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# CLINICAL RESPONSE OF A BRAND OF ARTEMETHER-LUMEFANTRINE IN CHILDREN BELOW FIVE YEARS OLD

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## ABSTRACT

*Malaria is a major health concern in children aged less than five years old, globally. In Nigeria, it was estimated that 300,000 children die annually from malaria. Thus, this study aims to evaluate the clinical response of a brand of arthemether-lumefantrine (AL) for clearing parasitaemia in children aged less than five years old. This was a prospective study of the clinical and parasitological responses to the treatment of uncomplicated Plasmodium falciparum (P. falciparum) malaria using a popular dispersible brand of AL 20/120 mg. A hundred participants within 6–59 months with P. falciparum malaria were enrolled in the study and participants who could not complete the follow-ups were excluded. The drug was administered to participants following same dosage regimen on days 0, 1, 2 and followed-up on days 3, 7, 14, 21 and 28 in which the participants were assessed clinically and parasitologically. Data was analysed using MS-Excel 2010 and SPSS version 18. Kaplan-Meier survival analysis was used to assess clinical outcomes. The study showed that 73 participants completed the 28 days follow-up while 27 participants were lost to follow-up. Clinical outcome revealed no early treatment failure (ETF), one late clinical failure (LCF), 10 parasitological failures and 62 adequate clinical and parasitological response (ACPF). Clinical response was 84.9%, cumulative success and failure rate was 93.6% and 6.4%, respectively, on day 28. The clinical response of AL was efficacious. The failure rate of 6.4% could likely be as a result of reinfection within the period of follow-up.*

***Keywords:*** Response, Children, *P. falciparum* malaria, Arthemeter-Lumefantrin, Brand

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## INTRODUCTION

Malaria continues to be a major public health problem in 97 countries and territories in the tropics and subtropics. Globally, it accounts for approximately 214 million cases annually and 3.2 billion people are at risk of infection (WHO 2015). Approximately 438,000 deaths were attributed to malaria in 2015, particularly in sub-Saharan Africa, where an estimated 90% of deaths occur (WHO 2015). As a critical target of the Millennium Development Goals, in 2005, the World Health Assembly established a goal of reducing cases and deaths by 75% between 2005 and 2015 (WHO 2005). Hence, over the past decade, there has been greatly renewed interest in research and innovations in diagnostic methods, drugs and vaccines, and the development of control measures for its eradication (Korenromp *et al.* 2013). As a result, between 2000 and 2013, the incidence of malaria fell by 30% globally and by 34% in Africa (Murray *et al*. 2014).

Globally, artemisinin combination therapy (ACT) are the recommended first-line treatment of uncomplicated *Plasmodium falciparum* (*P. falciparum*) malaria (WHO 2001) and has been adopted by most malaria endemic countries (Bosman and Mendis 2007). Reports of artemisinin resistance in some parts of Southeast Asia where ACT have been used for over a decade as first-line treatment has necessitated a continuous surveillance of the effectiveness and clinical response with ACTs in areas where resistance has not been reported (Lim *et al*. 2009; Carrara *et al*. 2009; Phyno *et al*. 2012). The consistent assessment of effectiveness and clinical response with antimalarials used as first-line drug is greatly essential in order to eliminate the disease completely due to its high mortality and morbidity in Nigeria (WHO 2010). The use of artemether-lumefantrine (AL) and artesunate-amodiaquine as first-line drugs was started in Nigeria in 2005 (FEDERAL MINISTRY OF HEALTH [FMOH] 2005). However, since such adoption, no study has been done to determine the clinical response to ACTs and their effectiveness in the southern part of Nigeria. We aim to assess the clinical response of AL in patients aged less than five years old with uncomplicated *P. falciparum* malaria.

