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## Pharmacovigilance of *Artemether-Lumefantrine* Among Cohort of Pregnant Women Treated for Uncomplicated Malaria in Selected Hospitals in Jos, Nigeria



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**Keywords:** Adverse drug reaction, Pregnancy, Artemether/lumefantrine, malaria, Nigeria

### ABSTRACT

**Background:** Malaria infection during pregnancy is a significant public health problem. Currently, artemisinin-based combination therapy (ACT) is the mainstay for the treatment of uncomplicated malaria. However, the safety profile of ACTs in pregnancy has not been adequately established. Antimalarial adverse effects are absent pregnancy registry in Nigeria, making it necessary to establish one, so the study aims to assess the safety profile of selected antimalarials among a cohort of pregnant women **Method:** There were two cohorts: Artemether-lumefantrine (AL) arm (ACT treatment arm) in line with Nigerian treatment guideline for uncomplicated malaria and the unexposed Sulfadoxine-Pyrimethamine arm for intermittent preventive therapy (SP IPTp); and the adverse drug events of ACT-exposed versus unexposed (SP IPTp) were compared. **Results:** A total of 392 pregnant women were enrolled in this study with the modal age of the participants being 20 - 29 years old. Adverse events observed among the pregnant women treated for malaria with artemether-lumefantrine fixed-dose combination include abdominal pain, dizziness, tinnitus, itching, skin rash, palpitation, and hallucination. Unlike in the AL group, there was a complete absence of skin rash, tinnitus, and hallucination in the SP group both within the first 3 days of therapy and after the first 3 days. **Conclusion:** The overall ADR severity classification was mild (95.6%), moderate (2.6%), and severe (1.8%). The result will be shared with the Nigerian National Pharmacovigilance Centre and to begin the antimalarial adverse effects pregnancy registry in Nigeria to promote the safe use of antimalarials in pregnancy thereby encouraging pharmacovigilance activities.

## INTRODUCTION

Malaria is a major global health burden causing high morbidity and mortality in the developing world; the parasite is transmitted to humans through the bite of a female *Anopheles* mosquito which thrives in humid and swampy areas. Sub-Saharan Africa continues to bear the burden of disease and Africa bears the heaviest burden<sup>1</sup>. In 2016, it caused 224,000 estimated deaths in West Africa with Nigeria accounting for 52% of these deaths<sup>2-3</sup>. Epidemiologically, malaria in Nigeria can be described as mesoendemic, implying regular seasonal transmission with greater intensity in the wet season than in the dry season.

Due to changes in the immune system during pregnancy, pregnant women are at high-risk of malaria<sup>4</sup>. Malaria infection during pregnancy is a significant public health problem<sup>3</sup>, with the prevalence of malaria in pregnancy in Nigeria being 17.4% to 73.1% (based on laboratory versus clinical diagnosis)<sup>5-6</sup>. Currently, artemisinin-based combination therapy (ACT) is the mainstay for uncomplicated malaria<sup>1,3,5-7</sup> and these have been included in the treatment guidelines of malaria in pregnancy in several countries including Nigeria. For the treatment of uncomplicated malaria in the 2<sup>nd</sup> or 3<sup>rd</sup> trimester of pregnancy, World Health Organization (WHO) recommends the use of ACT, but ACT can only be used in the first trimester if quinine is unavailable or if the benefit outweighs risk<sup>8</sup>.

However, the safety profile of ACTs in pregnancy has not been adequately established and major unresolved safety concerns exist about ACT use for malaria treatment in pregnant women, a group usually excluded from initial pre-licensing clinical trials of medicines including that of ACTs<sup>9-16</sup>.

Animal studies of artemisinin have shown embryo lethality and abnormalities<sup>17-20</sup>. A study of pregnant mice exposed to artemether-lumefantrine (AL) reported prolongation of the gestation period and a reduction in acetylcholine-mediated uterine contractions during labour<sup>21</sup>. Also, a high prevalence of congenital anomalies, including bent and or shortened long bones and also treatment-related heart defects, has been observed in rat litters<sup>22</sup>.

In humans, ACT use has been associated with several adverse drug events (ADEs), like dizziness in general populations, and among pregnant women treated for uncomplicated falciparum malaria were: asthenia, poor appetite, dizziness, abdominal pain, malaise, headache, general body weakness, dysphagia, fatigue, tinnitus, thrombocytopenia and vaginal bleeding. Others are elevation of serum levels of Na<sup>+</sup>, K<sup>+</sup>, creatinine and blood urea,

hallucination, and other behavioral changes; nausea, vomiting, cough, anorexia, diarrhea, drowsiness, generalized skin rash, pruritus, prolongation of the QT interval, the elevation of conjugated bilirubin, hallucination as well as congenital malformations in pregnancy<sup>9, 23-36</sup>, an experience which when associated with malaria burden in pregnancy is undesirable.

Although to our knowledge, there is still a paucity of safety data on the post-market use of ACTs in pregnancy worldwide, this being collaborated by others<sup>1, 23, 28, 31, 37-44</sup>. Studies done elsewhere outside Nigeria may not represent the true data for Nigerian pregnant women who are exposed to ACTs during the treatment of malaria due to reasons like genetic differences, for example in drug administration, distribution, elimination, and excretion (pharmacokinetics of the drug); and enzyme production (Pharmacogenomics) differences which may result in toxicity for drugs like proguanil. Also, a small number (300-3000) is exposed to a drug during the clinical trial in phase iii as compared to general use<sup>45</sup>. Hence the need for continuous post-marketing surveillance of their use in pregnancy in Nigeria and likely, additional ADRs may be uncovered since pharmacovigilance is an indispensable essential tool<sup>46-47</sup>.

