International Scholars Journals

African Journal of Parasitology Research ISSN: 2756-3391 Vol. 11 (3), pp. 001-011, March, 2023. Available online at https://internationalscholarsjournals.org/journal/ajproaj/articles?index=5 © International Scholars Journals

Full Length Research Paper

Artemether-Lumefantrine and Artesunate-Amodiaquine in routine use for the treatment of uncomplicated *Plasmodium falciparum* malaria in Senegal: Open randomized efficacy trial

Khadime Sylla*, Cheikh Binetou Fall, Souleye Lelo, Isaac Akhenaton Manga, Doudou Sow, Magatte Ndiaye, Kuaku Folly, Roger C.K Tine and Babacar Faye

Department of Parasitology-Mycology, Faculty of Medicine, Pharmacy and Odontology, University Cheikh Anta DIOP of Dakar (UCAD).

Received 30 November, 2022; Accepted 20 March, 2023

Abstract

Background: Prompt treatment of malaria attacks with artemisinin-based combination therapy (ACT) is an essential tool for malaria control. Several ACTs are currently being used in Senegal. A surveillance system aimed at monitoring antimalarial drug efficacy is established. This study was conducted to assess the efficacy of Artemether-Lumefantrine (AL) and Artesunate-Amodiaquine (ASAQ) under routine conditions. Methods: An open randomized trial was carried out during three malaria transmission seasons (2014 to 2016) in five malaria sentinel sites. The 2009 WHO protocol for antimalarial drug efficacy was used. The study end points included (i) PCR corrected adequate clinical and parasitological response (ACPR) at day 28, (ii) parasites and fever clearance time. Intention to treat (ITT) and per-protocol (PP) analysis were done. Results: Overall, 1118 patients with uncomplicated *Plasmodium falciparum* malaria were randomized to receive either AL (n=553) or ASAQ (n=565). In ITT analysis, PCR corrected ACPR at day 28 was at 96.1% [95%CI (88 – 99.9)] in the AL arm and 95.6% [95% CI (87.7 - 99.9)] in the ASAQ arm (p=0.7). PP analysis at day 28 showed 99.4% efficacy for both groups. Parasite clearance time and fever clearance time remained constant over the three transmission seasons and were obtained at 72 hours in both arms of the trial. Conclusion: Under operational conditions in Senegal, AL and ASAQ are still highly effective for the treatment of uncomplicated *P. falciparum* malaria. However, it's crucial to continue monitoring the efficacy of the drugs to further guide malaria treatment policy.

Keywords: Artemether–Lumefantrine, Artesunate–Amodiaquine, Efficacy, *Plasmodium falciparum*, Malaria, Senegal.

Khadime Sylla ORCID
https://orcid.org/0000-0003-3896-6997

Background

Malaria remains a major public health problem worldwide particularly in sub-Saharan Africa. According to the World Health Organization, an estimated 241 million malaria cases and 627,000 malaria deaths occurred worldwide in 2020. 92% of malaria cases and 93% of deaths are observed in Africa. Children under five are the most vulnerable group affected by malaria (WHO, 2021). Adequate management of malaria cases using rapid diagnostic test and effective drugs play a key role in reducing malaria burden. WHO recommend Artemisinin based-Combination Therapies (ACT) as reference treatment of uncomplicated malaria cases in high burden countries (WHO, 2015). ACTs are an effective drug that can reduce the morbidity and mortality related to malaria, prevent transmission of *Plasmodium falciparum* by acting on gametocytes

*Corresponding author Email:khadimesylla@yahoo.fr

and limit the spread of resistance (WHO, 2001., WHO, 2006., WHO, 2010). However, resistance to artemisinin was recently observed in western Cambodia (Dordon et al., 2006; Noedl et al., 2008).
In Senegal, significant decrease of malaria morbidity and mortality has been noted in recent years. This is due to the scaling-up of combined malaria control interventions by the National Malaria Control Programme (NMCP). ACT has been used as reference treatment for uncomplicated malaria cases since 2006 (NMCP SN, 2016). The efficacy of ACTs has been demonstrated in Sénégal previously (Faye et al, 2006., Tine et al, 2012., Faye et al, 2010., Sylla et al, 2013).
The reduction of malaria burden has guided the National Malaria Control Program to set the goal of pre-eliminating malaria in the country. One of the main strategies to achieve this objective is the management of malaria cases using rapid diagnostic test (RDTs) and artemisinin combination therapy (ACT) (NMCP SN, 2016). Thus, the monitoring of ACT efficacy become essential in order to prevent the spread of resistance.
It was in this context, we carried out this open randomized study to monitor the efficacy of artemether-lumefantrine (AL) and artesunate-Amodiaquine (ASAQ) used in routine conditions for the treatment of uncomplicated *Plasmodium falciparum* malaria in Senegal.

METHODS

Study sites

The study was conducted during three malaria transmission seasons (2014 to 2016) in five malaria sentinels sites located in four regions (Dakar, Kaolack, Kolda and Kedougou). In Dakar, the study was conducted in Deggo health post which is located at 20 km from the capital city. Malaria incidence in Dakar is moderate 5‰ to 15‰ habitants. Kaolack (Keur Soce Health post) is located in the central part of Senegal, 200 km from Dakar.
Kolda (Koukane health post) and Kedougou (Bandafassi and Tomboronkoto health posts) are located in the south-east of Senegal, 500 km and 740 km from Dakar respectively. Malaria incidence is high (>15‰ habitants) in Kaolack, Kolda and Kedougou. The stratification of region was done according to the National Malaria Control Program.
In these areas, malaria is highly seasonal during the rainy season (July to October) with a peak of transmission from September to December. *Plasmodium falciparum* is the predominant species and transmission is mainly due to *Anopheles gambiae s.l.* The enrollment of patients started in September 2014 and was completed in January 2017.

Study design

The study was designed as prospective open randomized trial assessing the efficacy of Artesunate-Amodiaquine (ASAQ) and Artemether-Lumefantrine (AL). The 2009 WHO protocol for antimalarial drug efficacy was used (WHO, 2009).The primary endpoint was the PCR adjusted adequate clinical and parasitological response (ACPR) at day 28. Secondary end points included: (i) parasite clearance time, (ii) gametocyte clearance time and (iii) the fever clearance time [13]. The study was conducted as part of a national surveillance program aiming at monitoring ACTs efficacy under routine conditions.

Patients

Only outpatients of different health posts were included in this study. Were eligible to be enrolled after informed consent, patients with age above 6 months who attended the health post with a history of fever in the preceding 24 hours or confirmed fever (axillary temperature ≥ 37.5°C), with uncomplicated *Plasmodium falciparum* malaria, parasitaemia between 1000 to 100000 trophozoites/µl, and patients able to take oral medication. Patients with severe and complicated malaria, according to the WHO definition (WHO, 2000), or mono-infection by another species or mixed infestation, severe vomiting, severe malnutrition, a woman with positive pregnancy test and patients who had a history of allergy to study drugs or did not give informed consent were excluded from the study.

