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Perceived Adverse Drug reactions to Artemether Lumefantrine and Artesunate Amodiaquine in Lagos, Nigeria

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ABSTRACT

Introduction: Medications produce a therapeutic effect that modulates a disorder and unwarranted effects that may be intrinsically harmful. Adverse drug reactions (ADRs) are undesirable effects that results from drug administration at usual doses and are the primary focus of regulatory agencies and post-marketing surveillance.

Aim and objectives: To evaluate ADRs to Artemisinin-based Combination Therapies (ACTs) such as Artemether-Lumefantrine (AL) and Artesunate-Amodiaquine (AA) among adults with the objectives of (i) estimating and comparing the frequency of ADRs associated with AL and AA and (ii) developing a list of classical adverse drug reactions to both antimalarials.

Materials and Methods: This cross-sectional, quantitative study was conducted from March to May 2013 at Ikorodu, a peri-urban settlement in Lagos State of Nigeria among 252 patients diagnosed with malaria and randomized into Artemether Lumefantrine (AL) arm and Artesunate Amodiaquine (AA) arm.

Results: The mean age (years) of all the study subjects was 34.4 (10.6) with 58% of them who attained secondary level education. About 50% of them took other non-antimalarial medication together with prescribed ACT during their illness. Overall mean duration of illness (days) before taking ACT was 2.8 (1.14) which was significantly longer (t-est=-3.57, P-value=0.0002) in AA arm (3.1 ± 1.2) than in AL arm (2.6 ± 1.0). In all, 234 (96.4%) and 169 (67.1%) severally completed the full dose of treatment and ate pre-medication fatty meal. Overall prevalence of ADRs was 47.6% - 27.8% in the AL arm and 69.8% in the AA arm. Among those who did not take fatty meal, the risk of ADRs was higher (χ^2=0.69, P-value=0.40, RR=1.26, 95% CI=0.72, 2.21) in the AA arm compared to the AL arm. Weakness, dizziness and headache were the most prevalent ADRs reported in both AL (25.9%, 13.8%, 15.5% respectively) and AA (50.0%, 10.0%, 16.4% respectively) arms.

Conclusion: In general, the frequency of ADRs, though mild or moderate in severity, was significantly higher in the AA arm than in the AL arm and the frequency of serious ADR was very low. The most prevalent ADRs reported were weakness/fatigue, headache and dizziness. Pre-medication consumption of fatty meal reduced the frequency of ADRs in both arms of the study. Programmes on the management of malaria with ACT should consider this baseline information for active surveillance for ADRs in Nigeria.

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Introduction

Medications generate varying effects, but typically a therapeutic effect is required for the treatment of a disorder. Other effects may be regarded as unwanted, regardless of if they are intrinsically harmful or not. The World Health Organization (WHO) defines these adverse drug reactions (ADRs) as noxious and unintended drug responses that occurs at doses used for prophylaxis, diagnosis, or therapy of disease, or for altering physiological function [1]. Although ubiquitous to most medications, most ADRs are relatively mild and transient, often abated once the drug is stopped or the dose reduced; some gradually subside as the body adjusts to the drug; while others are more serious and last longer. Digestive disturbances such as loss of appetite, nausea/vomiting, bloating and diarrhea are particularly common ADR because most drugs are taken orally and pass through the digestive tract [2]. However, almost any organ system can be affected. In older patient populations, neurological adverse effects are frequently observed, often reported as drowsiness and confusion. Reports have asserted

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that ADR are a significant cause of between 3-6% hospital admissions [3-5], contributing 5-10% of in-patient costs [6-8] as well as prolong hospital stay and consequent increase in the cost of disease management in patients [9]. However, there is a high index of suspicion that ADR is under-reported even in developed countries, not to mention in the developing parts of the world. As such, the actual prevalence could be higher than what is currently estimated [10,11]. An immediate outcome of ADRs is the withdrawal or restricted usage of otherwise efficacious drugs, leading to deficits in therapy.

Malaria is holo-endemic in Nigeria claiming the lives of millions of children and is a source of not only health but economic burden. An earlier study [12] reported that resistance of Plasmodium falciparum malaria parasites to antimalarial monotherapy such as chloroquine (CQ) [13,14] and sulphadoxine-pyrimethamine (SP) [15,16] could be prevented by combination of antimalarial targeting different sites of the parasite life-cycle. This led to the WHO endorsing Artemisinin-based combination therapy (ACT) in combating drug-resistant *Plasmodium falciparum*, the parasite that causes malaria [17]. From 2000 onwards, many malaria-endemic African countries, including Nigeria, acquired large volume of ACTs from organizations such as the Global Fund for Aids, Tuberculosis and Malaria (GFATM) and reviewed their National Anti-Malaria Treatment Policy with the objective of enabling those at risk of malaria to access antimalarial that is mostly acceptable, effective, affordable, safe, and of good quality [18]. The Federal Ministry of Health in Nigeria, following rigorous clinical studies, approved Artemether-Lumefantrin (AL) and Artesunate-Amodiaquine (AA) as first-line treatment of confirmed uncomplicated *Plasmodium falciparum* malaria [19]. In Nigeria and other African countries, malaria is associated with high morbidity and mortality particularly among children. The disease incapacitates the work-force from farming, trading and office work with high economic burden [20-22]. Recently, ADR to ACTs, especially AL and AA, has not received the attention it deserves and often get overshadowed by the drug effectiveness, disease-associated morbidity and the economic burden imposed on the population. Data on ADR to AL and AA in Nigeria are scant hence the objectives of this paper were (i) to estimate and compare the frequency of ADRs associated with AL and AA and (ii) to develop a list of classical adverse drug reactions to both antimalarials. Detailed drug history of the patient is critical in diagnosing ADR (Mahesh et al), thus, this study decided to evaluate ADRs to Artemisinin-based Combination Therapies (ACTs) such as Artemether Lumefantrine (AL) and Artesunate Amodiaquine (AA) among adults.

