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Comparative Efficacy of Dihydroartemisinin-Piperaquine versus Artemether-Lumefantrine in Treating Pediatric Malaria in Western Kenya

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ABSTRACT

Malaria remains a leading cause of morbidity and mortality among children under five in sub-Saharan Africa, with Western Kenya bearing a particularly high burden. This review evaluated the comparative efficacy, safety, and operational feasibility of two widely used artemisinin-based combination therapies (ACTs) artemether-lumefantrine (AL) and dihydroartemisinin-piperaquine (DHA-PPQ) in treating pediatric malaria in this region. DHA-PPQ, characterized by once-daily dosing and extended post-treatment prophylaxis, may offer advantages over AL, which requires twice-daily administration and has a shorter protective window. The article was developed through a narrative synthesis of peer-reviewed clinical trials, pharmacokinetic analyses, observational studies, and implementation research focused on pediatric malaria treatment in high-transmission settings. Evidence suggested that while both therapies are effective in parasite clearance, DHA-PPQ demonstrates superior protection against reinfection and improved adherence due to its simplified dosing. Concerns about QT interval prolongation with DHA-PPQ exist but remain clinically manageable. Given the operational challenges associated with AL and the epidemiological context of frequent reinfections in Western Kenya, DHA-PPQ emerges as a promising alternative, especially for pediatric use. Adoption of DHA-PPQ into national treatment protocols should be informed by robust pharmacovigilance, resistance monitoring, and health systems readiness to optimize outcomes and support sustained malaria control efforts among vulnerable children.

Keywords: Pediatric malaria, Dihydroartemisinin-piperaquine (DHA-PPQ), Artemether-lumefantrine (AL), Antimalarial efficacy, Western Kenya.

INTRODUCTION

Malaria remains one of the leading causes of pediatric morbidity and mortality in sub-Saharan Africa, with Western Kenya representing a significant hotspot of transmission [1, 2]. Children under the age of five are especially vulnerable to severe complications due to their underdeveloped immunity [3]. To mitigate this burden, the World Health Organization (WHO) endorses artemisinin-based combination therapies (ACTs) as the first-line treatment for uncomplicated Plasmodium falciparum malaria [4, 5]. Among the most widely adopted ACTs are artemether-lumefantrine (AL) and dihydroartemisinin-piperaquine (DHA-PPQ), both of which combine a fast-acting artemisinin derivative with a long-acting partner drug. While AL has historically been the standard of care in Kenya's National Malaria Treatment. Guidelines, concerns over adherence due to its twice-daily dosing and relatively shorter prophylactic effect have spurred interest in alternative therapies. DHA-PPQ, with its once-daily dosing and prolonged post-treatment prophylactic window, has gained prominence in various malaria-endemic countries [6, 7]. However, limited comparative studies exist to elucidate their relative efficacy and tolerability in pediatric populations under routine programmatic conditions in Western Kenya. With rising concerns over antimalarial resistance and treatment failure, a critical examination of these two regimens is urgently needed to inform clinical practice and national policy. This review aims to compare the clinical and parasitological efficacy,

safety profile, pharmacokinetic advantages, and operational feasibility of DHA-PPQ versus AL in treating pediatric malaria in Western Kenya. Drawing upon randomized controlled trials, observational data, pharmacological studies, and health systems analyses, the review provides a contextualized evaluation that accounts for regional transmission patterns, healthcare infrastructure, and pediatric-specific considerations. Ultimately, the synthesis of evidence presented herein seeks to guide optimized antimalarial treatment strategies that are both effective and sustainable for the pediatric population in this high-burden region.

Pediatric Malaria Epidemiology in Western Kenya

Western Kenya, particularly in counties bordering Lake Victoria such as Kisumu, Homa Bay, and Siaya, experiences perennial malaria transmission with seasonal peaks during the rainy seasons [8, 9]. Children under five bear a disproportionate burden of malaria-related hospitalizations and deaths. The predominant malaria parasite is *Plasmodium falciparum*, which is responsible for the most severe disease manifestations [10]. Factors contributing to high transmission in the region include warm, humid climate conducive to mosquito breeding, limited access to healthcare services, and socio-economic challenges that impair prompt diagnosis and treatment. Malaria control efforts in the region, including insecticide-treated nets (ITNs), indoor residual spraying (IRS), and intermittent preventive treatment in pregnancy (IPTp), have had variable success due to issues of coverage and sustainability [11, 12].