Treatment

After inclusion, all patients were randomized to receive Artemether-Lumefantrine (AL) or Artesunate-Amodiaquine (ASAQ) for three days. The drugs were administered under the direct supervision of the medical staff. In case of vomiting within the 30 minutes following the first administration, the same dose was administrated again. Participants who vomited a second time were excluded to the study and received intravenous quinine treatment in accordance with the National Malaria Control Program guidelines (25 mg/kg/day for seven days). The dosages of the study drugs were as follows:
Artesunate-Amodiaquine (ASAQ): the tablet contains 4mg/kg/day AS plus 10 mg/kg/day AQ. The drug was given once a day. The dosage was adjusted according to the weight: one tablet per day containing 25 mg/67.5 mg (4.5 - 9 kg), one tablet per day containing 50 mg/135 mg
(9 - 18kg), one tablet per day containing 100 mg/270 mg (18 - 36kg) and two tablets per day containing 100 mg/270 mg if weight was more than 36 kg.
Artemether-Lumefantrine (AL): the tablet contains 120 mg of Artemether plus 20 mg of Lumefantrine. The drug was given 2 times a day. The dosage was adjusted according the to weight: two tablets per day (5 – 14 kg); four tablets per day (15 – 24 kg); six tablets per day (25 – 45 kg) and eight tablets per day if weight was more than 45 kg.

Clinical follow up

After inclusion and first dose administration, all patients were followed at days 1, 2, 3, 7, 14, 21 and 28. At each follow up visit, a clinical examination and interview to evaluate the patient's clinical status as well as the occurrence of adverse events were done. Patients were seen by the medical team at any time if they did not feel well.
A blood sample was collected for thick and thin smears for all study patients from day 1 to day 28 and on a Whatman 3MM filter paper on day 0 and the day parasite reappearance for

DNA analysis.

Laboratory methods

Microscopy

Finger prick blood sample were collected to prepare thick and thin smears which were stained with May-Grünwald-Giemsa. Thick smear was used to determine parasite density. Thin smear was used to identify the parasite species. The parasite density was evaluated by counting the number of asexual parasites per 200 white blood cells and calculated per µl: number of parasites × 8000/200 assuming a white blood cell count of 8000 cells per µl. Thick and thin smears were negative after reading 100 fields microscopic.

PCR analysis

PCR analysis was performed to distinguish recrudescence from new infection in case of treatment failure. DNA was extracted from blood collected on filter paper by Chelex method (Wooden et al., 1993). Nested PCR was conducted to compare the genetic polymorphism of *P. falciparum* merozoite surface protein genes *msp1* and *msp2* and glutamate-rich protein (WHO, 2008).
Recrudescence was defined as at least one identical allele for each of the two markers in the pre-treatment and post-treatment samples. New infections were diagnosed when all alleles for at least one of the markers differed between the two samples.

Statistical methods

Sample size calculation

The sample size for each study arm was evaluated at 155 participants each year, based on an expected therapeutic effect of AL at 98% (Faye et al., 2006), assuming a non-inferiority margin of 7% (two side) and power at 80%, using a 95% confidence level and accounting for 10% of lost to follow up.

Data analysis

After data collection, data were entered in Excel software and the analysis was performed using Stata MP 14. Data were analyzed by estimation of difference in proportion according to a 95% confidence interval. Groups were compared using Chi Square test or Fisher exact test for categorical variables and Student's t-test for continuous variables when these tests were applicable. Otherwise, non- parametric tests (Mann-Whitney, Kruskall-Wallis) were used.
Intention to treat (ITT) and per protocol (PP) analysis were performed. Intention to treat analysis include all randomized subjects who took at least one full dose. Per protocol analysis comprised all subjects who received the three dose and attended follow up to the time of treatment failure or the end of the study (day 28). The cumulative incidence of failure rate was calculated in each group and compared using Kaplan Meier method. Statistical significance for all tests was set at 0.05 two side.

Ethical considerations

This study was conducted according to the Declaration of Helsinki and existing national legal and regulatory requirements. The protocol was reviewed and approved by the Senegalese Ethics Committee (Conseil National d'Ethique et de Recherche en Santé: CNERS). Approval number: 319MSAS/DPRS/CNERS (2014). Informed consent of parent or legal representative was required prior the participation to the study. To respect the confidentiality, an identification code was given to each participant.

RESULTS

General characteristics of study population at inclusion

Overall, 1118 patients with uncomplicated *P. falciparum* malaria infection were randomized to receive either AL (n=553) or ASAQ (n=565). Among participants, 1074 (96%) completed the study (534 in AL group and 540 in ASAQ group). During follow up a total 44 patients (4%) were lost to follow up or withdraw from the per protocol analysis. The trial profile is presented in Figure 1.
Mean age of study participant was 15.4±9 years in AL group and 22.2±11years in ASAQ group. Study population was mainly represented age group 10 to 20 years in both treatment arms. The sex ratio was 1.7 and 1.5 respectively in AL and ASAQ group. Mean temperature was 38.1°C in AL group and 38°C in ASAQ group. The proportion of subject with fever was 75.6% in AL group and 70% in ASAQ group. The parasitaemia was 32832.46 trophozoite/µl and 30620.11 trophozoite/µl respectively in AL and ASAQ arm. The proportion of patients with gametocytes was 1.8% in AL group and 0.7% in ASAQ group.
Overall, there was no significance difference ($p>0.05$) in terms of sex ratio, mean temperature, parasitaemia and proportion of patients with gametocyte in two different groups. However, mean age and weight were significantly higher in ASAQ group ($p<0.05$) (Table 1).

Therapeutic efficacy

Primary endpoint

The cure rate at day 28 before PCR corrected (ITT analysis) was 93.1% (95% CI: 85.5 – 99.9) and 94.7% (95% CI: 86.8 - 99.9) respectively in AL and ASAQ arms (p=0.16). The uncorrected PCR per protocol analysis at day 28 showed good efficacy: 97% in AL group and 99.1% in ASAQ group. The difference was not significative (p=0.06) (Table 2).
PCR corrected analysis showed 99.4% cure rate for both groups during per protocol. There was no early treatment failure. One case of late clinical failure was noted in AL group at day 21. Five cases of late parasitological failure were noted (2 in AL group and 3 in ASAQ group) (Table 3).
The Kaplan Meier survival analysis resulted in a very similar