Materials and Method

Study site

This study was conducted in Ikorodu, a semi-urban town located 30 km northwest of metropolitan Lagos in Nigeria. It is located along the largest Lagoon of Lagos on the Bight of Benin, and it is a traditional settlement of the Aworis, a sub-group of the Yorubas. The 2006 Census recorded its population as 535,619, though over the years, internal migration has increased the population density. The study population was characterized by ethnic homogeneity. The State Government has distributed free ACT to health facilities because of the town's high malaria endemicity. Prescription of ACT requires the patient to be diagnosed with malaria, using either microscopy or Rapid Diagnostic Test (RDT) kit.

Patient selection

Patients aged ≥18 years who were diagnosed either with microscope or with RDT, as having malaria and were given government approved ACT - AL and AA at three health facilities in Ikorodu for the treatment of acute malaria were included in the study. Those excluded from were pregnant and lactating women, patients on other antimalarials within 7 days of the commencement of the study, and chronically ill and hospitalized patients. Eligible patients were randomized to two groups to receive either AL or AA.

Data collection, procedures and analysis

Patient data for patients administered AL were obtained from Lagos State public health facilities in Ikorodu (as the State distributed only AL to public health facilities), while those treated with AA were retrieved from private health facilities. Patients were followed up, from the time they took the first dose, by visits from 5 trained field-workers who lived within the neighborhood of the health facilities and who were familiar with many of the inhabitants of the study area. Participants were interviewed by the fieldworkers that consisted of one monitoring and evaluation (M&E) officer, two Pharmacists and two Pharmacy assistants who were given a one-day training on best practices in administering and completing questionnaire. Data was entered into Excel spreadsheet, de-identified and coded before it was exported into NCSS2021 (Utah, USA) statistical software. Data collection and entry were processed concomitantly and quality of data was assured by double check where necessary. Variables obtained from participants included socio-demographic characteristics, patient-reported ADRs while receiving AL and AA, severity, duration and severity of ADR in each study arm and outcome of the ADR in each study arm. Patients in each arm were inquired on the type of meal consumed prior to medication administration as fatty meals significantly increases the bioavailability of ACT agents.

Sample size calculation and statistics

A prior pilot study in Lagos State showed a prevalence of 20.4% and 40.8% prevalence of ADR to AL and AA respectively [23] and these figures were used to calculate the sample size for each arm according to the formular of Altman (1991) as described by Whitley and Ball [24] as:

$$n = \frac{[p1(1-p1) + p2(1-p2)]}{(p1-p2)^2} \cdot C_{p1\ power}$$

where n represents the sample size to be determined and p1 and p2 the frequencies of ADR to AL and AA respectively as determined by the pilot study. The power of the study was set at 0.8 and the probability (1-β) of rejecting null hypothesis when it is false was taken as 0.8. At a significance level (α)

0.05, C_{p1} corresponds to 10.51 [24], thus the sample size was determined as

$$n = \frac{[(0.41(1-0.41) + 0.20(1-0.20)]}{(0.41-0.20)^2} X\ 10.51$$

or

96 in each arm

A simple random technique, using sample fraction, derive a sample size of 96 patients treated with AL and 96 treated with AA. Allowing for an attrition rate of 35%, the total sample size for each arm (AL, AA) was estimated at approximately 130.

The significance of association between two variables was determined by 2-tailed student's T-test and differences were considered significant when P-value was ≤0.05. Data were presented as Tables, Figures, Graphs and Charts.

Ethical approval and informed consent

The College of Medicine, University of Lagos, Nigeria, gave ethical approval to conduct the study (CM/COM/8/VOL.XX1 of 29th December 2010). Participants were informed of the study objectives before obtaining their written/verbal informed consent. Confidentiality of data was ensured, and participants were guaranteed that the data collected was for this study alone.

Results

Of the 256 patients recruited into the study, 4 (1.6%) were excluded due to antimalarial exposure a week prior to the study period (3 patients) and for being below the age criteria (1 patient). The remaining 252 (98.4%) patients, confirmed with Rapid Diagnostic Test (RDTm) for malaria at Ikorodu LGA of Lagos State, Nigeria, were randomized into AL arm (n-133) and AA arm (n=119). Study subjects' flow chart, as described above, is as shown in Figure 1.

