GLOBAL THERAPEUTIC INTERVENTION ON MALARIA.

ABSTRACT

Malaria is a vector borne infectious disease caused by distinct species of a single-celled parasite called Plasmodium. However, an infected adult female Anopheles 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 cause of deaths and diseases. It's transmission cuts across 86 countries with Africa recording approximately 95% deaths in 2020. Africa is mostly affected due to its weather conditions that support the easy spread of *Plasmodium falciparium.* Over the years, relevant interventions have been made by researchers in the diagnosis, prevention, and treatment of malaria, nevertheless there are still challenges in its treatment and management globally. This review article is focused on the therapeutic intervention of malaria globally. 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. To pick treatment best suitable as a first-line therapy, combination antimalarial therapy which consists of two or more antimalarial agents with different mechanisms of action was introduced and have been widely accepted and endorsed to prevent the development of drug resistance. To avoid progression of severe malaria which is progression of uncomplicated malaria that could result due to higher levels of parasitemia there should be complete elimination of the parasite in the pre-erythrocytic and erythrocytic stage of the human host as soon as possible. There is still the need to take malaria prophylaxis before or during travel and a period after departure from any malaria endemic country. The best measure for the eradication of malaria would be immunization as malaria is still one of the world's most tropical and deadly parasitic diseases with over 200 million new cases worldwide every year.

Keywords: Malaria, Immunization, Malaria Prophylaxis, *Plasmodium falciparium,* and Parasite.

1.0 INTRODUCTION

Malaria is a vector borne infectious disease caused by distinct species of a single-celled parasite called Plasmodium [1]. The species of Plasmodium that cause malaria in humans include *Plasmodium falciparum, Plasmodium malariae, Plasmodium vivax, Plasmodium ovale and Plasmodium knowlesi*[2]. The vector responsible for the transmission of malaria is an infected adult female Anopheles mosquito; only female mosquitoes feed on blood, while male mosquitoes feed on nectar and do not transmit the diseases [3]. Malaria can be severe and fatal, especially if it is caused by the *Plasmodium falciparum* which is also the most prevalent species [4]. It can be classified into 3: Asymptomatic, Uncomplicated and Severe malaria [5]. Malaria is also a transfusion transmitted disease, as the parasites can be transmitted in a pint of blood donated by an already infected individual [6]. The epidemiology of malaria is dependent on geographical location and its level to which it becomes endemic in these locations but is mostly found in the tropical region [7].

Over the years, the global impact of malaria cannot be overemphasized 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 Africa approximately recording 95% deaths in 2020 as reported by World Health organisation (WHO) [9], with a simple illustration made in figure 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 African countries incapacitated their ability to properly control the epidemic [10].

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

In continents like America and Asia where there is very low transmission of malaria, the residents develop little or no immunity against the disease and so 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].

According to the World Health Organisation's annual report on malaria last year, 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 outbreak which occurred almost same period. Hence, there is an urgent need to significantly fight back 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 in malaria, as globally attained in the past years.

1.1 Life Cycle of Malaria Parasite

The infected female Anopheles 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 [11]. During the asexual reproduction (schizogony), the parasite is replicated in the hepatic phase (pre-erythrocytic stage) without symptoms from the definitive host, tens of thousands of merozoites are produced [12], 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 [13].

In the erythrocytic stage, the merozoites mature into ring forms, trophozoites and schizonts respectively [14] which then produces other merozoites that burst out of the red blood cells, causing chills and rigor to the human host (symptomatic phase) [15]. 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 like fever due to the release and infection of merozoites to new red blood cells.

Some of the merozoites are in sexual forms called gametocytes; they differentiate and mature into male and female gametocytes [16]. The gametocytes are ingested from this infected human host during a blood meal from an uninfected adult female Anopheles mosquito, [17] 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 [18]. Generally, clinical symptoms are manifested between 7-14 days after the initial mosquito bite [3], this is also dependent on the specie of plasmodium that causes the infection.