### Prevalence of *P. falciparum* Malaria in Nigeria

Nigeria suffers the world's greatest malaria burden, with approximately 51 million cases and 207,000 deaths reported annually (approximately 30% of the total malaria burden in Africa), while 97% of the total population (approximately 173 million) is at risk of infection (WHO 2014). Moreover, malaria accounts for 60% of outpatient visits to hospitals and approximately 11% maternal mortality and 30% child mortality, especially among children aged less than five years old (WHO 2014; FMOH 2005).

Since 2008, the National Malaria Control Programme (NMCP) in Nigeria has adopted a specific plan, the goal of which is to reduce 50% of the malaria burden by 2013 (Ye *et al*. 2012). This is achieved by enforcing at least 80% coverage of long-lasting impregnated mosquito nets (LLINs), together with other measures, such as 20% of houses in targeted areas receiving indoor residual spraying (IRS) (Ye *et al*. 2012). Furthermore, the plan also emphasises treatment with two doses of intermittent preventative therapy (IPT) for 100% of pregnant women who visit antenatal care clinics (Ye *et al*. 2012). Because of these measures, the percentage of households with at least one LLIN increased to over 70% by 2010, compared to only 5% in 2008 (Oyeyemi, Alawode and Sogunro 2010).

## METHODS

### Study Design

The study was a prospective study on the clinical and parasitological responses to the treatment of uncomplicated *P. falciparum* malaria using AL following WHO (2009) protocol for investigating the clinical response to antimalarial. The standard protocol was drawn up and used to test the clinical response of subjects with *P. falciparum* treated with AL. A minimum of 50 patients is required within the ages of 6 to 59 months old in areas of high transmission and all patients ages over 6 months old in areas of low-to-moderate transmission with clinical and parasitological responses carried out on days 0, 1, 2, 3, 7, 14, 21 and 28 after drug administration. Treatment outcomes were classified as early treatment failure (ETF) which is defined as the presence of parasitaemia irrespective of axillary temperature or with a temperature greater than 37.5°C, late clinical failure (LCF) which is defined as the presence of parasitaemia on any day between day 4 and day 28), late parasitological failure (LPF) which is defined as the presence of parasitaemia between day 7 and day 28, and adequate clinical and parasitological response (ACPR) which is defined as absence of parasitaemia on day 28 irrespective of axillary temperature) (WHO 2009).

During follow-up, the patient's blood sample was collected and clinical condition examined on days 0, 1, 2, 3, 7, 14, 21 and 28 for the presence of parasitaemia. Patient treatment outcomes were classified as having ETF which is defined as the presence of danger signs (such as seizures, convulsion or severe weakness) or severe malaria on days 1, 2 or 3 in the presence of parasitaemia irrespective of axillary temperature or with a temperature greater than 37.5°C; LCF which is defined as the presence of danger signs (such as seizures, convulsions, severe weakness) or severe malaria in the presence of parasitaemia on any day between day 4 and day 28 with an axillary temperature greater than 37.5°C; LPF which is defined as the presence of parasitaemia between day 7 and day 28 with an axillary temperature less than 37.5°C; ACPR which is defined as absence of parasitaemia on day 28 irrespective of axillary temperature (WHO, 2009). The proportion of patients that showed treatment failure during follow-up was used to estimate the effectiveness/clinical response of the drug as defined by the ACPR. The day a patient was enrolled and received the first dose was designated as day 0.

### Study Area

This study was done in Eku Baptist General Hospital located in Ethiope East Local Government Area, Delta State, Nigeria. Eku Baptist General Hospital is one of the most popular healthcare facilities in the Ethiope east region (a region having a population of 200,792 people) (Report of Nigeria's National Population Commission Census 2007). It has developed a reputation of having well-trained specialists in diverse areas of medicine alongside excellent medical facilities, hence its use by neighbouring towns like Ughelli, Warri, Agbor, Sapele and Benin. Residents of this area engage mainly in farming and trading.

**Screening**

Patients were screened to identify those that met the enrolment criteria and the most important patient data captured were address, age, sex, temperature and parasite count. Examination of blood smear was performed on patients that met the enrollment criteria. The collected data for all screened patients were entered in a case screening form that was provided.