Socio-demographic characteristics of respondents. Table 1, Figures 2a-d, Figure 3

The overall mean age of the 252 study subjects was 34.4 years (± SD 10.6) with sex distribution of 99 males (39.3%) and 153 females (60.7%). The mean age of males was 32.8 years (± 10.8; range 17-63 years),) was significantly varied from that of females, 35.5 years (± 10.4; range 18-65 years) respectively (t-test=-1.97, P-value=0.03). Histogram and normal probability plot of age of males (Figures 2a, b) and females (Figures 2c, d), indicates that normality in ages of males (Shapiro-Wilk's test=0.910, P-value=0.0000, Alpha of 5%) and that of females (Shapiro Wilk's test=0.959, P-value=0.0002, Alpha of 5%), should be rejected. The figures also illustrate that majority (45, 50.0%) of the males were aged 20-29 years while majority (59, 38.6%) of the females were aged 30-40 years. More women (123, 80.4%) than men (75, 75.8%) were employed, though there was no significant difference in their proportion. Also, more women (n=8; 5.2%) than men (n=3; 3.0%) were professionals in occupation status. Only 3.6% of the survey population had no formal education, while 12.7% and 26.2% respectively had primary and tertiary levels of education. Over half (57.5%) of the respondents attained secondary education (Figure 3). Overall, there were no significant differences between the AL arm or AA arm of the study relative to age (years) or sex.

Duration of illness before taking ACT. Table 2, Figure 4

Overall, there was a significant variation (t-test=-3.57, P-value=0.0002) in the mean (± sd) duration (days) of febrile illness before taking either AL (2.6 days ± 1.0) or AA (3.1 days ± 1.2), driven mainly those aged 30-39 years (2.6 days ± 1.0) for AL and (3.3 days ± 1.1) for AA respectively (t-test=-3.39, P-value=0.0005), and those aged 40-49 years (2.4 years ± 1.1) for AL and 3.2 years ± 1.1) for AA respectively (t-test= -2.42,

