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REVIEW

Literature review: A comparison of the efficacy of Artemether-Lumefantrine (AL) versus Dihydroartemisinin-Piperaquine (DHP) for the treatment of uncomplicated malaria in patients

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Abstract

Background: Malaria, a life-threatening disease caused by Plasmodium parasites, poses a persistent global health challenge exacerbated by rising multidrug resistance (MDR). While Artemisinin-based Combination Therapies (ACTs) have significantly reduced malaria mortality, the threat of resistance highlights the need for optimised treatment strategies. **Objective:** This literature review compares the therapeutic efficacy of Artemether-Lumefantrine (AL) and Dihydroartemisinin-Piperaquine (DHP) in the treatment of uncomplicated malaria to inform treatment optimisation. **Method:** A review of literature published between 2019 and 2024 was undertaken, encompassing 13 peer-reviewed studies from PubMed, ScienceDirect, and Google Scholar. The findings were synthesised narratively. **Result:** Analysis reveals robust efficacy for both AL (96–98.6%) and DHP (98.8–100%), surpassing the World Health Organisation's 95% efficacy benchmark. Notably, DHP demonstrated superior results in most studies. **Conclusion:** The study highlights the consistent efficacy of AL and DHP, with DHP showing a slight advantage. These insights underscore the importance of maintaining sustained surveillance of antimalarial resistance and adhering to best practices in endemic regions.

Introduction

Malaria, primarily transmitted by mosquitoes, results from an infection with the protozoan parasite Plasmodium (Sumbe & Barkade, 2023). This parasite invades and replicates within human red blood cells. The disease typically starts with flu-like symptoms, including high fever, chills, and headaches (Bernad Julvian Zebua *et al.*, 2024). The annual Global Malaria Report revealed a concerning increase in malaria cases in 2022, with approximately 249 million cases recorded across 85 endemic nations. The incidence rate is now 58% higher than the targets set by the Global Technical Strategy for Malaria 2025. By comparison, 233 million cases were reported in 2019, highlighting a significant setback in malaria control efforts (Venkatesan, 2024).

The emergence of multidrug resistance (MDR) in Plasmodium, most notably in *Plasmodium falciparum*, presents a significant barrier to the global strategies for malaria control (Rasmussen *et al.*, 2022). This occurrence, marked by the parasite's resistance to various antimalarial medications, is driven by genetic mutations, significantly contributing to the rising incidence and fatality of malaria (Egwu *et al.*, 2022). To confront this global health challenge, the World Health Organisation recommends the use of Artemisinin-based Combination Therapies (ACTs), which have demonstrated outstanding efficacy in the treatment and prevention of malaria (Banek, 2019). ACTs combine artemisinin, a rapidly acting compound derived from Artemisia annua, with a longer-acting partner drug. This strategy has played a crucial role in alleviating the global impact of malaria, with a 37% decline observed

from 2000 to 2015. However, the ongoing threat of drug resistance necessitates continued efforts to develop new antimalarial agents and strategies (Ménard & Fidock, 2019).

The World Health Organisation advises that all national malaria control programs utilise antimalarial drugs that demonstrate a parasitological cure rate exceeding 95%, and that national policies should be revised if treatment failure rates reach 10% or more (World Health Organisation, 2014). This policy statement has prompted the initiation of efforts to track the development of resistance to antimalarial drugs through literature review studies. Given the limited research comparing the efficacy of Artemether-Lumefantrine (AL) and Dihydroartemisinin-Piperaquine (DHP) in treating uncomplicated *Plasmodium falciparum* malaria, further investigation is warranted (Apinjoh *et al.*, 2019). In light of these findings, this study evaluates the efficacy of AL and DHP, aiming to enhance our understanding and monitoring of the effectiveness of these antimalarial therapies.

Methods

A literature review was performed to assess and compare the therapeutic effectiveness of AL and DHP in managing uncomplicated malaria in patients. Scientific publications from 2019 to 2024 were retrieved from databases such as PubMed, ScienceDirect, and Google Scholar. The search terms employed were "*Artemether-Lumefantrine*", "*Dihydroartemisinin-Piperaquine*", "*Uncomplicated Malaria*", "*Mosquito-Borne Disease*", and "*Multidrug-resistance*".

