www.directivepublications.org

Journal of Biochemistry

ISSN 2995-6536

Mini Review

Piperaquine Resistance in Kenya: A Mini Review Following the Rollout of Duo-Cotecxin® as Second-Line Treatment for Uncomplicated Malaria.

Dancan M. Wakoli[a,c]*, Douglas O. Ochora[b], Bartholomew N. Ondigo[a], Hoseah M. Akala[c].

[a] *Department of Biochemistry and Molecular Biology, Egerton University, P.O. Box 536, Egerton-Njoro, Kenya.*
[b] *Department of Biological Sciences, School of Pure and Applied Sciences, Kisii University, P.O. Box 408-40200, Kisii, Kenya*
[c] *United States Army Medical Research Directorate-Africa/Kenya (USAMRD-A/K), Centre for Clinical Research, Kenya Medical Research Institute (KEMRI), P.O Box 20778, Kisumu, Kenya*

Abstract

Duo-cotecxin® is the second-line antimalarial drug for the treatment of uncomplicated malaria in Kenya. It is an artemisinin combined therapy (ACT) made up of dihydroartemisin and piperaquine (DHA-PPQ). This drug has shown good efficacy in chemotherapy, seasonal chemoprevention, and intermittent preventive treatment (IPT) of uncomplicated malaria. However, reports on emergence of DHA-PPQ resistance in Southeast Asia and later in South America have been attributed to the failing PPQ and artemisinin derivative efficacy. These findings, alongside recent increasing reports of partial artemisinin resistance in African countries, namely; Rwanda, Uganda, Eritrea, Tanzania, Ethiopia, Sudan, Namibia, and Zambia threaten the continued use of artemisinin-based combination therapy partner drugs such as piperaquine and lumefantrine in Kenya and across sub-Saharan Africa. Therapeutic efficacy studies (TES), molecular analyses, and *in vitro/ex vivo* drug susceptibility assays are the recommended tools for monitoring antimalarial drug resistance. Here, we review the existing literature on piperaquine resistance in Kenya utilizing TES, molecular signatures and *in vitro/ex vivo* susceptibility studies. Literature search was conducted on Scopus, PubMed, and Google Scholar databases using key words "piperaquine resistance in Kenya" or "antimalarial resistance in Kenya." Only articles written in English were included in the mini-review. We highlight the probable mode of action of PPQ, the molecular mechanism of piperaquine resistance, and the effectiveness of piperaquine against uncomplicated *P. falciparum* malaria. Efforts to strengthen the utilization of molecular and piperaquine survival assays as surveillance tools in Kenya are needed in order to adequately inform on piperaquine resistance as DHA-PPQ deployment increases in the Country amidst evolving artemisinin partial resistance.

Keywords : Dihydroartemisinin, Piperaquine, Duo-cotecxin, Antimalarial, Resistance, Kenya, Malaria.

INTRODUCTION

Malaria remains one of the deadly parasitic diseases globally if not treated. It infects over 260 million people causing more than 590,000 deaths annually. Sub-Saharan Africa (sSA) accounts for 94% of the disease burden and 95% of all the reported deaths ("World malaria report, 2024). In Kenya, malaria is a major public health problem, putting 75% of its population at risk, especially in the endemic Lake region of western Kenya (Musuva et al., 2017). The disease high burden is partly sustained by the rapid development of *P. falciparum* resistance to antimalarial drugs among other factors (Slater et al., 2021; "World malaria report, 2024), though malaria is preventable and treatable.

Malaria is caused by the protozoan *Plasmodium* species namely; *Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, Plasmodium ovale curtisi, Plasmodium ovale wallikeri,* and *Plasmodium knowlesi. Plasmodium falciparum* is responsible for the severe form of the disease and is widely distributed globally, especially in Sub-Saharan Africa. *P. vivax* is predominant in South America while both *P. vivax* and *P. falciparum* are widely spread across Asia (Slater et al., 2021). *Plasmodium falciparum* parasites are transmitted to human hosts by the female Anopheles mosquito during blood feeds (Meibalan and Marti, 2017). The parasites invade the liver cells where they mature into schizonts which rapture to release infective merozoites (Delves et al., 2012). Merozoites infect the erythrocytes where they transform into mature

***Corresponding Author:** **Dancan M. Wakoli,** Department of Biochemistry and Molecular Biology, Egerton University, P.O. Box 536, Egerton-Njoro, Kenya.
Email: dancanwakoli@gmail.com.
Received: 05-October-2025, Manuscript No. JOB-5163 **; Editor Assigned:** 06-October-2025 **; Reviewed:** 21-October-2025, QC No. JOB-5163 **;**
Published: 06-November-2025, **DOI:** 10.52338/job.2025.5163.
Citation: **Dancan M. Wakoli.** Piperaquine Resistance in Kenya: A Mini Review Following the Rollout of Duo-Cotecxin® as Second-Line Treatment for Uncomplicated Malaria. Journal of Biochemistry. 2025 November; 14(1). doi: 10.52338/job.2025.5163.
Copyright © 2025 **Dancan M. Wakoli.** This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

schizonts through ring and trophozoite stages 48 hours later (Tuteja, 2007). Mature schizonts rupture releasing merozoites, some of which commit to the sexual stage (gametocytes) and others reinvade more uninfected erythrocytes (Usui and Williamson, 2021). Mature gametocytes are ingested into the female Anopheles mosquito midgut during a blood meal (Talman et al., 2020). In the midgut, they develop into sporozoites through the zygote, ookinete, and oocyst stages (Bennink et al., 2016). Mature sporozoites migrate from the oocyst following rupture and make their way to the salivary glands ready to invade the next host (Baton and Ranford-Cartwright, 2005).

Antimalarial drugs alongside the recently approved RTS,S and R21 vaccines remains key interventions for malaria control in endemic areas. Artemisinin Combined Therapies (ACTs) are the approved current frontline antimalarials for the treatment of malaria in sSA. Artemether-lumefantrine (AL), and dihydroartemisinin-piperaquine (DHA-PPQ) are the recommended first line and second-line ACTs in Kenya ("World malaria report, 2024). These drugs have contributed immensely in bringing malaria cases down in sSA since their roll-out (Ashley and Phyo, 2018). However, the increase in malaria cases by 11 million globally in 2023 could be attributed to climate change, parasite HRP2 gene deletions, emerging new strains of mosquitoes, insecticides and drug resistance (Dereje et al., 2025; "World malaria report, 2024).

Emergence of partial artemisinin resistance in several countries in Africa alongside the suspected emerging signals of lumefantrine resistance (Tumwebaze et al., 2022; Uwimana et al., 2021; "World malaria report 2024," n.d.), an artemisinin partner drug is a threat to the continued use of ACTs in Kenya and sSA, particularly piperaquine since AL failure may lead to the switch in first-line treatment policies to DHA-PPQ (Organization, 2022). This trend warrants monitoring of the efficacy of artemisinin and piperaquine in Kenya. This study reviews literature on piperaquine resistance in Kenya since the roll out of Duo-cotecxin® as a second-line ACT for the treatment of uncomplicated malaria.