**Inclusion Criteria**

Children aged 6 to 59 months were screened for malaria parasite infection by microscopic examination of Giemsa-stained thick and thin blood films. Cases with positive outcomes and asexual parasite stages of 2,000–250,000 per µL of *P. falciparum* and who had not taken any antimalarial drugs or other drugs in the preceding seven days prior to screening were enrolled in this study. Other inclusion criteria include; mono-infection with *P. falciparum*, axillary temperature ≥37.5°C, ability to swallow oral medication, body weight >5 kg, informed consent form from the parent/guardian, ability and willingness to comply with study protocol for duration of study and comply to visit schedule, absence of danger signs (such as convulsion, seizure, severe weakness) or severe *P. falciparum* malaria (WHO 2009).

Observation of the patient was done 30 min after administration of the drug. A second dose was administered to patients who vomitted 30 min after administration and thereafter withdrawn from the study if vomiting re-occured.

Paracetamol syrup at a dose of 15 mg/kg 8 hourly was provided to help reduce body temperature and patients were advised to avoid herbal medicines during the study. Case screening form was used to record information and clinical observations on each patient enrolled.

Day 0 was designated as the day of enrollment and start of the first dose. Clinical assessment and follow-up was done and scheduled for days 0, 1, 2, 3, 7, 14, 21 and 28. Patients were advised of the need to return on days other than scheduled if symptoms got worse. Blood smear for parasite count was done on days 0, 1, 2, 3, 7, 14, 21 and 28 in which case patients were asked to return each time a blood sample was required.

Critical days during this study were days 1, 2 and 3 to ensure the safety of the patient and assessment of the clinical response by the researcher. Provision was made to locate the patient at home if not present as scheduled and pill count was carried out to determine adherence of caregivers to dosage schedule.

Criteria for withdrawal from this study included a patient who vomitted drug twice, failure to attend schedule visit during the first three days, serious adverse reactions prompting termination of treatment before 28 days, patient with severe malaria who were erroneously enrolled on day 0, detection of another malaria species, occurrence of another disease condition that could interfere with classification of treatment outcome, self-medication/third party administration of artemisinin drug or artesunate with antimalaria activity and consent withdrawal at any time without prejudices to further follow-up or treatment at other facility (WHO 2009).

### Physical Examination

This was done at baseline by a trained health personnel on day 0 before dosing and days 1, 2, 3, 7, 14, 21 and 28. Physical examination assessed the presence of danger signs (such as seizure, convulsions and severe weakness), axillary temperature, as well as complete medical history, demographic information and contact details.

Body temperature was measured at baseline on day 0 before dosing and on days 1, 2, 3, 7, 14, 21 and 28 using a clinical thermometer with a precision of 0.1°C.

Approval from Hospitals Management Board Ethical Committee with reference number EBGH/AD/112/REM/Vol.II/118 was obtained prior to the study.

### Microscopic Smear Examination and Counting

Thick and thin blood smears of parasite count were obtained and examined on day 0 prior to dose administration to confirm inclusion criteria of 2,000–250,000 per µL of *P. falciparum*. This smear was equally examined on days 0, 1, 2, 3, 7, 14, 21 and 28 and parasitological assessment was carried out. Each slide specimen was uniquely labelled with a study number, day of follow-up and date.

Parasite density was determined by counting the number of asexual parasite per 200 white blood cells and calculated per µL assuming a white blood cell count of 8,000 cell/µL. Sexual parasite count was done per 1,000 white blood cells. The smear was negative when thick field did not show presence of asexual parasite.

Exclusion of mixed infection was done by examination of 100 fields of second thick films. Confirmation was done using the film for the avoidance of doubt. Patient exclusion was done if examination was inconclusive.

