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Temporal Dynamic of Efficacy and Tolerability of Artemether–Lumefantrine for the Treatment of Uncomplicated *Plasmodium falciparum* Malaria in Bouna, Côte d'Ivoire

Running title: Surveillance of the efficacy of artemether–lumefantrine in Bouna, Côte d'Ivoire

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Abstract: Introduction: Therapeutic Efficacy Studies (TESs) are crucial for detecting early changes in *P. falciparum* susceptibility to antimalarial drugs. Artemether–lumefantrine is one of five first-line treatments for uncomplicated malaria in Côte d'Ivoire. This study aimed to assess the temporal dynamics of artemether–lumefantrine (AL) efficacy in managing uncomplicated malaria cases in Bouna, a sentinel site. **Methods:** This was a comparative analysis of two controlled, randomized, and open therapeutic trials based on a 28-day follow-up period, conducted according to the 2009 WHO protocol. The surveys were conducted in 2019 and 2023. Treatment response was measured and

defined following WHO guidelines, with analyses performed using intention-to-treat and per-protocol methods. **Results:** A 28-day follow-up was performed for 57 and 87 patients in 2019 and 2023, respectively. On day 28, the PCR-adjusted cure rates were higher in 2023 than in 2019, both in ITT analysis (96.6% versus 90.0%) and in PP analysis (97.7% versus 94.7%). However, more failures were observed after 28 days of follow-up in 2023 (23 cases) than in 2019 (9 cases). After PCR adjustment, nearly all cases were attributed to reinfection. In 2019, three cases of recurrence and six new infections were observed. In 2023, two recurrence events and 21 new infections were observed. In both surveys, AL was well-tolerated. **Conclusions:** This comparative assessment demonstrated that AL remains effective in treating uncomplicated malaria in Bouna. The high number of new infections highlights the need to strengthen preventive measures.

Keywords: malaria; efficacy; artemether–lumefantrine; Côte d'Ivoire

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1. Introduction

Plasmodium falciparum is resistant to most antimalarial drugs, including artemisinin derivatives. Regular monitoring of the efficacy of these drugs is crucial for detecting early changes in *P. falciparum* susceptibility [1]. The chemoresistance of *P. falciparum* poses a significant threat to malaria elimination efforts. Consequently, the World Health Organization (WHO) recommends routine monitoring through Therapeutic Efficacy Studies (TESs), which track clinical and parasitological outcomes in individuals receiving antimalarial treatment [2]. The results of TES are essential for countries to determine or review their national treatment policies [2].

In Côte d'Ivoire, the incidence of malaria was 266 per 1000 in the general population and 844 per 1000 in children under 5 years of age in 2022 [3]. This parasitic disease accounts for 33% of all outpatient visits and one-third of reported deaths in healthcare facilities [4]. This country, along with 28 other sub-Saharan countries, accounted for 96% of malaria cases and deaths globally in 2022 [2]. Since 2005, uncomplicated cases of malaria have been treated with Artemisinin-based Combination Therapies (ACTs) [5]. Artesunate–amodiaquine (AS + AQ) as a first-line treatment and artemether–lumefantrine (AL) as a second-line treatment were the ACTs recommended by the National Malaria Control Program (NMCP). Based on TES results indicating the same high efficacy rate for both combinations, the NMCP adopted both regimens as first-line treatments in 2013 [6]. In 2018, dihydroartemisinin–piperaquine (DHA-P) was introduced into the therapeutic arsenal as a first-line treatment, similarly to AS + AQ and AL [7]. Since 2022, the therapeutic management of uncomplicated cases of malaria recommended by NMCP is AS + AQ, AL, DHA-P, or artesunate–pyronaridine, all as first-line treatment [8]. However, only AS + AQ and AL combinations

are administered free of charge in public healthcare centers, which is why they are assessed using TESs. Other recommended ACTs are available in the private health sector.

Recent reports on mutations in the *Plasmodium falciparum* Kelch propeller domain 13 (pfk13) gene linked to artemisinin resistance in Rwanda and Tanzania [9–11] provide evidence to reinforce the surveillance of these antimalarial drugs, which remain a last resort in the treatment of malaria.

