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Effectiveness and safety of artemether–lumefantrine and dihydroartemisinin– piperaquine for the treatment of uncomplicated Plasmodium falciparum malaria in Franceville, Gabon

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Abstract

Background Artemether-lumefantrine (AL) and dihydroartemisinin-piperaquine (DHAPPQ) are the currently recommended first and second-line treatment for uncomplicated *Plasmodium falciparum* malaria in Gabon. Since 2017, no study assessing the efficacy of Artemisinin-based combinations (ACTs) was performed in Gabon, despite emerging signs of reduced efficacy of ACTs in parts of Africa. This study aimed to evaluate the effectiveness and safety of AL versus DHAPPQ for the treatment of uncomplicated *P. falciparum* malaria in Franceville, Gabon.

Methods We conducted a two-arm, open label, randomized controlled trial from July 2023 to April 2024 at Sino-Gabonese friendship hospital of Franceville. Children aged 6-144 months with uncomplicated *P. falciparum*malaria were enrolled, randomly assigned to receive AL or DHAPPQ and followed for 28 days, according to the WHO 2009 protocol. Recurrent infections were genotyped to distinguish recrudescence from new infection. The main outcomes were PCR uncorrected, PCR-corrected, day-3 parasitemia, and safety.

Results A total of 60 and 63 children were enrolled in the AL and DHAPPQ arms, respectively. during follow-up, 13.3% (n = 8/60) in AL and 14.3% (n = 9/63) in DHAPPQ arms were lost to follow-up or withdrew consent. The PCR-uncorrected ACPR was 92.3% (95% CI: 81.5-97.9%) for AL and 87.0% (95% CI:75.1-94.6%) for DHAPPQ, whereas day-28 PCR-corrected cure rates were 100% (92.6-100.0%) for AL and 100% (92.5-100.0%). All recurrent infections were classified as new infections. The proportion of patients with parasites on day 3 was 13.5% in AL and 16.7% in DHAPPQ arms. Both treatments were well tolerated with no serious adverse events occurred.

Conclusion Both AL and DHAPPQ remain highly effective and well-tolerated for the treatment of uncomplicated malaria in Gabon. However, the persistence of parasitemia on day 3 in both treatment arms is a warning signal that warrants sustained surveillance of effectiveness and efficacy of ACTs treatment in the country.

Background

Despite substantial progress in control and elimination efforts, including the development in diagnostic tools, advances in antimalarial drugs, immunizations, and vector control, malaria remains a major global public health concern, particularly in sub-Saharan African countries. In 2024, in the world malaria report, the World Health Organization (WHO) estimated 282 million malaria cases, and 610,000 related deaths worldwide [1]. The WHO African region continues to carry the heaviest burden, accounting for approximately 94% of cases and 95% of global malaria-related deaths. Children under five years old are the most affected and represented about 75% of all deaths due to malaria [1]. Malaria control strategy relies primarily on the prompt treatment of cases with effective antimalarial drugs [2].

Since the 2000s, the WHO recommended artemisinin-based combination therapy (ACTs) as the first line for the treatment of uncomplicated *P. falciparum* malaria in all endemic countries due to the emergence

and widespread of parasites resistant to once effective monotherapies such as chloroquine and sulfadoxine-pyrimethamine [3]. The six currently recommended artemisinin-based combination include artemether-lumefantrine (AL), artesunate-amodiaquine (AS-AQ), dihydroartemisinin-piperaquine (DHA-PPQ), artesunate-mefloquine (AS-MQ), artesunate-sulfadoxine-pyrimethamine (AS-SP) and artesunate-pyronaridine (AS-PY). The choice of ACTs by decision makers is based on robust local data regarding optimal efficacy, safety, parasite resistance, treatment adherence, and even cost-effectiveness.

ACTs are currently a critical component of global malaria control and elimination strategies, and addressing treatment failures is crucial to sustaining their long-term efficacy. In malaria endemic countries, WHO recommends regular surveillance every two years to assess the performance of first-line ACTs as well as second-line and those under consideration for future to inform treatment policies [4]. Thus, once the therapeutic efficacy of an first-line ACT falls below 90%, the WHO recommends a change in treatment regimen [5]. Recent published data from numerous therapeutic efficacy studies (TESs) have shown that AL and DHAPPQ remain highly efficacious and effective for the treatment of uncomplicated *P. falciparum* malaria in different endemic African countries [6, 7], although an increasing number of documents report a decline in efficacy in some areas [8–11]. Gabon adopted ACTs in 2003, and a subsequent national antimalarial medicine policy revision in 2013, recommended both AL and ASAQ as first-line regimens, whereas DHAPPQ was made second-line option. At that time, a single available comparative efficacy trial of AL and DHAPPQ in Gabon, conducted between 2007 and 2009, demonstrated a high efficacy for both treatments [12]. No subsequent therapeutic efficacy studies on these antimalarial combinations have been reported in the country. The most recent TES conducted in Lambaréné in 2017 noted the high therapeutic efficacy rate and excellent tolerability for AL [13]. A separated study performed in Franceville and Libreville between 2014 and 2015 likewise demonstrated high efficacy and safety for AL in *P. falciparum* malaria in Gabon [14].

Monitoring the efficacy of these ACTs in clinical practice, around 10 years after the start of their concomitant use in the national policy, is critical to determine if these drugs maintained their ability to treat uncomplicated malaria, and to provide up-to-date data able to assist policymakers. This study aimed to assess the effectiveness and safety of AL and DHAPPQ for the treatment of uncomplicated *P. falciparum* malaria, and to evaluate their protective effects against new infections among children in Franceville, Gabon.

Methods

Study site and period

The study was conducted from July 2023 to April 2024 at the Sino-Gabonese Friendship Hospital in Franceville, the capital of Haut-Ogooué province in southeastern Gabon. Franceville is the third largest city in the country, with an estimated population of approximately 110,000 according to the last official census of 2013 [15]. Malaria transmission in this region is mesoendemic, with an estimated parasite prevalence of approximately 20% and perennial transmission throughout the year [16–19].

