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Effectiveness of dihydroartemisinin-piperaquine for treating *Plasmodium falciparum* malaria from sub-Saharan Africa: a retrospective study

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ABSTRACT

Background: Artemisinin-based combination therapies (ACTs) are the recommended first-line treatment for uncomplicated malaria. However, growing reports of artemisinin resistance, particularly in Southeast Asia, raise concerns about the efficacy of ACTs. This study aimed to assess potential changes over time in the effectiveness of a three-day regimen of dihydroartemisinin-piperaquine (DHA-PPQ) for treating imported uncomplicated *Plasmodium falciparum* malaria.

Methods: A retrospective observational study was conducted. We reviewed the records of patients treated for uncomplicated *P. falciparum* malaria in a single centre in Italy (2013–2024). The inclusion criteria were treatment with DHA-PPQ and available data on parasitaemia at baseline and on day three. The primary objective was to determine the rate of parasitaemia clearance on day three.

Results: All 90 patients but one were infected in sub-Saharan Africa. We excluded the patient infected in Yemen to obtain a more homogenous cohort. Baseline median parasitaemia was 0.136 % (IQR 0.029–0.750). On day 3, only 6 patients (6.7 %) still had circulating parasites, though in absence of early treatment failure. Follow-up data (available for 63 patients) excluded also late parasitological failures. No significant trend in day-3 positivity was observed across the three study periods (2013–2015, 2016–2019, 2020–2023; $p = 0.339$).

Conclusions: This study revealed no significant reduction in the effectiveness of DHA-PPQ over time for the treatment of uncomplicated *P. falciparum* malaria imported from Africa. While ACT failure remains rare in sub-Saharan Africa, continued surveillance is essential, especially to monitor resistance trends and inform treatment protocols.

1. Introduction

As delineated in the World Health Organization (WHO) Guidelines for Malaria (2023), oral artemisinin-based combination therapy (ACT) remains the first-line treatment for uncomplicated malaria [1]. However, increasing concerns have emerged regarding the potential decline in their efficacy against *Plasmodium falciparum* infection due to the emergence of resistance [2–5].

From the clinical point of view, malaria is mainly classified as either severe or uncomplicated malaria.

According to the WHO definitions, therapeutic failures of malaria treatment can be classified into Early Therapeutic Failures and Late Therapeutic Failures. These failures may be due to various factors, including drug resistance, inadequate adherence to the treatment regimen, or individual pharmacokinetic profiles. Resistance to ACT may involve artemisinin derivatives, partner drugs, or both [2]; first identified in Cambodia in 2009 [6], it has since spread across the Greater Mekong Subregion [7,8], been detected at low frequency in India [9,10]

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and sub-Saharan Africa [11–18].

Partial artemisinin resistance, mediated by PfK13 mutations [18–20], manifests as delayed parasite clearance without complete loss of efficacy [21], while piperaquine resistance is linked to pm2/3 amplifications and PfCRT point mutations, the latter driving high-level resistance [22]; however, ACT failures may also result from subtherapeutic drug concentrations rather than genetic resistance alone [23].

Monitoring for treatment failure is also essential in nonendemic areas, both for documenting the emergence of resistance in the geographical areas of origin of patients and for evaluating the possible need for revision of national standard treatment regimen protocols. However, few studies have been conducted on the potential reduction in the efficacy of ACT regimens in nonendemic countries [24–30].

The aim of this study was to assess a possible change over time in the effectiveness of a three-day regimen of DHA-PPQ for treating uncomplicated *P. falciparum* malaria.

The primary objective of this study was to investigate the clearance of detectable parasitaemia, considering the asexual stages of the parasite, in peripheral blood smears on day three in patients treated with DHA-PPQ.

The secondary objectives of the study were as follows.

1) to compare the proportion of individuals with cleared parasitaemia on days one and two;
2) to identify early and late therapeutic failures.

2. Methods

This was a retrospective observational study. The study protocol received ethical clearance from the competent Ethics Committee "Comitato Etico Territoriale Sud Ovest Veneto" on June 5, 2024 (Prog. 300CET "EUREFF").

We reviewed the clinical records of all patients with uncomplicated *P. falciparum* malaria who were admitted to the Department of Infectious Tropical Diseases and Microbiology (DITM) of IRCCS Hospital Sacro Cuore Don Calabria (Negrar di Valpolicella, Verona, Italy) from September 2013 to March 2024. The diagnosis relied on microscopic detection of *P. falciparum* asexual forms.

For the definitions of severe and uncomplicated malaria, we referred to the WHO criteria [1].

Also, the definitions of Early and Late Therapeutic Failures were based on the criteria set by the WHO [1].