2.0 THERAPEUTIC INTERVENTIONS

Over the years, various research has made relevant interventions in the prevention, diagnosis, and treatment of malaria but there are still ongoing challenges that are faced mainly in the treatment and management globally. Targeting the parasites in the pre-erythrocytic phase, by preventing the progression to erythrocytic phase would appear to be an ideal approach [19] since the level of parasitemia is still low and patient is also still asymptomatic, but this may not be feasible 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 false negative result because the parasite has not been released to the blood stream.

Multiple organic compounds had been tried early in the 20th century to serve as a substitute for quinine, it started with methylene blue, then pamaquine and quinacrine, before chloroquine in 1934 [20]. It was until the near end of the Second World War, that the efficacy and value was recognized, after a re-evaluation in the United States and it became the drug of choice against malaria [21]. Although, monotherapy with either Sulphadoxine-pyrimethamine or chloroquine are cheap and readily available, there has been a rise in failure rates and resistance [22],

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 [23]. 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 [24]. 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 [25]; for instance, the use of chlorproguanil-dapsone, quinine-tetracycline, atovoaquine-proguil and artemisinin combined with other antimalarial drugs. However, for the treatment of *P. falciparum and P. vivax*, artemether-lumefantrine and artesunate-amodiaquine are commonly used [26].

Azithromycin, although an antibiotic offers promise as an additional option in a combination therapy due to its enhanced antimalarial properties *in vivo* and *in vitro* [27]. A multicenter study 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 with azithromycin, 9 of the 16 [56%], 14 of 16 [88%] for 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

the combination therapy of azithromycin-chloroquine was more effective than the monotherapy regimens in the treatment of acute uncomplicated *Plasmodium falciparum* malaria [23].

A randomized study on the effective treatment of uncomplicated *Plasmodium falciparum* malaria with azithromycin-quinine combination [28] agrees with the study on azithromycin alone and in combination with chloroquine on the treatment of acute uncomplicated *Plasmodium falciparum* malaria [23]. 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) is effective and yielded highly encouraging outcomes against multidrug resistant *Plasmodium falciparum* malaria, with seemingly better tolerance than quinine-doxycycline combination for 7 days [29]. It was reported in 2001, 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 [30].

In Africa and Asia, the use of Artemisinin-based Combination Therapy [ACT] has 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 [31]. 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 in malaria control with a fall in malaria transmission by reducing gametocyte carriage [32]. 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 exceed 95% [31]. Factors like efficacy, safety, cost easy administration and reduced reinfection rate should be considered in the selection of an appropriate ACT [33].

There are still occasional treatment failures in 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 [34]. However, a study in 2007 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 [35]. In 2011, another randomized study 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 [33] and the outcome agrees with the study done in 2007 (35). Participants from three countries were randomly picked from Cameroon in Central Africa, Senegal and Côte d'Ivoire in West Africa from ages two and above 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), 191patients 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 figures 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 is an advantage over the twice daily regimen of artemether-lumefantrine as patients are likely to be more compliant to treatment.

Another study 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* [36]. 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 $\geq 37.5^{O}C$ on enrollment. Group 1[mefloquine group] were administered a single dose of 15mg/kg mefloquine [MQ], while group 2 were given 15mg/kg of mefloquine and

4mg/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 rose 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 [36]. Contrary to this study, the rare use of mefloquine-artesunate, mainly because of the poor tolerance of the partnering drug-mefloquine was reported [37]. Artemether–lumefantrine commonly known by the trade name Coartem, compared to mefloquine-artesunate which is an extensively used artemisinin combination therapy across Africa [38]. An *in vivo* study which was done in western boarder of Thailand recorded a failure rate of about 46% in the use of mefloquine as a monotherapy regimen, this has attributed to the rise in mefloquine resistance thereby limiting its effectiveness to be used as a combination regimen in the artemisinin combination therapy [39]. Although, the addition of artesunate to mefloquine as an approved therapy in the region was recorded [40].

