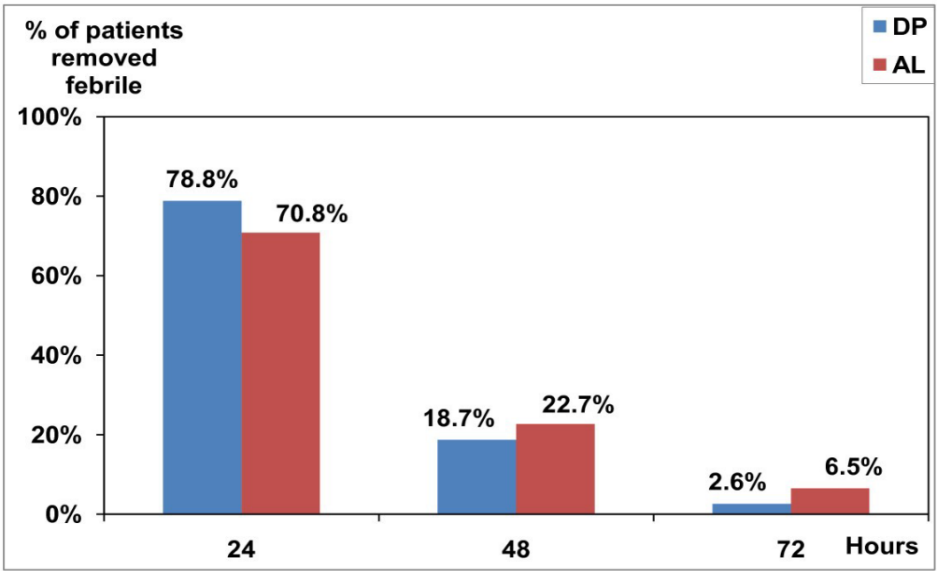

Fig. 2. Comparison of fever clearance in the treatment of *Plasmodium falciparum* using dihydroartemisinin-piperaquine (DP) and artemether-lumefantrine (AL) in the first 72 hours of treatment [35]

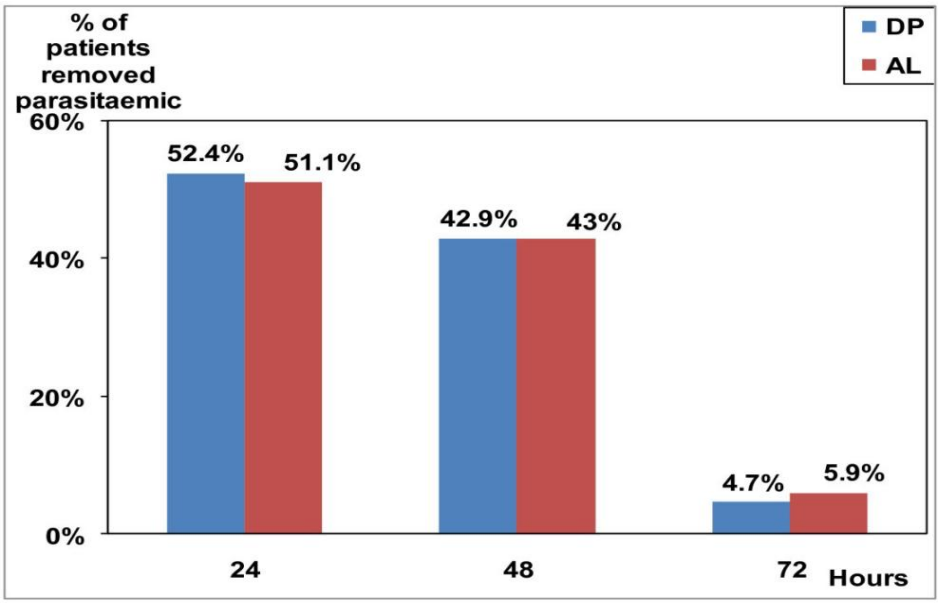

Fig. 3. Comparison of parasitaemia elimination in the treatment of *Plasmodium falciparum* using dihydroartemisinin-piperaquine (DP) and artemether-lumefantrine (AL) in the first 72 hours of treatment [35]