Post-market surveillance of drug and spontaneous reporting of ADRs is the cornerstone of pharmacovigilance and it is very important in maintaining patient safety<sup>8-49</sup>.

Antimalarial adverse effects are absent pregnancy registry in Nigeria as recommended by the in the year 2010 by WHO<sup>50</sup>, making it necessary to establish one, so the study aims to assess the safety profile of selected antimalarials among a cohort of pregnant women with a specific objective to monitor and document the occurrence and types of adverse events of these drugs during therapy among the pregnant women.

## **METHOD**

**Study design:** A multi-center prospective cohort study of antimalarials in pregnant women

### **Study setting**

Background of the study area: The study areas are three selected hospitals in Jos, Plateau State, Nigeria. The main site for the study was Jos University Teaching Hospital (JUTH; is a 642-bed tertiary hospital that provides a wide range of medical, surgical, diagnostic, outpatient, rehabilitative, and support services to residents of Jos and those referred from outside the city of Jos. It has a variety of units such as a functional accident and

emergency(which provides a 24hr service), others include pharmacy, Obstetrics, and Gynecology, pharmacovigilance, and drug safety center; pediatrics, general medicine, and surgery and laboratory services.

The second site is Plateau specialist hospital that is a secondary facility and the third is Bingham University Teaching Hospital (A tertiary hospital). The choice of these sites was to enable adequate coverage and facilitate the timely recruitment of participants. These facilities have an estimated 20,000 antenatal visits per year.

**Participants (Study Population) and exposure:** Pregnant women in their second (13th–24th week) or third trimester (25th–36th week) participated in the study. The first trimester was exploratory if there was inadvertent exposure or deliberate exposure if there was no suitable alternative treatment. There were two cohorts: Artemether-lumefantrine (AL) arm which is the ACT treatment is in line with Nigerian treatment guideline for uncomplicated malaria and the second is the unexposed Sulfadoxine-Pyrimethamine arm for intermittent preventive therapy (SP IPTp), and the adverse drug events of ACT-exposed versus unexposed (SP IPTp) were compared.

All pregnant women in the 2nd and 3rd trimesters who consent to participate were included while those who did not consent or those with comorbidities (like typhoid fever) and those who did not receive their antimalarials from the study sites were excluded.

The pregnant women received free AL for treatment of malaria at a dose of 80/480mg (Artemether/Lumefantrine fixed-dose combination, COARTEM<sup>®</sup>x 24 tablets each containing 20/120mg) initially, repeated eight hours later, then twelve hourly for three days or three tablets of SP (Sulfadoxine 500mg+ 25mg pyrimethamine) for IPT prophylaxis at a dose of 1500mg/75mgstat during this current pregnancy. The women were encouraged to report any untoward effect noticed following the use of these medicines that were not present at diagnosis of malaria or before the intake of the SP; and also to take the AL with milk to enhance the absorption of the medicines.

The sample size was calculated with OpenEpi, Version 3, to be 392with 20% attrition.

**Data collection and management:** Exposure data was collected based on antimalarial used in routine practice with the aid of a questionnaire tested through a pilot study of 60 questionnaires, adjustments were made where necessary until standardized using the Cronbach alpha for the reliability of the questionnaire. The sampling technique was

systematic and participant enrollment was according to the drug treatment choice of the physicians. Data were collected from patients' hospital case notes and folders and also from face-face and telephone interviews.

Data collection was done by researchers, trained research assistants, pharmacists, doctors, and nurses working at the study sites who were in constant contact with the researcher, using case report forms, questionnaires and stored in Microsoft Excel.

At baseline: Data such as date of recruitment, demographic data, parity, trimester, and maternal alcohol/tobacco intake status were collected.

There was a follow-up from the time of recruitment till 30 days and data for any adverse drug events during antimalarial therapy, and after therapy were obtained. To control for contamination, participants were asked if they had any antimalarial in a different setting.

Severity assessment was done using the modified Hartwig and Siegel scale where seven levels of adverse drug reactions were categorized into mild, moderate, and severe according to certain criteria. "ADR not requiring a change in the treatment of the suspected medicine and/or requires treatment with the suspected drug be held, discontinued, or otherwise changed and in addition, no antidote or other treatment was required, without an increase in length of stay is considered as mild. Moderate ADR is that which requires treatment with the suspected drug be held, discontinued, or otherwise changed and antidote or other treatment was required without an increase in length of stay/ADR which increases the length of stay by at least a day/ADR was the reason for hospitalization. Severe ADR is the ADR, which requires intensive medical care/cause permanent, harm to the patient/directly or indirectly led to the death of the patient"<sup>51</sup>.

### **Statistical Analysis**

Data were analyzed using Statistical Package for Social Sciences (IBM SPSS Statistics) version 23.0. Analytic methods: i. Descriptive analytic method: Frequencies, mean and standard deviation were generated for socio-demographic characteristics of participants and clinical variables where applicable. ii. Predictive Analytical method: to test for any statistically significant relationship using chi-square statistic, fishers exact test and t-test and a P-value  $\leq 0.05$  were considered statistically significant.