3.0 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 and the infection gets complicated, affecting other organs leading to acute kidney infection, hemolysis, hemoglobinuria among other symptoms that affects other organs, causing reduced immunity and drug resistance [41]. 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 [42]. Being the most common and fatal specie, *Plasmodium falciparum* has over the years developed resistance to almost all commonly used oral anti-malaria drugs [43]. This has presented and still is an ongoing challenge to the successful management in malaria-endemic regions.

It was suggested 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 [44]. It was added 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 [45]. Although in a later study in it was proposed that drugs with longer half-life provides post-treatment prophylaxis (a period of time in which reinfection is suppressed, usually after a successful completion of an antimalarial treatment regimen) [46]. For patients who are unable to tolerate orally, intravenous infusions can be administered, as seen in most severe cases of malaria [4].

In a randomized clinical trial, evaluated parasitaemia density of severe malaria treatment with intravenous artesunate or quinine stat and oral artemisinin-based combination therapy in Uganda children. The study was done on children living within an endemic region in Eastern Uganda. Subjects randomly were administered intravenous artesunate or intravenous quinine start dose, and full doses of artemether –lumefantrine (AL) or dihydroartemisinin-piperaquine (DP) were subsequently administered when they could tolerate orally [47].

3.1 MALARIA PROPHYLAXIS

Although in endemic countries, 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 [3]; 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 [48]. The use of IPTp with

sulfadoxine-pyrithamine (IPTp-SP) is recommended for pregnant women in moderate to high malaria endemic regions [42].

3.2 EMERGING THERAPIES

Without argument, with a devastating disease with over 200 million new cases worldwide every year [49], the best measure for the eradication of malaria would be 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 [50].

4.0 CONCLUSION

Despite all preventive measures and strategies like 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.

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. 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

4. Malaria.com. *Malaria Treatment – MALARIA.com*. [online]. 2021. Accessed 30 March 2021. Available at: http://www.malaria.com/overview/malaria-treatment-methods.

5. World Health Organization. Severe malaria. *Tropical Medicine and International Health*. 2014; **19**(1): 7–131.

6. 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;(42)1: 21-24.

7. Snow R, & Marsh K. The consequences of reducing transmission of Plasmodium falciparum in Africa. *Advances in Parasitology Journal.* 2002; 52:235-264. https://doi.org/10.1016/s0065-308x(02)52013-3

8. World Health Organization. World Malaria Report 2021. 2021. Accessed 26 of January 2022. Available at: 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 at: https://malariamustdie.com/thomas-story.

10. Centres for Disease Control and Prevention. Malaria's Impact Worldwide. 2021. Accessed on 23 October 2021. Available at: https://www.hhs.gov/U.S. Department of Health & Human Services.

11. Miller L, Ackerman H, Su, X, & Wellems T. Malaria biology and disease pathogenesis: insights for new treatments. *Nature Medicine.* 2013;(19): 156–167.

12. Cowman A, Healer J, Marapana D. & Marsh K. Malaria: biology and disease. *Cell*. 2016; 167(3): 610-624.

13. 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.
14. 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.
15. Clark, I., & Cowden, W. The pathophysiology of falciparum malaria. *Pharmacology & Therapeutics*. 2003; *99*(2): 221-260.
16. Baker D. Malaria gametocytogenesis. *Molecular and Biochemical Parasitology*. 2010; *172*(2): 57-65.
17. Waters A. Epigenetic Roulette in Blood Stream Plasmodium: Gambling on Sex. *PLOS Pathogens*. 2016; *12*(2): https://doi.org/10.1371/journal.ppat.1005353
18. 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.
19. Marques-da-Silva C, Peissig K, & Kurup S. Pre-Erythrocytic Vaccines against Malaria. *Vaccines.* 2020;*8*(3): 400.
20. Heyneman D. Antimalarial Agents. Chemistry and Pharmacology.Paul E. Thompson, Leslie M. Werbel. *The Quarterly Review of Biology*. 1973;*48*(2): 394-395.
21. Coatney G. Pitfalls in a Discovery: The Chronicle of Chloroquine. *The American Journal of Tropical Medicine and Hygiene*. 1963; *12*(2):121-128.
22. 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.
23. 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.
24. 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.
25. Wellems T, & Plowe C. Chloroquine□Resistant Malaria. *The Journal of Infectious Diseases.* 2001; *184*(6): 770-776.
26. 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): https://doi.org/10.1186/1475-2875-8-66
27. 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.