Results

The role of Artemisinin-based combination therapies in the treatment of malaria

Artemisinin is the most potent antimalarial agent currently available, capable of reducing *Plasmodium falciparum* parasite counts by up to 10,000-fold within 48 hours of treatment in infections caused by artemisinin-sensitive parasites (Tay, 2020). Artemisinin exhibits a rapid clearance rate, with a half-life of approximately one hour. While this necessitates a prolonged treatment course to eradicate the infection entirely, it also reduces the opportunity for drug-resistant parasites to proliferate over drug-sensitive ones (van der Pluijm *et al.*, 2021). The short half-life of this drug necessitates daily administration to achieve optimal therapeutic efficacy. However, short-term daily monotherapy (<7 days) has been associated with a relatively high rate of recrudescence, likely due to artemisinin-induced parasite dormancy (Peatey *et al.*, 2021).

ACT has been firmly established as a critical component of the global malaria treatment framework endorsed by the World Health Organisation, with implementation across more than 80 countries affected by malaria (de Haan *et al.*, 2023). Various alternatives to ACT exist, each offering distinct advantages in terms of patient tolerance, treatment adherence, cost-effectiveness, accessibility, and overall therapeutic efficacy (Baryakova *et al.*, 2023). Among the most recent and effective combinations are AL and DHP, which have demonstrated high tolerability and impressive efficacy in a wide range of clinical trials (Price, 2013). As shown in Table I, several studies indicate that the effectiveness of AL versus DHP is very high in various endemic countries.

Table I: Several studies on the efficacy testing of artemether-lumefantrine and dihydroartemisinin-piperaquine have been conducted

Author	Country	Sample	Result
(Hamaluba *et al.*, 2021)	Kenya	Total of 217 samples were collected: artemether-lumefantrine (n=72), arterolane-piperaquine-mefloquine (n=72), and arterolane-piperaquine (n=73). Out of 339 patients, 200 received DHA–PPQ and 139 received artemether-lumefantrine	The 42-day PCR-adjusted efficacy of artemether–lumefantrine was 96%, with 69 of 72 patients responding positively.
(Warsame *et al.*, 2019)	Somalia		The parasitological success rate for artemether-lumefantrine was 98.6%, while for dihydroartemisinin-piperaquine, it was 100%.
(Han *et al.*, 2020)	Myanmar	359 samples	The percentage of parasitological success for artemether-lumefantrine was over 96%, while for dihydroartemisinin-piperaquine, it was 100%.

Author	Country	Sample	Result
(Marwa *et al*., 2021)	Tanzania	205 samples. 116 children received artemether-lumefantrine, and 89 children received dihydroartemisinin-piperaquine	The study reported a parasitological success rate of 100% for both artemether-lumefantrine and dihydroartemisinin-piperaquine at day 28 and day 35 of follow-up.
(Omondi *et al*., 2019)	Kenya	334 samples. 168 children received dihydroartemisinin-piperaquine, and 166 children received artemether-lumefantrine	By day two, 6% of the artemether-lumefantrine group and 2.4% of the dihydroartemisinin-piperaquine group still had detectable asexual parasites. By day seven, none had detectable parasites, but by day 42, 14.1% of the AL group and 21.12% of the dihydroartemisinin-piperaquine group were still positive.
(Dorkenoo *et al*., 2024)	Togo	357 samples were used in this study. Specifically, there were 179 samples in the artemether-lumefantrine group and 178 samples in the dihydroartemisinin-piperaquine	Artemether-lumefantrine: 96.1% in Kouvé and 97.1% in Anié. Dihydroartemisinin-piperaquine: 98.8% in Kouvé and 100% in Anié.
(Sevene *et al*., 2019)	Malawi dan Mozambiq ue	221 patients	In children with uncomplicated *Plasmodium falciparum* malaria, artemether-lumefantrine and dihydroartemisinin-piperaquine effectively reduced gametocyte prevalence to 7.04% and 14.5%, respectively, by day 42. Artemether-lumefantrine exhibited a marginally shorter gametocyte carriage duration (4.5 vs. 5.1 days).
(Mairet-Khedim *et al*., 2021)	Cameroon	152 patients	Dihydroartemisinin-piperaquine offers excellent efficacy and tolerability, achieving a 100% cure rate. Its safety, convenient dosing, and effectiveness in low-drug pressure areas make it a sustainable care protocol for uncomplicated *Plasmodium falciparum* malaria.
(Abamecha *et al*., 2021)	Ethiopia	1,523 participants	The pooled PCR-corrected success rate for artemether-lumefantrine treatment was 98.7%.
(Asih *et al*., 2022)	Indonesia	A total of 195 samples were analyzed, comprising 114 *Plasmodium falciparum* cases and 81 P. vivax cases	Dihydroartemisinin-piperaquine is highly effective against both *Plasmodium falciparum* (97.9%) and *Plasmodium vivax* (97.1%) in Sumatra, offering rapid parasite clearance, reduced risk of delayed clearance, and a lower likelihood of resistance development. Its convenient dosing allows for shorter treatment courses and fewer side effects compared to quinine.
(Kpemasse *et al*., 2021)	Republik of Benin	58 patients received artemether lumefantrine, and 58 patients received dihydroartemisinin- piperaquine	Advantages of artemether lumefantrine**:** Prompt reduction of parasitemia and febrile states, strong gametocidal activity in resistant areas, and improved absorption with fatty meals. Advantages of dihydroartemisinin- piperaquine: Longer therapeutic effect for better parasite clearance, effective in reducing malaria transmission, and simpler dosing, which may enhance adherence.
(Derbie *et al.*, 2020)	Africa	115 patients were enrolled from Bohicon and 90 patients from Kandi, making up the total sample size of 205 participants	Artemether lumefantrine treatment of uncomplicated *Plasmodium falciparum* malaria in Bohicon showed a 91.3% ACPR, which improved to 96.3% after genotyping adjustment.
(Abamecha *et al*., 2020)	Ethiopia	8,320 patients	Artemether lumefantrine achieved >90% efficacy against uncomplicated *Plasmodium falciparum* malaria in all age groups, with a 28-day PCR-corrected cure rate exceeding 97%, confirming its robust antimalarial effectiveness.