DISCOVERY AND CLASSIFICATION OF PIPERAQUINE

Piperaquine was synthesized in 1960s independently by the Shanghai Pharmaceutical Industry Research in China and the Rhone Poulec in France (Davis et al., 2005). Being more effective against resistant parasites and well tolerated than chloroquine, it was included as a monotherapy in the Chinese treatment guidelines for the management of malaria to replace the failing chloroquine (Davis et al., 2005). However, development of piperaquine resistant parasites from 1970s (Small-Saunders et al., 2022), led to its withdrawal in China (Davis et al., 2005). After a decade (1990) it was rediscovered by the Chinese scientists as a potential candidate for combination with dihydroartemisinin to form a more effective ACT regimen Duo-Cotecxin (Davis et al., 2005; Hien et al., 2004).

Antimalarial drugs are classified based on their chemical structure such as quinoline derivatives, antifolates, and artemisinin derivatives (Belete, 2020; Slater et al., 2021), and the stage of the malaria parasite that they target (blood schizonticides, tissue schizonticides, and gametocytocidal) (Imrat et al., 2021). Quinoline derivatives act by blocking the parasite haem detoxification process (Sharma et al., 2015), antifolates target the parasite folate metabolic pathway that is vital for DNA biosynthesis (Müller and Hyde, 2010), while the artemisinin derivatives have a broad-spectrum action resulting in rapid clearance of the asexual parasite stages (Muangphrom et al., 2016). Blood schizonticides on the other hand act against the blood stages of *Plasmodium* parasites (Sharma et al., 2015), tissue schizonticides acts on the liver stages of the parasite preventing disease progression to the clinical stage in blood while gametocytocidal drugs clear gametocytes in the blood hence blocking their transmission to the mosquito (Sharma et al., 2015).

Piperaquine is a blood schizonticidal aminoquinoline belonging to the 4-aminoquinoline class, similar to chloroquine and amodiaquine. Structurally, it is a bisquinoline, composed of two quinoline units linked together (Belete, 2020). It is available in form of a piperaquine base or piperaquine phosphate or piperaquine tetraphosphate tetrahydrate salt (Davis et al., 2005).

HISTORY OF TREATMENT OF UNCOMPLICATED MALARIA IN KENYA

Treatment of malaria in Kenya using antimalarial drugs dates back to the colonial period. Before and partly during the World war II, quinine was used sparingly as a mainstay for the control of malaria ("Colonial policies to control malaria in Kenya," n.d.). However, due to the increased demand and cost of quinine alongside failure of the efforts by East African governments to produce it locally during the war (Ombongi and Rutten, 2010), its supply and availability diminished in Kenya motivating the shift to mepacrine in 1945 (Kenneth Ombongi et al., 1998). Quinine was later reintroduced as a first-line and a second-line antimalarial in some African countries due to the development of resistance to the conventional drugs by 2009 (Watsierah and Ouma, 2014; World Health Organization, 2009). One year later, mepacrine was replaced by paludrine due to its toxicity and skin paling side effect ("Colonial policies to control malaria in Kenya," n.d.). Between 1950 and 1960, paludrine was reported to be unable to offer total protection against malaria (Shanks et al., 2000) and was replaced by chloroquine and pyrimethamine as the first-line and prophylactic antimalarials, respectively (Ombongi and

Rutten, 2010). Chloroquine was effective until late 1970s when resistant malaria parasites emerged in Eastern and southern Africa (Bloland and Ettling, 1999). Chloroquine was replaced by the antifolate sulphadoxine-pyrimethamine (SP; Fansidar®) as a first-line drug in 1998 after over 10 years of declining efficacy in sub Saharan Africa (Shretta et al., 2000). Before this period, SP was a recommended second-line antimalarial for the treatment of uncomplicated malaria since 1983 (Terlouw et al., 2002). Nonetheless, emergence and widespread resistance to SP in Kenya (Certain et al., 2008), prompted change in the national malaria treatment policy to Artemether-Lumefantrine (AL) in 2004 which was rolled out widely in 2006 (Amin et al., 2007). To date, AL remains the recommended first-line antimalarial for the treatment of uncomplicated malaria in Kenya.

Artemether-lumefantrine is one of the artemisinin combination therapy (ACTs) recommended for the treatment of *P. falciparum* uncomplicated malaria in Kenya and sSA (Musuva et al., 2017). The principle of ACTs involves using two drugs with different mechanisms of action comprising of a rapid acting artemisinin derivative drug which has a short half-life often < 8 hrs (Slater et al., 2021), and a partner drug with a longer half-life (Martin et al., 2018). Currently, there are six ACTs recommended by WHO for treatment of malaria in sSA, namely; artemether-lumefantrine (AL), dihydroartemisinin-piperaquine (DHA-PPQ), artesunate-amodiaquine (ART-AQ), artesunate plus sulphadoxine-pyrimethamine (AS-SP), artesunate-mefloquine (AS-MQ) and artesunate-pyronaridine (AS-PND) (Ashley and Phyo, 2018; Organization, 2022). Malaria treatment guidelines vary geographically depending on the severity of the disease, cause, and resistance patterns (Slater et al., 2021). Artemether-lumefantrine (AL) and dihydroartemisinin-piperaquine (Duo-cotecxin®) are the recommended first-line and second-line regimens respectively, for the treatment of uncomplicated *P. falciparum* malaria in Kenya (Musuva et al., 2017). Duo-cotecxin® was adopted as the second-line regimen in 2009 (Ogutu et al., 2014), preferring the PPQ partner longer prophylactic period of 60-days after treatment (White, 2005). This shift in treatment policy aligns with the declining efficacy of AL (Dimbu et al., 2021; Ebohon et al., 2019; Ebong et al., 2021; "World malaria report 2024," n.d.), a trend that appears to usher in DHA-PPQ regimen as the next first-line treatment option in sSA beyond AL resistance (Assefa et al., 2021). However, emergence of resistance to DHA-PPQ in Southeast Asia and South America, and the recent reports of partial resistance to artemisinin and signals of lumefantrine resistance in some parts of Africa is a threat to the continued use of ACTs in sSA, particularly Kenya (Balikagala et al., 2021; Uwimana et al., 2021). This calls for the assessment of resistance status of these frontline antimalarials in the country to prevent spread of drug resistance (Sharma et al., 2015), since previous patterns of antimalarial drug resistance depicts that once resistance emerges in one part of the world, it spreads to other regions as was the case of chloroquine and SP resistance (Mita et al., 2009). **Table 1** summarizes antimalarials that have been used in Kenya and the year of resistance emergence.