The first study, which assessed the efficacy of ACT in Côte d'Ivoire, was conducted in 2009 [12]. Since then, six nationwide TESs, including both published and unpublished data, have been carried out at sentinel sites across the country [12–17]. These studies consistently reported that AS + AQ and AL remain effective and well-tolerated treatments for uncomplicated malaria in Côte d'Ivoire. However, no studies have compared the evolution of cure rates at the same site using the same antimalarial drugs over time. Since its addition to the list of sentinel sites, the site of Bouna has hosted only two TESs in 2019 and 2023. This study aimed to report the temporal dynamics of AL efficacy in managing uncomplicated malaria cases at Bouna, in Côte d'Ivoire.

2. Methods

2.1. Study Design

This study was a comparative analysis of two controlled, randomized, open therapeutic trials, each with a 28-day follow-up period. The first survey was conducted between February and July 2019, and the second from May to July 2023. The 2009 WHO protocol was used for these evaluations [18].

2.2. Study Site

Bouna is one of the 12 sentinel sites established by the NMCP for monitoring antimalarial efficacy. Initially, the NMCP had six sentinel sites starting from 1996; in 2017, six additional sites, including Bouna, were added. The Bouna site, which is in the northern savanna of the country, is bordered by Burkina Faso and Ghana (9°16′0″ North, 3°0′0″ West). The climate is tropical, with two seasons: a dry season from November to May and a rainy season from June to October. The transmission of malaria in Bouna and across Côte d'Ivoire occurs year-round, with a significant peak during the rainy season. Malaria cases in Côte d'Ivoire are predominantly caused by *P. falciparum* (95–99%) [4]. *Anopheles gambiae sensu stricto (s.s.)* and *Anopheles coluzzii* are the most important malaria vectors in this area [19]. The patients were enrolled at the General Hospital of Bouna, located in an area where malaria transmission occurs year-round. Molecular analyses were performed at the Malaria Research and Control Center (MRCC) of the National Institute of Public Health of Côte d'Ivoire.

2.3. Study Population

2.3.1. Selection Criteria

Both trials were focused on patients with uncomplicated malaria who met the study inclusion criteria, which were: a monospecific *P. falciparum* infection detected by microscopy, a parasitemia between 2000 and 200,000 asexual forms/μL, an axillary temperature $\geqslant$ 37.5 °C or a history of fever within the last 24 h, and an ability to take drugs *per os*. Additional criteria, such as the ability and willingness of the participant to comply with the protocol for the duration of the study and to respect the consultation scheduled study visits, as well as written informed consent of the parent or legal guardian and informed assent of all participants aged between 10 and 18, were also required. The ages of the recruited patients were between 6 months and 65 years and between 6 months and 12 years in the 2019 and 2023 surveys, respectively. Patients were not included in cases of signs or evidence of severe malaria as defined by the WHO [20], low body weight (<5 kg), signs of severe malnutrition defined by a brachial

perimeter at mid-height < 115 mm, intercurrent infectious disease, repeated vomiting, and history of previous serious side effects of the drugs used during the trial. The criteria for discontinuing the study were withdrawal of consent, occurrence of serious adverse effects, any finding of abnormal biological test results (>3 N), disease-related or not, unsatisfactory therapeutic response, protocol violation, loss during follow-up, and death.

2.3.2. Sample Size

For both surveys, the sample size was calculated using the World Health Organization guidelines for the assessment of antimalarial drugs [18]. A minimum of 50 and 73 patients was required in 2019 and 2023, respectively, based on the following criteria: proportion of probable clinical failures not higher than 10% (in 2019) and 5% (in 2023) based on the results of previous studies, level of confidence (P) of 95%, and precision (p) of 10%, considering patients who were excluded or lost to follow-up (20%).

2.4. Study Drug

The AL used in these clinical trials was provided through the NMCP by the Global Fund and PMI and was delivered free of charge at public-sector healthcare facilities. The names of the manufacturers, batch numbers, and expiration dates were recorded during the study. All of the antimalarial drugs were stored in a cool, dry place. Drugs were administered according to malaria therapeutic guidelines of NMCP [7,8].