In continents like America and Asia where there is very low transmission of malaria, the residents develop little or no immunity against the disease hence remain vulnerable to its infection which can be severe in most cases. However, pregnant women, children and immigrants (without adequate immunity to malaria) are the most affected population in regions with high transmission rate [10]. Malaria during pregnancy is a major public health problem with its antecedent on the woman, her fetus, and the newborn. Non-pregnant women are less susceptible to malaria when compared to pregnant women. However, the intensity of the infection depends on age, accumulation of malaria over a period of lifetime and parity. Furthermore, malaria during pregnancy increases the risk of maternal anemia which

leads to the delivery of low-birth-weight babies usually less than 2.5kg. To reduce the burden associated with malaria in pregnancy, it is recommended that early diagnosis and effective management of the infection is achieved, administration of intermittent preventive therapy (IPT) and proper use of insecticide treated nets (ITNs). This is evident in malaria endemic areas, where a dose of sulfadoxine -pyrimethamine is given during antenatal visit for prevention of malaria [11].

According to the World Health Organisation's annual report on malaria in 2021, the global death toll of malaria escalated between 2019 to 2021, with an additional 2% increase on the previous death rate of 4.8% recorded in 2019 [9]. This can be traced to a possible negligence of malaria control and therapeutic activities in affected regions, probably due to distractions by the Covid-19 pandemic which occurred within the period. Hence, there is an urgent need to significantly combat this surge by unveiling and implementing more therapeutic interventions relevant to malaria, especially in the tropics where malaria is endemic. This birthed the objective of this article, which is focused on collating vital information and critically reviewing several relevant and new therapeutic interventions on malaria, as globally attained in the past years.

1.1 Life Cycle of Malaria Parasite

The infected female *Anopheles* sp. mosquito is the definitive host of the parasite. During a blood meal from humans (secondary host), it injects sporozoites in the saliva that migrate through the blood vessels to the liver and infect the hepatocytes [12]. During the asexual reproduction (schizogony), the parasite is replicated in the hepatic phase (pre-erythrocytic stage) without symptoms from the definitive host, consequently tens of thousands of merozoites are produced [13]. These merozoites rupture from the host cells to the red blood cells (erythrocytic stage), still without causing symptoms to the human host, by wrapping itself in the cell membrane of the hepatic cells of the infected host thereby creating an adaptive and innate immune response [14].

In the erythrocytic stage, the merozoites mature into ring forms, trophozoites and schizonts respectively [15] which then produce other merozoites that burst out of the red blood cells, causing chills and rigor to the human host (symptomatic phase) [16]. This life cycle is repeated within the red blood cells periodically, thereby increasing the level of parasitemia in the human host resulting to clinical symptoms such as fever, due to the release and infection of merozoites on new red blood cells.

Some of the merozoites are in sexual forms called gametocytes. They differentiate and mature into male and female gametocytes [17]. The gametocytes are ingested from this infected human host during a blood meal by an uninfected adult female *Anopheles* sp. mosquito, [18] where another life cycle takes place till sporozoites are formed to be released into a human host during a subsequent blood meal and again the life cycle in humans is repeated [19]. Generally, clinical symptoms are manifested between 7-14 days after the initial mosquito bite [4]. This is also dependent on the specie of plasmodium that causes the infection.

The humid and warm environmental condition in tropical and Sub - tropical areas promotes the breeding and multiplication of *Anopheles* sp which are the carriers of *Plasmodium falciparum*. To control the spread of *Anopheles* sp which lay their eggs in water, it is important to treat or eliminate water pools, have proper water drainage, eliminate debris, use repellent and proper use of insecticide treated nets (ITNs). However, the environmental condition causes high resistance of pesticides [20,11].

2. THERAPEUTIC INTERVENTIONS

Over the years, several studies have made relevant interventions in the prevention, diagnosis, and treatment of malaria, but there are still global challenges in its treatment and management. Targeting the parasites in the pre-erythrocytic phase by preventing the progression to erythrocytic phase would appear to be an ideal approach [21] since the level of parasitemia would still be low and patient asymptomatic, but this may be difficult, considering the absence of symptoms in the first place. This approach is only possible and effective if the merozoites have not migrated to the red blood cells, a blood smear done at this time would yield a negative result because the parasite would not have been released into the blood stream.