Table 1. Summary of all the antimalarial drugs that have been used in Kenya for malaria control and the year resistance was first reported.

Antimalarial drugs	Drug Class	Year First used in Kenya	Year resistance was first reported in Kenya	References
Quinine	Quinoline derivative	1900	----------	Ombongi & Rutten, 2010
Mepacrine	Acridine derivative	1945	----------	Ombongi et al., 1998
Paludrine		1946	----------	Shanks et al., 2000
Chloroquine	Quinoline derivative	1950	1978	Bloland & Ettling, 1999, Ombongi & Rutten, 2010
Pyrimethamine	Antifolate	1950	1988	Certain et al., 2008, Ombongi & Rutten, 2010
Sulfadoxine-pyrimethamine	Antifolates	1998	2003	Amin et al., 2007, Shretta et al., 2000
Artemisinin- Lumefantrine	Endoperoxide and Quinoline	2004	----------	Amin et al., 2007
Dihydroartemisin-Piperaquine	Artemisinin and quinoline derivatives	2009	----------	Musuva et al., 2017; Ogutu et al., 2014

MECHANISM OF ACTION OF PIPERAQUINE AGAINST *PLASMODIUM* PARASITES

The exact mechanism of action of piperaquine (PPQ) remains incompletely understood (Tarning et al., 2008). Nonetheless, accumulating evidence suggests multiple potential modes of action (de Villiers and Egan, 2021; Dhingra et al., 2017; Martin et al., 2018; Pandey et al., 2001). One widely supported hypothesis is that PPQ blocks heme detoxification within the *Plasmodium*

falciparum digestive vacuole. During intraerythrocytic development, the parasite digests host hemoglobin via a cascade of aspartic proteases, notably the plasmepsin (*pfpm*) family, producing amino acids and free heme (Ke et al., 2014). Free heme is toxic to the parasite, and its detoxification via polymerization into hemozoin is essential for parasite survival (Ke et al., 2014). PPQ is believed to inhibit this detoxification process by binding to free heme and preventing its conversion to hemozoin (de Villiers and Egan, 2021; Dhingra et al., 2017). Supporting this, introduction of the C101F mutation in the *pfcrt* gene encoding the chloroquine resistance transporter has been shown to confer resistance to piperaquine, implicating digestive vacuole transport in PPQ activity (Dhingra et al., 2017).

In addition to heme detoxification inhibition, blockade of hemoglobin proteolysis has been proposed as a complementary mechanism (Dhingra et al., 2017). As a lipophilic weak base, piperaquine passively diffuses into the acidic food vacuole, where it accumulates and may inhibit one or more enzymatic steps in hemoglobin degradation (Ashley and Phyo, 2018; Dhingra et al., 2017). This results in the accumulation of both toxic free heme and undigested hemoglobin, ultimately contributing to parasite death (Martin et al., 2018). Furthermore, amplification of the *pfpm2* and *pfpm3* genes has been associated with reduced PPQ susceptibility, suggesting that piperaquine may directly or indirectly target these proteases.

MECHANISM OF PIPERAQUINE RESISTANCE

Resistance of *Plasmodium falciparum* to piperaquine (PPQ) has emerged as a growing concern, particularly in regions where DHA–PPQ is deployed as a first-line antimalarial therapy. This resistance is driven by both single nucleotide polymorphisms (SNPs) and copy number variations (CNVs) in multiple parasite genes (Duru et al., 2016; Leroy et al., 2019). The earliest reports of piperaquine resistance date back to the 1980s in China (18). In Southeast Asia (SEA) and parts of South America, declining efficacy of DHA–PPQ has been attributed to reduced sensitivity to both artemisinin and piperaquine (Mok and Fidock, 2024; Nsanzabana, 2019).

PPQ resistance is recognized as a multigenic trait, caused by mutations in several genes, including *pfpm2, pfpm3, pfcrt, pfmdr1, pfexo, and pfk13* (Dhingra et al., 2017; Leroy et al., 2019; Martin et al., 2018; Nsanzabana, 2019; Ross et al., 2018; Silva et al., 2020) (**Table 2**). Amplification of the *plasmepsin-2* and *plasmepsin-3* genes has been most consistently associated with PPQ resistance in SEA (Amato et al., 2017; Duru et al., 2016; Martin et al., 2018). Increased copy number of these genes enhances hemoglobin catabolism, supplying excess amino acids for parasite growth and thereby diminishing the efficacy of piperaquine, which is thought to act in part by interfering with hemoglobin degradation and heme detoxification (Amato et al., 2017). It has also been suggested that *pfpm2/3* amplification may modify the parasite food vacuole environment, limiting drug accumulation (Amato et al., 2017; Witkowski et al., 2017). However, studies in Africa have shown that while *pfpm2* amplification is increasingly prevalent and unassociated with clinical or *in vitro* PPQ resistance (Leroy et al., 2019). This observation suggests that *pfpm2/3* amplification alone may not be sufficient to drive piperaquine resistance in African parasite populations, suggesting the role of regional genetic backgrounds or drug pressure differences.

Table 2. Summary of known genetic resistance markers in Plasmodium falciparum that confer resistance to piperaquine.

Drug	Loci	Polymorphism linked with resistance	References
Piperaquine	*Pfpm2*	Overexpression/increased gene copy number	Amato et al., 2017, Duru et al., 2015, Martin et al., 2018, Silva et al., 2020
	Pfpm3	Overexpression/increased gene copy number	Amato et al., 2017, Martin et al., 2018, Silva et al., 2020
	Pfmdr1	Single copy number variation	Duru et al., 2015
	Pfcrt	H97Y, C101F, F145I, M343L, C350R & G353V	Boonyalai et al., 2020, Dhingra et al., 2017, Duru et al., 2015, Rose et al., 2018, Wicht et al., 2020
	Pfexo	E415G	Amato et al., 2017, Boonyalai et al., 2020, Diakite et al., 2019, Duru et al., 2015
	Pfk13	C580Y, I543T, P553L, R539T, Y493H & P574L	Duru et al., 2015, Mok & Fidock, 2024

Pfpm2- Plasmodium falciparum plasmepsin 2 gene and *Pfpm3- Plasmodium falciparum* plasmepsin 3 gene*, Pfmdr1- Plasmodium falciparum* multi drug resistance gene 1*, Pfcrt- Plasmodium falciparum* chloroquine resistance gene*, Pfexo-Plasmodium falciparum* exonucleases*, Pfk13-Plasmodium falciparum kelch 13*