### Data Analysis

Clinical response was classified as ETF, LCF, LPF and ACPR. The Kaplan-Meier survival analysis of primary outcome was used. This was equally used to estimate the risk of treatment failure and of new infection. Descriptive statistics such as percentage, mean, standard deviation and range was employed. Data was analysed using IBM SPSS version 18 (2009, IBM SPSS Inc., Chicago, Illinois).

## RESULTS

### Baseline Characteristics of Study Population at Enrolment

From the total of 93 patients screened, 55.9% were male, while 44.1% were female. The mean age of the study population was 23 ± 14.23 months with a class range of 6–59 months. The mean body temperature of the study group was 37.40°C with a class range of 37.5°C–38.5°C. The mean parasite density was 1,910.26 ± 1,478.73 cells/µL with a range of 1,000 to 10,000 cells/µL. Table 1 shows the baseline characteristics of the study population.

**Table 1:** Baseline characteristics of study population.

| Variables | Mean ± SD | Range |
|---|---|---|
| Age (months) | 23.18 ± 14.23 | 6–59 |
| Temperature (°C) | 37.51 ± 0.53 | 37.5–38.5 |
| *Parasite density (µL) | 1,910.26 ± 1,478.73 | 1,000–10,000 |

*Note*: *Carried out on day 0.

### Survival Analysis of Clinical Response

The treatment response as presented by the survival analysis from the Kaplan Meier plot is presented in the Figure 1.

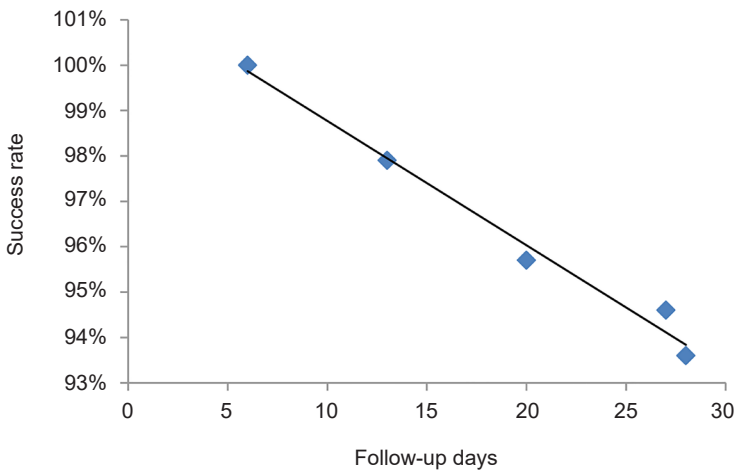


**Figure 1:** Survival analysis of clinical response.

The survival analysis shows estimates of success cumulative incidence of 1.00 from day 0 to day 6, 0.9790 from day 7 to day 13, 0.9570 from day 14 to day 20, 0.9460 from day 21 to day 27 and finally 0.9360 in day 28. Clinical response was 84.9%, cumulative success and failure rate was 93.6% and 6.4%, respectively, on day 28.

Conversely, the failure cumulative incidence increased from 0.00 in day 0 to day 6, 0.021 in day 7 to day 13, 0.048 in day 14 to day 20, 0.054 in day 21 to day 27, and finally 0.064 in day 28.

### Classification of Clinical and Parasitological Response

The study outcome per protocol analysis showed that there was no ETF. However, there was one case of LCF, 10 case of LPF and 62 case of ACPR as shown in Table 2.

**Table 2:** Classification of clinical and parasitological response.

| Clinical outcome | Number of patients | Percentage |
|---|---|---|
| ETF | 0 | 0 |
| LCF | 1 | 1.4 |
| LPF | 10 | 14.0 |
| ACPR | 62 | 84.9 |

The absence of ETF indicates that no patient developed severe malaria on days 1, 2 or 3 in the presence of parasitaemia and there was no parasitaemia on day 2 or day 3 irrespective of axillary temperature or with a temperature greater than 37.5°C. The presence of one LCF indicates that there was parasitaemia on any day between day 4 and day 28 with an axillary temperature greater than 37.5°C or history of fever in patients who did not previously meet any of the criteria for ETF. Furthermore, the presence of 10 late parasitological failure posits that there were 10 participants with parasitaemia between day 7 and day 28 with an axillary temperature less than 37.5°C in patients who did not previously meet any of the criteria for ETF or LCF.