**Ethical approval** was sought and obtained from the three site institutional ethics committees. Informed consent was obtained from the participants before recruitment into the study. Data

were anonymized before analysis and no result from participants is reported individually to maintain confidentiality.

## RESULTS

A total of 392 pregnant women were enrolled in this study with the modal age of the participants being 20 - 29 years old (table 2). Participants were recruited from three Health Facilities within Jos metropolis. This included Jos University Teaching Hospital (71.9%), Plateau State Specialist Hospital (19.1%), and Bingham University Teaching Hospital (8.9%) respectively with Jos University Teaching hospital recording the highest number (71.9%) of participants (Table 1). Among the women enrolled, 6.4% had primary, 24.7% had secondary, 37% had tertiary level of education and 3.1% had no formal education. The majority were married women (82.9%) and in terms of occupation, the housewives were more in number (Figure 1). Three (3) of the women (0.8%) reported intake of alcohol and only one (1) smoke cigarettes on the average of one stick per day (Table 2). Parity: Majority (56%) was multigravidae (Figure 2).

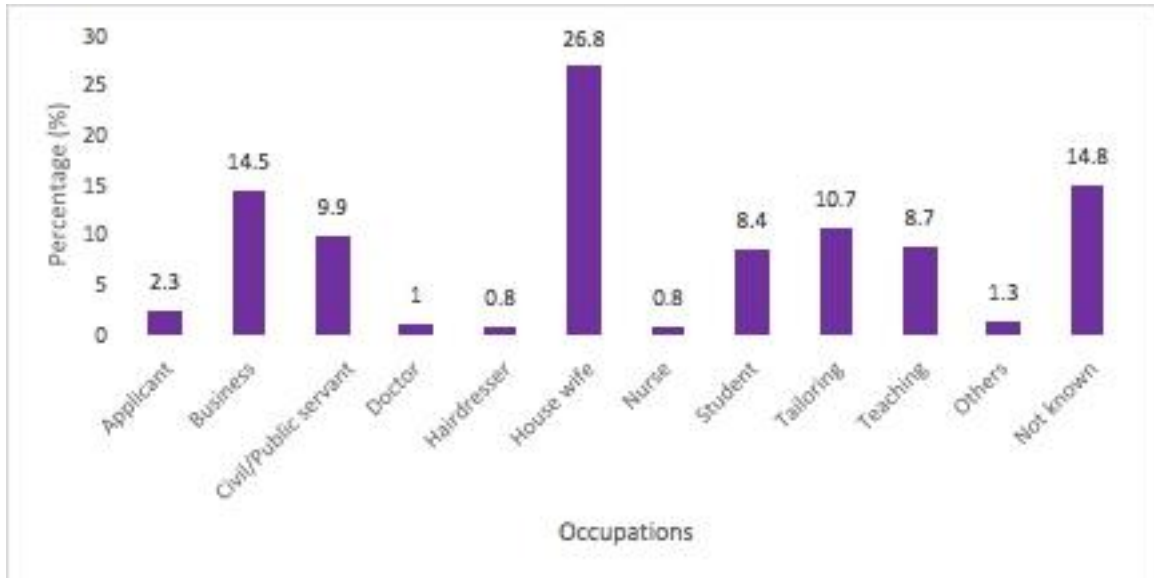
Diagnosis of malaria was majorly (83.7%) based on clinical signs and symptoms (Figure 3). The study showed that most participants had uncomplicated malaria while 45(11.5%) experienced severe malaria in pregnancy and 219(55.9%) used AL drugs apart from routine hematinic while 173(44.1%) used SP (Table 3).

A pattern of AL and SP used per Trimester: Out of the participants that took AL, 8.5%, 34.5%, and 57% used it in the 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> trimester respectively. SP use was 4.4%, 29.2%, and 66.4% in the 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> trimester respectively.

**Table no 1: Participants' recruitment by facility**

Facility	F	%
JUTH	282	71.9
PSSH	75	19.1
BINGHAM	35	8.9
Total	392	100.0

**Key:** Jos University Teaching Hospital (JUTH), Plateau Specialist Hospital (PSSH), Bingham University Teachinh Hospital (BINGHAM).



**Figure No 1: Distribution of participants by occupations (n = 392)**



**Table no 2: Demographic characteristics of participants (n = 392)**

Variable	f	%	
<b>Age group (years)</b>			Mean±Std.Dev
<20	8	2.0	29.3±5.7
20-29	173	44.1	
30-39	148	37.8	
40-49	9	2.3	
Not known	54	13.8	
<b>Education</b>			
No formal education	12	3.1	
Primary	25	6.4	
Secondary	97	24.7	
Tertiary	145	37.0	
Not known	113	28.8	
<b>Marital status</b>			
Married	389	99.2	
Single	3	0.8	
<b>Is this woman a twin?</b>			
Yes	5	1.3	
No	387	98.7	
Primigravidae	173		
Multigravidae	219	55.9	
<b>Alcohol intake</b>			
Yes	3	.8	
No	320	81.6	
Not specified	69	17.6	
<b>Does the woman smoke</b>			
Yes	1	0.3	
No	322	82.1	
Not specified	69	17.6	
<b>If yes, number of Sticks of</b>			