Study design

The study was a two-arm, open-label, randomized controlled trial designed to assess the effectiveness and safety of AL and DHAPPQ in children with uncomplicated *P. falciparum* malaria. Patients were followed for 28 days' period with a series of scheduled follow-up visits, clinical and laboratory assessments according to the standard WHO 28-day efficacy protocol [20], except that only the first dose of each antimalarial regimen was directly supervised by clinical staff. Enrolled children were randomly assigned to receive either AL or DHAPPQ.

Patients enrollment

All children of either sex, aged from 6 months to 12 years, who attended the Sino-Gabonese Friendship Hospital and fulfilled all the following criteria were enrolled in the study: (i) presenting with fever (axillary temperature ≥ 37.5°C), or history of fever within the past 24 hours; (ii) confirmed mono-infection with asexual *P. falciparum;* (iii) parasitemia ranging from > 1000 to ≤ 200 000 asexual parasites/ μL ; (iv) ability to ingest tablets orally (v) ability and willingness to comply with the protocol for the duration of the study and to follow the consultation schedule (vi) written informed consent from parent or legal guardian. Parents or guardians were instructed to supervise home-based treatment and to ensure compliance with schedules post-treatment clinical and laboratory assessments. Additional eligibility criteria were applied in accordance with WHO standard protocol [20].

Sample size estimation

The required sample size estimate were informed by the results of previous studies conducted in Gabon in 2009 [12] and 2015 [13, 14] assessing AL and DHAPPQ. Per the WHO protocol a PCR-corrected treatment failure rate of 5% was assumed for both AL and DHAPPQ treatment arms. Using a confidence level of 95% and an estimate precision of 6%, a minimum sample size of 51 participants was estimated for each treatment arm. To account for an anticipated 20% loss to follow-up and withdrawals during the 28-day follow-up period, 62 participants were targeted per treatment arm, for a total of 124 participants.

Drug administration and follow-up

Enrolled patients were treated either with AL (Artefan®, Ajanta pharma limited, Mumbai, India) or DHAPPQ (Malacur®, Ciron drugs and pharmaceuticals Pvt. Ltd., India, for Laboratorios Salvat). Treatments were administrated orally based on body weight, in line with the manufacturer recommendations. AL oral tablets were administrated as fixed-doses combinations of 20 mg/120 mg or 40 mg/240 mg or 60 mg/360 mg or 80 mg/480 mg, whereas DHA-PPQ oral tablets were supplied in fixed-dose combinations available in three dosages forms: 20 mg/160 mg, 40 mg/320 mg and 60 mg/480 mg (Table S1, supplementary data). Both regimens were administrated over three consecutive days: AL as six doses given twice daily, while DHAPPQ as three doses given once daily.

Enrolled patients were followed-up for a period of 28 days with scheduled visits on days 1, 2, 3, 7, 14, 21, and 28 (day 0 was counted as day of the first drug intake), or at any unscheduled day within the 28 days' follow-up period if malaria-like symptoms emerged or when child felt unwell. Each follow-up visit involved clinical assessment and blood collect for parasitological evaluation, hemoglobin level measurement, and filter paper storage.

Study outcomes

The primary treatment outcomes were day 3 parasitemia and per-protocol PCR-uncorrected and PCR-corrected efficacy outcomes for AL and DHA-PPQ at 28 days' follow-up period. Treatment outcomes analyzed were classified in accordance with the WHO protocol[20] as early treatment failure (ETF), late clinical failure (LCF), late parasitological failure (LPF), or adequate clinical and parasitological response (ACPR), before and after PCR correction. Secondary outcomes included parasite clearance after treatment initiation, fever resolution, changes in mean hemoglobin level, the occurrence of adverse events and serious adverse events in both treatment groups during the 28 days' follow-up period. All adverse events that occurred during follow-up were recorded at each scheduled or unscheduled visit through interviews with parents or guardians about the nature and frequency of any events that occurred at home between follow-up visits. For each patient, adverse events were recorded in individual case report forms.

Microscopy

Parasitological assessment consisted of quantification of malaria asexual parasites and *Plasmodium* species identification to confirm compliance with inclusion criteria. At enrollment, two slides were collected for each patient: one thick smear stained with 20% Giemsa for 20 minutes and examined by microscopy to detect presence and an estimated parasite density, and a thin smear stained with RAL kit, according with the manufacturers recommendations, for *Plasmodium* species identification. Thin smears were also prepared on the day of recurrent infections. Thick blood smears were further examined during the follow-up period on days 1, 2, 3, 7, 14, 21 and 28. Parasites density expressed in parasites per µl of blood was estimated by counting the number of asexual parasites against 200 leucocytes in thick blood films, then by multiplying the total count by a factor of 30, assuming an average count of leucocytes of 6000 in a µl of blood.[21] A slide was declared free malaria parasite if at least 100 high power fields were read and did not reveal the presence of malaria parasite. All malaria blood slides were examined independently by two qualified microscopists, and any discordant readings (in the presence or absence of parasites, in species diagnosis or parasite density) were reviewed by a third independent microscopist. For each patient, the final parasite density was considered as the average of the first two counts, or by averaging the two closest parasitemias in the case of discordant results from the first two microscopists.

Hematological assessment

Hemoglobin levels were measured on days 0, 7, 14, 21 and 28, using a SFRI HEMIX 3–60 automated hematology analyzer (SFRI Medical Diagnostics, France).

Molecular analysis

Plasmodium genomic DNA was extracted from dried blood spots (DBS) using the Quick-DNA™ Miniprep Plus Kit (Zymo Research, USA), according to the manufacturer's instructions. Purified DNA was eluted in 100 µl of elution buffer and stored at -20°C until downstream assays.

To distinguish recrudescence from reinfection, paired samples from patient who presented with a recurrent parasitemia (day 0 and the day of recurrent infection) were genotyped by PCR targeting polymorphic regions of *P. falciparum* merozoite surface protein 1 (*msp*-1) and merozoite surface protein 2 (*msp*-2)[22, 23]. The three *msp*-1 allelic families (MAD20, RO33, K1) and the two *msp*-2 allelic families (FC27, 3D7) were amplified using family-specific nested PCR. Genotypic profiles obtained from amplification baseline samples (day 0) and on the day of recurrent parasitemia were compared for each allelic family based on DNA fragment size. Cases were classified as recrudescence by the presence of a least one shared allele at each locus between both paired samples for either of the two marker genes. A new infection was defined when there were no shared alleles between pre- and post-treatment samples for a least one of the two markers.