Mutations in the *pfcrt* gene particularly H97Y, C101F, F145I, M343L, C350R, and G353V are considered key determinants of PPQ resistance (Amato et al., 2017; Duru et al., 2016; Wicht et al., 2020). These mutations likely mediate reduced drug accumulation in the parasite's digestive vacuole by enhancing drug efflux, thereby preventing PPQ from reaching concentrations sufficient to inhibit heme detoxification (Dhingra et al., 2017; Leroy et al., 2019; Martin et al., 2018; Ross et al., 2018). These SNPs have been strongly associated with elevated PPQ 50% inhibition concentration (IC_{50}) values and decreased *in vitro* sensitivity

(Boonyalai et al., 2020). Although *pfmdr1* single-copy variants have been linked to piperaquine resistance in SEA (Duru et al., 2016), recent studies, including that by Ansbro et al. (2022), demonstrate that not all piperaquine resistant isolates harbor single-copy *pfmdr1* (Ansbro et al., 2020). This observation suggests that *pfmdr1* may not be a primary driver of PPQ resistance. Further, mutations in the *pfk13* propeller domain, namely; C580Y, I543T, P553L, R539T, Y493H, and P574L are associated with artemisinin resistance by causing delayed parasite clearance in Southeast Asia (Duru et al., 2016). However, these mutations are not directly linked to PPQ resistance and have not been commonly detected in African isolates (Leroy et al., 2019).

A non-synonymous SNP, E415G, in the *pfexo* gene encoding a putative exonuclease has been linked to elevated piperaquine IC_{50} values, suggesting a potential role in resistance phenotypes (Duru et al., 2016). This polymorphism has been increasingly reported in SEA, particularly in Cambodia (Duru et al., 2016), and has also been detected at low frequencies in field isolates from Mali (Diakité et al., 2019). However, its relevance in African parasite populations remains unclear (Diakité et al., 2019), and further studies are needed to determine whether the presence of E415G correlates with *in vitro* piperaquine susceptibility as measured by the piperaquine survival assay (PSA).

Studies on Cambodian samples show the combination of *pfcrt* mutations and *pfexo* E415G, even in the absence of *pfpm2* amplification, is sufficient to confer piperaquine resistance (Boonyalai et al., 2020). Conversely, disruption of *pfpm2/3* genes has been associated with increased parasite sensitivity to PPQ, while overexpression does not appear to significantly affect drug susceptibility (Mukherjee et al., 2018). Although the precise role of *Plasmepsin-2/3* amplification in piperaquine resistance remains unclear (Silva et al., 2020), its presence has been associated with resistance, particularly in parasites carrying polymorphisms in *Pfcrt, Pfmdr1*, and *Pfexo*. It has been proposed that *Plasmepsin-2/3* gene amplification may confer low-level resistance, facilitating the emergence of highly resistant parasites when combined with *Pfcrt* mutations (Ross and Fidock, 2019).

CURRENT STATUS OF PIPERAQUINE RESISTANCE IN KENYA

Emerging signals of piperaquine resistance have been monitored in Africa, though not yet widespread (Leroy et al., 2019; Wakoli et al., 2022). In Kenya no cases of PPQ resistance have been documented yet. A previous longitudinal study assessing the sensitivity of Kenyan *P. falciparum* isolates to antimalarial drugs using the *ex vivo* and *in vitro* growth inhibition assays (malaria SYBR Green and Piperaquine survival assay) has reported *in vitro* piperaquine IC_{50}s below the resistance cut-off point and 85% of isolates with PSA rate below 10% suggesting piperaquine effectiveness in the country (Cowell and Winzeler, 2019; Mwai et al., 2009). Genomic analyses in the country have revealed a low frequency of *Pfpm2/3* and *Pfmdr1* single copy, key markers for PPQ resistance in SEA but this did not associate with PPQ IC_{50} and PSA resistance data (Mwai et al., 2009; Wakoli et al., 2022). *Pfcrt* (H97Y, F145I, M343L, C350R and G353V) mutations implicated in PPQ resistance in SEA have not been detected in the African parasite population (Delandre et al., 2024). These findings corroborate, several studies in Kenya assessing the efficacy of DHA-PPQ vs AL (Agarwal et al., 2013; Chebore et al., 2020; Ogutu et al., 2014; Westercamp et al., 2022). Specifically, a therapeutic efficacy study (TES) conducted in Siaya County between 2010 and 2011 among children aged 6 to 59 months reported a 96% PCR-corrected adequate clinical and parasitological response (ACPR) at day 42 (Agarwal et al., 2013). Similarly, a study by Ogutu and colleagues in Kisumu County during the same period in children of the same age group demonstrated a 98.7% ACPR at day 42 (Ogutu et al., 2014). Five years later, another TES conducted in Siaya County showed a DHA-PPQ ACPR of 93% (Westercamp et al., 2022). In the same year, Chebore et al. (2020) analyzed samples from a TES evaluating the efficacy of DHA-PPQ vs AL. Their findings revealed that recrudescent samples from the DHA-PPQ arm did not harbor *Pfpm2* mutations, markers associated with piperaquine resistance, supporting the conclusion that piperaquine remains effective for malaria treatment in Kenya. Additionally, a study conducted between 2019 and 2021 in Kenya and Malawi evaluated malaria chemoprevention in pregnant women living with HIV who were receiving daily co-trimoxazole. The study assessed the use of monthly intermittent preventive treatment with dihydroartemisinin-piperaquine and found that this regimen significantly improved malaria prevention among women residing in areas with high sulfadoxine-pyrimethamine (SP) resistance (Barsosio et al., 2024).

Furthermore, a recent systematic review by Roh et al. (2025) comparing DHA-PPQ with SP for intermittent preventive treatment during pregnancy reported that in areas where *Plasmodium falciparum* exhibits high SP resistance, DHA-PPQ demonstrates superior antimalarial efficacy (Pernaute-Lau et al., 2025). Findings from the TES and DHA-PPQ chemoprevention trials further support the continued effectiveness of piperaquine in the treatment and prevention of uncomplicated malaria in Kenya.

CONCLUSION

Piperaquine remains effective against *Plasmodium falciparum* parasites in Kenya, even as partial resistance to artemisinin-based combination therapies (ACTs) rises across parts of

Africa. This sustained efficacy highlights its potential as a viable alternative for first-line malaria treatment. However, the growing use of Duo-Cotecxin® in Kenya may increase the risk of selecting for piperaquine-resistant parasites, driven by drug pressure and diminishing artemisinin potency. As such, enhancing Kenya's antimalarial resistance surveillance systems using the novel established piperaquine survival assay and molecular tools is critical to detect and respond to emerging piperaquine resistance in a timely manner.

CRediT authorship contribution statement

Dancan M. Wakoli: Conceptualization, Led the literature search, Writing the review & editing. Douglas O. Ochora: Writing review & editing. Bartholomew N. Ondigo: Supervision, writing-review & editing. Hoseah M. Akala: Conceptualization, Supervision, writing-review & editing.