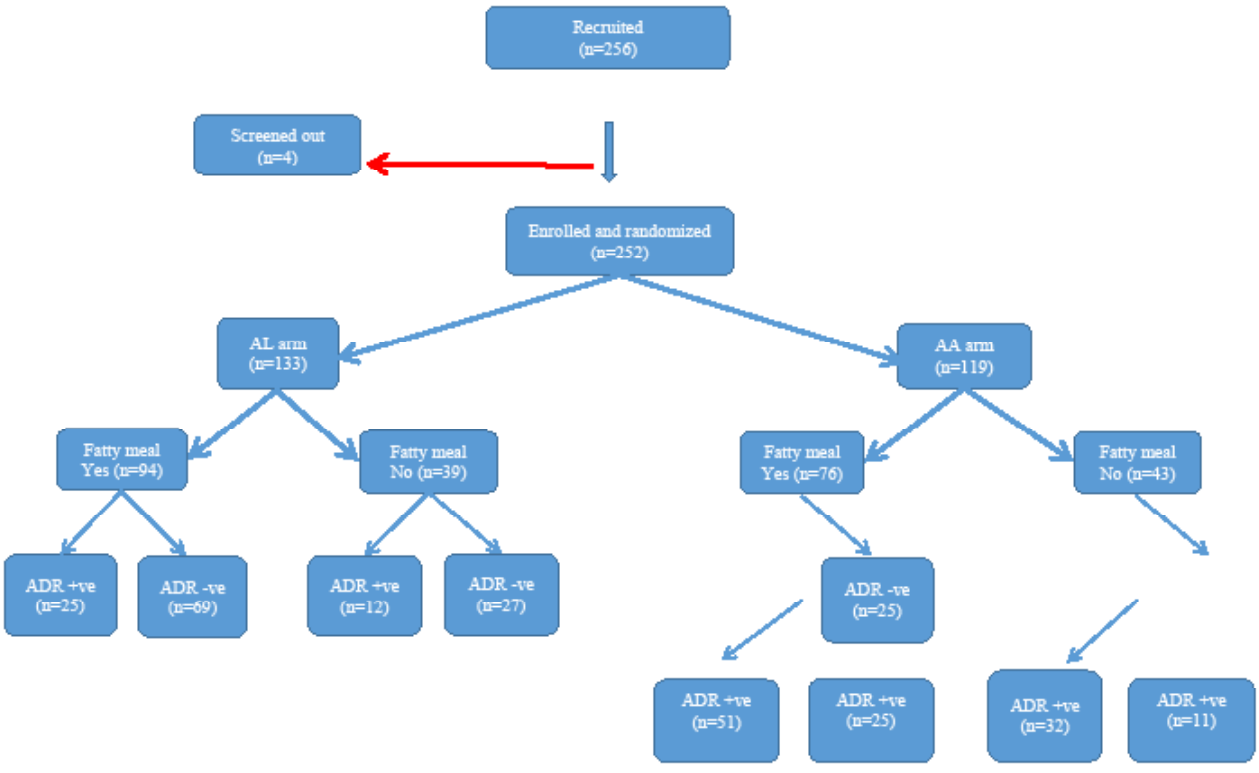
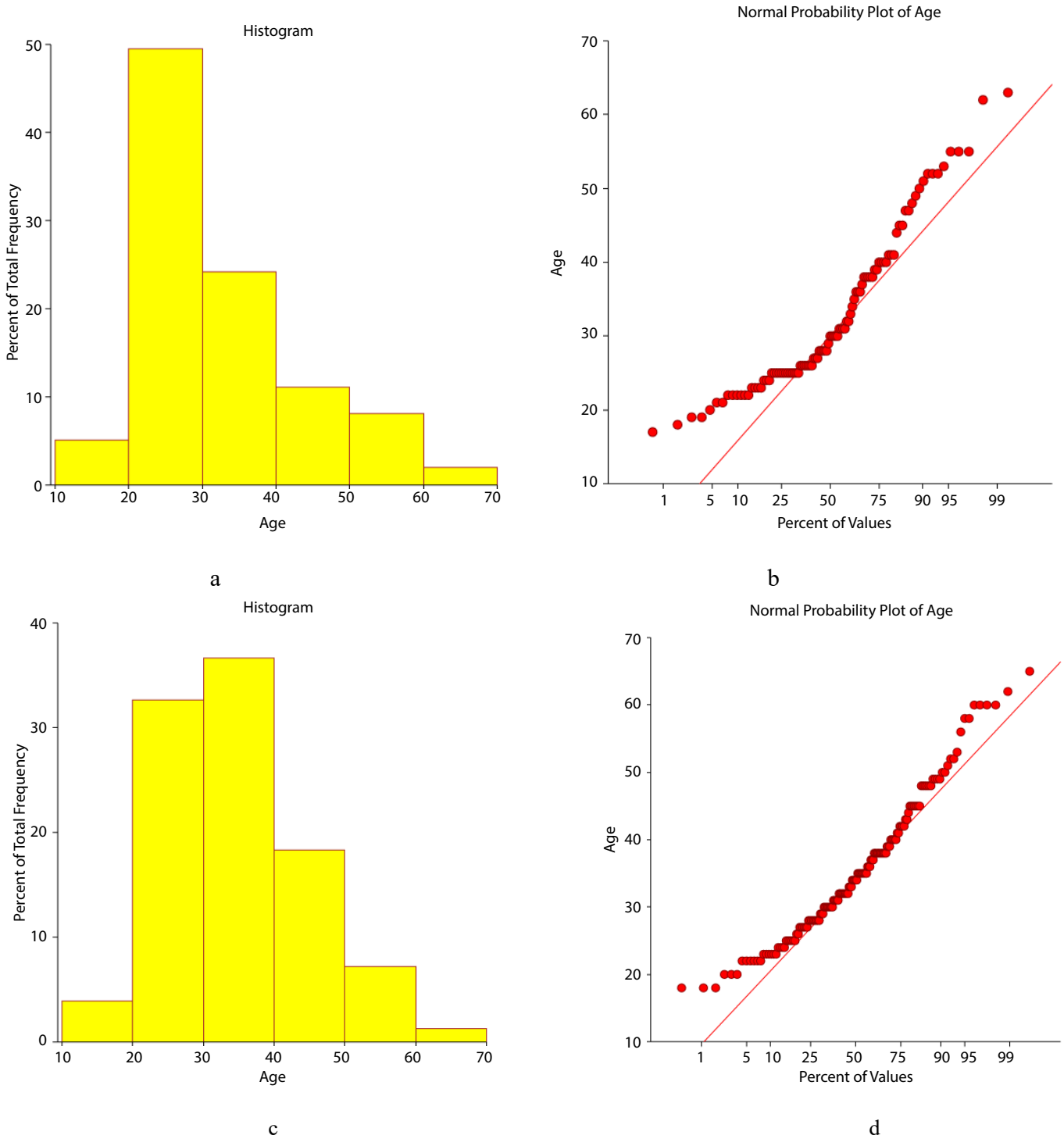


Figure 1: Study subjects' flow chart.



Figures 2a-d: Histogram and normal probability plot of age of males (a, b) and females (c,d).

P-value=0.010). Mean duration of illness was significantly longer (t-test= -2.32, 0.01) in females in AA arm (3.0 (1.0)) than among those in AL arm (2.6 (0.9)). Interestingly, study subjects with secondary level of education had notable variation (t-test=-3.09, P-value=0.001) in the mean duration of illness before taking AL (2.5 (0.8)) or AA (3.0 (1.1)). Duration of time before taking any antimalarial was 1 day, 2 days, 2.5 days, 3 days, 4 days 5 days and 6 days in 25 (9.2%), 82 (32.5%), 3 (1.2%), 79 (31.4%), 40 (15.9%), 19 (7.5%) and 6 (1.6%) study subjects, respectively. Duration of time before taking AL was 1 day, 2 days, 2.5 days, 3 days, 4 days 5 days and 6 days in 16 (12.0%), 48 (36.1%), 2 (1.5%), 45 (33.8%), 15 (11.3%), 6 (4.5%) and 1 (0.8%) study subjects, respectively. Duration of time before taking AA was 1 day, 2 days, 2.5 days, 3 days, 4 days 5 days and 6 days in 9 (7.6%), 34 (28.8%), 1 (0.8%), 34 (28.6%), 25 (21.0%), 13 (10.9%) and 3 (2.5%) study subjects, respectively (Figure 4a-c).