Data management and statistical analysis

Data were collected using the WHO standardized Microsoft Excel data collection sheet. Data were double-entered by two independent operators, and any discrepancies were reviewed and corrected by a third reviewer. Statistical analyses were performed using RStudio software (v2025.09.2 + 418; Posit software PBC, Boston, MA, USA). Day 3 parasitemia was defined as the proportion of patients with detectable parasitemia on day 3. A univariate logistic regression model was fitted to estimate the association between baseline parasite density and the risk of persistent parasitemia on day 3. The Kaplan-Meier survival analysis was used to estimate and visualize both unadjusted and PCR-adjusted cumulative probabilities of adequate clinical and parasitological response (ACPR) up to day 28. Patients lost to follow up, those who withdrew consent, or those experiencing reinfection were censored at the last visit day or the day of last negative microscopy result. The per-protocol analysis focused only patients who reached therapeutic endpoint. The pattern of fever, parasites clearance, mean hemoglobin level, and adverse events frequencies were compared between treatment arms. Proportions, mean, standard deviation and range were reported as appropriate. Proportions were compared using the Chi-square or Fisher's exact test, and the comparisons of means using Student's t-test for. statistical significance was set at p-value < 0.05.

Ethical considerations

This study was approved by the National Ethics Committee of Gabon and registered under number: PROT N° 0023/2023/PR/SG/CNER. The informed consent form in French was entirely read and the full scope of the study was explained to parents or legal guardians. The study's purpose, objectives,

methodology, potential benefits, and limitations were clearly explained, along with their right to withdraw their children from the study at any time during the follow-up period. Written informed consent was obtained for each child before enrolment.

Results

Patient characteristics

Out of 910 febrile children screened, 123 met the inclusion criteria, and were enrolled into the study (Fig. 1). The remaining 787 children who did not met the inclusion criteria were not included in the study. The 123 enrolled children were randomly assigned to receive either AL (n = 60) and DHAPPQ (n = 63). In the AL group, among the 60 participant included in the intention-to-treat analysis, 8 were subsequently excluded due to loss to follow-up (n = 3) and withdrawal of consent (n = 5). Thus, 52 children were included in the per-protocol analysis. Similarly, in the DHAPPQ group, 63 participants were included in the intention-to-treat analysis while 54 participants were retained in the per-protocol analysis after the exclusion of 09 children for loss to follow-up (n = 5) and withdrawal of consent (n = 4).

Baseline characteristics of enrolled children are summarized in Table 1. Overall, girls accounted for 56,1% of enrolled children, and the sex ratio (male/female) did not differ between treatment groups (p = 1.00). The mean age of children in the AL group (80.3 ± 46.9 months) and in DHAPPQ group (69.7 ± 40.7 months) were not statistically different when compared (p = 0.19). The proportion of children under 5 years of age recruited into the study was nearly identical between treatment group (38.3% vs 41.3%, p = 0.74). Mean axillary temperatures and geometric mean parasite density at enrolment (at day 0) did not differ significantly across treatment arms (both $p > 0.05$). No statistically significant differences were observed in any of the other baseline variables assessed.

Table 1
patients screened and baseline characteristics of patients enrolled in the therapeutic efficacy study

Characteristics	**Overall (n = 123)**	**Treatment group**		***P-value***
		AL	**DHAPPQ**	
		n = 60	**n = 63**	
Sex ratio (Male/Female)	0.78	0.77	0.80	1,00
Age in months, mean (SD),	74.88 (43.96),	80.34 (46.9)	69.7 (40.7)	0.186
Range,	7.0-144.0	8.0-144.0	7.0-144.0	
95% CI	95% CI:67.0-82.8	95% CI:68.1–92.6	95% CI:59.4–80.0	
Age group (month), n (%)	49 (39.8)	23 (38.3)	26 (41.3)	0.74
< 60				
60–144	74 (60.2)	37 (61.7)	37 (58.7)	0.74
Weight (kg), mean (SD),	21.3 (10.1),	23.19 (11.53);	19.7 (8.31);	0.051
Range,	7.0–58.0,	7.0–58.0	7.0–46.0	
95% CI	95% CI:19.5–23.2	95% CI:20.3–26.0	95% CI:17.5–21.7	
Height in cm, mean (IQR)	115.2 (27.7)	118.5 (30.3)	112.1 (24.9)	0.21
Range,	60–165	60–165	60–165	
95% CI	95% CI : 110.2-120.2	95% CI: 111.0-128.0	95% CI: 106–119	
Temperature at day0 (°C), mean(SD),	37.7 (1.13),	37.7 (1.08),	37.6 (1.18),	0.74
Range	36.0-40.9	36.0-40.2	36.0-40.9	
95% CI	95% CI: 37.5–37.9	37.4–38.0	37.3–37.9	
Hemoglobin at day0, mean (SD)	10.1 (1.4)	10.08 (1.43),	10.12 (1.38),	0.88
Range,	8.0–14.0	8.0–14.0,	8.0-13.1,	
95% CI	95% CI:9.84–10.35	95% CI:9.7–10.5	95% CI:9.8–10.5	
Parasitemia at day 0, geometric mean*,	8257.6	8429.5	8097.1	0.72
(95% CI)	95% CI:6367.7-10708.3	95% CI:6219.7-12277.5	95% CI:5506.7-11901.9	

geometric mean *: parasite density (asexual parasites/μl); IQR: interquartile range; n: number of patients; SD: standard deviation; 95% CI: 95% confidence interval.

Primary outcomes evaluation of in-vivo effectiveness of AL and DHAPPQ

Table 2 summarizes the unadjusted and PCR-adjusted treatment outcomes at day 28. In the unadjusted data, no ETF occurred in either treatment arm. Three patients (2.8%) experienced LCP, including 1 in the AL arm and 2 in the DHAPPQ arm. LPF was found in 3 (5.8%) and 5 (9.3%) patients receiving AL and DHAPPQ, respectively. The unadjusted ACPR rates were 92.3% (95% CI: 81.5–97.9) for AL and 87.0% (95% CI: 75.1–94.6) for DHAPPQ, with no statistically significant difference between groups ($p = 0.37$). After PCR correction, no ETFs, LCF and LPF occurred in both treatment arms. Subsequently, the PCR-adjusted cure rates at day 28 were 100% (95% CI: 92.6–100.0) for AL and 100% (95% CI: 92.5–100.0) in DHAPPQ arm.