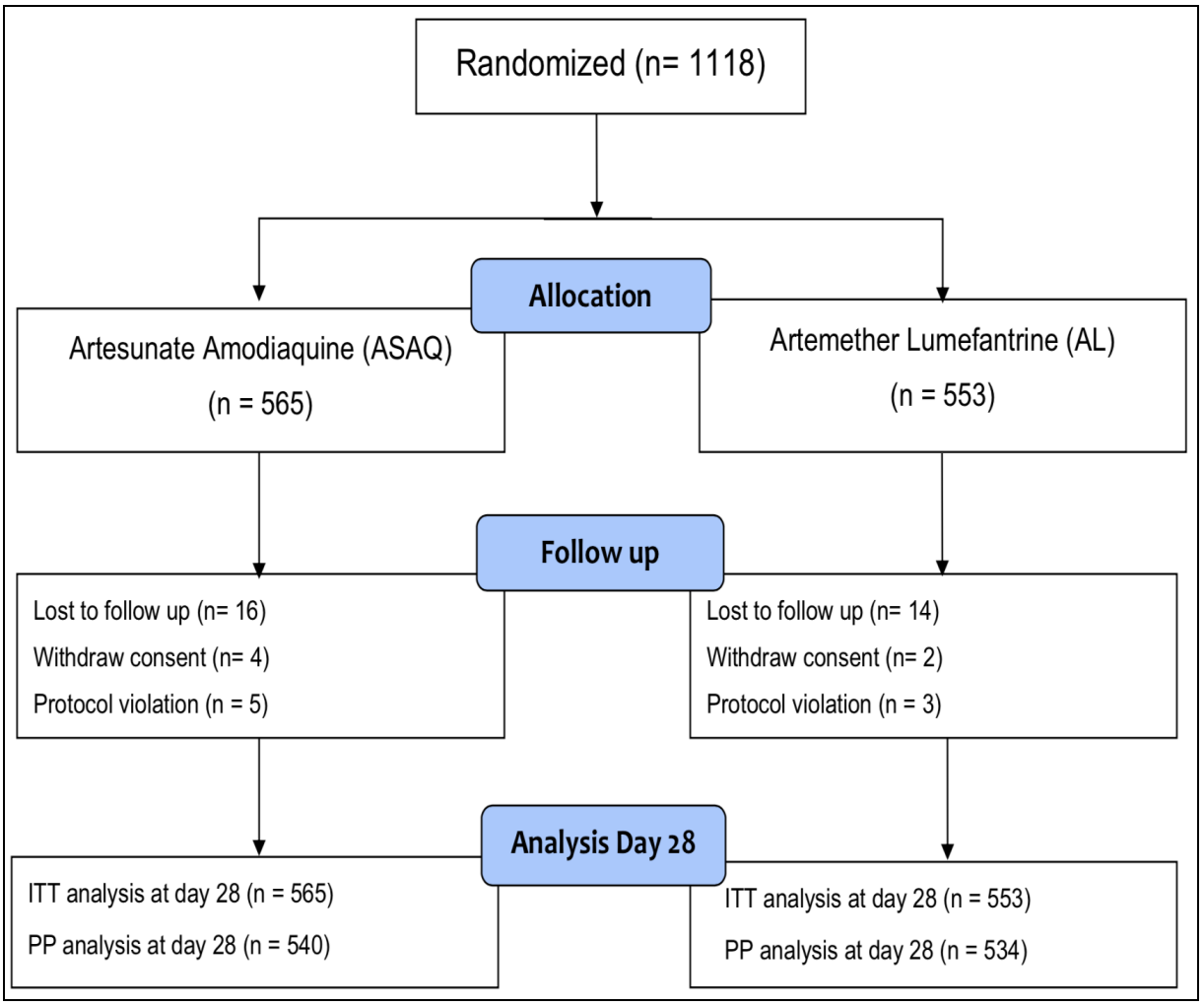

Figure 1: Trial profile.

cumulative incidence failure rate at day 28 two groups (log rank test, p = 0.33) (Figure 2).

Secondary endpoints

Parasite and fever clearance time remained constant over the three transmission seasons. At inclusion parasitaemia was 33141.15 trophozoites/µl in AL group, versus 31424.6 trophozoites/µl in ASAQ group. The parasitemia decreased to 2444.6 trophozoites/µl in AL group, and 1901.7 trophozoites/µl in ASAQ group, 24 hours after first treatment. The proportion of patients with parasites at day 1 was 34% in AL group and 39.5% in ASAQ group. At day 2, this proportion was 2% and 1.8% respectively in both groups. Parasite clearance was obtained at 72 hours in both groups (Figure 3).

At inclusion, the proportion of febrile patients was 75.6% in AL and 70% in ASAQ group. After first dose administration, this proportion was 12.5% in AL group and 4.6% ASAQ group. Fever clearance was obtained at 72 hours in both arms (Figure 4). Regarding gametocyte carriage, the number of patients with gametocyte at inclusion was 10 in AL group and 4 in ASAQ group.

The gametocyte clearance was obtained at day 28 in ASAQ. However, in AL group one patient remained gametocyte carrier at the end of follow up (Figure 5).

DISCUSSION

Malaria is still public health concern in Sub-Saharan Africa. Prompt treatment of uncomplicated malaria cases using Artemisinin Combination Therapy (ACT) is essential component of malaria control strategies. In Senegal, scaling up of ACTs was effective since 2006 with implementation of efficacy monitoring system. This study was carried out in this context.

The therapeutic efficacy obtained was 96.1% in the AL group versus 95.6% in the ASAQ group in ITT and 99.4 in both groups in per protocol. Previous studies have described similar results. In Senegal, a study conducted by Sylla et al when assessing the efficacy of artemisinin-based combination therapies between 2011 and 2012 showed 99.41% efficacy in ASAQ group and 100% in AL group (Sylla et al., 2013). Faye et al during a multicenter study (Cameroon, Côte d'Ivoire and Senegal) in children under five years of age, noted a

Table 1: Baseline characteristics of study participant at the inclusion.

Parameters	AL (n=553)	ASAQ (n=565)	P value
Mean age (± SD, 95%), years	15.4±9 (14.6 – 16/2)	22.2±11 (19.3 – 21.3)	< 0.05
Age group (%, 95 CI)			
Under 10 years	24.4% (20.4 – 28.9)	12.1% (9.3 – 15.3)	< 0.05
10 – 20 years	54.6% (48.6 – 61.1)	51.5% (45.7 – 57.7)	
> 20 years	21% (17.3 – 21.2)	36.5% (31.6 – 41.8)	
Sex ratio (M/F)	1.7 (354/208)	1.5 (344/221)	0.6
Mean weight (± SD, 95% CI), kg	43±12 (42 - 44)	46.8±14 (45.7 – 48.1)	< 0.05
Mean temperature (± SD, 95% CI), °C	38.1±1.1 (38 – 38.2)	38±1.2 (37.8 – 38.1)	0.27
Patients with fever (%, 95% CI)	75.6% (68.5 – 83.2)	70% (63.3 – 77.4)	0.04
Median parasitaemia (trophozoïte/µl)	32832.46	30620.11	0.75
Patients with gametocytes (%, 95% CI)	1.8%	0.7%	0.16

Table 2: Efficacy of ASAQ and AL and at day 28 before PCR correction, ITT and PP analysis.