2.5. Procedures

2.5.1. Follow-Up Procedure

Patients with uncomplicated malaria who met the inclusion criteria were recruited and treated with AL. Drug administration was supervised by the research team during the first three days. Patients were monitored for 28 days, with primary efficacy analysis at D28. Follow-up consisted of a series of scheduled visits for clinical and laboratory tests. The visiting days were as follows: Days 1, 2, 3, 7($\pm$1), 14($\pm$1), 21($\pm$1), and 28($\pm$2) for the 2023 survey. In 2019, follow-up was carried out for 42 days, including two more visit days: 35($\pm$2) and 42($\pm$2). Visits were also allowed on any other day when the patient felt unwell and parasitological re-evaluation was required.

2.5.2. Clinical Procedure

Each recruited patient underwent a guided interview and a complete physical examination, including clinical signs and symptoms of malaria, vital signs, and body temperature. This complete physical examination was performed at inclusion, before any treatment on day 0, and then on the visit day.

2.5.3. Biological Procedure

Sample Collection

Venous whole-blood samples were collected from each patient using an ethylenediaminetetraacetic acid (EDTA) tube. Samples were collected on day 0, before any treatment, and then on each visit day to confirm malaria for the follow-up of the efficacy of ACTs. Venous samples were used to prepare thick and thin blood smears, as well as Dried Blood Spots (DBSs).

Parasitological Analyses

To confirm *Plasmodium* carriage and determine parasitemia, thick and thin blood smears were prepared for each sample. Parasitemia was determined by counting the number of asexual parasites against 200 white blood cells per μL., i.e., number of parasites × 6000/200, assuming a white blood cell mean of 6000 cells per μL, as recommended by the WHO when the patient's exact white blood cell count is not available [21]. Double-check readings were performed on all slides. All of the slides were independently interpreted by two qualified laboratory technicians, and parasitemia were calculated by averaging the two counts. Smears with discordant results (differences between the two technicians' results for species diagnosis, parasitemia > 50%, or presence of *Plasmodium*) were re-examined by a third independent technician, and parasitemia was determined by averaging the two closest counts. Negative results were considered after evaluating at least 100 microscopic fields.

Hematology Analyses

The hemoglobin level was determined using a hemoglobinometer (HemoCue® Hb 301, Ängelholm, Sweden) from a drop of fingertip blood. This test was performed on day 0 to avoid including a patient with a low hemoglobin level corresponding to the WHO criteria for severe malaria [20] and if necessary, on other follow-up days.

Plasmodium falciparum Genotyping

Molecular analysis was performed to distinguish between recurrence and new infection. Parasite DNA was extracted using the Chelex-based method [22] and subjected to nested PCR, as previously described [23]. The latter was used to determine the length of polymorphisms in the genes encoding merozoite surface protein-1 (*msp1*) and merozoite surface protein-2 (*msp2*).

2.5.4. Tolerability Evaluation

Safety was assessed by recording the type and incidence of adverse events and serious adverse events. An adverse event was defined as any sign, symptom, syndrome, or unexpected illness in a participant that did not necessarily have a causal relationship with the trial intervention [24].

2.5.5. Endpoints

Treatment response was measured and defined according to WHO guidelines [25]. Primary and secondary endpoints have been described previously [14]. The primary efficacy parameter was the cure rate on day 28. Clinical or biological signs not present at the time of inclusion that appeared during follow-up, or any sign present on day 1 that worsened thereafter, were considered adverse events.

2.5.6. Ethical Approval

Both surveys were approved by the National Committee of Ethics and Life and Health Sciences [French Comité National d'Ethique et des Sciences de la Vie et de la Santé] (certificate numbers: N° 049/MSLS/CNER-dkn, 2019 and 167-22/MSHPCMU/CNESVS-kM, 2023). Surveys were conducted in accordance with the principles of the Declaration of Helsinki. Free and written informed consent was obtained from the patients, parents, or legal guardians before enrolment.

2.6. Statistical Analysis

All data were recorded using IBM SPSS Statistics version 21. Comparison of different parameters in both surveys was performed using Fisher's exact test. The intention-to-treat (ITT) analysis included all recruited subjects who had taken at least one full dose, even those who were not followed up with until the end of the study. The per-protocol (PP) analysis included all subjects who received six doses of AL and were followed up with until the end of the study. The level of significance for statistical tests was set at $p < 0.05$.