Multiple organic compounds had been tried earlier in the 20th century to serve as a substitute for quinine. It started with methylene blue, then

pamaquine and quinacrine, before chloroquine in 1934 [22]. It was not until towards the end of the Second World War, that the efficacy and value of chloroquine was recognized, after a re-evaluation in the United States and it became the drug of choice against malaria [23]. Although, monotherapy with either Sulphadoxine-pyrimethamine or chloroquine is cheap and readily available, there has been a rise in failure rates and resistance [24], especially in *P. falciparum* cases. This took a major toll in endemic areas where it was used as the drug of choice for malaria due to its therapeutic value. This in turn affected patient's health [25]. There are several considerations to look at in picking a treatment best suitable as a first-line therapy.

Combination antimalarial therapy usually consists of two or more antimalarial agents with different mechanisms of action [26]. In the treatment of malaria, combination therapies have been widely accepted and endorsed to prevent the development of drug resistance and to regain the value of older compounds [27]; such combination include the use of chlorproguanil-dapsone, quinine-tetracycline, atovoaquine-proguil and artemisinin combined with other antimalarial drugs for the treatment of malaria. However, for the treatment of *P. falciparum* and *P. vivax*, artemether-lumefantrine and artesunate-amodiaquine are commonly used [28].

Azithromycin, although an antibiotic, offers hope as an additional option in a combination therapy due to its enhanced antimalarial properties *in vivo* and *in vitro* [29]. A multicenter study [25] was carried out in India on azithromycin alone and in combination with chloroquine on the treatment of acute uncomplicated *Plasmodium falciparum* malaria. Ninety-six (96) of the participants who tested positive for P. *falciparum* with rapid diagnostic test [RDT] and peripheral blood smears were assigned to 3 groups: Azithromycin Monotherapy, Chloroquine Monotherapy and Azithromycin-Chloroquine combination therapy. On the third day of treatment, 9 of the 16 [56%] participant of azithromycin, 14 of 16 [88%] participant of chloroquine and 61 of 64 [95%] participants of the combined therapy of azithromycin-chloroquine were cured. On the 7th day, one of participants from the combination therapy regimen dropped out, but the results were still the same, as 61 of 63 [97%] were cured, while 10 of 16 [63%] and 14 of 16 [88%] were cured with azithromycin and chloroquine respectively. On the final day of monitoring [day 28], two of the thirty two participants did not make it for follow up, one from each monotherapy regimen group, with 5 of 15 [33%] of azithromycin and 4 of 15 [27%] of chloroquine participants cured, 21 of the 30 failed [relapses inclusive], 61 of 63 participants were cured with substantial improvements clinically and resolution of parasitaemia, showing that combination therapy of azithromycin-chloroquine was more effective than the monotherapy regimens in the treatment of acute uncomplicated *Plasmodium falciparum* malaria [25].

A randomized study on the effective treatment of uncomplicated *Plasmodium falciparum* malaria with azithromycin-quinine combination [30] agrees with the study on azithromycin alone and in combination with chloroquine on the treatment of acute uncomplicated *Plasmodium falciparum* malaria [25]. In comparison with quinine-doxycycline, a second line malaria therapy, azithromycin-quinine regimen with higher doses of azithromycin (1-1.5grams/day 2 or 3 times daily) was effective and yielded highly encouraging outcomes against multidrug resistant *Plasmodium falciparum* malaria, with seemingly better tolerance than quinine-doxycycline combination for 7 days [31]. A study in 2001 (32) reported, that some of the most multidrug resistant strains of *Plasmodium falciparum* malaria can be found in the western boarder of Thailand and the combination therapy of quinine-azithromycin shows promising results in terms of its efficacy [32].

In Africa and Asia, the use of Artemisinin-based Combination Therapies [ACT] have been widely accepted as they are reliably and rapidly effective in the treatment of *Plasmodium falciparum* malaria due to increased cases of clinical failure and resistance to sulfadoxine-pymethamine and chloroquine [33]. With the aim of complete elimination and treatment of P. *falciparum* malaria, the efficacy of the ACT of choice is of utmost importance as it has made relevant contribution to malaria control with a fall in malaria transmission by reducing gametocyte carriage [34]. It was suggested that the efficacy of an ACT is also dependent on the partnering agent to the artemisinin derivative and the use of artemether–lumefantrine (AL), artesunate–mefloquine), and dihydroartemisinin-piperaquine. Their efficacy usually exceeds 95% [33]. Factors like efficacy, safety, cost, ease of administration and reduced reinfection rate should be

considered in the selection of an appropriate ACT [35].