Outcome	**Before corrected PCR**		
	AL (N=553)	**ASAQ (N=565)**	**p-value**
	% [95% CI]	**% [95% CI]**	
IPP analysis			
NA	22/553 (3.9%)	25/565 (4.4%)	
Late clinical failure	3/553 (0.5%)	1/565 (0.2%)	
Late parasitological failure	13/553 (2.4%)	4/565 (0.7%)	
ACPR	515/553 (93.1%)	535/565 (94.7%)	0.16
	[85.5 – 99.9]	[86.8 - 99.9]	
Per protocol analysis	**AL (N=534)**	**ASAQ (N=540)**	
	% [95% CI]	**% [95% CI]**	
Late clinical failure	3/534 (0.6%)	1/540 (0.2%)	
Late parasitological failure	13/534 (2.4%)	4/540 (0.7%)	
ACPR	518/534 (97%)	535/540 (99.1%)	0.06
	[88.8 - 99.9]	[90.8 - 99.9]	

NA: Not Applicable, ACPR: Adequate Clinical and Parasitological Response.

therapeutic efficacy after PCR correction at day 28 of 98.7% for ASAQ and 96.9% for AL (Faye et al., 2012). 98.9% and 96.7% efficacy were noted by Ndiaye et al, in a study conducted from 2007 to 2009 respectively in ASAQ and AL group after PCR correction at day 28 (Ndiaye et al., 2011). Same trends noted in other studies conducted in Africa. Touré et al in Côte d'Ivoire in 2014, have noted an adjusted efficacy rates of 96.8% and 99% for ASAQ and AL respectively. In the per protocol analysis, the efficacy after PCR correction was 100% for each combination (Touré et al., 2014). In a systematic

Table 3: Efficacy of ASAQ and AL and at day 28 after PCR correction, ITT and PP analysis.

Outcome	**After corrected PCR**		
	AL (N=553)	**ASAQ (N=565)**	**P value**
	% [95% CI]	**% [95% CI]**	
ITT analysis			
NA	19/553 (3.4%)	22/565 (3.9%)	
Late Clinical failure	1/553 (0.2%)	00	
Late parasitological failure	2/553 (0.4%)	3/565 (0.5%)	
ACPR	531/553 (96.1%)	540/565 (95.6%)	0.7
	[88 – 99.9]	[87.7 - 99.9]	
Per protocol analysis	**AL (N=534)**	**ASAQ (N=540)**	
	% [95% CI]	**% [95% CI]**	
Late clinical failure	1/534 (0.2%)	00	
Late parasitological failure	2/534 (0.4%)	3/540 (0.5%)	
ACPR	531/534 (99.4%)	537/540 (99.4%)	1
	[91.2 - 99.9]	[91.2 - 99.9]	

NA: Not Applicable, ACPR: Adequate Clinical and Parasitological Response.

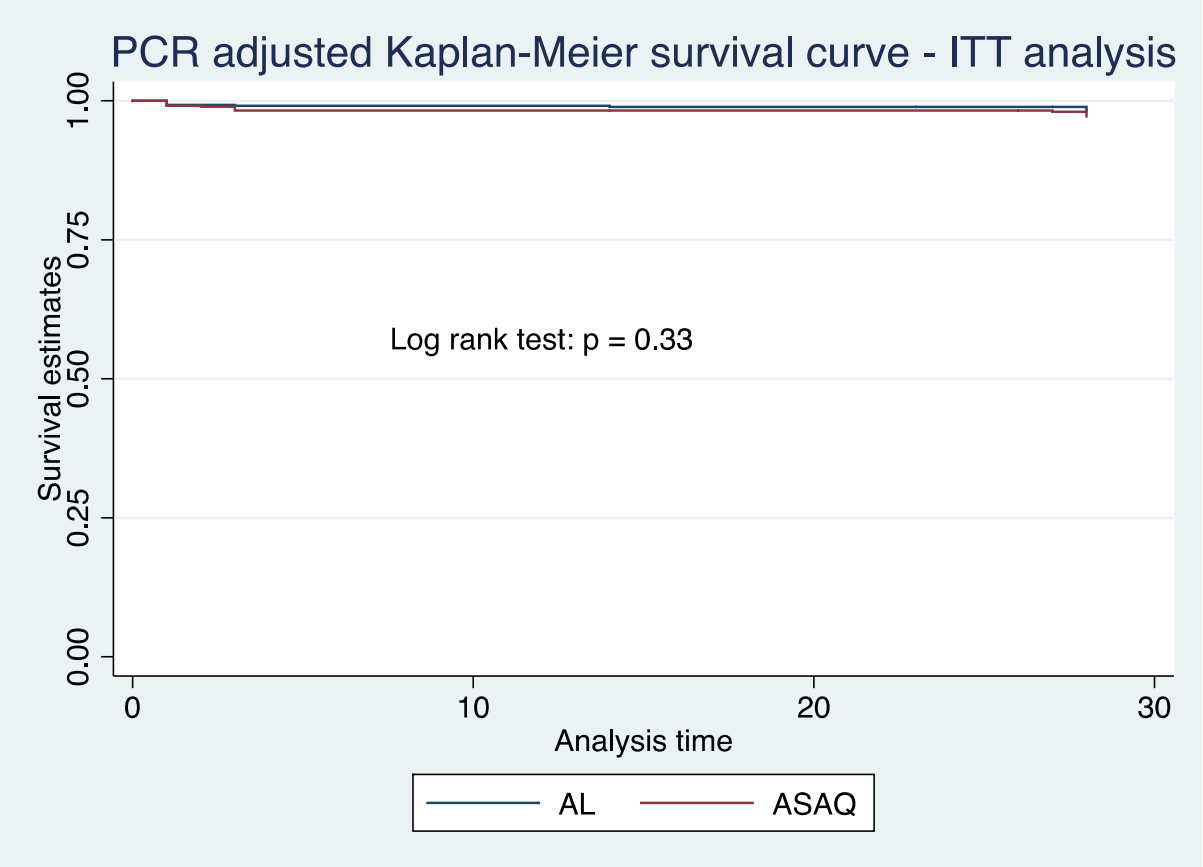

Figure 2: Kaplan-Meier Survival analysis.

review performed by Marwa et al, the cure rates noted after PCR correction were 98% for AL and 99% for ASAQ (Marwa et al., 2022). Another review conducted by Derbie et al and concerning the efficacy of AL, have noted after 28 days of follow-up, the pooled PCR uncorrected and corrected APCR was at 87% and 97% respectively (Derbie et al., 2020). In Bénin, when evaluating the efficacy of arthemether-lumefantrine for the treatment of uncomplicated *P. falciparum* malaria, Ogouyèmi-Hounto et al have showed 87% efficacy rates before PCR correction and 100% after PCR correction

