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EFFICACITY AND TOLERABILITY OF ARTESUNATE AMODIAQUINE (ASAQ) VERSUS ARTHEMETHER LUMEFANTRINE (AL) IN THE TREATMENT OF UNCOMPLICATED *PLASMODIUM FALCIPARUM* MALARIA AMONG CHILDREN FROM 0 TO 60 MONTHS IN THREE PROVINCES IN CHAD

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ABSTRACT
The Chadian government recommends three artemisinin-based combinations for the treatment of uncomplicated *Plasmodium falciparum* malaria: Artemether–Lumefantrine (AL), Artesunate–Amodiaquine (ASAQ). Due to the treatment of emerging anti-malarial drug resistance, it is important to periodically monitor the efficacy of artemisinin-based combination therapy (ACT). This study evaluated these medications therapeutic efficacy in Massakory, Mondo, and Dourbali Provinces. Enrollment occurred between January and April 2020. Study participants were children with *P. falciparum* monoinfection from each provincial capital. Participants received a 3-day course of a quality-assured artemisinin based combination and were monitored for 28 days (AL and ASAQ arms). We recruited 1130 children of whom 570 (ASAQ group) and 560 (AL group) were fully followed-up. The cure rates for ASAQ and AL treatments were 95.8% and 92.5% on day 28 respectively. Overall, both drugs were well tolerated at the clinical and biological level, no late parasitological failures have been recorded in AL and ASAQ groups. This study shows that ASAQ and AL are still effective and well tolerated. Accordingly, they can continue being used to treat uncomplicated malaria in Chad. However, monitoring of their efficacy should remain a priority for health authorities.

KEYWORDS: Malaria, Efficacy, *Plasmodium falciparum*, Artesunate-Amodiaquine, Artemether-Lumefantrine.

INTRODUCTION
Malaria is the principal cause of morbidity and mortality in Chad and is endemic throughout the country and remains a major public health problem (Issa *et al.*, 2017). The WHO estimated in 2019 that malaria disease led to more than three million cases and 380 000 deaths in Africa. Reports from the National Malaria Control Program (NMCP) in Chad indicate that malaria is responsible for 43% of all causes of outpatient visits and one third of reported deaths in health facilities (NMCP., 2014). In recent years, the country has made significant gains in reducing malaria burden with aggressive preventive measures, case management, and surveillance (Issa *et al.*, 2017). Artemisinin-based combination therapy (ACT) comprises an Artemisinin derivative plus a partner drug; the Artemisinin component has a relatively short half-life and acts quickly to reduce parasite burden, while the partner drugs have longer half-lives and suppress parasitaemia for weeks post-treatment. These pharmacological differences are important when monitoring for drug resistance and inadequate clearance of parasitaemia in the first few days after treatment signals a possible problem with the Artemisinin component of an ACT, while recurrent parasitaemia later on points more towards an issue with the partner drug. Worldwide, malaria elimination efforts is threatened by resistance of *Plasmodium falciparum* to most of antimalarial drugs including artemisinin derivatives. Artemisinin resistance has already been confirmed in five countries of the Greater Mekong subregion: Cambodia, the Laouse People's Democratic Republic, Myanmar, Thailand, and Vietnam (Chavatte *et al.*, 2015 and Matubi *et al.*, 2015). This phenomenon risks following the same historical trajectory from Asia to Africa seen previously with chloroquine resistance (Schindler *et al.*, 2019). Indeed, a case of indigenous artemisinin-resistant *P. falciparum* has recently emerged in a patient from Equatorial Guinea, Africa (Schindler *et*