Declaration of competing interests

The authors declare that there are no competing interests.

REFERENCES

1. Agarwal, A., McMorrow, M., Onyango, P., Otieno, K., Odero, C., Williamson, J., Kariuki, S., Kachur, S.P., Slutsker, L., Desai, M., 2013. A randomized trial of artemether-lumefantrine and dihydroartemisinin-piperaquine in the treatment of uncomplicated malaria among children in western Kenya. Malaria Journal 12, 254. https://doi.org/10.1186/1475-2875-12-254

2. Amato, R., Lim, P., Miotto, O., Amaratunga, C., Dek, D., Pearson, R.D., Almagro-Garcia, J., Neal, A.T., Sreng, S., Suon, S., Drury, E., Jyothi, D., Stalker, J., Kwiatkowski, D.P., Fairhurst, R.M., 2017. Genetic markers associated with dihydroartemisinin–piperaquine failure in Plasmodium falciparum malaria in Cambodia: a genotype–phenotype association study. The Lancet Infectious Diseases 17, 164–173. https://doi.org/10.1016/S1473-3099(16)30409-1

3. Amin, A.A., Zurovac, D., Kangwana, B.B., Greenfield, J., Otieno, D.N., Akhwale, W.S., Snow, R.W., 2007. The challenges of changing national malaria drug policy to artemisinin-based combinations in Kenya. Malar J 6, 72. https://doi.org/10.1186/1475-2875-6-72

4. Ansbro, M.R., Jacob, C.G., Amato, R., Kekre, M., Amaratunga, C., Sreng, S., Suon, S., Miotto, O., Fairhurst, R.M., Wellems, T.E., Kwiatkowski, D.P., 2020. Development of copy number assays for detection and surveillance of piperaquine resistance associated plasmepsin 2/3 copy number variation in Plasmodium falciparum. Malar J 19, 181. https://doi.org/10.1186/s12936-020-03249-x

5. Ashley, E.A., Phyo, A.P., 2018. Drugs in Development for Malaria. Drugs 78, 861–879. https://doi.org/10.1007/s40265-018-0911-9

6. Assefa, D.G., Zeleke, E.D., Bekele, D., Tesfahunei, H.A., Getachew, E., Joseph, M., Manyazewal, T., 2021. Efficacy and safety of dihydroartemisinin-piperaquine versus artemether-lumefantrine for treatment of uncomplicated Plasmodium falciparum malaria in Ugandan children: a systematic review and meta-analysis of randomized control trials. Malar J 20, 174. https://doi.org/10.1186/s12936-021-03711-4

7. Balikagala, B., Fukuda, N., Ikeda, M., Katuro, O.T., Tachibana, S.-I., Yamauchi, M., Opio, W., Emoto, S., Anywar, D.A., Kimura, E., Palacpac, N.M.Q., Odongo-Aginya, E.I., Ogwang, M., Horii, T., Mita, T., 2021. Evidence of Artemisinin-Resistant Malaria in Africa. N Engl J Med 385, 1163–1171. https://doi.org/10.1056/NEJMoa2101746

8. Barsosio, H.C., Madanitsa, M., Ondieki, E.D., Dodd, J., Onyango, E.D., Otieno, K., Wang, D., Hill, J., Mwapasa, V., Phiri, K.S., Maleta, K., Taegtmeyer, M., Kariuki, S., Schmiegelow, C., Gutman, J.R., ter Kuile, F.O., 2024. Chemoprevention for malaria with monthly intermittent preventive treatment with dihydroartemisinin–piperaquine in pregnant women living with HIV on daily co-trimoxazole in Kenya and Malawi: a randomised, double-blind, placebo-controlled trial. Lancet 403, 365–378. https://doi.org/10.1016/S0140-6736(23)02631-4

9. Baton, L.A., Ranford-Cartwright, L.C., 2005. Spreading the seeds of million-murdering death*: metamorphoses of malaria in the mosquito. Trends in Parasitology 21, 573–580. https://doi.org/10.1016/j.pt.2005.09.012

10. Belete, T.M., 2020. Recent Progress in the Development of New Antimalarial Drugs with Novel Targets. Drug Design, Development and Therapy 14, 3875–3889. https://doi.org/10.2147/DDDT.S265602

11. Bennink, S., Kiesow, M.J., Pradel, G., 2016. The development of malaria parasites in the mosquito midgut. Cell Microbiol 18, 905–918. https://doi.org/10.1111/cmi.12604

12. Bloland, P.B., Ettling, M., 1999. Making malaria-treatment policy in the face of drug resistance. Annals of Tropical Medicine & Parasitology 93, 5–23. https://doi.org/10.1080/00034983.1999.11813390

13. Boonyalai, N., Vesely, B.A., Thamnurak, C., Praditpol, C., Fagnark, W., Kirativanich, K., Saingam, P., Chaisatit, C., Lertsethtakarn, P., Gosi, P., Kuntawunginn, W., Vanachayangkul, P., Spring, M.D., Fukuda, M.M., Lon, C., Smith, P.L., Waters, N.C., Saunders, D.L., Wojnarski, M., 2020. Piperaquine resistant Cambodian Plasmodium falciparum clinical isolates: in vitro genotypic and phenotypic characterization. Malaria Journal 19, 269. https://doi.org/10.1186/s12936-020-03339-w

14. Certain, L.K., Briceño, M., Kiara, S.M., Nzila, A.M., Watkins, W.M., Sibley, C.H., 2008. Temporal patterns of pyrimethamine resistance haplotypes in Kilifi, Kenya. J Infect Dis 197, 1743–1751. https://doi.org/10.1086/588198

15. Chebore, W., Zhou, Z., Westercamp, N., Otieno, K., Shi, Y.P., Sergent, S.B., Rondini, K.A., Svigel, S.S., Guyah, B., Udhayakumar, V., Halsey, E.S., Samuels, A.M., Kariuki, S., 2020. Assessment of molecular markers of anti-malarial drug resistance among children participating in a therapeutic efficacy study in western Kenya. Malar J 19, 291. https://doi.org/10.1186/s12936-020-03358-7

16. Colonial policies to control malaria in Kenya: The early years (1896-1926) [WWW Document], n.d. URL https://1library.net/article/colonial-policies-control-malaria-kenya-early-years.yn6pd50q (accessed 7.28.25).