There are still occasional treatment failures with respect to drug resistance, especially from the artemisinin-based combination therapies that evolved from similar basic compounds. An example is the report of increased treatment failure with artemisinin-based combination therapy dihydroartemisinin-piperaquine against *Plasmodium falciparum,* and this could be linked to cross resistance between piperaquine and chloroquine [36]. However, a study in 2007 [37] disagrees as a randomized open study to assess the efficacy and tolerability of dihydroartemisinin-piperaquine for the treatment of uncomplicated P. *falciparum* malaria in Cambodia proved to be highly effective and well tolerated in Southeast Asia [37]. In 2011, another randomized study [35] in sub-Saharan Africa, comparing the multicentric assessment of the efficacy and tolerability of dihydroartemisinin-piperaquine (DP) to artemether-lumefantrine (AL) in the treatment of uncomplicated *Plasmodium falciparum* malaria was done [35] and the outcome agrees with a study conducted in 2007 [37]. Participants from three countries were randomly picked from Cameroon in Central Africa, Senegal and Côte d'Ivoire in West Africa, the participant were from ages two and above and they were chosen based on positive blood smear malaria results from P*. falciparum*. A total of 374 patients successfully completed the trial to the last day (day 28), 191 patients were administered DP once daily for three days and 183 in the AL group were administered artemether-lumefantrine twice daily also for three days. Follow up visits to evaluate the density of the parasites and clinical well-being of the patients were done on days one to four and subsequent visits on days 7, 14, 21 and 28. Although two recurrences with P. falciparum infection occurred, one was a recrudescence while the other was a new infection in the DP group while the two recurrences in the AL group were as a result of recrudesces. As shown in Figs. 2 and 3 respectively, located in the appendix, more than 90% of the patients recovered quickly from fever and parasitaemia in the first two days of both treatments. Adverse effects from both drugs did not interrupt or affect the course of treatment as they were both tolerated. However, the once daily regimen of dihydroartemisinin-piperaquine was an advantage over the twice daily regimen of artemether-lumefantrine as patients are likely to be more compliant to treatment.

Another study [38] was carried out in the Amazon region of Bolivia to ascertain the efficacy of mefloquine and mefloquine-artesunate for the treatment of uncomplicated *Plasmodium falciparum* malaria. The results indicated a combination therapy with mefloquine more effective against P. *falciparum* [38]. Ninety-six of the 149 participants who enrolled were males across four different cities in Bolivia: Porvenir, Puerto Rico, Guayaramerin and Riberatta. More than 50% of the 149 had fever with a temperature ≥37.5°C on enrollment. Group 1[mefloquine group] were administered a single dose of 15 mg/kg mefloquine [MQ], while group 2 were given 15 mg/kg of mefloquine and 4 mg/kg of artesunate [MQ-AS] daily for three days. By day 2 of treatment, only 5 of the 149 participants still had fever, 3 from MQ group and 2 from MQ-AS group, with a rapid and significant fall in parasite density as 39 of the patients in group 1 and 55 in group 2 were negative for *P. falciparum* malaria after a laboratory confirmation with a blood smear. On day 3, there was no account of fever documented in both groups; the fall in parasite density was greater than day 2 as the number of subjects treated with MQ in group1 had gone up to 59 from 39 and in group 2, there was a rise from 55 to 64 subjects with negative blood smear results. By day 7, all patients had no *P. falciparum* malaria parasites in their systems but still attended follow up visits on days 14, 21 and 28. The results of this study led the Ministry of Public Health in Bolivia to change the treatment policy for uncomplicated P. *falciparum* malaria in the Amazon region to the artemisinin combination therapy using mefloquine-artesunate as it is more effective than the monotherapy with mefloquine and would help to prevent or delay the chances of resistance [38]. Contrary to this study, the rare use of mefloquine-artesunate, mainly because of the poor tolerance of the partnering drug-mefloquine was reported [39]. Artemether–lumefantrine commonly known by the trade name Coartem, compared to mefloquine-artesunate which is an extensively used artemisinin combination therapy across Africa [40]. An *in vivo* study which was done in western border of Thailand recorded a failure rate of about 46% in the use of mefloquine as a monotherapy regimen. This was attributed to the rise in mefloquine resistance thereby limiting its effectiveness to be used as a combination regimen in the artemisinin combination therapy [41]. Although, the addition of artesunate to mefloquine as an approved therapy in the region was recorded [42].