Table 2
Measures of therapeutic efficacy of AL before and after PCR correction

Treatment outcome	Total	Treatment group		*P-value*
	n (%; 95% CI)	AL	DHAPPQ	
		n (%; 95% CI)	n (%; 95% CI)	
PCR uncorrected				
Day 3 Parasitemia*	10 (9.4; 5.21–16.5)	5 (9.6; 4.2–20.6)	5 (9.3; 4.0-19.9)	1.00
ETF	0 (0, 0.0-3.4)	0 (0, 0.0-6.9)	0 (0, 0.0-6.6)	1.00
LCF	3 (2.8, 0.6-8.0)	1 (1.9, 0.0-10.3)	2 (3.7, 0.5–12.7)	1.00
LPF	8 (7.6, 3.3–14.4)	3 (5.8, 1.2–15.9)	5 (9.3, 3.1–20.3)	0.72
ACPR	95 (89.6, 82.1–94.9)	48 (92.3, 81.5–97.9)	47 (87.0, 75.1–94.6)	0.37
Total for per-protocol	106	52	54	
Withdrawn	9 (7.32)	5 (8.3)	4 (6.4)	0.74
Lost to follow-up	8 (6.5)	3 (5.0)	5 (7.9)	0.72
Total at baseline	123	60	63	
PCR corrected				
Day 3 Parasitemia*	16 (15.1; 9.5–23.1)	7 (13.5; 6.7–25.3)	9 (16.7; 9.0-28.7)	0.65
ETF	0 (0.0, 0.0-3.8)	0 (0.0, 0.0-7.4)	0 (0.0, 0.0-7.5)	1.00
LCF	0 (0.0, 0.0-3.8)	0.0 (0.0, 0.0-7.4)	0 (0.0, 0.0-7.5)	1.00
LPF	0 (0.0, 0.0-3.8)	0 (0.0, 0.0-7.4)	0 (0.0, 0.0-7.5)	1.00
ACPR	101 (100.0, 96.2–100.0)	48 (100.0, 92.6–100.0)	47 (100.0, 92.5–100.0)	1.00
Total for per-protocol	106	48	47	
Withdrawn	9 (7.32)	5 (8.3)	4 (6.4)	0.74
Lost to follow-up	8 (6.5)	3 (5.0)	5 (7.9)	0.72
Re-infection	8 (7.5)	3 (5.8)	5 (9.3)	0.72
Unknown PCR[†]	3 (2.8)	1 (1.9)	2 (3.7)	1.00
Total at baseline	123	60	63	

*: day 3 parasitemia included all patient who reached day 3 follow up; †: cannot be resolved after PCR because results were inconsistent; n; sample size; ACPR: adequate clinical and parasitological response; ETF: early treatment failure; LCF: late clinical failure; LPF: late parasitological failure; n: number of patients enrolled on day 0 or followed-up until the day 28; 95% CI: confidence interval at 95%; AL: Artemether-Lumefantrine; DHAPPQ: Dihydroartemisinin-Piperaquine.

Day-3 *P. falciparum* parasitemia persisted in 9.6% (5/52; 95% CI: 4.2–20.6) of patients in AL group and in 9.3% (5/54; 95% CI: 4.0-19.9) of patients screened in DHAPPQ group using microscopy, whereas by PCR, the proportion of day-3 parasitemia were found in 13.5% (7/52; 95% CI: 6.7–25.3) and 16.7% (9/54; 95% CI: 9.0-28.7) in AL and DHAPPQ groups, respectively. Univariate logistic regression analysis showed a positive association between baseline parasite density and day-3 positivity, and that each ten-fold increase in baseline parasite density was associated with an approximately two-fold increase in the risk of persistent day 3 parasitemia (*OR* = 2.1, 95%CI: 0.9–4.9). However, this association was not statistically significant (*p* = 0.087).

Kaplan-Meier survival estimates of ACPR and recurrent parasitemia risk for AL versus DHAPPQ

The cumulative probability of ACPR at day 28 were compared between AL and DHAPPQ arms. Kaplan-Meier survival analysis using the PCR-unadjusted data showed that children treated with AL had a lower cumulative treatment success incidence that those treated with DHAPPQ, but difference was not statistically different (log-rank *p-value* = 0.185; Fig. 2). PCR-adjusted cumulative treatment success incidence was 100% in both groups (Fig. 2). The cumulative risk of recurrent parasitemia by day 28 was also compared between the two groups. Based on PCR-unadjusted data, the log-rank test of indicated a recurrent infection incidence of 7.69% in AL arm and 12.96% in DHAPPQ arm. After PCR adjustment, incidence rates dropped to 5.77% and 9.26% for AL and DHAPPQ, respectively. No significant difference was observed between AL and DHAPPQ groups in the probability of a new infection, whether based on unadjusted data (*RR* = 1.68, 95% CI [0.52–5.42], *p* = 0.53) or with PCR-adjusted data (*RR* = 1.61, 95% CI [0.40–6.38], *p* = 0.72) (Fig. 3).

Evaluation of parasitemia clearance, fever resolution, hemoglobin, and adverse events post treatment

Parasite clearance between day 0 and day 3 was comparable across the two treatment arms (P > 0.05; Table 3). The proportion of children with detectable parasitemia on day 1 was 74.1% in AL arm and 80.0% DHAPPQ arm. By day 2, these proportions decreased to 32.7% and 21.8% for AL and DHAPPQ, respectively.

The proportion of children with measured fever (axillary temperature ≥ 37.5°C) at baseline (on day 0) was similar between treatment arms (57.6% in AL arm vs 53.2% in DHAPPQ arm; *p* = 0.761). By day 1, fever resolution was more pronounced among children treated with AL than those treated with DHAPPQ, with

fever prevalence of 1.9% compared 12.7%, respectively, although the difference was not statistically significant ($p = 0.061$). On day 2, fever persisted in two children in the AL arm, whereas in the DHAPPQ arm no child remained febrile. On day 3, fever had resolved in all patients in both treatment groups. Three children - two in DHAPPQ arm and one in AL arm - with fever on day 14 were found to have new *P. falciparum* infection.