Figure 1 presents the mechanism of malaria infection in the human body. When an infected mosquito feeds, it transmits sporozoites through its saliva, which enter the bloodstream and migrate to the liver within approximately 30 minutes. There, they infect liver cells (hepatocytes) and undergo a multiplication phase that lasts about 6 to 15 days, producing thousands of merozoites. This multiplication causes the host cells to rupture, releasing merozoites into the bloodstream. The erythrocytic phase involves red blood cells (RBCs) where merozoites multiply asexually and rupture the RBCs, releasing more merozoites into the bloodstream. Each rupture triggers a fever episode, allowing newly released merozoites to infect additional RBCs, which leads to further amplification.

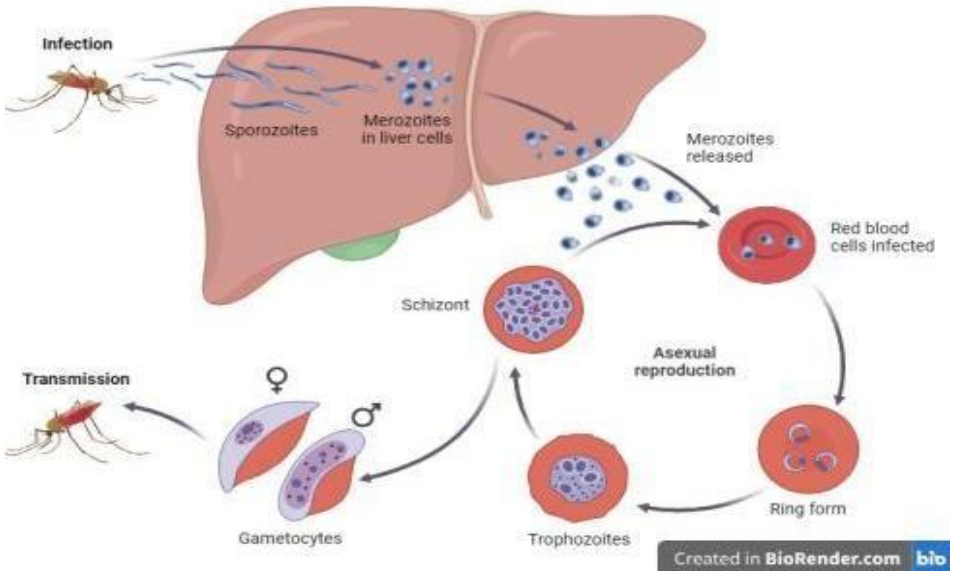

Figure 1: Mechanism of malaria infection

Discussion

Chemical stability of artemether-lumefantrine and dihydroartemisinin-piperaquine

Artemether-lumefantrine exhibits good chemical stability and retains its effectiveness even after its expiration date (Nyarko *et al.*, 2024). These results provide compelling evidence to reconsider the two-year shelf life criteria established by regulatory agencies, with the potential to extend shelf life and improve drug availability in areas where it is needed (Bate *et al.*, 2009). Additionally, DHP shows that both whole and half tablets of DHP remain stable when stored under tropical conditions (30°C and 70% relative humidity) for up to three months (Osarfo, 2016). Both active ingredients, dihydroartemisinin and piperaquine, maintain levels above 95% of their initial concentrations in both light and dark conditions (Wells *et al.*, 2015). These findings provide assurance for malaria control programs considering DHP, highlighting the importance of drug stability in mass treatment and reducing the waste of unused tablets (Maria Hodel *et al.*, 2017).

Bioavailability of both drugs

The oral bioavailability of lumefantrine (LR) in Artemether-Lumefantrine (AL) studies is significantly variable and influenced by multiple factors, including the timing and method of administration (Kajubi *et al.*, 2016). In a study involving children from Kampala, Uganda, lumefantrine showed an exceptionally high maximum plasma concentration (C_max) of 6,757 ng/ml, with a corresponding area under the concentration-time curve (AUC_0–∞) of 210 µg·h/ml (Mwesigwa *et al.*, 2010). This suggests that, despite artemether being more lipid-soluble and subject to irregular absorption, its combination with lumefantrine provides an effective therapeutic outcome (Das *et al.*, 2018). The bioavailability of DHP indicates that dihydroartemisinin achieves a maximum concentration (Cmax) of approximately 357 ng/mL with a time to maximum concentration (Tmax) of around 1.27 hours (Malmberg, 2013). Piperaquine has a Cmax of approximately 300 ng/mL, with varying Tmax values (Joel Leong *et al.*, 2018). Overall, the bioavailability of DHP demonstrates a favourable profile for malaria treatment, with stable and safe pharmacokinetic parameters (Chotsiri *et al.*, 2017).