3. Results

A total of 60 and 88 patients were included in the 2019 and 2023 evaluations, respectively. The inclusion rates were 1.9% (60/3192) and 27.8% (317/88) in 2019 and 2023 surveys, respectively. A 28-day follow-up was achieved for 57 patients in 2019 and 87 patients in 2023. The trial profiles are presented in Figures 1 and 2.

Females were predominant (51.7%; sex ratio, 0.94 in 2019; 54.5%; sex ratio, 0.83 in 2023). Their mean age was 6.3 years (SD = 6.8; range: 0.50–32) in the 2019 survey and 4.7 years (SD = 2.4; range: 0.80–12) in 2023. The infection rate among children under five years old was 60% (2019) and 60.2% (2023) in the two surveys. The geometric mean parasitemia was 65187.8 parasites/μL (SD = 55,251) (range: 116–41,2461) in 2019 and 41,340.8 parasites/μL (SD = 42,196.9) (range: 2486–198,478) in 2023. The baseline characteristics of the patients included in each survey are shown in Table 1.

The analyses were performed in ITT and PP on day 28 for both surveys and on day 42 only for the 2019 evaluation. On day 28, the PCR-adjusted cure rates were higher in 2023 than in 2019, both in the ITT analysis (96.6% versus 90.0%) and in the PP analysis (97.7% versus 94.7%). On day 42, the PCR-adjusted cure rates were 88.3% and 93.0% following ITT and PP analyses, respectively.

After 28 days of follow-up, more failures (23) were observed in 2023 than in 2019 (9).

On day 28, four of nine failure cases were classified as late clinical failure (LCF), whereas the other five were described as late parasitological failure (LPF) in the 2019 survey. In 2023, 14 cases of LCF and nine cases of LPF were observed. After 42 days of follow-up in the 2019 survey, 10 failures were observed. Five of these ten cases were LCF, while the other five were LPF. Overall, none of the patients experienced an early treatment failure (ETF).

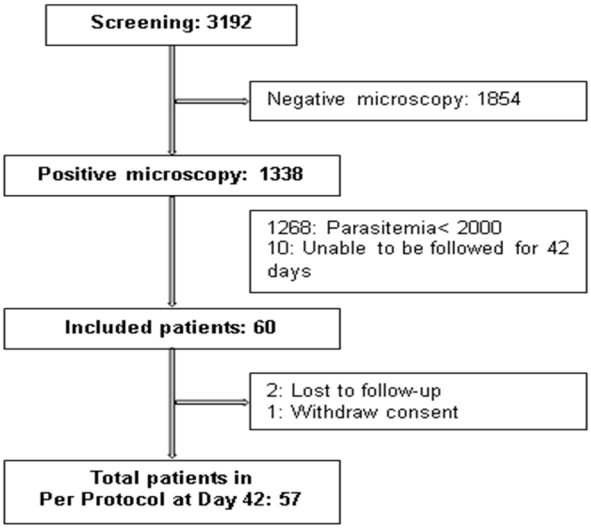

Figure 1: Trial profile in Bouna, 2019.

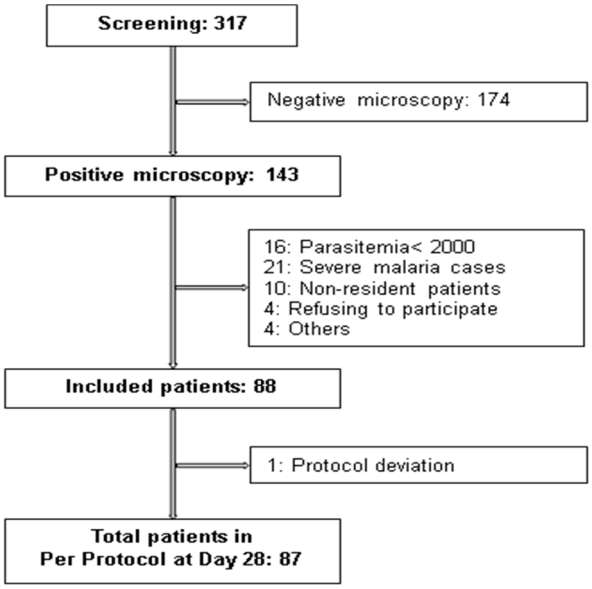

Figure 2: Trial profile in Bouna, 2023.