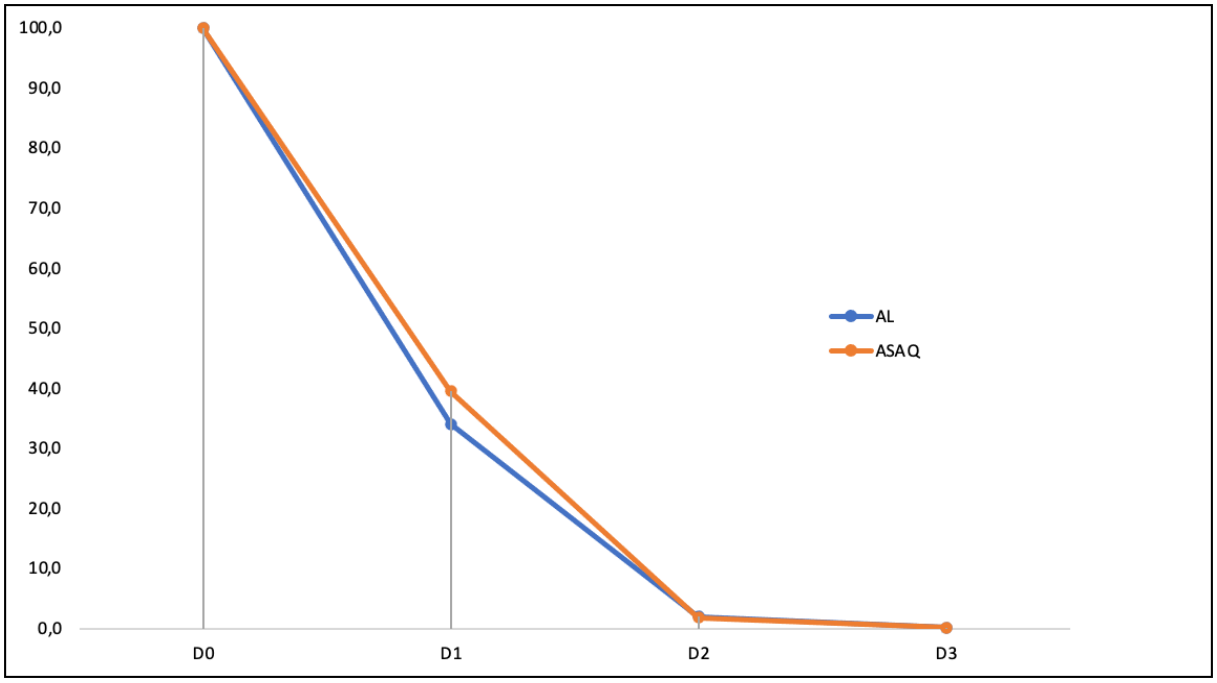

Figure 3: Proportion of patients with parasites during the first tree treatment day.

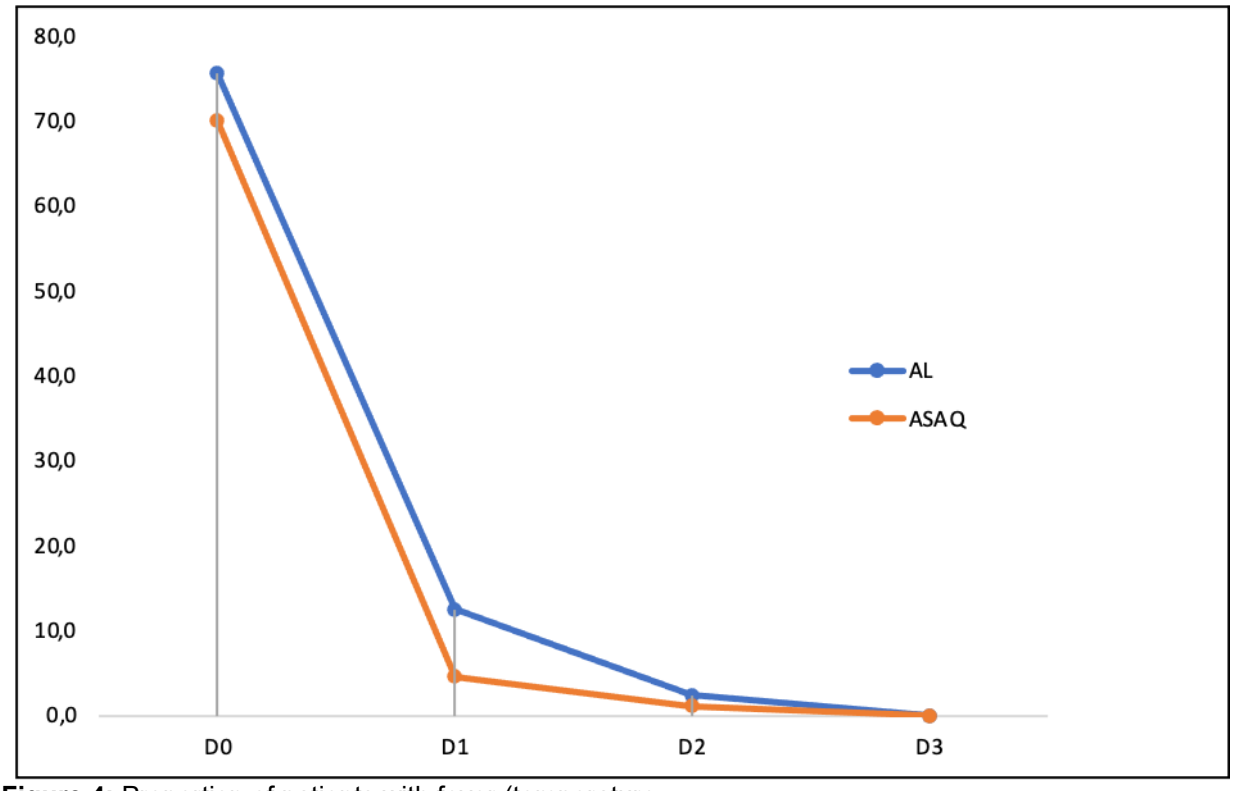

Figure 4: Proportion of patients with fever (temperature.

(Ogouyèmi-Hounto et al., 2016). Similar results were found in Ethiopia with 94.7% (95% CI: 87.1–98.5) and 96% (95% CI: 88.8–99.2) efficacy for AL during PCR-uncorrected and-corrected analysis (Abamecha et al., 2020). When evaluating the effectiveness of ASAQ versus AL for home-based treatment of uncomplicated *Plasmodium falciparum* malaria among children 6–120 months in Cameroon, Niba et al have noted that the PP PCR adjusted day 28 cure rates were