According to the routine procedures performed in clinical practice at the DITM, parasitaemia was calculated as the number of asexual parasites counted per 200 white blood cells on the thick blood smear or as the number of parasitised red blood cells in a total of at least 1000 red blood cells on the thin blood smears. The choice of either method depends on the parasitaemia level. Patients with parasitaemia greater than 10 % were classified as having severe malaria, according to the WHO definition [1]. For the evaluation of parasitaemia clearance, only the asexual forms of the parasite were considered.

All patients diagnosed with malaria were hospitalised via routine protocols followed at DITM. The inclusion criteria were treatment with DHA-PPQ and available data on parasitaemia at baseline and on day three.

The exclusion criteria were severe malaria; malaria caused by *Plasmodium* species other than *P. falciparum* or mixed infections; malaria treated with other or additional antimalarial drugs.

We reviewed paper (from 2013–2015) and electronic records (from 2016–2024) and collected the following variables: date of diagnosis; dates of first dose of treatment; duration of treatment; parasitaemia at baseline, on days one, two, and three and on following days if parasitaemia on day three was still positive; follow-up parasitaemia from day seven until day 42; presence of axillary temperature greater than 37.5 °C on day one, two, and three; DHA-PPQ dosage (number of tablets per day); age; sex; body weight; country of infection; country of origin; reason for the travel; chronic diseases (diabetes, cardiopathy, chronic obstructive pulmonary disease, hypertension, chronic liver disease, chronic kidney disease, malignancies); past splenectomy, history of malaria prophylaxis.

3. Statistical analysis

A convenience sample of eligible records was used for the study. Continuous variables are presented as medians, interquartile ranges (IQRs) as well as minimum and maximum values. Categorical variables are presented as numbers and percentages. The chi-square test with a simulated p value was used to compare the proportions of positive cases after different days of treatment between years of treatment (2013–2015, 2016–2019, 2020–2023) and the Kruskal-Wallis rank sum test was used to compare levels of parasitaemia across years of treatment (2013–2015, 2016–2019, 2020–2023).

4. Results

89 patients had acquired the infection in Africa, and only one patient had acquired it in Yemen. For this reason, to strengthen the internal consistency of the study and ensure uniformity, we excluded the patient who had contracted malaria in Yemen from the subsequent analyses. Among the 89 patients enrolled, 26 (29.2 %) were female. The median age was 45 years (IQR 31–53), and the median weight was 77 kg (IQR 66–88, min: 14.6, max: 113).

The patient population primarily consisted of visiting friends and relatives (VFR) (67 patients, 75.3 %), tourists (14 patients, 15.7 %), missionaries and non-governmental organization workers (eight patients, 9 %); comorbidities were reported by 42 out of 89 (47.2 %). The most common comorbidities were: arterial hypertension (17 patients, 19.1 %), diabetes mellitus (8 patients, 9 %), chronic liver disease (2 patients, 2.2 %), and splenectomy (1 patient, 1.1 %). Three patients had taken chemoprophylaxis with mefloquine, which was however discontinued before the end of the trip. The African countries where each patient acquired the infection are shown in Fig. 1. A total of 93.3 % of patients completed the 3-day standard treatment with DHA-PPQ. Among the remaining patients, four (4.5 %) and two (2.2 %) received four and five days of therapy, respectively. One of the patients who received the treatment for five days had positive parasitaemia on day three; the reason for prolonging DHA-PPQ treatment for more than three days was not clearly stated in the medical records of the remaining five patients.

Overall, the median parasitaemia at baseline was 0.136 % (IQR 0.029–0.750), on day one was 0.011 % (IQR: 0.001–0.129, 88 valid cases), on day two was 0 % (IQR: 0–0.001, 80 valid cases), and on day three was 0 % (IQR: 0–0, 90 valid cases).

On day three, 83/89 patients (93.3 %) had cleared parasitaemia, whereas 6/98 patients (6.7 %) were still parasitaemic (max: 0.67 %, min: 0 %).

Of these six patients, two had acquired their infection in Nigeria, two in Ghana, one in Burkina Faso, and one in Togo. Considering that the number of DHA-PPQ tablets is administered in relation to body weight, an underdosage of the therapy was observed in one patient (body weight 110 kg, tablets administered: 4 per day). Only one of these patients with persisting parasitaemia received a prolonged (i.e. more than three-day) treatment course.

No statistically significant correlation was detected between parasitaemia positivity on day three and the year in which the patient was treated (p value 0.339), even when the periods were stratified into three-time intervals (2013–2015, 2016–2019, and 2020–2023), as shown in Table 1.

When the patient with underdosage was excluded, the analyses did not reveal significant correlations either.