Mean hemoglobin levels on days 28 were significantly higher than pre-treatment values in both treatment groups. In AL group, mean hemoglobin increased from 10.12 g/dL (95% CI: 9.72–10.5) at baseline to 12.23 (95% CI: 11.8–12.6) at day 28 ($p < 0.0001$), corresponding to a mean increase of 2.11 g/dL (95% CI: 1.56–2.66). Similarly, in DHAPPQ group the changes observed from 10.1 g/dL (95% CI: 9.72–10.5) at baseline to (12.1 95% CI: 11.8–12.6) at day 28 was significant ($p < 0.0001$), with a mean recovery of 2.0 g/dL (95% CI: 1.45–2.55).

At least one adverse event occurred in 6 children (10.0%) in AL group and 6 children (9.5%) in DHAPPQ group. None of the reported adverse events during the follow-up led to withdrawal from the study. Vomiting and nausea were the most frequently reported adverse events, with vomiting occurring in 6.7% of patients and 4.8% in AL and DHAPPQ arms, respectively. The occurrence of others adverse events including, nausea, pruritus, cough or allergic reactions were comparable between treatment arms. No serious adverse event was documented (Table 3).

Table 3
Frequency of fever, parasitemia and adverse events in AL and DHAPPQ arms.

Category	Outcome	Treatment		*p-value*
		AL	DHAPPQ	
Parasite clearance	Parasitemia on day 1, n (%)	40 (74.1)	44 (80.0)	0.46
	Parasitemia on day 2, n (%)	18 (32.7)	12 (21.8)	0.18
Fever clearance	Fever on day 0, n (%)	34 (56.7)	33 (52.4)	0.63
	Fever on day 1, n (%)	1 (1.9)	7 (13.0)	0.06
	Fever on day 2, n (%)	2 (3.7)	0.0	0.50
	Fever on day 3, n (%)	0.0	0.0	-
Hemoglobin	Hemoglobin recovery, mean (SD)	2.11 (1.97)	2.00 (1.98)	0.78
Auto-medication	With antimalarial n (%)	13 (22.0)	8 (12.9)	0.19
Adverse events	Vomiting, n (%)	4 (7.4)	3 (5.5)	0.72
	Diarrhea, n (%)	1 (1.9)	2 (3.6)	1.00
	Nausea, n (%)	1 (1.9)	0.0	0.50
	Pruritus, n (%)	1 (1.9)	1 (1.8)	1.00
	Cough, n (%)	1 (1.9)	1 (1.8)	1.00
	Anorexia, n (%)	1 (1.9)	0.00	0.50
	Epistaxis, n (%)	1 (1.9)	0.00	0.50
	Allergy, n (%)	0.00	1 (1.8)	1.00

n: sample size; SD: standard deviation; Only participants who completed the treatment and were present on day 3 post-treatment where included in the analysis of fever resolution, parasite clearance and adverse events.

Discussion

Although the implementation of ACTs against uncomplicated *P. falciparum* malaria has been done in Gabon, the effectiveness of these ACTs was not often evaluated; prior studies were primarily carry out under supervised clinical conditions. The present study assessed the effectiveness and safety of Artemether-lumefantrine (AL) and dihydroartemisinin-piperaquine (DHAPPQ)in children under 12 years of age presenting with uncomplicated *P. falciparum* malaria in Franceville. An home-based treatment administration and follow-up approach was adopted to mimic community-level behaviors and practices, rather than the standard follow-up in health care for monitoring the efficacy of ACTs [20].

The results showed a PCR-adjusted day-28 cure rate of 100% for both AL and DHAPPQ, exceeding the WHO benchmark of 90.0% [20]. These findings are consistent with day-28 PCR-adjusted ACPR rates range of 96.4% – 98.6%, previously reported in Gabon [12–14], and support sustained high therapeutic effectiveness of AL and DHAPPQ two decades and one decade, respectively, after their nationwide implementation as first- and second-line therapy for uncomplicated *P. falciparum* malaria. The sustainability of effectiveness for AL at this level is remarkable given the context of prolonged and widespread drug pressure, as AL remains the main ACTs used for uncomplicated malaria in the study region. The adjusted PCR cure rate for AL is higher than the range of 88 to 96% registered in Cameroon, Ghana, Angola, Rwanda and Equatorial Guinea in unsupervised conditions and supervised clinical trials. In Uganda, in the districts of Arua and Busia, even lower PCR-adjusted cure rates for AL, of 81.5% and 82.1%, were recorded [8]. At the continental level, some studies have reported comparable PCR-adjusted AL cure rates of 100.0% in some regions in Tanzania [24], Liberia [25], or Mozambique [26], but such findings are uncommon [9, 10, 27–32]. Aggregated data over the past two decades indicate a PCR-adjusted efficacy of AL consistently maintained at around 97% in sub-Saharan Africa [11, 33].

Similarly, systematic reviews and meta-analysis on therapeutic efficacy of ACTs in sub-Saharan Africa, showed pooled PCR-adjusted cure rates maintained high at around 99% for DHAPPQ. The adjusted PCR cure rate of the present study is similar to high adjusted PCR cure rates for DHAPPQ reported from Rwanda [30], Togo [34], Ghana [35], or Mozambique [36]. Importantly, ten years after introduction of DHAPPQ as second-line treatment in the national malaria treatment policy, its use has remained quite limited, accounting for around 4% of prescribed antimalarial treatments. In Cameroon [37] and Angola [38], where DHAPPQ is deployed as first-line therapy, excellent therapeutic efficacy has been demonstrated, suggesting preserved efficacy despite heightened drug pressure. Nevertheless, lower PCR-adjusted cure rates than those in the present study, have been reported in Uganda [39], Democratic Republic of Congo [40], and Burkina Faso [41].