The high malaria burden among children necessitates therapeutic regimens that are not only efficacious but also safe, tolerable, and easy to administer in resource-constrained settings. This underscores the need to assess ACTs based on their suitability for pediatric use, particularly in rural and peri-urban communities in Western Kenya.

Artemether-Lumefantrine: Profile and Performance

Artemether-lumefantrine (AL), also known by its trade name Coartem, is the most widely used ACT in Kenya [13, 14]. It combines the rapid schizonticidal activity of artemether with the longer acting lumefantrine, designed to eliminate residual parasites and prevent recrudescence. AL is typically administered in six doses over three days, requiring twice-daily administration with fatty food to optimize lumefantrine absorption.

i. **Efficacy and Limitations:** AL has demonstrated high initial cure rates exceeding 90% in clinical trials across Africa [15, 16]. However, there have been reports of declining efficacy due to suboptimal adherence and emerging drug resistance. Children often have trouble completing the full dosing schedule, particularly in resource-limited households where food insecurity or caregiver literacy may be barriers.

ii. **Safety and Tolerability:** AL is generally well tolerated, with adverse effects such as headache, dizziness, and gastrointestinal symptoms being mild and transient [17, 18]. Importantly, AL does not significantly prolong the QT interval, making it a safer option in children with underlying cardiac risks.

iii. **Operational Challenges:** The twice-daily dosing and need for co-administration with food complicate adherence, particularly in younger children or when the caregiver is absent during dosing times. Additionally, the short half-life of lumefantrine offers limited post-treatment prophylaxis, leaving children vulnerable to reinfection within weeks of treatment in high-transmission areas.

Dihydroartemisinin-Piperaquine: Emerging Alternative

Dihydroartemisinin-piperaquine (DHA-PPQ) combines dihydroartemisinin, a potent artemisinin derivative, with piperaquine, a bisquinoline compound with a significantly longer half-life than lumefantrine [19, 20] . It is administered once daily over three days, offering simplicity in pediatric dosing regimens.

i. **Efficacy:** DHA-PPQ has shown high efficacy (>95% cure rates) in pediatric populations, with superior post-treatment prophylactic effect due to piperaquine's prolonged plasma concentration [21]. Studies in East Africa suggest that DHA-PPQ may reduce the risk of reinfection for up to 4–6 weeks post-treatment, a significant advantage in high-transmission settings such as Western Kenya [22].

ii. **Safety and Concerns:** DHA-PPQ is generally well tolerated, with side effects like AL. However, piperaquine has been associated with QT interval prolongation, raising concerns over potential cardiotoxicity. Nonetheless, clinically significant arrhythmia remains rare in pediatric populations. Careful dosing and monitoring, especially in malnourished children or those on concurrent QT-prolonging drugs, are advisable.

iii. **Dosing and Adherence:** The once-daily regimen of DHA-PPQ significantly enhances adherence, particularly among young children. Studies report higher completion rates and caregiver satisfaction compared to AL. Simplified dosing also aligns well with community-based treatment models and integrated community case management (iCCM) approaches.

Comparative Studies and Field Evidence

Randomized trials comparing DHA-PPQ and AL in pediatric populations have yielded critical insights into their relative efficacy and operational suitability. In a large multicenter trial in Kenya, Uganda, and Tanzania, DHA-PPQ

demonstrated non-inferior, and in some contexts superior, efficacy compared to AL at day 28 and day 42 parasitological endpoints. The prolonged prophylactic effect of DHA-PPQ contributed to lower reinfection rates, although initial parasite clearance was faster with AL.