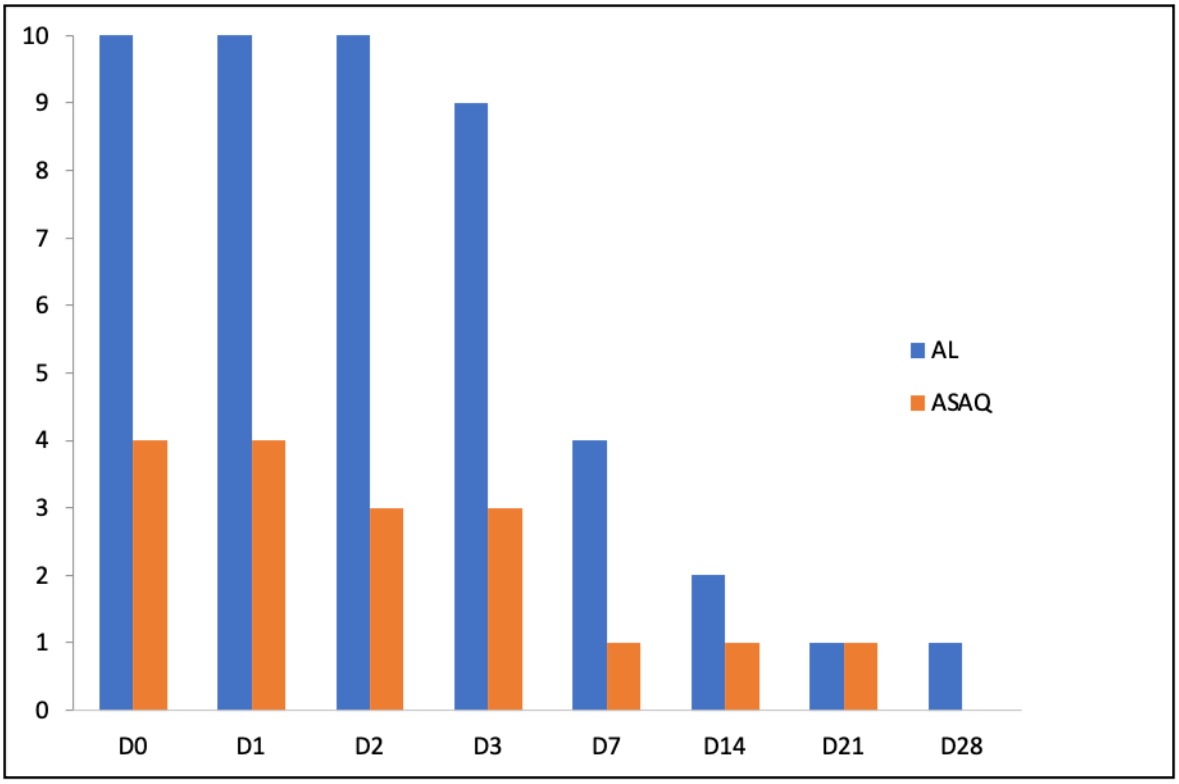

Figure 5: Number of patients with gametocytes during the follow up.

96.9% for ASAQ treatment versus AL 95.5% for AL treatment (Niba et al., 2022).

Concerning Artesunate-Amodiaquine combination, PCR-adjusted efficacy of 97.1% was noted at day 28 by Diarra et al during ACT efficacy trial performed in Mali (Diarra et al., 2021). In Ghana, Abuaku et al have demonstrated an efficacy of ASAQ between 96.7% et 97.7% in children with uncomplicated *P. falciparum* malaria (Abuaku et al., 2017). The ASAQ efficacy observed in Mauritania was more than 98% in two different sites (Ouldabdallahi et al. 2014). In Niger, 95.8% and 96% efficacy were noted respectively for AL and ASAQ at day 28 after PCR correction (Ibrahima et al., 2020).

In Burkina Faso Tinto et al, during an efficacy trial of ASAQ versus AL for malaria treatment have noted adjusted clinical and parasitological adequate response of 89.7% for ASAQ and 89.8% for AL (Tinto et al., 2014). A study conducted in Republic of Congo, have demonstrated good efficacy of ASAQ (94.2%) and AL (98.2%) combinations in different studies conducted in children (Pembet Singana et al., 2022). Other studies conducted in Burkina Faso and Cameroon have shown similar results on the efficacy of ASAQ and AL combinations for the treatment of uncomplicated *P. falciparum* malaria (Lingani et al., 2020; Nji et al., 2015).

A rapid decrease in parasitemia was noted in our study. Parasite clearance was obtained at day 3 in both AL and ASAQ treatment groups. Studies by other authors have shown similar results in Senegal where Faye et al in 2008 (Faye et al., 2010), Ndiaye et al (Ndiaye et al. 2011) in 2007-2009 and Sylla et al al in 2011-2012 have obtained parasite clearance at day 3 for AL and ASAQ combinations (Sylla et al., 2013). When assessing the efficacy of AL and ASAQ in Guinea, Beavogui et al have noted that all slides were negative in both arms at day 3 of follow-up (Beavogui et al., 2020). A disappearance of parasitaemia at day 3 after treatment with ASAQ and AL was noted in a study evaluating the efficacy of two combinations in patients with uncomplicated malaria in Angola (Davlantes et al., 2018). In Uganda Yeka et al had effective parasite clearance at D3 for ASAQ and AL (Yeka et al., 2014).

The results of our study, showed fever clearance was obtained at day 3 two treatment groups. This has been previously demonstrated by Sylla et al and Ndiaye et al (Sylla et al., 2013; Ndiaye et al., 2011). A study carried out by Faye et al on the efficacy of AL and ASAQ in Cameroon, Senegal and Ivory Coast reported a clearance of fever at day 2 for both treatments (Faye et al., 2012). In Tanzania, a disappearance of fever 36 hours after treatment with AL was reported (Mhamilawa et al., 2020).

The gametocyte clearance was obtained at day 28 in ASAQ. However, in AL group one patient remained gametocyte carrier at the end of follow up. This is in line with was previously described in Senegal (Faye et al, 2010). In Madagascar, gametocytes were undetectable from day 14 for AL arm while for ASAQ arm, gametocyte carriage was gradually decreased but persisted until day 21 (Rakotoarisoa et al, 2022).

The results of our study showed that both combination therapies used remain effective and lead to a rapid disappearance of fever after their administration.

CONCLUSION

The results from this study showed that Artemether-Lumefantrine and Artesunate-Amodiaquine combinations are

still highly effective for the treatment of uncomplicated Plasmodium falciparum malaria in Senegal since the scaling up of Artemisinin based Combinations Therapies. The APCR of two combinations are above the 90% WHO acceptable cut-off. It is however crucial to continue to monitor the efficacy of these first line drugs in order to further guide malaria treatment policy in Senegal.

FUNDINGS

This study was funded by the National Malaria Control Programme in collaboration with the department of Parasitology-Mycology of the faculty of Medicine, Pharmacy and Odontology, University Cheikh Anta Diop of Dakar

ACKNOWLEDGMENTS

We would like to thank all the patients and staff at all trial sites who participated in this study. We also would like to thank the National Malaria Control Progamme for providing the ACTs.

Conflicts of Interest

There is no conflict of interest related to the publication of this research manuscript.

Author contribution

KS and BF conceived and designed the study. KS, CBF monitored the data collection. KF collected data in the site. KS analyzed the data. MN was responsible for the PCR analysis. KS wrote the first draft of the manuscript. All authors read and approved the final manuscript.

Data Availability

The data used for this research article are available from the corresponding author upon request.

REFERENCES

Beavogui, A.H., Camara, A., Delamou, A. Malar J 19Davlantes, E., Dimbu, P.R., Ferreira, C.M. Plasmodium falciparum Malar J 17Diarra, Y., Koné, O., Sangaré, L. et al. Therapeutic efficacy of artemether–lumefantrine and artesunate–amodiaquine for the treatment of uncomplicated Plasmodium falciparummalaria in Mali, 2015–2016. Malar J 20, 235 (2021). https://doi.org/10.1186/s12936-021-03760-9Lingani, M., Bonkian, L.N., Yerbanga, I. /Malar J 19Mhamilawa, L.E., Ngasala, B., Morris, U. et al. Parasite clearance, cure rate, post-treatment prophylaxis and safety of standard 3-day versus an extended 6-day treatment of artemether–lumefantrine and a single low-dose primaquine for uncomplicated Plasmodium falciparum malaria in Bagamoyo district, Tanzania: a randomized controlled trial. Malar J 19, 216 (2020). https://doi.org/10.1186/s12936-020-03287-5 et al. versus Plasmodium falciparum Malar J 14Pembet Singana, B., Casimiro, P.N., Matondo Diassivi, B. et al. Prevalence of malaria among febrile patients and assessment of efficacy of artemether-lumefantrine and artesunate-amodiaquine for uncomplicated malaria in Dolisie, Republic of the Congo.Malar J 21, 137 (2022). https://doi.org/10.1186/s12936-022-04143-4Rakotoarisoa, M.A., Fenomanana, J., Dodoson, B.T. Comparative effect of artemether-lumefantrine and artesunate-amodiaquine on gametocyte clearance in children with uncomplicated Plasmodium falciparum malaria in Madagascar. Malar J 21, 331 (2022). https://doi.org/10.1186/s12936-022-04369-2