On day three, no patient was febrile, nor had parasitaemia greater than 25 % of the pre-treatment value. Parasitaemia on day two did not

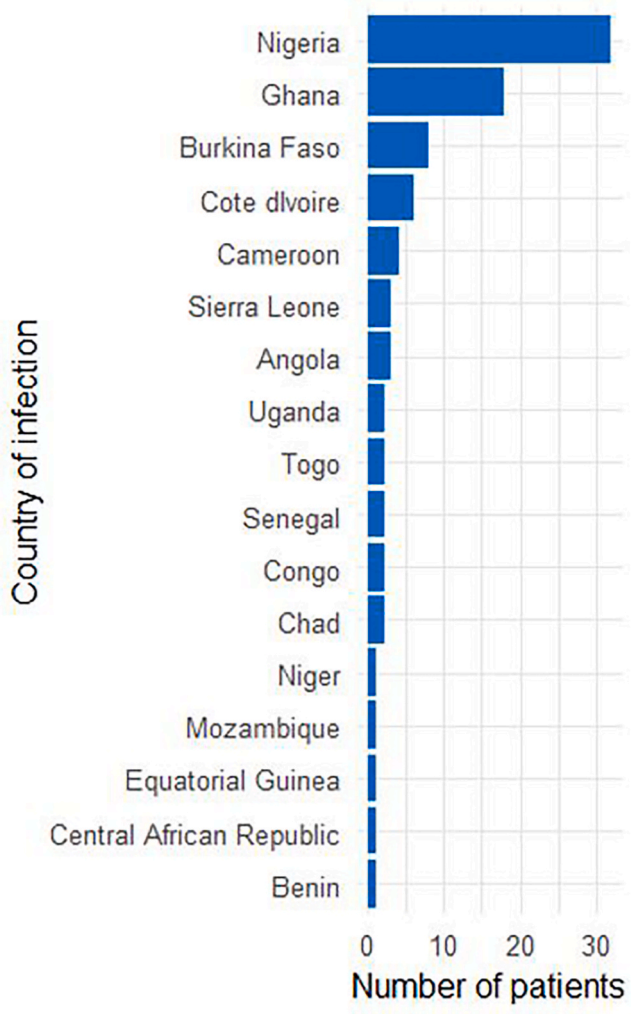

Fig. 1. Country of infection: countries where *Plasmodium falciparum* infection was acquired.

exceed the pre-treatment levels in any of the 80 patients for whom the data were available. Overall, none of the six patients with positive parasitaemia on day three met the criteria for early treatment failure [2].

Parasitaemia in at least one time point from day 7 to day 42 was available for 63 patients, and was negative in all cases. Therefore, none of the patients for whom follow-up data were available after the end of therapy met the WHO definition of late parasitological failure.

5. Discussion

In Europe, treatment failure to therapeutic drug regimens containing artemisinin derivates has seldom been reported, mostly concerning artemether-lumefantrine [27,28,34,35]. The first case of DHA-PPQ failure reported in Europe in an uncomplicated *P. falciparum* case was detected in 2014 [31]. A few other cases were reported afterwards, though some of them were probably caused by under-dosing rather than gene mutations [32]. A case report published in 2022 described a patient returning from Côte d'Ivoire with a diagnosis of severe malaria, who experienced recrudescence after treatment with intravenous artesunate followed by DHA-PPQ. Molecular analysis did not detect molecular markers of antimalarial drug resistance, and the relapse was attributed either to impaired intestinal absorption or poor manufacturing practices. In this case, however, unlike the patients in our study, the malaria was severe and was initially treated with intravenous artesunate and only subsequently with DHA-PPQ [33].

Our findings did not show an increasing trend in parasitological failure of uncomplicated malaria cases imported from African countries treated with DHA-PPQ, which is in line with the findings of previous meta-analyses [34,35]. It should however be considered that most studies conducted in Africa have analysed the response to artemether-lumefantrine (A-L), which is the drug most widely used [36,37], and this entails greater community exposure and an increased risk of resistance transmission compared to DHA-PPQ [23].

Specifically, a meta-analysis conducted in 2013 evaluated the trends in early parasitological response following treatment with ACT for uncomplicated malaria, comparing studies from 2000–2005 with those from 2006–2011 [34]. In 95 % of the analysed studies, the proportion of patients with peripheral parasitaemia was less than 6 % at 72 h. Excluding studies from Cambodia, no patients presented with positive

Table 1
Median parasitaemia at the different time points in the three-time intervals.