Table 1: Baseline characteristics of patients at inclusion.

	AL, 2019 N = 60	**AL, 2023 N = 88**
Sex ratio (M/F)	0.94	0.83
Male, n (%)	29 (48.3)	40 (45.5)
Female, n (%)	31 (51.7)	48 (54.5)
Mean Age (SD), years	6.3 (6.8)	4.7 (2.4)
Min–Max	0,50-32	0.80-12
[0.5–5[, n (%)	36 (60)	53 (60.2)
[5–15[, n (%)	19 (31.7)	35 (39.8)
[15–63], n (%)	5 (8.3)	0 (0.0)
Mean Temperature (SD), °C	39 (0.7)	38.8 (0.8)
Min–Max	37.5–41.4	37.5–40.0
[37.5–38.5[, n (%)	18 (30)	30 (54.2)
[38.5–41.2], n (%)	42 (70)	58 (45.8)
Mean Parasitemia (SD), trophozoite/μL	65,187.8 (55,251)	41340.8 (42,196.9)
Min–Max	3776–199,208	2486–198,478

After PCR adjustment, nearly all cases were reinfections. In 2019, three cases of recurrence and six cases of new infections were observed. In 2023, two recurrence events and 21 new infections were observed. The single case of failure observed between days 28 and 42 in the 2019 survey was classified as a recrudescence case. However, no significant differences were observed between the two surveys.

In addition, no patient presented with parasites on day 3 in either survey.

Treatment outcomes are summarized in Table 2.

Table 2: Treatment outcomes on days 28 and 42.

	ITT Analysis					PP Analysis				
	AL, 2019		AL, 2023			AL, 2019		AL, 2023		
	n/N	%	n/N	%	* *p*-Value	n/N	%	n/N	%	* *p*-Value
DAY 28										
Enrolled patients	60	-	88	-	-	-	-	-	-	-
Patients fully followed up with on day 28	57/60	95.0	87/88	98.9	-	57	-	87	-	-
Patients missing	3/60	5.0	1/88	1.1	-	3/57	-	1/88	-	-
Crude failure rate on day 28	12/60	20.0	24/88	27.3	0.34	9/57	15.8	23/88	26.1	0.16
Crude cure rate on day 28	48/60	80.0	64/88	72.7	0.34	48/57	84.2	65/88	73.9	0.16
PCR-adjusted failure rate on day 28	6/60	10.0	3/88	3.4	0.16	3/57	5.3	2/88	2.3	0.38
PCR-adjusted cure rate on day 28	54/60	90.0	85/88	96.6	0.16	54/57	94.7	86/88	97.7	0.38
DAY 42										
Patients fully followed up with on day 42	57/60	95.0	-	-	-	57	-	-	-	-
Patients missing	3/60	5.0	-	-	-	3/57	-	-	-	-
Crude failure rate on day 42	13/60	21.7	-	-	-	10/57	17.5	-	-	-
Crude cure rate on day 42	47/60	78.3	-	-	-	47/57	82.5	-	-	-
PCR-adjusted failure rate on day 42	7/60	11.7	-	-	-	4/57	7.0	-	-	-
PCR-adjusted cure rate on day 42	53/60	88.3	-	-	-	53/57	93.0	-	-	-

* Fisher's exact test.

Overall, a similar evolution in the proportion of patients with parasitic infections was observed during follow-up in both surveys. In both surveys, AL facilitated rapid parasite clearance (Figure 3).