The comparison of *in vivo* effectiveness on day 28 did not showed any significant difference between AL and DHAPPQ. This is consistent with findings previously reported across the continent in numerous effectiveness and efficacy studies, which showed closet efficacy rates between the two treatment [12, 30, 34, 42]. Nevertheless, while both ACTs continues to demonstrate high therapeutic performance, aggregated data indicate a long-term trend of higher overall efficacy for DHAPPQ compared with AL [5, 6, 8, 33]. The recent and limited deployment of DHAPPQ likely contributes, at least in part, to its preserved high efficacy.

In both treatment arms, parasitemia declined progressively by day 3. However, neither regimen demonstrated particularly rapid parasite clearance. The proportion of patients with positive parasitemia decreased to 76.9–80.0% on day 1, and further to 21.8–32.7% on day 2. Similar day-2 positivity rates have been reported in Angola[9] and Uganda [27]. Conversely, these findings contrast with those reported in most sub-Saharan Africa studies, which document faster parasite clearance kinetics by day 2 following ACT treatment.[6, 38, 42, 43] Day-3 parasitemia rates were relatively high in both groups, reaching 16.7% in the DHAPPQ arm. Although such day-3 positivity rates have become less uncommon

in recent years for AL in Africa [8, 29, 44–47], this appears to be a unexpected finding for DHAPPQ. Parasite density on admission is one of the main known factors affecting parasite clearance [5, 48]. In our cohort, the risk of persistent parasitemia on day 3 was not significant associated with baseline parasite density. This finding in consistent with the observations of Tadele et *al*., in Ethiopia [49], Unsupervised drug administration and potential non-compliance with the recommended treatment schedule, could also explain these high rates of positive parasite on day 3. The difference in therapeutic response between unsupervised and supervised antimalarial drug administration has been previously described in the literature,[50, 51] although some studies report no significant difference between the two conditions [52]. Other known factors, including drug bioavailability, multiplicity of infection, age, nutritional status, and host immunity, also influence antimalarial drug efficacy and effectiveness [53–56]. Additionally, the use of PCR in addition to microscopy on day 3 likely enhanced the detection of residual parasitemia, including submicroscopic infections, and even gametocytes or residual DNA in the absence of viable parasites as documented elsewhere [46, 47, 49]. Nevertheless, treatments based on ACTs typically results in a rapid clearance of parasitemia by day 3 after treatment initiation. Consequently, delayed parasite clearance raises concerns about possible artemisinin partial resistance. The WHO considers that in therapeutic efficacy studies, a day-3 parasite positivity rate above 10% is an indicator of suspected artemisinin partial resistance in an area [5]. Further investigation is needed to understand the underlying reasons, particularly at the genetic level, given day 3 parasite positivity. In Southeast Asia [57] and, more recently, in select African countries [8, 45, 47], delayed parasite clearance on day 3 has been associated with mutations in *Pfkelch-13* gene. Notably, despite delayed clearance, all patient subsequently achieved complete parasites elimination, and no recrudescence was observed.

The study recorded a relatively high number of reinfection cases compared with those observed elsewhere [8, 35, 42, 58]. The rates of new infections were comparable between both treatment arms, with a risk of new infection only 1.6-fold higher in DHAPPQ arm compared with AL arm. These findings do not corroborate previous findings observed elsewhere in Africa,[6, 8, 30, 33] which reported a higher risk of new infections occurred in children treated with AL compared with those treated with DHAPPQ. It is well established that the risk of post-treatment reinfection is strongly influenced by the pharmacodynamics and pharmacokinetic characteristics of the non-artemisinin partner drug in ACTs. Piperaquine has a substantially longer elimination half-life (approximately 2–4 weeks) [59, 60] than lumefantrine (3–4 days) [59, 61], enabling sustained therapeutic plasma concentration and providing extended post-treatment prophylactic protection against subsequent infections. An additional advantage of DHAPPQ is its once-daily dosing schedule, which enhance adherence. In this context, our findings appear unexpected given the intrinsic advantages of DHAPPQ and the comparative aggregated data available to date. Importantly, however, a high reinfection rate does not necessarily suggest reduced therapeutic efficacy; rather, it may reflect intense local transmission and sustained exposure to *Plasmodium* infections.

Both treatments showed an excellent ability to clear fever as expected. In DHAPPQ arm fever was cleared by day 2, whereas in children treated with AL fever was fully resolved by day 3. These findings are consistent with what is generally observed in others studies conducted in Gabon [58, 62] and elsewhere

[35, 42, 43, 63], although in Cameroon [29] or in Ethiopia [64] persistent fever on day 3 and even beyond after treatment with AL have already been documented. Also, mean hemoglobin levels significantly increased in both treatment arms. Hemoglobin recovery levels were comparable between the two groups, highlight the capacity of both treatments to improve patients' overall health.

Both treatment appeared to be globally safe and well tolerated, with comparable profiles, although adverse events were slightly more frequent and diversified in the AL group compared with DHAPPQ group. The adverse events found corresponded to the established safety spectra of both treatments, were infrequent, and generally mild. The most commonly recorded adverse events were vomiting and diarrhea. No serious adverse events occurred during follow-up period in either treatment arm, in agreement with the data described elsewhere in Africa [10, 29, 63, 64].

This study presented some limitations that warrant consideration. First, its single-center, and urban design may not be representative of the diversity of malaria transmission setting at the provincial or national level, and restrict the generalizability of findings. Second, following the first supervised dose, subsequent treatment was administered at home without direct clinical oversight. Third, gametocyte carriage was not systematically assessed in all participants and was therefore not retained in the analysis. Finally, the cumulative exclusion of seventeen participants across both arms owing to consent withdrawal or loss to follow-up resulted in reduced sample size, which may have limited statistical power.

Conclusion

Our findings support that AL and DHPPQ remains highly effective in Gabon since its introduction as first- and second-line therapy for uncomplicated *P. falciparum* malaria within the national treatment policy. Both treatments were generally well tolerated, with no serious adverse events documented. The high prevalence of day-3 *P. falciparum* parasitemia exceeding 10% in both AL and DHAPPQ calling for a regular and sustained surveillance of the ACTs of malaria national regimen.

Abbreviations

ACT
Artemisinin-based combination therapy
DHAPPQ
Dihydroartemisinin–piperaquine
AL
Artemether–lumefantrine
ACPR
Adequate clinical and parasitological response
ETF
Early treatment failure

LCF
Late clinical failure
LPF
Late parasitological failure
PCR
Polymerase chain reaction
mg
Milligram
Kg
Kilogram
CI
Confidence interval
WHO
World Health Organization.