cigarettes/day

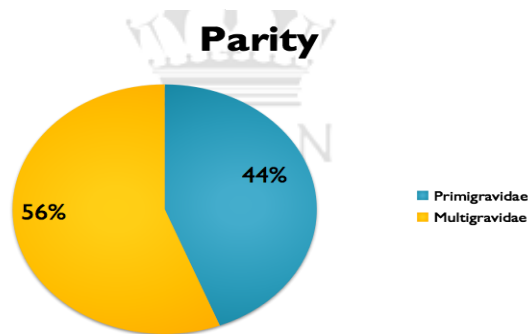
1

**Is the father of this baby  
the same as that of the  
first, second, etc. as it  
may apply**

	1	0.3
Yes	208	53.1
No	115	29.3
Not specified	69	17.6

**Table no 3: AL and SP prescription pattern**

Study groups	F	%
AL	219	55.9
SP	173	44.1
Total	392	100.0



**Figure no 2: Parity**

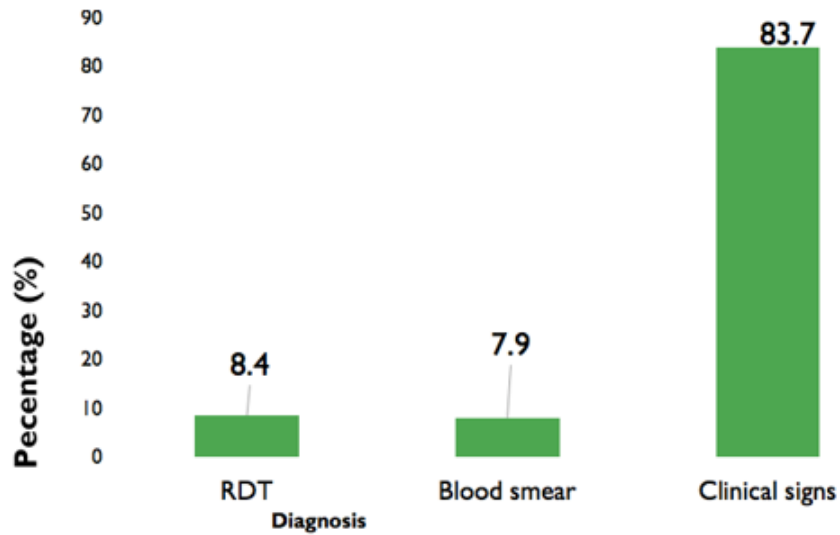


Figure no 3: Method of diagnosis N = 392

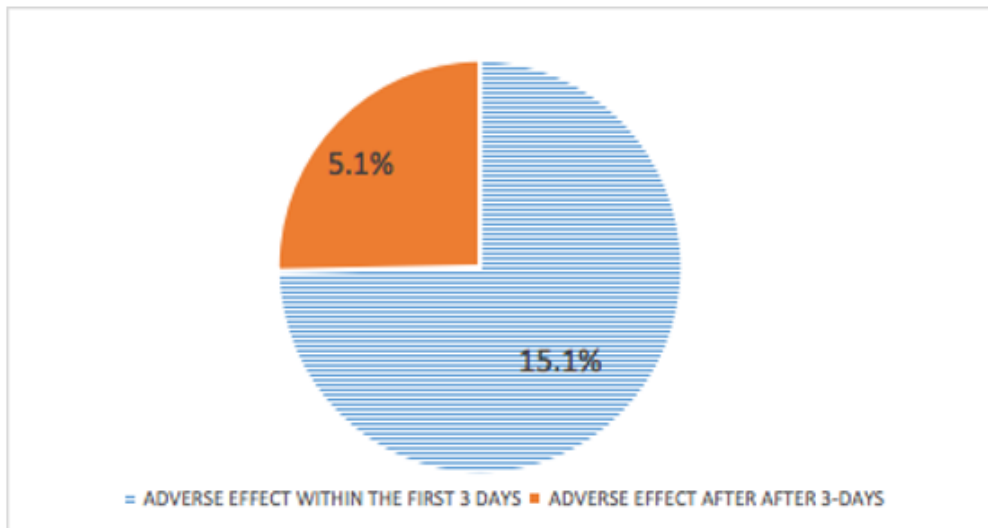
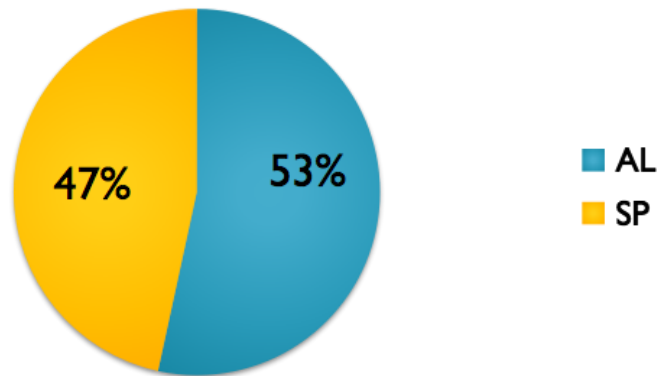


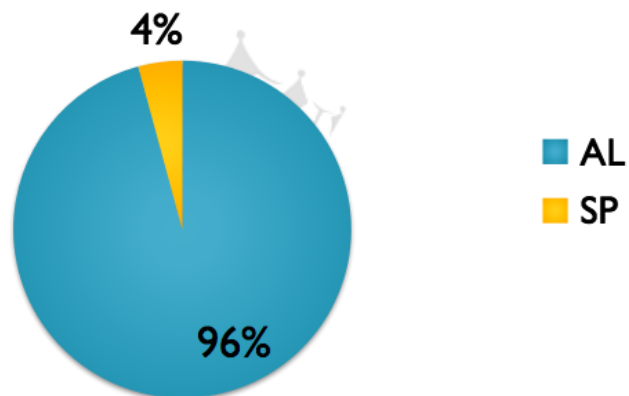
Figure no 4: Overall adverse effects for participants before and after therapy