The development of drug resistance to artemether-lumefantrine and dihydroartemisinin-piperaquine

In a 2021 study, Gansane assessed the effectiveness of AL and DHP for the treatment of uncomplicated *Plasmodium falciparum* malaria in children aged 6 to 59 months in Burkina Faso (Gansané *et al.*, 2021). Conducted across three sites, the study followed 672 children for a period of 42 days. Both AL and DHP demonstrated suboptimal efficacy. Notably, AL's efficacy rates fell below 90% at two sites by day 28 (Keighley *et al.*, 2021). DHP showed better performance but also dropped below 90% at two sites by day 42. Molecular markers of artemisinin resistance, such as the *Pfk13* mutation, were not detected (Diarra *et al.*, 2021). However, inadequate post-treatment prophylaxis for AL was suggested to be associated with reduced lumefantrine susceptibility (Byakika-Kibwika

et al., 2010). The data indicate that there may be a pressing need to reassess the current first-line ACT in Burkina Faso, as resistance issues continue to emerge (Kokori *et al.*, 2024)

Emerging evidence highlights the rising risk of resistance to AL and DHP, which presents a substantial obstacle to effective malaria control, particularly in regions with a high incidence of the disease (Duru *et al.*, 2016). Evidence suggests that an increase in the copy number of the Pfmdr1 gene is associated with resistance to AL. In contrast, elevated copy numbers of the Pfpm2 gene are associated with resistance to DHP (Gupta *et al.*, 2018). Although some areas report high PCR-corrected efficacy rates, specific locations, such as Nanoro and Gourcy in Burkina Faso, have shown efficacy levels below 90%, indicating insufficient effectiveness (Rasmussen & Ringwald, 2021). Although no mutations in the Pfkelch13 gene, known to be associated with artemisinin resistance, were identified in this study, the observed treatment failure rates exceeding 10% with AL raise significant concerns, highlighting the importance of sustained monitoring and potential revisions to future malaria treatment strategies (Dorkenoo *et al.*, 2024).

Conclusion

The efficacy of DHP was significantly greater (97.9% for *Plasmodium falciparum* and 97.1% for *Plasmodium vivax*) compared to AL, and it also resulted in a lower incidence of delayed parasite clearance and a reduced potential for the development of resistance. These outcomes provide valuable information to enhance malaria treatment protocols in the face of growing challenges from drug resistance.

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