Concurrent medication taken simultaneous in each arm of the study (Table 3).

Only 1 person in AL arm, a 45-year-old female professional, who ate fatty meal before taking the recommended ACT, but did not complete the full dose, developed 5 ADRs which included moderately severe palpitation that started later on

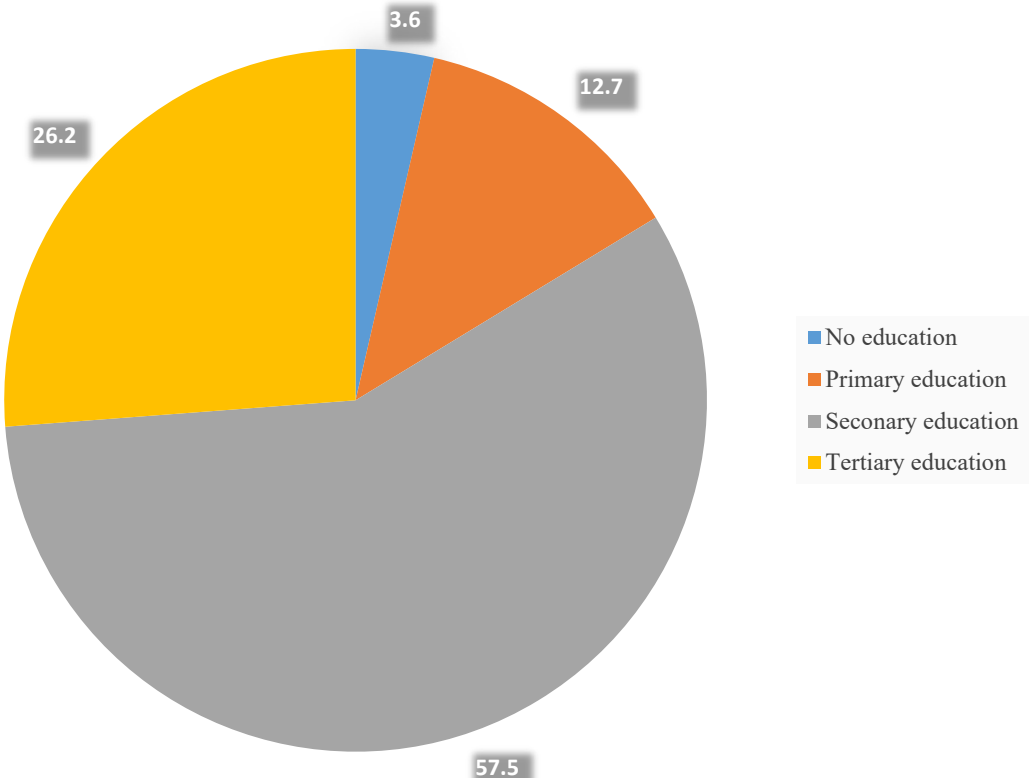
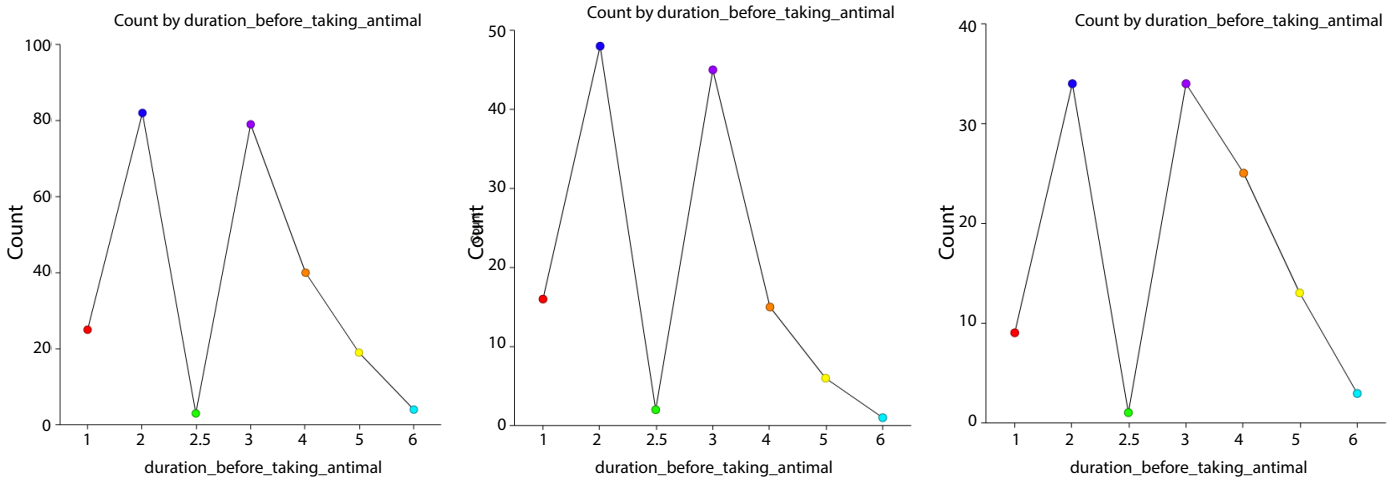


Figure 3: Percent distribution of educational status of study participants.