**Rate of occurrence of adverse effects within first 3 days**

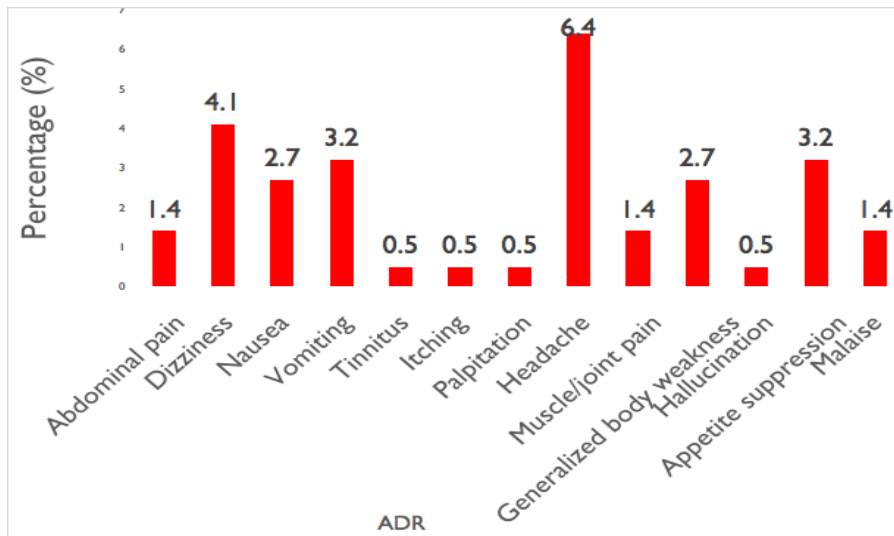


**Figure no 5: Rate of occurrence of adverse effects within first 3 days n = 116**

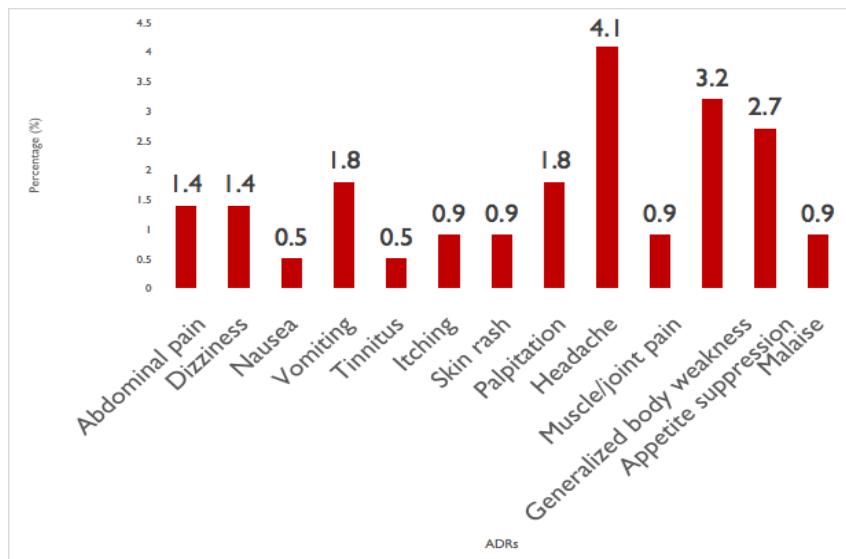
**Rate of occurrence of adverse effects after first 3 days**



**Figure no 6: Rate of occurrence of adverse effects after first 3 days n=48**



**Figure no 7: Adverse effects of drugs within the first three (3) days among patients that took AL n= 62**



**Figure no 8: Adverse effects of drugs after the first three (3) days for AL category n= 46**

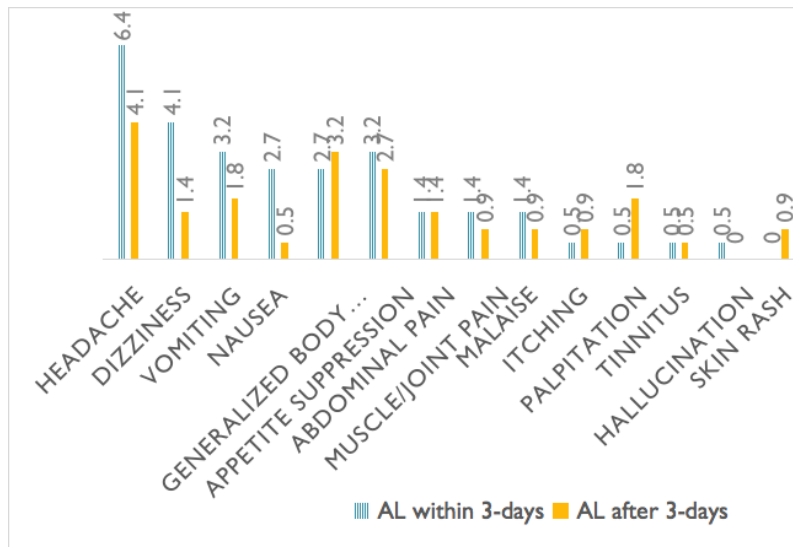


Figure no 9: Comparing ADR within the first 3-days with ADR After the first 3-days for the AL category