al., 2019). Therefore, World Health Organization (WHO) recommends routine monitoring of the therapeutic efficacy of Artemisinin-based combination therapies (ACTs) that is essential to ensure timely changes in treatment policy and to help detect early changes in *P. falciparum* susceptibility to antimalarial drugs (WHO, 2004). Artesunate-Amodiaquine (ASAQ), Artemether-Lumefantrine (AL) and Sulfadoxine-Pyriméthamine (SP) for pregnant (women were recommended in 2005 by the National Malaria Control Program (NMCP) of Chad for treatment of uncomplicated cases as first-line and second-line respectively. The first studies were conducted on both drug combinations in 2009, 2011 at three sentinel sites by Tchonfiene *et al*., 2013; and Tailor *et al*., 2013. Also in 2018 Issa *et al* had conducted the same study in one site in South of Chad. Survey reports estimated combined (ASAQ) and (AL) treatment failure rates of 0.7% in 2011 and 0% in 2018 (Issa *et al*., 2018), indicating a same and high efficacy. These results were followed by the adoption of both regimens as first-line treatments since 2005. However, owing to patients complaints following the use of ASAQ frequently reported by physicians, a greater use of (AL) compared to (ASAQ) is common (Mohammed *et al*., 2018**)** , posing a high risk of selection of resistant strains by (AL). Failure rate is one of the main indicators of drug resistance (Gabriels *et al*., 2004). In this context, a non-inferiority assessment of efficacies of both combinations after this therapeutic change and its impact on failures rates was finally due. The aim of this study was to evaluate the efficacy of (ASAQ) and (AL) for the treatment of uncomplicated *falciparum* malaria in three regions in Chad.

MATERIAL AND METHODS

Study area: This study was conducted from January to April 2020 at three district-level hospitals of Mondo (province of Kanem), Massakory (province of Hadjer-Lamis) and Dourbali (province of Chari-Baguirmi) (Figure 1). The all three sites are characterized by two seasons: one rainy season (from June to October) and one dry season (from November to June). The transmission of malaria occurs throughout the year, with a peak in the rainy season from July to October.

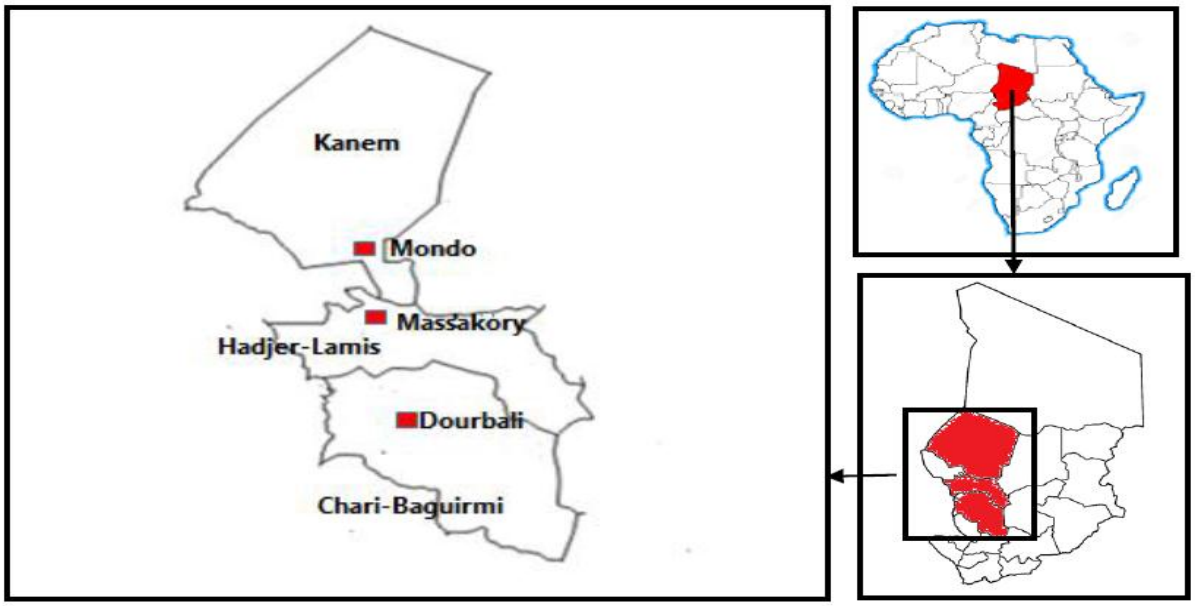

Figure 1: Represent the study area.