Figures 4a, b, c: Frequency distribution of duration of illness overall (a) and before taking AL (b) or AA (c).

Duration of illness before taking any antimalarial was 1 day, 2 days, 2.5 days, 3 days, 4 days 5 days and 6 days in 25 (9.2%), 82 (32.5%), 3 (1.2%), 79 (31.4%), 40 (15.9%), 19 (7.5%) and 6 (1.6%) study subjects, respectively; before taking AL was 1 day, 2 days, 2.5 days, 3 days, 4 days 5 days and 6 days in 16 (12.0%), 48 (36.1%), 2 (1.5%), 45 (33.8%), 15 (11.3%), 6 (4.5%) and 1 (0.8%) study subjects, respectively and before taking AA was 1 day, 2 days, 2.5 days, 3 days, 4 days 5 days and 6 days in 9 (7.6%), 34 (28.8%), 1 (0.8%), 34 (28.6%), 25 (21.0%), 13 (10.9%) and 3 (2.5%) study subjects, respectively.

the same day she took AL and lasted for 3 days as well as mild restlessness, moderate fatigue, moderate loss of appetite and profuse sweating all of which started the day after taking the AL and which lasted for 4 days respectively. In all, 116 (96.7%) of the study subjects who developed ADR recovered fully and only 4 (3.3%) had a perceived life-threatening experience.

Risk ratio assessment of fatty meal consumption and development of ADR to AL and AA (Table 5).

In all, 94 (70.7%) of the 133 study subjects in AL arm took fatty meal before taking the antimalarial and 39 (29.3%) did not take fatty meal. In the AA arm, 76 (63.9%) took fatty meal while 43 (36.1%) did not. Of the 94 that took fatty meal in the AL arm, 25 (26.6%) developed ADR while 69 (73.4%) did not; of the 39 that did not take fatty meal, 12 (30.8%) developed ADR while 27 (69.2%) did not. The relative risk (RR) of ADR among study subjects who did not take fatty meal in AL arm was higher (χ^2 =0.24, P-value= 0.63, RR=1.15, 95% CI=0.66, 2.03) than among those who took fatty meal (χ^2 =0.24, P-value= 0.63, RR=0.94, 95% CI=0.73, 1.21). The RR of ADRs among study subjects who

Table 1: Socio-demographic characteristics of respondents relative to gender and antimalarial taken.

Variable	Sub-variable	Statistics	All	Male	Female	AL arm	AA arm	χ^2	P-value	OR	95% CI
Age (years)	All	Freq. (%)	252 (100.0)	99 (39.3)	153 (60.7)	133 (52.8)	119 (47.2)	-	-	-	-
		Mean (± sd)	34.4 (10.6)	32.8 (10.8)	35.5 (10.4)	-	-	-	-	-	-
	<20	Freq. (%)	7 (2.3)	4 (4.0)	3 (2.0)	4 (3.0)	3 (2.5)	0.00*	1.00	1.20	0.26, 5.47
		Mean (± sd)	18.1 (0.7)	18.3 (1.0)	18.0 (0.0)	-	-	-	-	-	-
	20-29	Freq. (%)	90 (35.7)	45 (45.5)	45 (29.4)	44 (33.1)	46 (38.7)	0.85	0.36	0.78	0.47, 4.31
		Mean (± sd)	24.9 (2.4)	24.8 (2.2)	25.1 (2.7)	-	-	-	-	-	-
	30-39	Freq. (%)	84 (33.3)	25 (25.3)	59 (38.6)	53 (39.9)	51 (42.9)	0.23	0.63	0.88	0.53, 1.46
		Mean (± sd)	34.2 (3.1)	34.1 (3.4)	34.3 (3.0)	-	-	-	-	-	-
	40-49	Freq. (%)	45 (17.9)	14 (14.1)	31 (20.3)	20 (15.0)	25 (16.8)	1.52	0.22	0.67	0.35, 1.27
		Mean (± sd)	44.2 (3.3)	43.2 (3.4)	44.5 (3.2)	-	-	-	-	-	-
	≥50	Freq. (%)	26 (10.3)	11 (11.1)	15 (9.8)	12 (9.0)	14 (11.8)	0.51	0.48	0.74	0.33, 1.68
		Mean (± sd)	55.6 (4.6)	54.5 (4.3)	56.5 (4.8)	-	-	-	-	-	-
Sex	Male	Freq. (%)	99 (39.3)	-	-	54 (40.6)	45 (37.8)	0.20	0.65	1.12	0.68, 1.87
	Female		153 (60.7)	-	-	79 (59.4)	74 (62.2)				
Employed	Yes	Freq. (%)	198 (78.6)	75 (75.8)	123 (80.4)	115 (86.5)	83 (69.7)	10.38	0.001	2.77	1.47, 5.22
	No		50 (19.8)	23 (23.2)	26 (17.0)	16 (12.0)	34 (28.6)	10.76	0.001	0.34	0.18, 0.66
	No response		4 (1.6)	1 (1.0)	4 (2.6)	2 (1.5)	2 (1.7)	0.00	1.00	0.89	0.12, 6.44
Occupational status (ISCO)	Professional	Freq. (%)	11 (4.6)	3 (3.0)	8 (5.2)	8	3	1.10*	0.30	2.47	0.64, 9.55
	Technician		3 (1.2)	2 (2.0)	1 (0.7)	2	1	0.00*	1.00	1.80	0.16, 20.13
	Clerical support		29 (12.1)	10 (10.1)	19 (12.4)	10	19	4.38	0.04	0.43	0.19, 0.96
	Service and Sales		118 (49.2)	24 (24.2)	94 (61.4)	69	49	2.88	0.09	1.54	0.94, 2.54
	Craft and related trades workers		10 (4.2)	7 (7.1)	3 (2.0)	3	7	1.32*	0.25	0.37	0.09, 1.46
	Plant and machine operators, and assemblers		20 (8.3)	19 (19.2)	1 (0.7)	13	7	1.30	0.25	1.73	0.67, 4.50
	Elementary occupations		13 (5.4)	12 (12.1)	1 (0.7)	7	6	0.006	0.94	1.05	0.34, 3.21
	Armed forces occupations		1 (0.4)	1 (1.0)	0 (0.0)	0	1	0.003*	0.96	0.00	undefined
	Student		30 (12.5)	16 (16.2)	14 (9.1)	9	21	7.06	0.007	0.34	0.15, 0.77
	Housewife		4 (1.7)	0 (0.0)	4 (2.6)	0	4	2.65*	0.10	0.00	undefined
	No answer		13 (5.2)	5 (5.0)	8 (5.2)	12	1	7.00*	0.008	11.70	1.50, 91.43