3. MANAGEMENT OF SEVERE MALARIA

Severe malaria (also known as complicated malaria) is a progression of uncomplicated malaria, which could result due to parasitaemia levels higher than 100,000 per mm^3. This rise in parasitemia level leads to complicated infection which affects other organs and leads to acute kidney infection, hemolysis, hemoglobinuria among other symptoms that affects other organs, causing reduced immunity and drug resistance [43]. The aim of treatment is the complete elimination of the parasite in the pre-erythrocytic and erythrocytic stage of the human host as soon as possible, in order to avoid its progression to severe malaria, other life-threatening complications and in worse case scenarios death [44]. Being the most common and fatal specie, *Plasmodium falciparum* has over the years developed resistance to almost all commonly used oral anti-malaria drugs [45]. This has presented and still is an ongoing challenge in the successful management of malaria in the endemic regions.

It was reported that agents with longer half-life of weeks or months like chloroquine, mefloquine and piperaquine, have the tendency to be unsuccessful due to parasite resistance as the half-life of an antimalarial agent plays a vital role in the emergence of drug resistance [46]. It was also reported in a study, that the exposure of parasites to drug concentration residues in the human host from drugs with longer half-life and slow elimination would not occur if drugs were eliminated in about 2 days of the parasite's life cycle [47]. In a later study [48], it was proposed that drugs with longer half-life provide post-treatment prophylaxis (a period of time in which reinfection is suppressed, usually after a successful completion of an antimalarial treatment regimen) [48]. For patients who are unable to tolerate oral administration, intravenous infusions can be administered, as seen in most severe cases of malaria [3].

In a randomized clinical trial [49], evaluated parasitaemia density of severe malaria treatment with intravenous artesunate or quinine stat and oral artemisinin-based combination therapy in Uganda children was carried out. The study was done on children living within an endemic region in Eastern Uganda. Subjects randomly were administered intravenous artesunate or intravenous quinine stat dose and full doses of artemether –lumefantrine (AL) or dihydroartemisinin-piperaquine (DP) were subsequently administered when they could tolerate orally [49].

3.1 Malaria Prophylaxis

In endemic countries, although, tremendous progress has been made in the prevention and control of malaria with the use of long-lasting insecticide-treated and insecticide-repellant bed nets [4], there is still the need to take malaria prophylaxis before or during travel and a period after departure from any malaria endemic country. Some of the drugs of choice include atoqvaquone-proguil, primauine, doxycycline and mefloquine [50]. The use of IPTp with sulfadoxine-pyrithamine (IPTp-SP) is recommended for pregnant women in moderate to high malaria endemic regions [44]. A causal mechanism of prophylaxis has several distinct advantages, including the fact that it targets a smaller number of parasites (before they complete a four-log amplification in the liver) and clinically that it requires just 1, not 4, weeks of postexposure dosing [51]. The risk of contracting malaria is dependent on the region visited, length of stay, immunity or level of protection, exposure which depends on the type of activity, and compliance with prophylaxis. Individuals including children who have undergone splenectomy are at higher risk of malaria and should avoid malaria endemic areas. Cases where traveling is unavoidable for such individual, it is important they take adequate chemoprophylaxis and avoid mosquito bites [52].

3.2 Emerging Therapies

Inarguably, for a devastating disease with over 200 million new cases worldwide every year [53], the best measure for the eradication of malaria is immunization. In the year 2021, the World Health Organization approved the use of RTS,S/AS01 malaria vaccine among children in sub-Saharan Africa and other regions with moderate to high *P. falciparum* malaria transmission after a successful pilot scheme in Ghana, Kenya and Malawi [54].