Declarations

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Authors' contributions

JBLD, SLOL, RKIL, SSO and INDN conceived and designed the study. SLOL, RKIL, SSO and INDN implemented the study and supervised data collection. JBLD, SLOL and RKIL coordinated the study. INDN and SSO performed the fieldwork, data entry, and supervised the enrolment and follow-up of patients. NCA, LCK and NDM provided technical support in the interpretation of results. All authors participated in the preparation of the manuscript. All authors read and approved the manuscript.

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Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

Data supporting the conclusions of this article are included within the article.

The datasets analysed are available upon request to the corresponding author.

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Figures

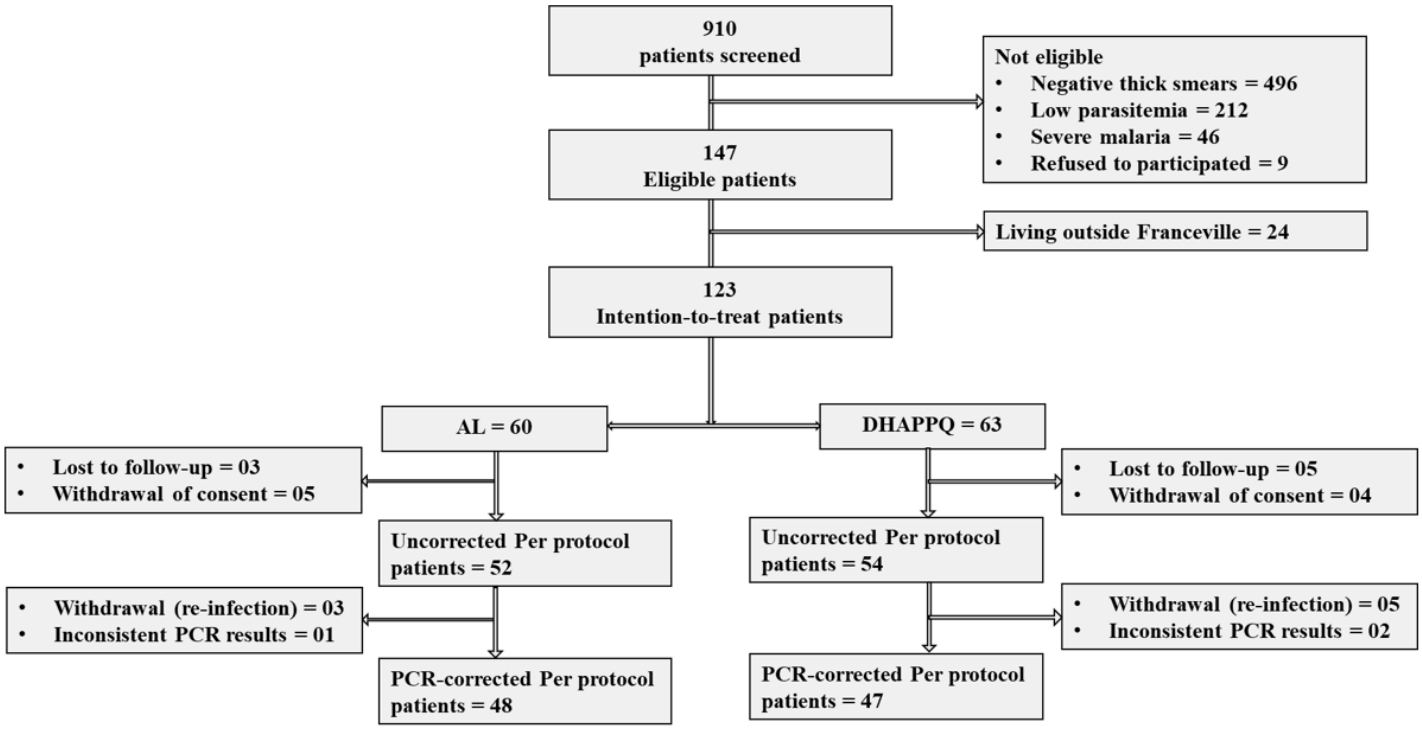


Figure 1

Trial profile showing the flow of patient during the screening, enrolment and follow-up.