* Fisher's exact

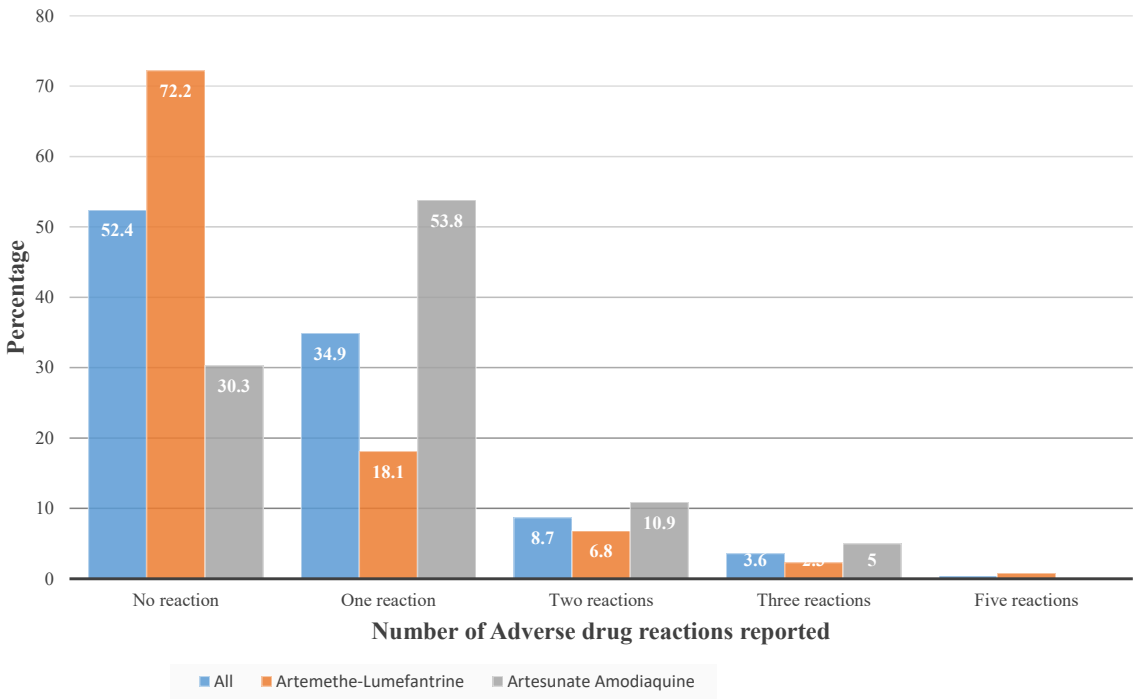


Figure 5: Percent distribution of ADRs to Artemether Lumefantrine and Artesunate Amodiaquine.

Table 2: Mean (±) duration (days) of illness before taking prescribed ACT relative to socio-demographic characteristics.