Abamecha A, Yilma D, Addisu W, El-Abib H, Ibenthal A, Noedl H, Yewhalal D, Moumni M, Abdissa A. (2020). Therapeutic efficacy of artemether-lumefantrine in the treatment of uncomplicated Plasmodium falciparum malaria in Chewaka District, Ethiopia. Malaria Journal. 19, 240. https://doi.org/10.1186/s12936-020-03307-4

Abuaku BK, Mensah BA, Ofori MF, Myers-Hansen J, Derkyi-Kwarteng AN, Essilfie F, Dokurugu M, Amoakoh E, Koram KA, Ghansah A (2017). Efficacy of Artesunate/Amodiaquine in the Treatment of Uncomplicated Malaria among Children in Ghana. American Journal of Tropical Medicine and Hygiene. 97(3):690-695.

Adjei GO, Kurtzhals JA, Rodrigues OP, Alifrangis M, Hoegberg LC, Kitcher ED, Badoe EV, Lamptey R, Goka BQ (2008). Amodiaquine-artesunate vs artemether-lumefantrine for uncomplicated malaria in Ghanaian children: a randomized efficacy and safety trial with one year follow-up. Malaria Journal. 11;7:127.

Beavogui, A.H., Camara, A., Delamou, A. et al. Efficacy and safety of artesunate–amodiaquine and artemether–lumefantrine and prevalence of molecular markers associated with resistance, Guinea: an open-label two-arm randomised controlled trial.Malar J 19, 223 (2020). https://doi.org/10.1186/s12936-020-03290-w

Davlantes, E., Dimbu, P.R., Ferreira, C.M. et al. Efficacy and safety of artemether–lumefantrine, artesunate–amodiaquine, and dihydroartemisinin–piperaquine for the treatment of uncomplicated Plasmodium falciparum malaria in three provinces in Angola, 2017. Malar J 17, 144 (2018). https://doi.org/10.1186/s12936-018-2290-9

Derbie A, Mekonnen D, Adugna M, Yeshitela B, Woldeamanuel Y, Abebe T (2020). Therapeutic Efficacy of Artemether-Lumefantrine (Coartem®) for the Treatment of Uncomplicated Falciparum Malaria in Africa: A Systematic Review. Journal of Parasitology Research. 20; 7371681.

Diarra, Y., Koné, O., Sangaré, L. et al. Therapeutic efficacy of artemether–lumefantrine and artesunate–amodiaquine for the treatment of uncomplicated *Plasmodium falciparum* malaria in Mali, 2015–2016. Malar J 20, 235 (2021). https://doi.org/10.1186/s12936-021-03760-9

Dondorp AM, Nosten F, Yi P, Das D, Phyo AP, Tarning J, Lwin KM, Ariey F, Hanpithakpong W, Lee SJ, Ringwald P, Silamut K, Imwong M, Chotivanich K, Lim P, Herdman T, An SS, Yeung S, Singhasivanon P, Day NP, Lindegardh N, Socheat D, White NJ (2006). Artemisinin resistance in Plasmodium falciparum malaria. New England Journal of Medicine. 361:455–467.

Faye B, Kuété T, Kiki-Barro CP, Tine RC, Nkoa T, Ndiaye JL, Kakpo CA, Sylla K, El Menan H, Gaye O, Faye O, Same-Ekobo A, Moussa K (2012). Multicentre study evaluating the

non-inferiority of the new paediatric formulation of artesunate/amodiaquine versus artemether/lumefantrine for the management of uncomplicated Plasmodium falciparum malaria in children in Cameroon, Ivory Coast and Senegal. Malarial Journal. 27;11:433.

Faye B, NDiaye JL, Dieng Y, Faye O, Gaye O (2006). Efficacy and tolerability of four antimalarial combinations in the treatment of uncomplicated Plasmodium falciparum malaria in Senegal. Malaria Journal. 6:80.

Faye B, Offianan AT, Ndiaye JL, Tine RC, Toure W, Djoman K, Sylla K, Ndiaye PS, Penali L, Gaye O (2010). Efficacy and tolerability of artesunate-amodiaquine (Camoquin plus) versus artemether-lumefantrine (Coartem) against uncomplicated Plasmodium falciparum malaria: multisite trial in Senegal and Ivory Coast. Tropical Medicine and International Health. 15:608–613.

Gbotosho GO, Sowunmi A, Happi CT, Okuboyejo TM (2011). Therapeutic efficacies of artemisinin-based combination therapies in Nigerian children with uncomplicated falciparum malaria during five years of adoption as first-line treatments. American Journal of Tropical Medicine and Hygiene. 84(6):936-43.

Ibrahima I, Laminou IM, Adehossi E, Maman D, Boureima S, Harouna HK, Hamidou HH, Mahamadou A, Yacouba I, Hadiza J, Tidjani IA (2020). Safety and Efficacy of Artemether-Lumefantrine and Artesunate-Amodiaquine in Niger]. Bulletin de la Société de Pathologie Exotique, ;113(1):17-23.

Kobbe R, Klein P, Adjei S, Amemasor S, Thompson WN, Heidemann H, Nielsen MV, Vohwinkel J, Hogan B, Kreuels B, Bührlen M, Loag W, Ansong D, May J (2008). A randomized trial on effectiveness of artemether-lumefantrine versus artesunate plus amodiaquine for unsupervised treatment of uncomplicated Plasmodium falciparum malaria in Ghanaian children. Malaria Journal. 7:261.

Lingani, M., Bonkian, L.N., Yerbanga, I. et al. In vivo/ex vivo efficacy of artemether–lumefantrine and artesunate–amodiaquine as first-line treatment for uncomplicated falciparum malaria in children: an open label randomized controlled trial in Burkina Faso.Malar J 19, 8 (2020). https://doi.org/10.1186/s12936-019-3089-z

Marwa K, Kapesa A, Baraka V, Konje E, Kidenya B, Mukonzo J, Kamugisha E, Swetberg G. (2022) Therapeutic efficacy of artemether-lumefantrine, artesunate-amodiaquine and dihydroartemisinin-piperaquine in the treatment of uncomplicated *Plasmodium falciparum* malaria in Sub-Saharan Africa: A systematic review and meta-analysis. PLoS ONE 17(3): e0264339. https://doi.org/10.1371/journal.pone.0264339

Mhamilawa, L.E., Ngasala, B., Morris, U. et al. Parasite clearance, cure rate, post-treatment prophylaxis and safety of standard 3-day versus an extended 6-day treatment of artemether–lumefantrine and a single low-dose primaquine for uncomplicated Plasmodium falciparum malaria in Bagamoyo district, Tanzania: a randomized controlled trial. Malar J 19, 216 (2020). https://doi.org/10.1186/s12936-020-03287-5

National malaria control program Senegal (2016). Strategic plan against malaria, Ministry of Health Senegal 2016–2020.