		Treatment period			p-value
	Overall	2013–2015	2016–2019	2020–2023	
	N = 89	N = 29	N = 44	N = 16	
Parasitaemia day0 (n/200 WBC)					0.593[a]
Median (IQR)	0.1362 (0.0286, 0.7500)	0.1362 (0.0367, 0.6166)	0.0972 (0.0243, 0.7278)	0.3664 (0.0344, 1.4878)	
Min, Max	0.0009, 4.4300	0.0009, 2.4000	0.0014, 4.4300	0.0016, 3.3000	
Parasitaemia day1 (n/200 WBC)					0.595[a]
Median (IQR)	0.0110 (0.0014, 0.1286)	0.0128 (0.0029, 0.1288)	0.0094 (0.0010, 0.1283)	0.0076 (0.0007, 0.1170)	
Min, Max	0, 3.8500	0, 0.9000	0, 3.8500	0, 1.3200	
Cases with clearance of parasitaemia on day 1, n/N, %	7/88, 8.0 %	1/29, 3.4 %	4/43, 9.3 %	2/16, 12.5 %	0.524[b]
Parasitaemia day2 (n/200 WBC)					0.64[a]
Median (IQR)	0 (0, 0.0007)	0 (0, 0.0007)	0 (0, 0.0008)	0 (0, 0.0007)	
Min, Max	0, 0.4000	0, 0.0038	0, 0.0359	0, 0.4000	
Cases with clearance of parasitaemia on day 2, n/N, %	49/89, 55.1 %	16/29, 55.2 %	21/44, 47.7 %	12/16, 75.0 %	0.171[b]
Parasitaemia day3 (n/200 WBC)					0.167[a]
Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
Min, Max	0, 0.6657	0, 0	0, 0.0016	0, 0.6657	
Cases with clearance of parasitaemia on day 3, n/N, %	83/89, 93.3 %	29/29, 100.0 %	40/44, 90.9 %	14/16, 87.5 %	0.127[b]

[a] Kruskal-Wallis rank sum test.
[b] Pearson's Chi-squared test.

parasitaemia on the third day of treatment [34].

In fact, a reduction in the efficacy of ACT has been reported mainly in Southeast Asia, primarily in Cambodia, Thailand, and Vietnam [6–8,38,39]. Reports of therapeutic failure in sub-Saharan Africa are rare, and if they are attributed to drug resistance, the underlying suspected mechanism is resistance to the partner drug [9]. Notably, the patients enrolled in our study were mainly VFR or travelers to sub-Saharan Africa. No patient had contracted malaria in Southeast Asia. This could explain the low rate of failure reported in our study.

Of note, underdosing plays a substantial role in the resistance to artemisinin derivatives, primarily causing late failures [38]. This is an issue specifically for patients weighing more than 80 kg who receive DHA-PPQ; for these individuals, the WHO guidelines recommend a higher dosage compared to that reported in the package leaflet, to reduce the risk of treatment failure [1].

This study has some limitations. First, the small number of cases per year and their uneven distribution across the years. The retrospective design might have resulted in poorer quality of the collected data and limited some sub-analyses due to a lack of information; for example, we were unable to assess any late clinical failure and we had no data on the possible presence of resistance-associated mutations in the samples from the six patients who still had positive parasitaemia on the third day of treatment. Overall, parasitaemia at baseline was relatively low in all patients, partly due to the decision to enroll only those with uncomplicated malaria. However, this may have led to an underestimation of the number of patients still parasitaemic on day 3 of therapy. Parasitaemia levels at baseline and follow-up were assessed by different microbiologists as part of routine care, which may introduce variability and operator-dependent results.

6. Conclusions

In conclusion, our study revealed no difference over time in the frequency of DHA-PPQ failure for the treatment of uncomplicated malaria. However, we must consider that the sample size was small and that no cases were from Southeast Asia, where the highest proportion of ACT failures is currently reported. Monitoring possible treatment failures is important to establish an alert in the case of expansion of areas with the emergence of ACT-resistant parasites. Regular surveillance studies, such as the present work, are essential for the early detection of emerging antimalarial resistance. They serve as critical early-warning tools, enabling timely identification of resistance trends and potential geographic spread, thereby informing public health strategies and guiding effective malaria control interventions.

CRediT authorship contribution statement

Federica Ciminelli: Writing – original draft, Data curation. **Dora Buonfrate:** Writing – review & editing, Conceptualization. **Cristina Mazzi:** Methodology, Formal analysis. **Andreas Neumayr:** Writing – review & editing. **Daniel Camprubí-Ferrer:** Writing – review & editing. **Federico Gobbi:** Writing – review & editing, Supervision, Data curation, Conceptualization.

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Declaration of competing interest

The authors have declared no conflicts of interest.

List of abbreviations

WHO: World Health Organization.
ACT: artemisinin-based combination therapy.
DHA-PPQ: dihydroartemisinin-piperaquine.
PPQ: piperaquine
pm2/3: Plasmepsin 2 and 3.
DITM**:** Department of Infectious Tropical Diseases and Microbiology.
VFR: visiting friends and relatives.
IQR: interquartile range.
A-L: artemether-lumefantrine.

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