

Mini Review

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

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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 dihydroartemisinin 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 rupture to release infective merozoites (Delves et al., 2012). Merozoites infect the erythrocytes where they transform into mature

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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 Phyto, 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 Poulenc 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 tetrakisphosphate 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 Phyto, 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 *pfcr*t 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 *pfpm*2 and *pfpm*3 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; Nsanabana, 2019).

PPQ resistance is recognized as a multigenic trait, caused by mutations in several genes, including *pfpm*2, *pfpm*3, *pfcr*t, *pfmdr*1, *pfexo*, and *pfk*13 (Dhingra et al., 2017; Leroy et al., 2019; Martin et al., 2018; Nsanabana, 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 *pfpm*2/3 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 *pfpm*2 amplification is increasingly prevalent and unassociated with clinical or *in vitro* PPQ resistance (Leroy et al., 2019). This observation suggests that *pfpm*2/3 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	<i>Pfpm</i> 2	Overexpression/increased gene copy number	Amato et al., 2017, Duru et al., 2015, Martin et al., 2018, Silva et al., 2020
	<i>Pfpm</i> 3	Overexpression/increased gene copy number	Amato et al., 2017, Martin et al., 2018, Silva et al., 2020
	<i>Pfmdr</i> 1	Single copy number variation	Duru et al., 2015
	<i>Pfcr</i> t	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
	<i>Pfexo</i>	E415G	Amato et al., 2017, Boonyalai et al., 2020, Diakite et al., 2019, Duru et al., 2015
	<i>Pfk</i> 13	C580Y, I543T, P553L, R539T, Y493H & P574L	Duru et al., 2015, Mok & Fidock, 2024

*Pfpm*2- *Plasmodium falciparum* plasmepsin 2 gene and *Pfpm*3- *Plasmodium falciparum* plasmepsin 3 gene, *Pfmdr*1- *Plasmodium falciparum* multi drug resistance gene 1, *Pfcr*t- *Plasmodium falciparum* chloroquine resistance gene, *Pfexo*-*Plasmodium falciparum* exonucleases, *Pfk*13- *Plasmodium falciparum* kelch 13

Mutations in the *pfcr*t 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 (Diakit   et al., 2019). However, its relevance in African parasite populations remains unclear (Diakit   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 *pfcr*t 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 *Pfcr*t, *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 *Pfcr*t 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). *Pfcr*t (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 recrudescence 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.

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