Study procedures: Patients with malaria-like symptoms were received at selected health centers. Meticulous clinical examinations of the patients and laboratory investigations were conducted immediately after inclusion. Patients who met baseline inclusion criteria were randomly assigned to one of the two treatment groups. Drug administration was supervised by a member of the research team and patients were kept under observation. After the initial dose, patients had a follow-up within 28 days. All data collected from this study were recorded in a personal and confidential. Each patient was scheduled for follow-up examinations on day 0, 1, 2, 3, 7, 14, 21, 28, any other time the participant felt unwell during the study period it will be treated. On each visit day, the following information was collected: 1) clinical data, 2) biological data (diagnosis of malaria and determination of parasitemia), 3) any details about drug adverse events. In case of treatment failure, are placement therapy was offered according to the national treatment guidelines.

Laboratory analysis: Blood smear were obtained to check the presence of *P. falciparum* and to estimate the parasitaemia at day 0 (before inclusion) and at each scheduled or unscheduled visit. Thick and thin blood films were prepared, dried and Giemsa-stained according to standard operating procedures and examined under light microscopy at 1000-time magnification. Parasite

density was calculated by counting the number of asexual parasites per 200 white blood cells (WBC) in the thick blood film, based on an assumed WBC of 8000/µl. One hundred high-powered fields (HPF) were examined (independent of presence or absence of asexual parasite stages). The parasite density per microliter was calculated using the following formula: W Parasite density/µI = (number of parasites counted × 8000)/-number of leukocytes counted- Blood smears were examined by two readers. Hemoglobin level was measured at day 0, 14, 28.

Patients and Inclusion criteria

During the study period, all male and female patients aged 6 to 59 months inclusive, with fever (axillary temperature ≥ 37.5 °C) or history of fever in the last 24 h, visiting the peripheral health centers of Massakory, Dourbali and Mondo health districts. Children weighing less than 5 kg or more, with a confirmed *P. falciparum* (parasitaemia ≥ 4000/µL to 200,000/µL) mono-infection, hemoglobin level above 5.0 g/dl, and agreed to participate whenever applicable by giving their assent and if their parents or guardian provided written informed consent. Patients were not included if they were not willing to participate or had participated to any drug trial within the last 30 days, or had known hypersensitivity to the study drug, or were severely malnourished (defined as weight for height < 70% of the median NCHS/WHO reference), or had severe malaria. Patients were excluded after randomization if slide re-evaluation demonstrated a parasite density or species outside the inclusion criteria, if the patient experienced repeated vomiting of study medications on day 0, anti-malarial drug intake outside the study protocol during the follow up period, or a voluntary consent withdrawal. For each included participant, five milliliters of venous blood were collected in EDTA tubes for hemoglobin assessments.

Outcome measures

Early Treatment Failures (ETF) in case of significant parasitaemia at day 2 or 3 or parasites and fever at day 3, Late Clinical Failures (LCF) for cases with parasites and fever during follow-up after day 3 and Late Parasitological Failures (LPF) for parasite infections with/without fever during the follow-up period. Cases which remained negative during follow-up were considered to be Adequate Clinical and Parasitological Responses (ACPR). These were modified from WHO guidelines 12- 13.

Ethical considerations

Artemether–lumefantrine and Artesunate plus amodiaquine are the first and second line anti-malarial treatments in Chad. The study protocol was reviewed and approved by the National Malaria Control Program (NMCP) in Chad. Informed consent and written informed consent were obtained from the children's parents before entering the study. The study was conducted according to the WHO Good Clinical Practices guidelines and according to the Chadian ministry of health regulations.

Statistical analysis: All data were recorded using IBM SPSS Statistics, version 25, comparisons of different parameters in both arms were done using, Fisher's exact test, and the independent samples t-test. The level of significance for statistical tests was set at 0.05.

RESULTS

Baseline characteristics of enrolled participants**:** a total of 1130 children were enrolled over the study period and treated with either AL or ASAQ for three days. About 49.55% of the participants treated with AL and 50.44% of those treated with ASAQ. Children from 4-5 months were more represented in AL group followed by children from 2-3 years from ASAQ group. Mean of parasitimia was 11720.24 and 17834.84 respectively in AL and ASAQ groups. Other characteristics are described in Table 1.

Table I: Characteristics of study population.