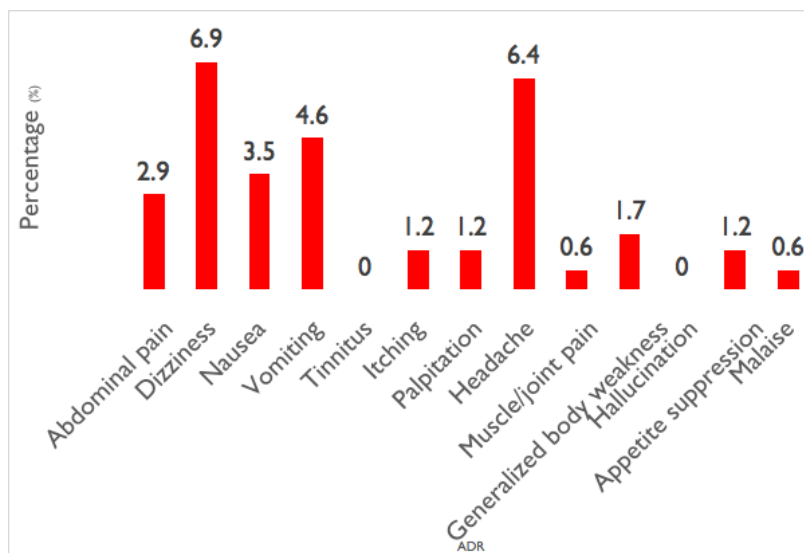


Figure no 10: Adverse effects of drugs within the first three (3) days among patients that took SP. n= 54

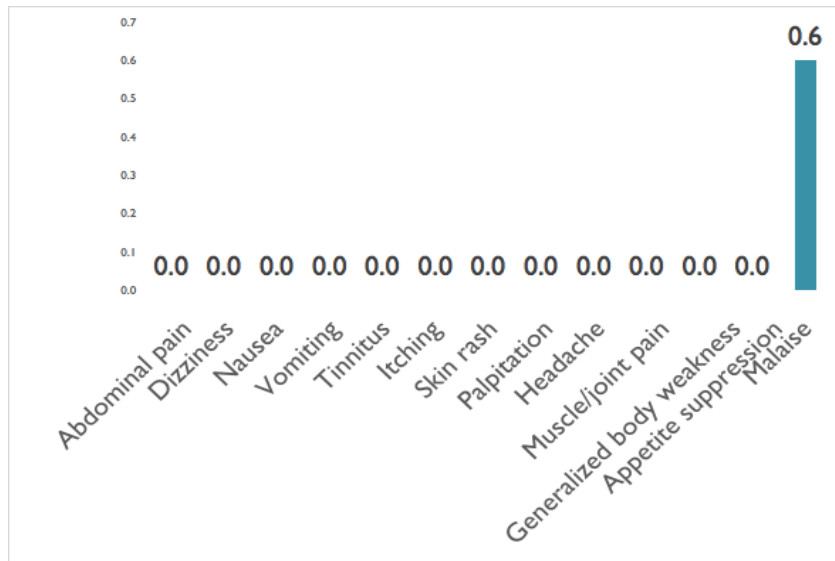


Figure no 11: Adverse effects of drugs after the first three (3) days for SP category n=1

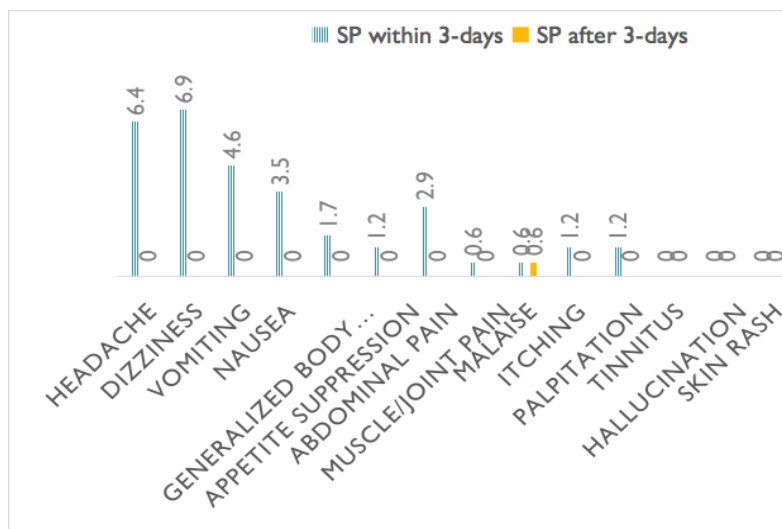


Figure no 12 Comparing ADR within the first 3-days with ADR After the first 3-days for the SP category