28. 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.
29. 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.
30. 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.
31. François N, & White N. Artemisinin-based combination treatment of falciparum malaria. *The American Journal of Tropical Medicine and Hygiene*. 2007; 77(6):181–192.
32. 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, https://doi.org/10.1371/journal.pmed.0040309
33. 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): https://doi.org/10.1186/1475-2875-10-198 .
34. 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.
35. 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.
36. 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.
37. 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.
38. 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) https://doi.org/10.1186/1475-2875-10-64
39. 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.
40. 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.
41. 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.
42. World Health Organization. *Guidelines for the treatment of malaria*, 3rdedition. 2015. Accessed 28th November, 2021. Available at: https://apps.who.int/iris/bitstream/handle/10665/162441/9789241549127_eng.pdf?sequence=1.
43. Tschan S, Kremsner P & Mordmüller B. Emerging drugs for malaria. *Expert Opinion on Emerging Drugs*. 2012; 17(3):319-333.

44. 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.
45. White, N. Antimalarial drug resistance. *Journal of Clinical Investigation*. 2004;113(8), 1084-1092.
46. White, N. How antimalarial drug resistance affects post-treatment prophylaxis. *Malaria Journal*. 2008:*7*(9). https://doi.org/10.1186/1475-2875-7-9

47. Byakika-Kibwika P, Achan J, Lamorde M, Karera-Gonahasa C, Kiragga A. N. & 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
48. Schwartz E. Prophylaxis of malaria. *Mediterranean journal of hematology and infectious diseases*. 2012;*4*(1): Prophylaxis of Malaria - PMC (nih.gov)

49. 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 at: Malaria eradication: benefits, future scenarios and feasibility. Executive summary of the report of the WHO Strategic Advisory Group on Malaria Eradication.

50. World Health Organization. Malaria Vaccine Implementation Programme. 2022. Accessed on June 23 2022. Available at: Malaria vaccine implementation programme (who.int).