Characteristics	AL (N=560)	ASAQ (N=570)
Site		
Masakory	230	220
Dourbali	180	190
Mondo	150	160
Sexe		
Masculin n (%)	320 (57.15)	320(56.14)
Feminin n (%)	240 *(42.85)*	250(43.85)
Age		
mean	4.33	3.70
interval	0.5	0.4
Weight		
mean	15.26	13.13
interval	7.55	6.42
Temperature in C^0		
mean	38.66	38.55
interval	37.50-40.50	35.60-40.80
Parasitemia		
mean	11720.24	17834.84
interval	**2000.200000**	**2000.200000**

Legend: AL= Arthemether lumefantrin; ASAQ= Artesian amodiaquine; N=General population of study; n= Number of population examinated ; (%)= Parcentage.

Treatment efficacy: the early treatment failure over the 28 days follow up period have been recorded in all treatment groups respectively 7(1.25%) in AL and 5(0.87%) in ASAQ. Early clinical failures were recorded in all groups: 6(0.53) in AL and 3(0.26)% in ASAQ group meaning that patients treated with AL were more likely to have earlier clinical failure compared to patients treated with ASAQ. On the other hand, no late parasitological failures have been recorded in AL and ASAQ groups; finally treatment was significantly successful in ASAQ group (Table 2) compared to AL group (97.67% versus 98.59%, p=0.0008).

Table II: Treatment responses.

Treatment response for treatment	Masakory n (%)	Dourbali n (%)	Mondo p-value n (%)
Artemether ETF Lumefantrine ECF	2(0 .35) 2(0.35)	2(0.35) 3(0.53)	3(0.53) 0.001 1(0.17)
N= 560 LPF	0(0)	0(0)	0(0)
ACPR	**226(40.3)**	**175(31.25)**	**146(26.07)**
Artesunate ETF Amodiaquine ECF	1(0.17) 1(0.17)	2(0.35) 1(0.17)	2(0.35) 0.06 1(0.17)
N=570 LPF **ACPR**	**0(0)** **218(38.24)**	**0(0)** **187(32.80)**	**0(0)** **157(27.54)**

Legend: ETF= Earlier treatment failure; ECF= Earlier clinical failure, LPF: Late parasitoloical failure; ACPR= Adequate clinical and parasitological responses; N=General population of study; n= Number of population examinated ; (%)= Parcentage.

Treatment tolerability**:** over the study period, we found no serious adverse event. The registered adverse events were mild to moderate and none required active treatment or intervention's discontinuation. Common adverse events were weakness in either group.

DISCUSSION

This is probably the first publication on the AL and ASAQ in the treatment of uncomplicated falciparum malaria in children from 6 months to five years. The study showed a full efficacy (97.67%) of the AL and (98.59%) of ASAQ for the treatment of uncomplicated falciparum malaria in these regions, and no cases of late parasitological failure detected during the 28-day follow-up period. Recently, a full efficacy of the AL and ASAQ was reported in an area of unstable malaria transmission in South of Chad by (Issa *et al.*; 2018). In order study in Mali, the AL and ASAQ had shown 91.0% and 97.1% efficacy in children with uncomplicated falciparum malaria (Souleyiman *et al.;* 2017). In Burkina faso (Matubi *et al*., 2015) reported that the efficacy of AL and ASAQ for the treatment of children with uncomplicated falciparum malaria was 97% and 85.2% respectively.

Previously (AL) and (ASAQ) is available in the form of tablets and the patients had to swallow up to 24 tablets and the idea of this simple form (suspension) was emerged to enhance the compliance. Recently, the bioavailability of chloroquine suspension was comparable with that of chloroquine syrup as standard (Chindlar *et al.,* 2019). Yet, due to the spread of chloroquine resistance, the chloroquine suspension might not be the preferred choice. The preliminary data on artemisinin suggested artemether as an optimum candidate 8 and the combination was emerged. Due to the age factor, it was difficult to monitor or detect the adverse effects in the studied children. However, abdominal pain; nausea and mild diarrhea were reported in sixty two children. It had been reported that .There was twenty one case of gametocytaemia during the follow-up period. The ability of Artesunate to reduce the post-treatment gametocytaemia is important, as it may reduce transmission (Nosten *et al*., 2002).

CONCLUSION

Artemether-lumfantrine (AL) and Artesian-Amodiaquine (ASAQ) suspension appears to be efficacious and safe for the treatment of uncomplicated malaria in Chad.

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