4. CONCLUSION

Despite all preventive measures and strategies such as vector control and the use of artemisinin-based combinations, Malaria is still one of the world's most tropical and deadly parasitic diseases. Although treatable and preventable, the management of the disease is a major barrier in the complete eradication of malaria globally. After years of research and studies, there are

just two vaccines that have shown promise in the eradication of malaria, although some are still undergoing trials. The use of artemisinin combination therapy (ACT) is still very effective.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Ashley E, Pyae-Phyo A, Woodrow C. Malaria. The Lancet. 2018;391(10130): 1608-1621.
2. Freimanis G, Sedegah S, Owusu-Ofori S, Kumar J, Allain P. Investigating the prevalence of transfusion transmission of plasmodium within a hyper endemic blood donation system. Transfusion. 2013;53(7): 1429-1441.
3. Malaria.com. Malaria Treatment – MALARIA.com. [online]. 2021. Accessed 30 March 2021 Available:http://www.malaria.com/overview/malaria-treatment-methods.
4. Phillips M, Burrows J, Manyando C, van Huijsduijnen R, Van Voorhis W, Wells T. Malaria. Nature Reviews Disease Primers. 2017;3(17050). DOI: 10.1038/nrdp.2017.50
5. Okocha E, Ibeh C, Ele P, Ibeh N. The prevalence of malaria parasitemia in blood donors in a Nigerian teaching hospital. Journal of Vector Borne Diseases. 2005; 1(42): 21-24.
6. World Health Organization. Severe malaria. Tropical Medicine and International Health. 2014;19(1):7–131.
7. Snow R, Marsh K. The consequences of reducing transmission of *Plasmodium falciparum* in Africa. Advances in Parasitology Journal. 2002;52:235-264. Available:https://doi.org/10.1016/s0065-308x(02)52013-3
8. World Health Organization. World Malaria Report 2021. 2021. Accessed on 26 January 2022 Available:World malaria report 2021 (who.int).
9. Churcher T. World Malaria Report 2021 - a more accurate picture of the malaria burden in Africa; 2021. Accessed on 23 October 2021 Available:https://malariamustdie.com/thomas-story.
10. Centre for Disease Control and Prevention. Malaria's Impact Worldwide; 2021. Accessed on 23 October 2021 Available:https://www.hhs.gov/U.S. Department of Health & Human Services
11. Ogwunga CC, Ahumibe NC, Ogwunga JN, Iwunze FN. Knowledge, attitudes and practices towards malaria prevention among pregnant women attending Federal Medical Centre Owerri. International Journal for Research and Development in Technology. 2019;12(2):73-85.
12. Miller L, Ackerman H, Su, X, Wellems T. Malaria biology and disease pathogenesis: Insights for new treatments. Nature Medicine. 2013;19:156–167.
13. Cowman A, Healer J, Marapana D. & Marsh K. Malaria: biology and disease. Cell. 2016;167(3):610-624.
14. Liehl P, Zuzarte-Luís V, Chan J, Zillinger T, Baptista F, Carapau D, et al. Host-cell sensors for Plasmodium activate innate immunity against liver-stage infection. Nature Medicine. 2013;20(1):47-53.
15. Paul A, Egan E, Duraisingh M. Host–parasite interactions that guide red blood cell invasion by malaria parasites. Current Opinion in Hematology. 2015;22(3):220-226.
16. Clark I, Cowden W. The pathophysiology of falciparum malaria. Pharmacology & Therapeutics. 2003;99(2):221-260.
17. Baker D. Malaria gametocytogenesis. Molecular and Biochemical Parasitology. 2010;172(2):57-65.
18. Waters A. Epigenetic roulette in blood stream plasmodium: Gambling on sex. PLOS Pathogens. 2016;12(2). Available:https://doi.org/10.1371/journal.ppat.1005353
19. Perkins D, Were T, Davenport G, Kempaiah P, Hittner J, Ong'echa J. Severe Malarial Anemia: Innate Immunity and Pathogenesis. International Journal of Biological Sciences. 2011;7(9):1427-1442.
20. Mosquito Control. Anopheles Mosquitoes. Accessed on 25 July 2022. Available:https://mosquitocontrol.net/anopheles-mosquitoes/
21. Marques-da-Silva C, Peissig K, Kurup S. Pre-Erythrocytic Vaccines against Malaria. Vaccines. 2020;8(3):400.
22. Heyneman D. Antimalarial agents. chemistry and pharmacology. Paul E. Thompson, Leslie M. Werbel. The Quarterly Review of Biology. 1973;48(2): 394-395.
23. Coatney G. Pitfalls in a discovery: The chronicle of chloroquine. The American

Journal of Tropical Medicine and Hygiene. 1963;12(2):121-128.