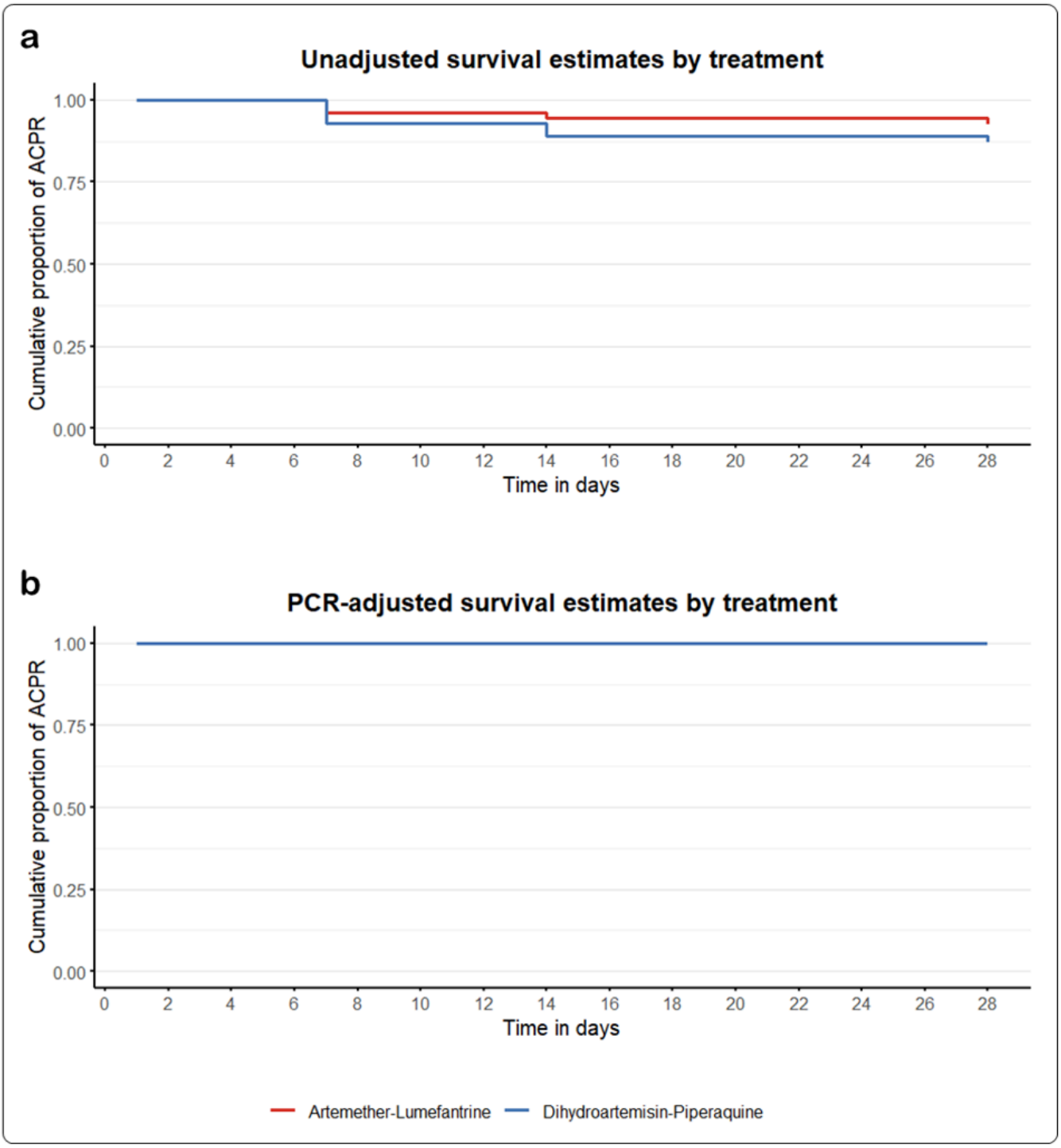


Figure 2

Kaplan-Meier cumulative proportion of ACPR before and after PCR correction.

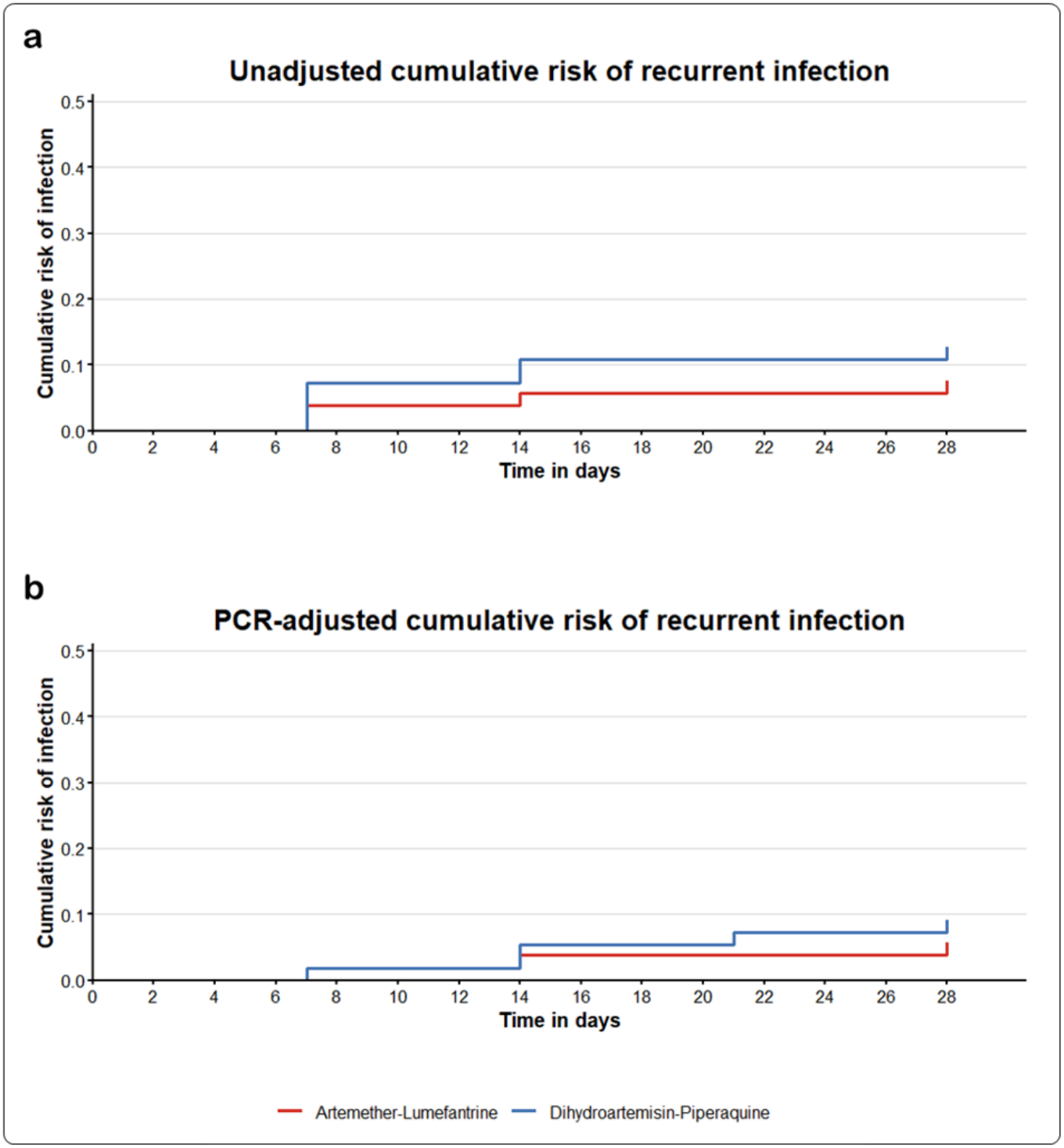


Figure 3

Cumulative risks of recurrent parasitemia by 28 before and after PCR correction, following Artemether-lumefantrine and Dihydroartemisinin-piperaquine treatments.

Supplementary Files

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