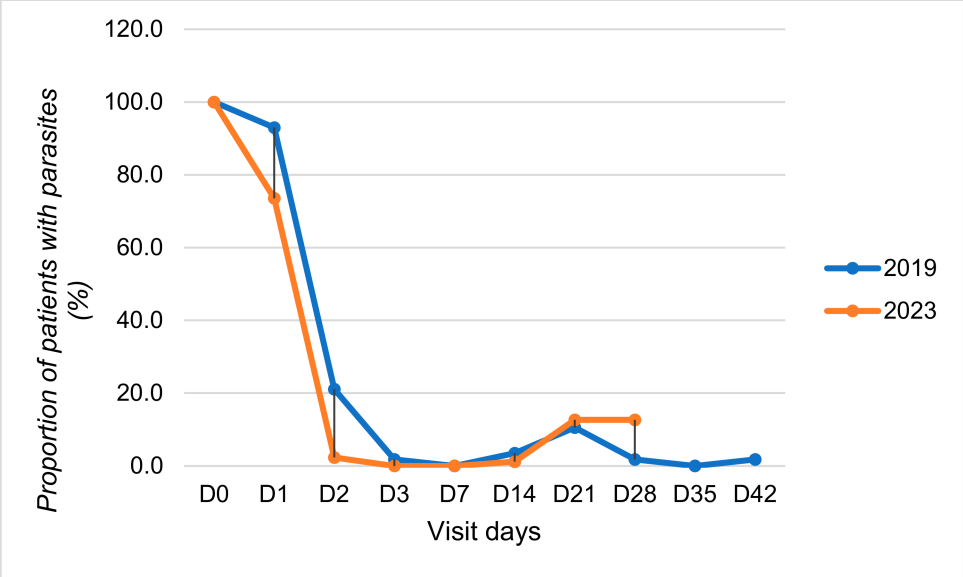

Figure 3: Proportion of patients with parasites according to visit days.

A decrease in fever during follow-up was noticed in both surveys, but it was faster in 2013 than in 2019 (Figure 4).

At the clinical level, seven cases of adverse events were detected in 2019: two cases of vomiting, one of nausea, one of asthenia, one of diarrhea, one of abdominal pain, and one of abdominal distension. No adverse events were reported in 2023.

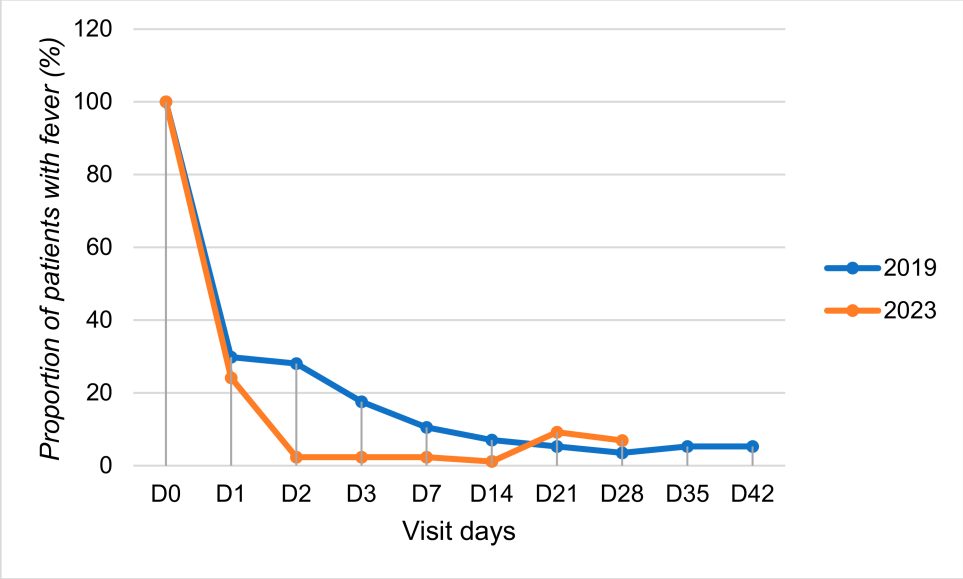

Figure 4: Proportion of patients with fever according to visit days.

4. Discussion

Therapeutic Efficacy Studies (TESs) are crucial for detecting early changes in *P. falciparum* susceptibility to antimalarial drugs and are useful for countries to best determine or review their national treatment policies [2]. Since the beginning of TESs in Côte d'Ivoire, only two TESs have been carried out at the sentinel site of Bouna. This study presents the results of the two TESs. This study compared the evolution of cure rates observed after AL administration for the management of uncomplicated malaria cases in Bouna.