24. Vestergaard L, Ringwald P. Responding to the challenge of antimalarial drug resistance by routine monitoring to update National Malaria Treatment Policies. The American Journal of Tropical Medicine and Hygiene. 2007;77(6):153-159.
25. Dunne M, Singh N, Shukla M, Valecha N, Bhattacharyya P, Dev V. A multicenter study of azithromycin, alone and in combination with chloroquine, for the treatment of acute uncomplicated *Plasmodium falciparum* malaria in India. The Journal of infectious diseases. 2005; 191(10):1582–1588.
26. White N, Olliaro P. Strategies for the prevention of antimalarial drug resistance: Rationale for combination chemotherapy for malaria. Parasitology Today. 1996; 12(10):399-401.
27. Wellems T, Plowe C. Chloroquine-resistant malaria. The Journal of Infectious Diseases. 2001;184(6):770-776.
28. Nankabirwa J, Zurovac D, Njogu J, Rwakimari J, Counihan H, Snow R, Tibenderana J. Malaria misdiagnosis in Uganda – implications for policy change. Malaria Journal. 2009;8(1). Available:https://doi.org/10.1186/1475-2875-8-66
29. Andersen S, McGreevy P, Schuster B, Ager A, Ohrt C, Berman J. et al. Activity of Azithromycin as a Blood Schizonticide against rodent and human plasmodia in vivo. The American Journal of Tropical Medicine and Hygiene. 1995;52(2):159-161.
30. Miller R, Wongsrichanalai C, Buathong N, McDaniel P, Knirsch C, Walsh D, Ohrt C. Effective treatment of uncomplicated *Plasmodium falciparum* malaria with azithromycin-quinine combinations: A randomized, dose-ranging study. The American Journal of Tropical Medicine and Hygiene. 2006;74(3):401-406.
31. Karbwang J, Na-Bangchang K, Thanavibul A, Ditta-in M, Bunnag D, Harinasuta T. Comparative clinical trial of artesunate and the combination of artesunate-mefloquine in multidrug-resistant falciparum malaria. Clinical Drug Investigation. 1996;11(2):84-89.
32. Wongsrichanalai C, Sirichaisinthop J, Karwacki JJ, Congpuong K, Miller RS, Pang L, Thimasarn K. Drug resistant malaria along the Thai-Myanmar and Thai-Cambodia borders. Southeast Asian Journal of Tropical Medicine and Public Health. 2001;32:41–49.
33. François N, White N. Artemisinin-based combination treatment of falciparum malaria. The American Journal of Tropical Medicine and Hygiene. 2007;77(6):181–192.
34. Bhattarai A, Ali A, Kachur S, Mårtensson A, Abbas A, Khatib R. et al. Impact of Artemisinin-Based Combination Therapy and Insecticide Treated Nets on Malaria Burden in Zanzibar. Plos Medicine. 2007; 4(11):309. Available:https://doi.org/10.1371/journal.pmed.0040309
35. Yavo W, Faye B, Kuete T, Djohan V, Oga S, Kassi R. et al. Multicentric assessment of the efficacy and tolerability of dihydroartemisinin-piperaquine compared to artemether-lumefantrine in the treatment of uncomplicated *Plasmodium falciparum* malaria in sub-Saharan Africa. Malaria Journal. 2011:10(1). Available:https://doi.org/10.1186/1475-2875-10-198
36. Karunajeewa H, Mueller I, Senn M, Lin E, Law I, Gomorrai P. et al. A trial of combination antimalarial therapies in children from Papua New Guinea. New England Journal of Medicine. 2008; 359(24):2545-2557.
37. Janssens B, Van Herp M, Goubert L, Chan S, Uong S, Nong S. et al. A randomized open study to assess the efficacy and tolerability of dihydroartemisinin-piperaquine for the treatment of uncomplicated falciparum malaria in Cambodia. Tropical Medicine & International Health. 2007; 12(2):251-259.
38. Avila J, Villaroel R, Marquino W, Zegarra J, Mollinedo R, Ruebush T. Efficacy of mefloquine and mefloquine-artesunate for the treatment of uncomplicated Plasmodium falciparum malaria in the Amazon region of Bolivia. Tropical Medicine and International Health. 2004; 9(2):217-221.
39. Sirima S, Ogutu B, Lusingu J, Mtoro A, Mrango Z, Ouedraogo A. et al. Comparison of artesunate–mefloquine and artemether–lumefantrine fixed-dose combinations for treatment of uncomplicated Plasmodium falciparum malaria in children younger than 5 years in sub-Saharan Africa: A randomised, multicentre, phase 4