17. Cowell, A.N., Winzeler, E.A., 2019. The genomic architecture of antimalarial drug resistance. Brief Funct Genomics 18, 314–328. https://doi.org/10.1093/bfgp/elz008

18. Davis, T.M.E., Hung, T.-Y., Sim, I.-K., Karunajeewa, H.A., Ilett, K.F., 2005. Piperaquine: a resurgent antimalarial drug. Drugs 65, 75–87. https://doi.org/10.2165/00003495-200565010-00004

19. De Villiers, K.A., Egan, T.J., 2021. Heme Detoxification in the Malaria Parasite: A Target for Antimalarial Drug Development. Acc Chem Res 54, 2649–2659. https://doi.org/10.1021/acs.accounts.1c00154

20. Delandre, O., Pradines, B., Javelle, E., 2024. Dihydroartemisinin–Piperaquine Combination in the Treatment of Uncomplicated Plasmodium falciparum Malaria: Update on Clinical Failures in Africa and Tools for Surveillance. Journal of Clinical Medicine 13, 6828. https://doi.org/10.3390/jcm13226828

21. Delves, M., Plouffe, D., Scheurer, C., Meister, S., Wittlin, S., Winzeler, E.A., Sinden, R.E., Leroy, D., 2012. The Activities of Current Antimalarial Drugs on the Life Cycle Stages of Plasmodium: A Comparative Study with Human and Rodent Parasites. PLOS Medicine 9, e1001169. https://doi.org/10.1371/journal.pmed.1001169

22. Dereje, N., Fallah, M.P., Shaweno, T., Duga, A., Mazaba, M.L., Raji, T., Folayan, M.O., Ngongo, N., Ndembi, N., Kaseya, J., 2025. Resurgence of malaria and artemisinin resistance in Africa requires a concerted response. Nat Med 1–2. https://doi.org/10.1038/s41591-024-03439-z

23. Dhingra, S.K., Redhi, D., Combrinck, J.M., Yeo, T., Okombo, J., Henrich, P.P., Cowell, A.N., Gupta, P., Stegman, M.L., Hoke, J.M., Cooper, R.A., Winzeler, E., Mok, S., Egan, T.J., Fidock, D.A., 2017. A Variant PfCRT Isoform Can Contribute to Plasmodium falciparum Resistance to the First-Line Partner Drug Piperaquine. mBio 8, e00303-17. https://doi.org/10.1128/mBio.00303-17

24. Diakité, S.A.S., Traoré, K., Sanogo, I., Clark, T.G., Campino, S., Sangaré, M., Dabitao, D., Dara, A., Konaté, D.S., Doucouré, F., Cissé, A., Keita, B., Doumbouya, M., Guindo, M.A., Toure, M.B., Sogoba, N., Doumbia, S., Awandare, G.A., Diakité, M., 2019. A comprehensive analysis of drug resistance molecular markers and Plasmodium falciparum genetic diversity in two malaria endemic sites in Mali. Malaria Journal 18, 361. https://doi.org/10.1186/s12936-019-2986-5

25. Dimbu, P.R., Horth, R., Cândido, A.L.M., Ferreira, C.M., Caquece, F., Garcia, L.E.A., André, K., Pembele, G., Jandondo, D., Bondo, B.J., Nieto Andrade, B., Labuda, S., Ponce de León, G., Kelley, J., Patel, D., Svigel, S.S., Talundzic, E., Lucchi, N., Morais, J.F.M., Fortes, F., Martins, J.F., Pluciński, M.M., 2021. Continued Low Efficacy of Artemether-Lumefantrine in Angola in 2019. Antimicrob Agents Chemother 65, e01949-20. https://doi.org/10.1128/AAC.01949-20

26. Duru, V., Witkowski, B., Ménard, D., 2016. Plasmodium falciparum Resistance to Artemisinin Derivatives and Piperaquine: A Major Challenge for Malaria Elimination in Cambodia. Am J Trop Med Hyg 95, 1228–1238. https://doi.org/10.4269/ajtmh.16-0234

27. Ebohon, O., Irabor, F., Ebohon, L.O., Omoregie, E.S., 2019. Therapeutic failure after regimen with artemether-lumefantrine combination therapy: a report of three cases in Benin City, Nigeria. Rev Soc Bras Med Trop 52, e20190163. https://doi.org/10.1590/0037-8682-0163-2019

28. Ebong, C., Sserwanga, A., Namuganga, J.F., Kapisi, J., Mpimbaza, A., Gonahasa, S., Asua, V., Gudoi, S., Kigozi, R., Tibenderana, J., Bwanika, J.B., Bosco, A., Rubahika, D., Kyabayinze, D., Opigo, J., Rutazana, D., Sebikaari, G., Belay, K., Niang, M., Halsey, E.S., Moriarty, L.F., Lucchi, N.W., Souza, S.S.S., Nsobya, S.L., Kamya, M.R., Yeka, A., 2021. Efficacy and safety of artemether-lumefantrine and dihydroartemisinin-piperaquine for the treatment of uncomplicated Plasmodium falciparum malaria and prevalence of molecular markers associated with artemisinin and partner drug resistance in Uganda. Malar J 20, 484. https://doi.org/10.1186/s12936-021-04021-5

29. Hien, T.T., Dolecek, C., Mai, P.P., Dung, N.T., Truong, N.T., Thai, L.H., An, D.T.H., Thanh, T.T., Stepniewska, K., White, N.J., Farrar, J., 2004. Dihydroartemisinin-piperaquine against multidrug-resistant Plasmodium falciparum malaria in Vietnam: randomised clinical trial. The Lancet 363, 18–22. https://doi.org/10.1016/S0140-6736(03)15163-X

30. Imrat, Verma, A.K., Mina, P.R., Imrat, Verma, A.K., Mina, P.R., 2021. Recent Advances in Antimalarial Drug Discovery: Challenges and Opportunities, in: Plasmodium Species and Drug Resistance. IntechOpen. https://doi.org/10.5772/intechopen.97401

31. Ke, H., Sigala, P.A., Miura, K., Morrisey, J.M., Mather, M.W., Crowley, J.R., Henderson, J.P., Goldberg, D.E., Long, C.A., Vaidya, A.B., 2014. The heme biosynthesis pathway is essential for Plasmodium falciparum development in mosquito stage but not in blood stages. J Biol Chem 289, 34827–34837. https://doi.org/10.1074/jbc.M114.615831

32. Kenneth Ombongi, M Dobson, M Malowany, R W Snow, 1998. The East African Medical Journal: its History and Contribution to Regional Malaria Research during the last 75 years. 75, 10–19.