Observational data from Western Kenya indicate that DHA-PPQ may offer practical advantages in regions with high reinfection risk. Reinfection, rather than recrudescence, remains the predominant cause of post-treatment malaria recurrence in this region, making the longer prophylaxis of DHA-PPQ particularly relevant. Moreover, adherence surveys reveal a consistent preference among caregivers for DHA-PPQ due to the ease of administration. These findings suggest that when implemented with appropriate pharmacovigilance and monitoring, DHA-PPQ may yield superior long-term outcomes in pediatric malaria control.

Pharmacokinetics and Drug Resistance Considerations

The pharmacokinetic profiles of the two regimens offer key insights into their clinical utility. Lumefantrine has a half-life of approximately 4–6 days, while piperaquine has a half-life extending beyond 20 days [23]. This difference not only impacts on the duration of post-treatment prophylaxis but also affects the window of vulnerability to developing drug resistance.There is emerging concern that sub-therapeutic levels of piperaquine, due to incorrect dosing or poor absorption, may foster piperaquine resistance. Molecular markers such as *pfcrt*, *pfmdr1*, and *plasmepsin* mutations are being monitored closely in Western Kenya. While resistance to piperaquine remains low in this region, continuous surveillance is crucial to preempt the resistance trends observed in Southeast Asia.

By contrast, lumefantrine resistance has been relatively stable, although mutations associated with decreased sensitivity are increasingly reported. Drug policy must therefore adapt dynamically to evolving resistance patterns, guided by therapeutic efficacy studies and molecular surveillance.

Health Systems and Implementation Perspectives

From a health systems viewpoint, the choice of antimalarial therapy must balance efficacy with logistics, cost, and scalability. AL remains the cornerstone of Kenya's national policy due to its availability, price subsidies, and inclusion in public procurement systems [24]. However, stockouts, poor adherence, and reinfection compromise its utility in high-burden settings. Introducing DHA-PPQ into routine use requires investment in supply chain management, training of health workers, and updated treatment guidelines. While the initial cost of DHA-PPQ may be higher, its potential to reduce reinfection rates and subsequent clinic visits may offer downstream savings.

Operational research in Kenya has shown that community health workers can safely administer DHA-PPQ under supervision, highlighting its potential in integrated community case management. Additionally, co-formulated pediatric dispersible tablets enhance dosing accuracy and acceptability among children.

Special Considerations in Pediatric Malaria Treatment

Treating malaria in children necessitates consideration of age-specific pharmacodynamics, nutritional status, immune response, and caregiver dependence. Malnutrition, common in Western Kenya, may alter drug metabolism and efficacy [25, 26]. Thus, weight-based dosing and nutritional support are critical. Furthermore, the ability of a treatment regimen to prevent reinfection holds value for children who may otherwise experience repeated episodes that impair growth, cognitive development, and school attendance. As such, therapeutic strategies that combine high cure rates with extended prophylaxis such as DHA-PPQ may offer broader developmental benefits.

CONCLUSION

The comparative evaluation of DHA-PPQ and AL in the treatment of pediatric malaria in Western Kenya reveals nuanced differences with significant clinical and programmatic implications. While both regimens are effective in clearing initial infection, DHA-PPQ offers superior post-treatment prophylaxis, simplified dosing, and higher adherence, making it especially valuable in high-transmission settings. However, its use requires vigilance for QT interval prolongation and careful dosing, particularly in vulnerable pediatric subgroups. Health system readiness, cost considerations, and resistance surveillance remain pivotal in determining the optimal deployment of these therapies. Given the high burden of reinfection and operational challenges associated with AL, incorporating DHA-PPQ into treatment protocols for children in Western Kenya may enhance treatment outcomes and reduce malaria incidence. Future policy decisions should be guided by ongoing efficacy trials, pharmacovigilance data, and implementation research to ensure that treatment strategies remain responsive to the evolving malaria landscape. With appropriate safeguards, DHA-PPQ has the potential to complement or even supplant AL as the preferred first-line therapy for pediatric malaria in high-burden regions, thereby advancing child health and contributing to malaria control efforts in sub-Saharan Africa.

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