Ndiaye JL, Faye B, Gueye A, Tine R, Ndiaye D, Tchania C, Ndiaye I, Barry A, Cissé B, Lameyre V, Gaye O (2011). Repeated treatment of recurrent uncomplicated Plasmodium falciparum malaria in Senegal with fixed-dose artesunate plus amodiaquine versus fixed-dose artemether plus lumefantrine: a randomized, open-label trial. Malaria Journal. 12;10:237.

Niba PTN, Nji AM, Ali IM, Akam LF, Dongmo CH, Chedjou JPK, Fomboh CT, Nana WD, Oben OLA, Selly-Ngaloumo AA, Moyeh MN, Ngu JA, Ludovic AJ, Aboh PM, Ambani MCE, Omgba PAM, Kotcholi GB, Adzemye LM, Nna DRA, Douanla A, Ango Z, Ewane MS, Ticha JT, Tatah FM, Dinza G, Ndikum VN, Fosah DA, Bigoga JD, Alifrangis M, Mbacham WF (2022). Effectiveness and safety of artesunate-amodiaquine versus artemether-lumefantrine for home-based treatment of uncomplicated Plasmodium falciparum malaria among children 6-120 months in Yaoundé, Cameroon: a randomized trial. BMC Infectious Diseases, 22(1):166.

Nji, A.M., Ali, I.M., Moyeh, M.N. et al. Randomized non-inferiority and safety trial of dihydroartemisin-piperaquine and artesunate-amodiaquine versus artemether-lumefantrine in the treatment of uncomplicated Plasmodium falciparum malaria in Cameroonian children. Malar J 14, 27 (2015). https://doi.org/10.1186/s12936-014-0521-2

Noedl H, Se Y, Schaecher K, Smith BL, Socheat D, Fukuda MM (2008). Evidence of artemisinin-resistant malaria in western Cambodia. New England Journal of Medicine. 359:2619–2620.

Ogouyèmi-Hounto A, Azandossessi C, Lawani S, Damien G, de Tove YS, Remoue F, Kinde Gazard D (2016). Therapeutic efficacy of artemether-lumefantrine for the treatment of uncomplicated falciparum malaria in northwest Benin. Malaria Journal. 22;15:37.

Ouldabdallahi M, Alew I, Salem MSOA, Dialaw BM, Boukhary AOMS, Khairy MLO, Aziz MBA, Ringwald P, Basco LK, Niang SD, Lebatt SM (2014). Efficacy of artesunate-amodiaquine for the treatment of acute uncomplicated falciparum malaria in southern Mauritania. Malaria Journal, 13, 496 https://doi.org/10.1186/1475-2875-13-496

Pembet Singana, B., Casimiro, P.N., Matondo Diassivi, B. et al. Prevalence of malaria among febrile patients and assessment of efficacy of artemether-lumefantrine and artesunate-amodiaquine for uncomplicated malaria in Dolisie, Republic of the Congo.Malar J 21, 137 (2022). https://doi.org/10.1186/s12936-022-04143-4

Rakotoarisoa, M.A., Fenomanana, J., Dodoson, B.T. et al. Comparative effect of artemether-lumefantrine and artesunate-amodiaquine on gametocyte clearance in children with uncomplicated Plasmodium falciparum malaria in Madagascar. Malar J 21, 331 (2022). https://doi.org/10.1186/s12936-022-04369-2

Sylla K, Abiola A, Kouly Tine RC, Faye B, Sow D, Ndiaye JL, Ndiaye M, Lo AC, Folly K, Ndiaye LA, Gaye O (2013). Monitoring the efficacy and safety of three artemisinin based-combinations therapies in Senegal: results from two years surveillance. *BMC* Infectious Diseases, 13:598.

Tine RCK, Faye B, Sylla K, Ndiaye JL, Ndiaye M, Sow D, Lo AC, Abiola A, Ba MC, Gaye O (2012). Efficacy and tolerability of a new formulation of artesunate- mefloquine for

the treatment of uncomplicated malaria in adult in Senegal: open randomized trial. Malaria Journal. 11:416.

Tinto H, Diallo S, Zongo I, Guiraud I, Valea I, Kazienga A, Kpoda H, Sorgho H, Ouédraogo JB, Guiguemdé TR, D'Alessandro U (2014). Effectiveness of artesunate-amodiaquine vs. artemether-lumefantrine for the treatment of uncomplicated falciparum malaria in Nanoro, Burkina Faso: a non-inferiority randomised trial. Tropical Medicine and International Health. 19(4):469-75.

Toure OA, Assi SB, N'Guessan TL, Adji GE, Ako AB, Brou MJ, Ehouman MF, Gnamien LA, Coulibaly MA, Coulibaly B, Beourou S, Bassinka I, Soumahoro A, Kadjo F, Tano MA (2014). Open-label, randomized, non-inferiority clinical trial of artesunate-amodiaquine versus artemether-lumefantrine fixed-dose combinations in children and adults with uncomplicated falciparum malaria in Côte d'Ivoire. Malaria Journal. 19;13:439.

WHO (2000). Severe falciparum malaria. World Health Organization, Communicable Deseases Cluster. Transaction Royal Society of Tropical Medicine and Hygiene. 37:105–125.

WHO (2001)**.** Antimalarial drug combination therapy: Report of WHO Technical Consultation. https://apps.who.int/iris/handle/10665/66952

WHO (2006). Guidelines for the treatment of malaria. WHO/HTM/MAL/2006.1108. https://infonet-biovision.org/sites/default/files/1571.treatmentguidelines20061.pdf

WHO (2008). Methods and techniques for clinical trials on antimalarial drug efficacy: genotyping to identify parasite populations. https://apps.who.int/iris/handle/10665/43824

WHO (2009). Methods for surveillance of antimalarial drug efficacy. Geneva. https://www.who.int/docs/defaultsource/documents/publications/gmp/methods-for-surveillance-of-antimalarial-drug-efficacy.pdf?sfvrsn=29076702_2

WHO (2010). Guidelines for the treatment of malaria. 2nd edition. WHO ISBN 978 (92), 4. Geneva. https://www.paho.org/en/documents/guidelines-treatment-malaria-second-edition-2010

WHO (2021). World Malaria Report. Licence: CC BY-NC-SA 3.0 IGO. (https://www.who.int/publications/i/item/9789240040496)

WHO .(2015) Guidelines for the treatment of malaria, 3rd ed. World Health Organization. https://apps.who.int/iris/handle/10665/162441

Wooden J, Kyes S, Sibley CH (1993). PCR and strain identification in Plasmodium falciparum. Parasitology today. 1;9(8):303-5.

Yeka A, Lameyre V, Afizi K, Fredrick M, Lukwago R, Kamya MR, Talisuna AO (2014). Efficacy and safety of fixed-dose artesunate-amodiaquine vs. artemether-lumefantrine for repeated treatment of uncomplicated malaria in Ugandan children. PLoS One. 9(12):e113311.*NA: Not Applicable, ACPR: Adequate Clinical and Parasitological Response.*