33. Leroy, D., Macintyre, F., Adoke, Y., Ouoba, S., Barry, A., Mombo-Ngoma, G., Ndong Ngomo, J.M., Varo, R., Dossou, Y., Tshefu, A.K., Duong, T.T., Phuc, B.Q., Laurijssens, B., Klopper, R., Khim, N., Legrand, E., Ménard, D., 2019. African isolates show a high proportion of multiple copies of the Plasmodium falciparum plasmepsin-2 gene, a piperaquine resistance marker. Malar J 18, 126. https://doi.org/10.1186/s12936-019-2756-4

34. Martin, R.E., Shafik, S.H., Richards, S.N., 2018. Mechanisms of resistance to the partner drugs of artemisinin in the malaria parasite. Current Opinion in Pharmacology 42, 71–80. https://doi.org/10.1016/j.coph.2018.07.010

35. Meibalan, E., Marti, M., 2017. Biology of Malaria Transmission. Cold Spring Harb Perspect Med 7, a025452. https://doi.org/10.1101/cshperspect.a025452

36. Mita, T., Tanabe, K., Kita, K., 2009. Spread and evolution of Plasmodium falciparum drug resistance. Parasitology International 58, 201–209. https://doi.org/10.1016/j.parint.2009.04.004

37. Mok, S., Fidock, D.A., 2024. Determinants of piperaquine-resistant malaria in South America. The Lancet Infectious Diseases 24, 114–116. https://doi.org/10.1016/S1473-3099(23)00564-9

38. Muangphrom, P., Seki, H., Fukushima, E.O., Muranaka, T., 2016. Artemisinin-based antimalarial research: application of biotechnology to the production of artemisinin, its mode of action, and the mechanism of resistance of Plasmodium parasites. J Nat Med 70, 318–334. https://doi.org/10.1007/s11418-016-1008-y

39. Mukherjee, A., Gagnon, D., Wirth, D.F., Richard, D., 2018. Inactivation of Plasmepsins 2 and 3 Sensitizes Plasmodium falciparum to the Antimalarial Drug Piperaquine. Antimicrob Agents Chemother 62, e02309-17. https://doi.org/10.1128/AAC.02309-17

40. Müller, I.B., Hyde, J.E., 2010. Antimalarial drugs: modes of action and mechanisms of parasite resistance. Future Microbiol 5, 1857–1873. https://doi.org/10.2217/fmb.10.136

41. Musuva, A., Ejersa, W., Kiptui, R., Memusi, D., Abwao, E., 2017. The malaria testing and treatment landscape in Kenya: results from a nationally representative survey among the public and private sector in 2016. Malar J 16, 494. https://doi.org/10.1186/s12936-017-2089-0

42. Mwai, L., Kiara, S.M., Abdirahman, A., Pole, L., Rippert, A., Diriye, A., Bull, P., Marsh, K., Borrmann, S., Nzila, A., 2009. In Vitro Activities of Piperaquine, Lumefantrine, and Dihydroartemisinin in Kenyan Plasmodium falciparum Isolates and Polymorphisms in pfcrt and pfmdr1. Antimicrobial Agents and Chemotherapy 53, 5069–5073. https://doi.org/10.1128/aac.00638-09

43. Nsanzabana, C., 2019. Resistance to Artemisinin Combination Therapies (ACTs): Do Not Forget the Partner Drug! Trop Med Infect Dis 4, 26. https://doi.org/10.3390/tropicalmed4010026

44. Ogutu, B.R., Onyango, K.O., Koskei, N., Omondi, E.K., Ongecha, J.M., Otieno, G.A., Obonyo, C., Otieno, L., Eyase, F., Johnson, J.D., Omollo, R., Perkins, D.J., Akhwale, W., Juma, E., 2014. Efficacy and safety of artemether-lumefantrine and dihydroartemisinin-piperaquine in the treatment of uncomplicated Plasmodium falciparum malaria in Kenyan children aged less than five years: results of an open-label, randomized, single-centre study. Malaria Journal 13, 33. https://doi.org/10.1186/1475-2875-13-33

45. Ombongi, K., Rutten, M., 2010. Dashed hopes and missed opportunities: Malaria control policies in Kenya (1896-2009). pp. 109–143. https://doi.org/10.1163/9789004201286_006

46. Organization, W.H., 2022. WHO guidelines for malaria, 3 June 2022, in: WHO Guidelines for Malaria, 3 June 2022.

47. Pandey, A.V., Bisht, H., Babbarwal, V.K., Srivastava, J., Pandey, K.C., Chauhan, V.S., 2001. Mechanism of malarial haem detoxification inhibition by chloroquine. Biochem J 355, 333–338. https://doi.org/10.1042/0264-6021:3550333

48. Pernaute-Lau, L., Recker, M., Tékété, M., de Sousa, T.N., Traore, A., Fofana, B., Sanogo, K., Morris, U., Inoue, J., Ferreira, P.E., Diallo, N., Burhenne, J., Sagara, I., Dicko, A., Veiga, M.I., Haefeli, W., Björkman, A., Djimde, A.A., Borrmann, S., Gil, J.P., 2025. Decreased dihydroartemisinin-piperaquine protection against recurrent malaria associated with Plasmodium falciparum plasmepsin 3 copy number variation in Africa. Nat Commun 16, 2680. https://doi.org/10.1038/s41467-025-57726-5

49. Ross, L.S., Dhingra, S.K., Mok, S., Yeo, T., Wicht, K.J., Kümpornsin, K., Takala-Harrison, S., Witkowski, B., Fairhurst, R.M., Ariey, F., Menard, D., Fidock, D.A., 2018. Emerging Southeast Asian PfCRT mutations confer Plasmodium falciparum resistance to the first-line antimalarial piperaquine. Nat Commun 9, 3314. https://doi.org/10.1038/s41467-018-05652-0

50. Ross, L.S., Fidock, D.A., 2019. Elucidating Mechanisms of Drug-Resistant Plasmodium falciparum. Cell Host Microbe 26, 35–47. https://doi.org/10.1016/j.chom.2019.06.001

51. Shanks, G.D., Biomndo, K., Hay, S.I., Snow, R.W., 2000. Changing patterns of clinical malaria since 1965 among a tea estate population located in the Kenyan highlands. Trans R Soc Trop Med Hyg 94, 253–255. https://doi.org/10.1016/s0035-9203(00)90310-9

52. Sharma, C., Awasthi, S.K., Sharma, C., Awasthi, S.K., 2015. Recent Advances in Antimalarial Drug Discovery — Challenges and Opportunities, in: An Overview of Tropical Diseases. IntechOpen. https://doi.org/10.5772/61191

53. Shretta, R., Omumbo, J., Rapuoda, B., Snow, R.W., 2000. Using evidence to change antimalarial drug policy in Kenya. Trop Med Int Health 5, 755–764. https://doi.org/10.1046/j.1365-3156.2000.00643.x

54. Silva, M., Calçada, C., Teixeira, M., Veiga, M.I., Ferreira, P.E., 2020. Multigenic architecture of piperaquine resistance trait in Plasmodium falciparum. Lancet Infect Dis 20, 26–27. https://doi.org/10.1016/S1473-3099(19)30689-9

55. Slater, L., Betson, M., Ashraf, S., Sargison, N., Chaudhry, U., 2021. Current methods for the detection of antimalarial drug resistance in Plasmodium parasites infecting humans. Acta Tropica 216, 105828. https://doi.org/10.1016/j.actatropica.2021.105828