trial. The Lancet Infectious Diseases. 2016;16(10):1123-1133.
40. Ngasala B, Malmberg M, Carlsson A, Ferreira P, Petzold M, Blessborn D, et al. Effectiveness of artemether-lumefantrine provided by community health workers in under-five children with uncomplicated malaria in rural Tanzania: an open label prospective study. Malaria Journal. 2011;10(1).
Available:https://doi.org/10.1186/1475-2875-10-64
41. Nelson A, Miller R, Sriwichai S, Buathong N, Purfield A, Uthaimongkol N, et al. Pfmdr1 Genotyping and in vivo mefloquine resistance on the Thai-Myanmar border. The American Journal of Tropical Medicine and Hygiene. 2005;72(5):586-592.
42. Rojanawatsirivet C, Congpuong K, Vijaykadja S, Thongphua S, Thongsri K, Na-Bangchang K, Wilairatana P, Wernsdorfer W. Declining mefloquine sensitivity of *Plasmodium falciparum* along the Thai-Myanmar border. Southeast Asian Journal Tropical Medicine Public Health. 2004;35:560–565.
43. Wassmer S, Taylor T, Rathod P, Mishra S, Mohanty S, Arevalo-Herrera M, et al. Investigating the pathogenesis of severe malaria: A multidisciplinary and cross-geographical approach. The American Journal of Tropical Medicine and Hygiene. 2015;93(3):42-56.
44. World Health Organization. Guidelines for the treatment of malaria, 3rd edition; 2015.
Accessed 28th November, 2021
Available:https://apps.who.int/iris/bitstream/handle/10665/162441/9789241549127_eng.pdf?sequence=1
45. Tschan S, Kremsner P, Mordmüller B. Emerging drugs for malaria. Expert Opinion on Emerging Drugs. 2012;17(3): 319-333.
46. Hastings I, Watkins W, White N. The evolution of drug–resistant malaria: The role of drug elimination half–life. Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences. 2002;357(1420):505-519.
47. White N. Antimalarial drug resistance. Journal of Clinical Investigation. 2004; 113(8):1084-1092.
48. White N. How antimalarial drug resistance affects post-treatment prophylaxis. Malaria Journal. 2008:7(9).
Available:https://doi.org/10.1186/1475-2875-7-9
49. Byakika-Kibwika P, Achan J, Lamorde M, Karera-Gonahasa C, Kiragga AN, Mayanja-Kizza H, et al. Intravenous artesunate plus artemisnin based combination therapy (ACT) or intravenous quinine plus ACT for treatment of severe malaria in Ugandan children: A randomized controlled clinical trial. BMC Infectious Diseases. 2017;17(1):794.
50. Schwartz E. Prophylaxis of malaria. Mediterranean journal of hematology and infectious diseases. 2012;4(1). Prophylaxis of Malaria - PMC (nih.gov).
51. Bakshi RP, Tatham LM, Savage AC, Tripathi AK, Mlambo G, Ippolito MM, Nenortas E, Rannard SP, Owen A, Shapiro TA. Long-acting injectable atovaquone nanomedicines for malaria prophylaxis. Nature communications. 2018;9(1):1-8.
52. Malaria Site. Malaria Prophylaxis; 2015.
Accessed 25th July, 2022
Available:http://www.malariasite.com/prophylaxis/
53. World Health Organization. Malaria Eradication: Benefits, Future Scenarios & Feasibility. In A Report of the Strategic Advisory Group on Malaria Eradication; WHO: Geneva, Switzerland; 2018.
Accessed on 24 October, 2021
Available:Malaria eradication: Benefits, future scenarios and feasibility. Executive summary of the report of the WHO Strategic Advisory Group on Malaria Eradication.
54. World Health Organization. Malaria Vaccine Implementation Programme; 2022.
Accessed on June 23, 2022
Available:Malaria vaccine implementation programme (who.int)

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/89600