## DISCUSSION

The treatment of choice for uncomplicated *P. falciparum* malaria is ACT according to WHO (2006). ACTs are combinations consisting of an artemisinin derivative and another effective long-acting schizontocidal antimalarial drug given according to body weight and age. This study was carried out to assess the clinical response of patients to AL for the treatment of uncomplicated *P. falciparum* malaria in children aged less than five years old. In the study majority of the patients were males. This is due to the large turnout of caregivers with male children and not due to the prevalence of the disease in males. This is similar to the gender distribution of patients in similar study by Falade *et al.* (2005) in which 51.9% were males and 48.1% were females. In another study by Salah *et al.* (2006) the proportion of male patients was 68.2%. The mean body temperature was 37.51 ± 0.53. This was slightly lower than that obtained by Assefa *et al.* (2010) which was 38°C ± 0.86. The mean parasite density of the study group was 1,910 cells/μL ± 1,479 with a range of 1,000 and 10,000 cells/μL, this is in contrast to a study by Umar (2014) whose mean parasite density was 3,768 cells/μL ± 265 with a range of 2,001 and 14,000 cells/μL. The low parasite density as defined in this study is due to the fact that the parasite clearance time was lower. The parasite clearance time is the time between starting therapy and the first negative blood test, when negativity persist for more than 48 hours.

The treatment outcome from the analysis recorded that there was no ETF, 1.4% LCF, 14.0% LPF and 84.9% ACPR. In a similar study conducted in Kaduna state north-west of Nigeria, there was no ETF, but one LCF, one LPF and 41 ACPR (Umar 2014). The absence of ETF and the one LPF are similar in both studies. However, the differences lies in the LPF and ACPR. Furthermore, this study recorded 84.9% ACPR slightly lower than that of Falade *et al.* (2005) which recorded 88.7% ACPR. The difference in treatment outcomes could be traced to the high occurence of malaria in the study area as the study population live in a malaria endemic region. Thus, the high parasitological failure of 14% accounts for the lower ACPR of 84.9%.

Another study on the clinical response to AL for the treatment of uncomplicated *P. falciparum* malaria in rural endemic area of Ethiopia showed ACPR of 95.8% and 96.2% in two study sites (Assefa *et al.* 2010). This is much higher than the 84.9% reported in this study. The adequate clinical response of AL reported may be due to differences in malaria exposure and late adoption of AL in Ethiopia.

The cure rate of the drug on day 14 was 97.90%. This is in concert with the *in-vivo* response of *P. falciparum* to artemisinin derivatives which were shown to have more than 90% cure rate on day 14 when they were first introduced as first-line drug for treatment in Nigeria (FMOH 2005). The result of the Kaplan-Meier analysis showed that there was a cure rate of 100% from day 0 to day 6. This is evident in the absence of ETF. The cure rate began to decrease gradually from 95.70% to 94.60% from day 21 to day 27, reaching 93.60% by day 28 and a failure rate of 6.4%. This is in contrast to the result obtained by Falade *et al.* (2005) which recorded a cure rate of 100% in both first and second week and 88.7% in the fourth week of the study. The reason for this is that as the therapeutic concentration of the drug decreases with time, the cure rate also reduces.

## LIMITATIONS

This study has provided more information on antimalarial clinical response in Southern Nigeria, cooperation of the caregivers, guardians and other health care personnel in the follow-up protocol was poor thus making the research much more challenging.

## CONCLUSION

The clinical response of AL in children aged less than 5 years old was adequate. The failure rate of 6.4% could likely be due to inappropriate dosing frequency of the drug and probable re-infection during the follow-up period.

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