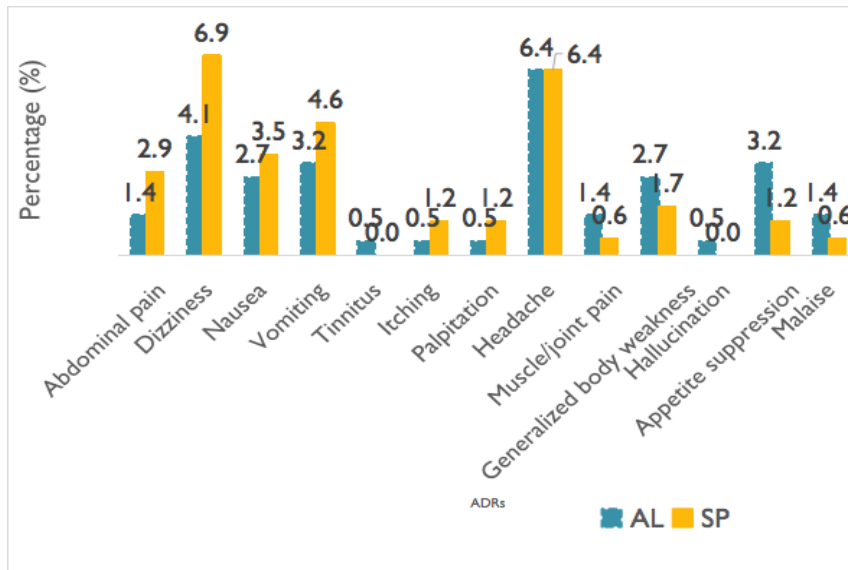


Figure no 13: Adverse effects of drugs within the first three (3) days for both AL and SP

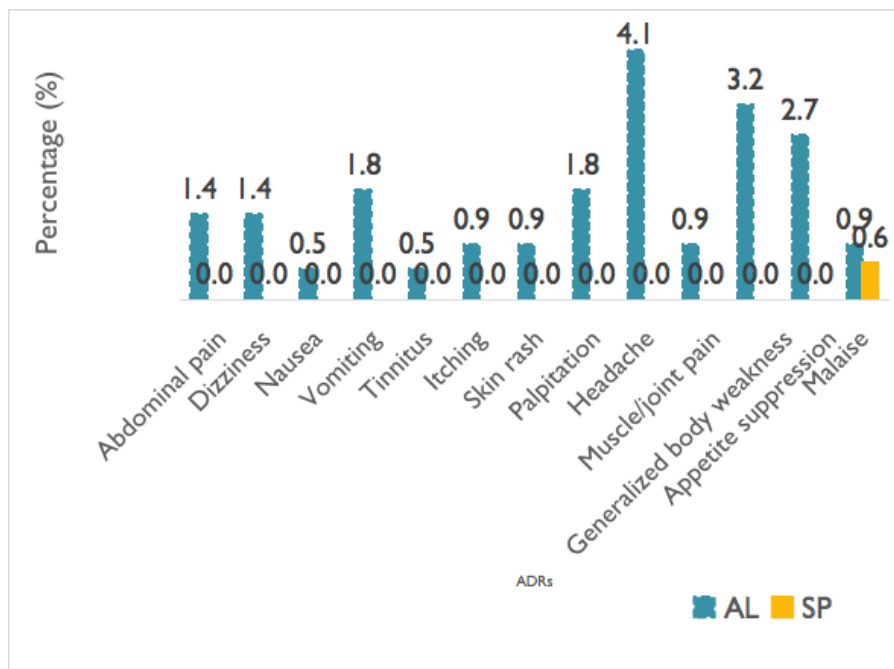


Figure no 14: Adverse effects of drugs after the first three (3) days for AL and SP

Of the 219 people that took AL, the adverse effects prevented some (7 being 3.2%) from completing their drugs and in most cases, vomiting was the main reason for non-compliance. ADR severity classification (Hartwig): Mild (95.6%), Moderate (10 people/ 2.6%) and Severe (7 / 1.8%).

Association of ADR and sociodemographic profile: There was no association between age, marital status, education, parity, being a twin, alcoholic intake, and ADR. However, there were more ADRs among the age group of 20-39 years, 30 and 20 school leavers' group, and among primigravidae (during therapy) and the married than the other groups. Interestingly after the first 3 days of antimalarial medication, both the Primigravidae and Multigravidae each had 50% adverse effects.

Significance of ADR within 3 days of therapy and after 3 days to 1 month following therapy: There was no statistical difference in the ADR between the two groups within 3 days ( $\chi^2 = 2.876$ ,  $p = 0.090$ ). There was a statistically significant difference in ADR between the two groups after 3 days of use ( $\chi^2 = 13.090$ ,  $p = 0.000$ ). There was a significant drop from the overall 15.1% to 5.1%. This suggests that more adverse effects were recorded during medication use compared to after therapy.

ADR and trimester of use of antimalarials: Within the first 3 days, more adverse effects were recorded in the 3rd trimester compared to the second, but there was no statistical difference ( $\chi^2 = 1.747$ ,  $p = 0.417$ ). After the first 3 days, unlike in the first 3 days, more adverse effects were recorded in the 2nd Trimester and there was also no significant difference ( $\chi^2 = 5.746$ ,  $p = 0.057$ ).

## DISCUSSION

A total of 392 pregnant women were enrolled in this study with the modal age of the participants being 20 - 29 years old. Among the women enrolled, 6.4% had primary, 24.7% had secondary, 37% had tertiary level of education and 3.1% had no formal education. More participants had tertiary education maybe because this study was conducted in a place with ready access to many educational facilities. The majority were married women (82.9%) and in terms of occupation, the housewives were more in number. Three (3) of the women (0.8%) reported intake of alcohol and only one (1) smoke cigarettes on the average of one stick per day (Table 2).

Parity: Majority (56%) was multigravidae (Figure 2). This study agrees with other studies which reported that most of their participants were multigravidae<sup>9, 52</sup>.