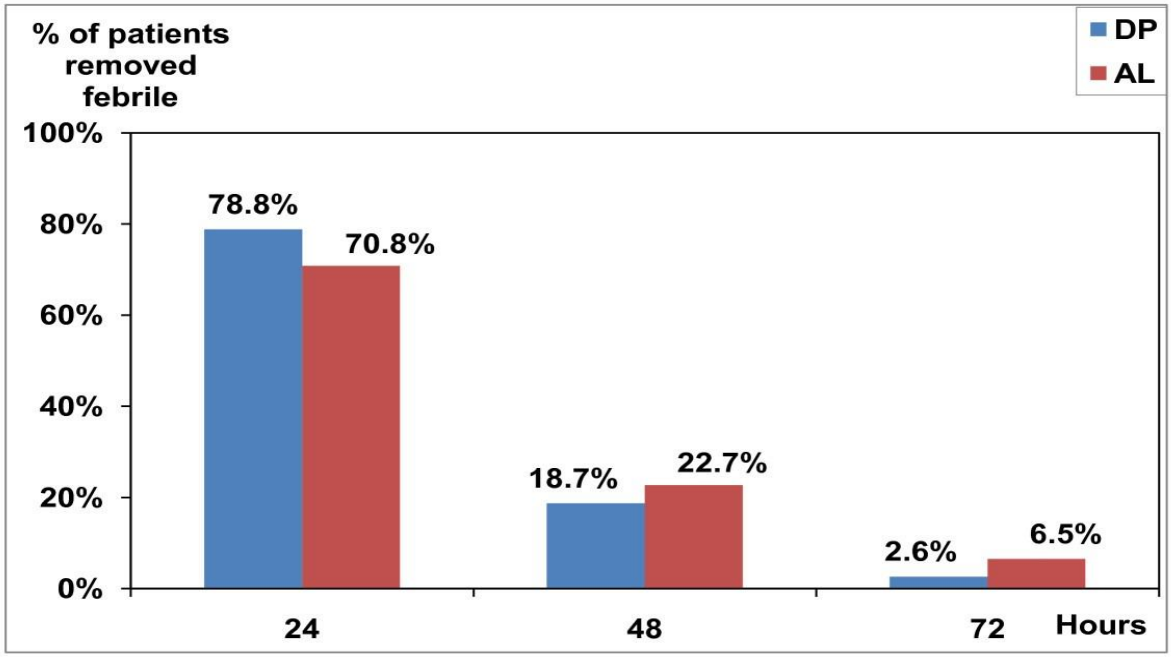

Figure 2: Comparison of fever clearance in the treatment of *Plasmodium falciparum* using dihydroartemisinin-piperaquine (DP) and artemether-lumefantrine (AL) in the first 72hours of treatment [33].

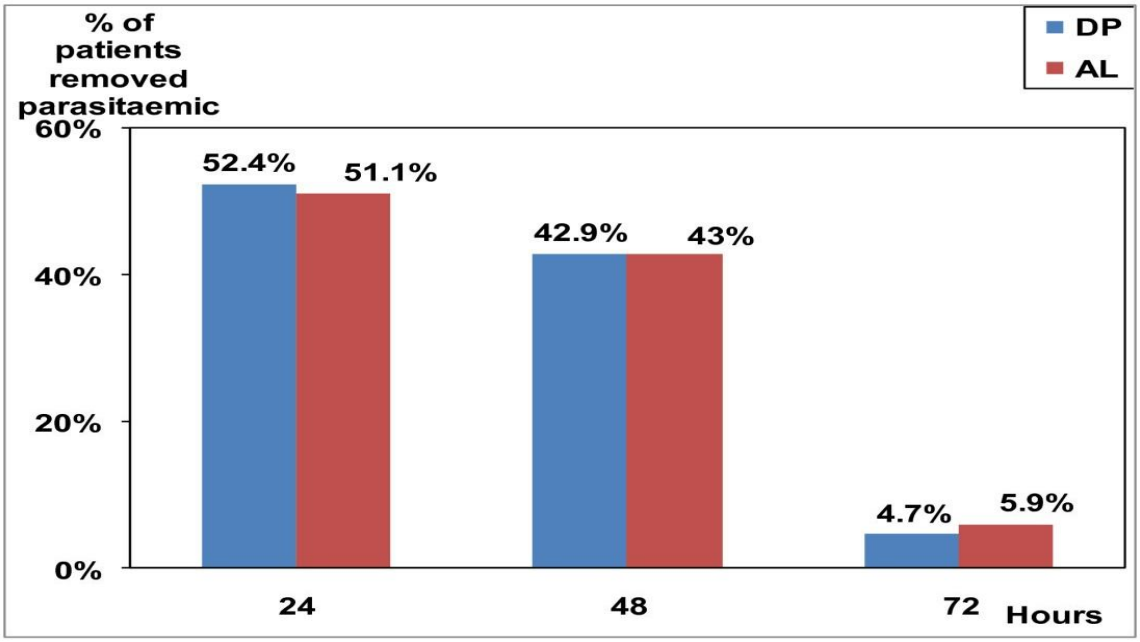

Figure 3: Comparison of parasitaemia elimination in the treatment of *Plasmodium falciparum* using dihydroartemisinin-piperaquine (DP) and artemether-lumefantrine (AL) in the first 72hours of treatment [33].