In Côte d'Ivoire, malaria occurs more frequently among vulnerable populations, such as pregnant women and children under the age of five [4]. In the present study, children under five years old were more likely to be infected in the two surveys. This age group is more frequently infected because of their immature immune system and increased exposure to malaria parasites [26].

Artemether–lumefantrine (AL) and AS + AQ are ACTs administered free of charge in public-sector healthcare establishments. In most health facilities in Côte d'Ivoire, AL is prescribed at higher rates than ASAQ because of patients' complaints following the use of the latter [27]. Globally, AL is also the most widely used ACT, followed by AS + AQ [28].

Overall, the efficacy of AL remained relatively unchanged over time, with 94.7% PCR-corrected efficacy in 2019 and 97.7% in 2023 after 28 days of follow-up. The therapeutic efficacy of AL in the two surveys was well above the 90% threshold recommended by the WHO [18]. This result is in line with previous studies conducted in Côte d'Ivoire [13–15] and other African countries [29,30]. In addition, prompt parasite clearance was observed during the early days. Delayed parasite clearance at 72 h is an in vivo predictor of subsequent treatment failure with ACTs and an indicator of choice for routine monitoring of suspected artemisinin resistance in *P. falciparum*. The proportion of patients with persistent parasitemia on day 3 after ACTs is a useful indicator as a simple and readily measurable marker in the setting of drug efficacy surveillance studies [31]. In the current study, none of the

patients presented with parasites on day 3, as observed previously in the country [16], indicating rapid parasite clearance from patients following artemether–lumefantrine in Bouna. These results should encourage the PNLP to maintain AL as the first-line treatment for uncomplicated malaria in Bouna and Côte d'Ivoire.

Despite the high cure rates, concerns remain. Indeed, a high level of failure was observed in 2023 compared with 2019. Antimalarial treatment failure is a useful indicator for assessing ACT resistance [1] and may be caused by many factors other than the intrinsic susceptibility of *P. falciparum* to the drug being tested [32]. Crude failure rates are higher in 2023. Several studies that compared AL with ACT regimens consisting of longer-acting partner drugs demonstrated a shorter time to reinfection for AL. The mean protection provided by AL is estimated at 13.8 days . In most health facilities in Côte d'Ivoire, AL is prescribed more than AS + AQ because of patient complaints following the use of the latter [27].

After PCR correction, most cases of failure were classified as new infections in both surveys, showing a high level of exposure of patients to malaria. The number of new infestations is expected to increase by 2023. This result may be attributed to the study period. In 2019, the survey was conducted mainly during the dry season (February, March, April, and May), unlike in 2023, when the survey was conducted at the beginning of the rainy season, when transmission was high in the country. Populations are more exposed to mosquito bites during the rainy season, posing a high risk of infection in vulnerable populations if no preventive tools are adopted. This result demonstrates the importance of reinforcing community mobilization and behavioral change mechanisms, which could be significant for the success of all malaria prevention activities implemented in the country [33].

As reported in most studies [13–15,34–36], prompt fever clearance was observed during the early days of treatment with AL.

In addition, AL is well tolerated without serious adverse events, as usually reported [13–15,35,36]. At the clinical level, seven cases of adverse events were detected between 2019 and 2023. This gap could be explained by the fact that in 2019, people aged up to 65 years were included, contrary to 2023, where patients aged no more than 12 years were included, expressing less concern about the effects experienced.

A limitation of this study is the non-availability of 42 days of follow-up data from the 2023 survey, causing a lack of comparison of the long-lasting protective action of partner drugs in ACTs.

5. Conclusion

AL remains effective and well-tolerated for the therapeutic management of uncomplicated malaria in Bouna, Côte d'Ivoire. Furthermore, the increase in new infections suggests the need to strengthen preventive measures at this sentinel site. In any case, monitoring ACTs should remain a high priority at the national level.

Author Contributions: W.Y., H.E.M., and O.A.T. supervised the study. M.T.D., V.A.B.-T., and A.K.-T. supervised the sample collection. A.K.-T. analyzed the data and wrote this paper. All authors contributed to the drafting of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no competing interests.

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