### **Adverse drug events recorded during therapy:**

Out of the 392 pregnant women enrolled in the study, 59 (15.1%) had adverse drug events within the first 3 days of therapy. The rate of occurrence of these adverse drug events was 116 (as some women had more than one adverse drug event) with 53% of this occurring in the AL group and 47% recorded from the SP group (Figure 4 and 5). A study in Nigeria reported that 40% (4 out of 10) of the pregnant women who participated in their study and took either AL or Amodiaquine had adverse drug reactions within the first three days of therapy. However, the contribution of each of these drugs to the adverse drug reactions was not stated<sup>28</sup>. A study of the safety of AL and quinine in pregnancy reported that a total of 141 adverse events were observed<sup>27</sup>.

Most of the reactions were either resolved within the first 3 days or decreased after the first 3 days with 96% of the unresolved adverse drug events after the first 3 days seen from the AL group. From figure 4 and 6, after the first 3 days of therapy, 20 (5.1%) of the participants had adverse drug events with a statistically significant difference in the rate of occurrence of 48 with 96% of these from the AL group and 4% from the SP group ( $p = 0.000$ ).

The majority of the women who had adverse drug events within the first 3 days were in their third trimester of pregnancy (51.4%) while those that had adverse drug events after the first 3 days were mainly those in their second trimester (61.5%). However, these differences were not statistically significant.

From figures 7-14:

The summary of adverse events observed among the women in the AL group includes abdominal pain, dizziness, nausea, vomiting, tinnitus, itching, palpitation, headache, Muscle/Joint pain, generalized body weakness, hallucination, appetite suppression, malaise, and skin rash. However, the type of adverse events observed in this study was more compared to the reported adverse events of palpitations, dizziness, drowsiness, and generalized skin rash in the AL arm in a different study<sup>26</sup>. Also, women were reported to have said that “ACT cause fast heartbeat which will lead to some form of worry” in another study<sup>32</sup>. This “fast heartbeat” can be interpreted to mean palpitation.

Of the adverse effects experienced by the AL group, the headache was the highest (6.4%), This is similar to a study that reported headache and influenza-like syndrome being the highest in the AL group<sup>27</sup>. Also, another study reported headache was experienced by 26% is

the highest observed in their patients who took AL for the treatment of malaria<sup>25</sup>. But different from a study carried out in Uganda where abdominal pain (33%) was the highest<sup>53</sup>. However, in our study, abdominal pain was higher in the SP group (2.9%) than in the AL group (1.4%). Dizziness was observed during the first three days of therapy in 4.1% of participants who took AL and this is lower than the 15% Genet and colleagues reported along with Cough (25%), anorexia (12%), and diarrhea (9%) which were not reported by any of our participants<sup>25</sup>.

Vomiting was seen in 7.8% [lower in AL group (3.2%) than the SP (4.6%)], this is in is different from a study in Zambia in which 0.4% of the population had vomiting<sup>54</sup>. and in a multicentre study that reported vomiting in 11.2% in the AL group<sup>23</sup>.

The summary of adverse events observed in the SP group was dizziness, headache, nausea, vomiting, generalized body weakness, appetite suppression, malaise, palpitation, muscle/joint pain, abdominal pain, and itching. In the SP group, dizziness was highest (6.9%) [higher than in AL group 4.1%], followed by headache (6.4%).

Of the adverse drug events observed within the first 3 days of therapy, there were more abdominal pain, dizziness, vomiting, itching, and palpitation in the SP group than in the AL group while muscle/joint pain, generalized body weakness, appetite suppression, and malaise were more in the AL group.

Itching occurred in both groups, but the itching in the SP group resolved within the first 3 days of therapy. The itching continued to skin rash after 3 days of therapy in the AL group indicating delayed drug reaction of skin rash. Other delayed drug reactions observed by an increase in the number of participants who reported these observations after the first 3 days of therapy with AL were generalized body weakness, itching, palpitation, and skin rash. Nevertheless, the skin rash was absent in all the participants within the first 3 days of therapy.

Unlike in the AL group, there was a complete absence of skin rash, tinnitus, and hallucination in the SP group both within the first 3 days of therapy and after the first 3 days. All the reactions observed within the first 3 days in the SP group were resolved within the first 3 days except for malaise which continued after 3 days but was all resolved within one month.

Of the 219 people that took AL, the adverse effects prevented some (7 being 3.2%) from completing their drugs and in most cases, vomiting was the main reason for non-adherence to therapy.

ADR severity classification<sup>51</sup>: Most of the reactions were mild (95.6%) while others were moderate (10 people/ 2.6%) and those that had severe reactions were 7 (1.8%).

## CONCLUSION

Adverse drug events observed among the pregnant women treated for malaria with artemether-lumefantrine fixed-dose combination include abdominal pain, dizziness, nausea, vomiting, tinnitus, itching, palpitation, headache, Muscle/Joint pain, generalized body weakness, hallucination, appetite suppression, malaise, and skin rash while those observed in the SP group were Dizziness, headache, nausea, vomiting, generalized body weakness, appetite suppression, malaise, palpitation, muscle/joint pain, abdominal pain, and itching.

These adverse drug events will be documented and used to kick-start the antimalarial adverse effects pregnancy registry in Nigeria to promote the safe use of antimalarials in pregnancy and enhance pharmacovigilance activities.

**ACKNOWLEDGMENT:** Special appreciation to the Physicians, Pharmacists, Nurses, record clerks in all the study sites especially those who work in the Obstetrics and gynecology department for their roles in recruitment and adverse drug events monitoring and detection.

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