56. Small-Saunders, J.L., Hagenah, L.M., Wicht, K.J., Dhingra, S.K., Deni, I., Kim, J., Vendome, J., Gil-Iturbe, E., Roepe, P.D., Mehta, M., Mancia, F., Quick, M., Eppstein, M.J., Fidock, D.A., 2022. Evidence for the early emergence of piperaquine-resistant Plasmodium falciparum malaria and modeling strategies to mitigate resistance. PLOS Pathogens 18, e1010278. https://doi.org/10.1371/journal.ppat.1010278

57. Talman, A.M., Ouologuem, D.T.D., Love, K., Howick, V.M., Mulamba, C., Haidara, A., Dara, N., Sylla, D., Sacko, A., Coulibaly, M.M., Dao, F., Sangare, C.P.O., Djimde, A., Lawniczak, M.K.N., 2020. Uptake of Plasmodium falciparum Gametocytes During Mosquito Bloodmeal by Direct and Membrane Feeding. Front Microbiol 11, 246. https://doi.org/10.3389/fmicb.2020.00246

58. Tarning, J., Ashley, E.A., Lindegardh, N., Stepniewska, K., Phaiphun, L., Day, N.P.J., McGready, R., Ashton, M., Nosten, F., White, N.J., 2008. Population Pharmacokinetics of Piperaquine after Two Different Treatment Regimens with Dihydroartemisinin-Piperaquine in Patients with Plasmodium falciparum Malaria in Thailand. Antimicrobial Agents and Chemotherapy 52, 1052–1061. https://doi.org/10.1128/aac.00955-07

59. Terlouw, D.J., Aidoo, M.A., Udhayakumar, V., Kolczak, M.S., Oloo, A.J., Kager, P.A., Lal, A.A., Nahlen, B.L., Kuile, F.O. ter, 2002. Increased Efficacy of Sulfadoxine-Pyrimethamine in the Treatment of Uncomplicated Falciparum Malaria among Children with Sickle Cell Trait in Western Kenya. The Journal of Infectious Diseases 186, 1661–1668. https://doi.org/10.1086/345363

60. Tumwebaze, P.K., Conrad, M.D., Okitwi, M., Orena, S., Byaruhanga, O., Katairo, T., Legac, J., Garg, S., Giesbrecht, D., Smith, S.R., Ceja, F.G., Nsobya, S.L., Bailey, J.A., Cooper, R.A., Rosenthal, P.J., 2022. Decreased susceptibility of Plasmodium falciparum to both dihydroartemisinin and lumefantrine in northern Uganda. Nat Commun 13, 6353. https://doi.org/10.1038/s41467-022-33873-x

61. Tuteja, R., 2007. Malaria − an overview. The FEBS Journal 274, 4670–4679. https://doi.org/10.1111/j.1742-4658.2007.05997.x

62. Usui, M., Williamson, K.C., 2021. Stressed Out About Plasmodium falciparum Gametocytogenesis. Front Cell Infect Microbiol 11, 790067. https://doi.org/10.3389/fcimb.2021.790067

63. Uwimana, A., Umulisa, N., Venkatesan, M., Svigel, S.S., Zhou, Z., Munyaneza, T., Habimana, R.M., Rucogoza, A., Moriarty, L.F., Sandford, R., Piercefield, E., Goldman, I., Ezema, B., Talundzic, E., Pacheco, M.A., Escalante, A.A., Ngamije, D., Mangala, J.-L.N., Kabera, M., Munguti, K., Murindahabi, M., Brieger, W., Musanabaganwa, C., Mutesa, L., Udhayakumar, V., Mbituyumuremyi, A., Halsey, E.S., Lucchi, N.W., 2021. Association of Plasmodium falciparum kelch13 R561H genotypes with delayed parasite clearance in Rwanda: an open-label, single-arm, multicentre, therapeutic efficacy study. Lancet Infect Dis 21, 1120–1128. https://doi.org/10.1016/S1473-3099(21)00142-0

64. Wakoli, D.M., Ondigo, B.N., Ochora, D.O., Amwoma, J.G., Okore, W., Mwakio, E.W., Chemwor, G., Juma, J., Okoth, R., Okudo, C., Yeda, R., Opot, B.H., Cheruiyot, A.C., Juma, D., Roth, A., Ogutu, B.R., Boudreaux, D., Andagalu, B., Akala, H.M., 2022. Impact of parasite genomic dynamics on the sensitivity of Plasmodium falciparum isolates to piperaquine and other antimalarial drugs. BMC Med 20, 448. https://doi.org/10.1186/s12916-022-02652-2

65. Watsierah, C.A., Ouma, C., 2014. Access to artemisinin-based combination therapy (ACT) and quinine in malaria holoendemic regions of western Kenya. Malar J 13, 290. https://doi.org/10.1186/1475-2875-13-290

66. Westercamp, N., Owidhi, M., Otieno, K., Chebore, W., Buff, A.M., Desai, M., Kariuki, S., Samuels, A.M., 2022. Efficacy of Artemether-Lumefantrine and Dihydroartemisinin-Piperaquine for the Treatment of Uncomplicated Plasmodium falciparum Malaria among Children in Western Kenya, 2016 to 2017. Antimicrobial Agents and Chemotherapy 66, e00207-22. https://doi.org/10.1128/aac.00207-22

67. White, N.J., 2005. Intermittent Presumptive Treatment for Malaria. PLOS Medicine 2, e3. https://doi.org/10.1371/journal.pmed.0020003

68. Wicht, K.J., Mok, S., Fidock, D.A., 2020. Molecular Mechanisms of Drug Resistance in Plasmodium falciparum Malaria. Annu Rev Microbiol 74, 431–454. https://doi.org/10.1146/annurev-micro-020518-115546

69. Witkowski, B., Duru, V., Khim, N., Ross, L.S., Saintpierre, B., Beghain, J., Chy, S., Kim, S., Ke, S., Kloeung, N., Eam, R., Khean, C., Ken, M., Loch, K., Bouillon, A., Domergue, A., Ma, L., Bouchier, C., Leang, R., Huy, R., Nuel, G., Barale, J.-C., Legrand, E., Ringwald, P., Fidock, D.A., Mercereau-Puijalon, O., Ariey, F., Ménard, D., 2017. A surrogate marker of piperaquine-resistant Plasmodium falciparum malaria: a phenotype–genotype association study. The Lancet Infectious Diseases 17, 174–183. https://doi.org/10.1016/S1473-3099(16)30415-7

70. World Health Organization, 2009. Global antimalarial drug policies database—WHO African region, September ed. Geneva, Switzerland.

71. World malaria report 2024 [WWW Document], n.d. URL https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2024 (accessed 7.28.25).