		All				AL arm				AA arm				T-test	P-value
Variable	Sub-variable	Duration	Min.	Max.	95% CI	Duration	Min.	Max.	95% CI	Duration	Min.	Max.	95% CI		
Age (years)	All	2.8 (1.14)	1.0	6.0	2.69, 2.97	2.6 (1.0)	1.0	6.0	2.44. 2.79	3.1 (1.2)	1.0	6.0	2.84, 3.28	-3.57	0.0002
	<20	2.9 (1.07)	2.0	5.0	1.87, 3.85	2.7 (0.5)	2.0	3.0	1.95, 3.55	3.0 (1.7)	2.0	5.0	-1.30, 7.30	-0.30	0.40
	20-29	2.6 (1.11)	1.0	6.0	2.41, 2.88	2.6 (1.1)	1.0	6.0	2.27, 2.93	2.7 (1.2)	1.0	6.0	2.34, 3.03	-0.41	0.34
	30-39	2.8 (1.09)	1.0	5.0	2.60, 3.08	2.6 (1.0)	1.0	5.0	2.29, 2.86	3.3 (1.1)	2.0	5.0	2.90, 3.68	-3.39	0.0005
	40-49	2.8 (1.15)	1.0	5.0	2.50, 3.19	2.4 (1.1)	1.0	5.0	1.94, 2.96	3.2 (1.1)	1.0	5.0	2.70, 3.62	-2.42	0.010
	≥50	3.4 (1.30)	1.0	6.0	2.86, 3.91	3.1 (0.9)	2.0	5.0	2.51, 3.66	3.6 (1.5)	1.0	6.0	2.75, 4.54	-1.05	0.15
Sex	Male	2.9 (1.26)	1.0	6.0	2.63, 3.13	2.7 (1.2)	1.0	6.0	2.35, 3.02	3.1 (1.3)	1.0	6.0	2.72, 3.50	-1.58	0.06
	Female	2.8 (1.06)	1.0	6.0	2.63, 2.96	2.6 (0.9)	1.0	5.0	2.37, 2.77	3.0 (1.2)	1.0	6.0	2.76, 3.30	-2.32	0.01
Employed	Yes	2.8 (1.11)	1.0	6.0	2.64, 2.95	2.7 (1.1)	1.0	6.0	2.47, 2.86	3.0 (1.2)	1.0	6.0	2.73, 3.23	-1.80	0.04
	No	3.0 (1.30)	1.0	6.0	2.61, 3.35	2.4 (0.9)	1.0	5.0	1.90, 2.85	3.3 (1.4)	1.0	6.0	2.78, 3.76	-2.74	0.004
	No response	2.6 (0.89)	2.0	4.0	1.49, 3.71	2.0 (0.0)	2.0	2.0	-	3.0 (1.0)	2.0	4.0	0.51, 5.48	-1.41	0.20
Educational status	No formal education	3.4 (1.24)	2.0	5.0	2.49, 4.39	3.3 (1.3)	2.0	5.0	1.25, 5.25	3.6 (1.3)	2.0	5.0	1.93, 5.27	-0.34	0.37
	Primary	3.0 (1.18)	1.0	5.0	2.54, 3.39	2.9 (1.1)	1.0	5.0	2.25, 3.60	3.0 (1.2)	1.0	5.0	2.40, 3.60	-0.24	0.40
	Secondary	2.7 (1.01)	1.0	6.0	2.56, 2.89	2.5 (0.8)	1.0	5.0	2.32, 2.69	3.0 (1.1)	1.0	6.0	2.70, 3.25	-3.09	0.001
	Tertiary	2.9 (1.36)	1.0	6.0	2.57, 3.23	2.7 (1.3)	1.0	6.0	2.23, 3.11	3.2 (1.3)	1.0	6.0	2.69, 3.74	-1.54	0.06
Occupational status (ISCO classification)	Professional	2.1 (0.94)	1.0	4.0	1.46, 2.72	1.9 (0.8)	1.0	3.0	1.18, 2.57	2.7 (1.2)	2.0	4.0	-0.20, 5.54	-1.07	0.19
	Technician	2.0 (1.00)	1.0	3.0	-0.48, 4.48	2.0 (1.4)	1.0	3.0	-10.71, 14.71	2.0 (0.0)	2.0	2.0	-	-	-
	Clerical support	3.5 (1.13)	1.0	6.0	3.07, 3.93	2.9 (1.1)	1.0	4.0	2.11, 3.69	3.8 (1.0)	2.0	6.0	3.31, 4.32	-2.16	0.02
	Service and Sales	2.9 (1.11)	1.0	6.0	2.65, 3.06	2.8 (1.1)	1.0	6.0	2.49, 3.01	3.0 (1.1)	1.0	6.0	2.67, 3.33	-0.88	0.19
	Craft and related trades workers	3.1 (1.37)	1.0	6.0	2.12, 4.08	2.3 (1.2)	1.0	3.0	-0.54, 5.20	3.4 (1.4)	2.0	6.0	2.14, 4.72	-1.26	0.13
	Plant and machine operators, and assemblers	2.7 (0.88)	1.0	4.0	2.24, 3.06	2.6 (0.8)	2.0	4.0	2.15, 3.08	2.7 (1.1)	1.0	4.0	1.69, 3.74	-0.21	0.42
	Elementary occupations	3.4 (1.45)	1.0	5.0	2.51, 4.26	3.0 (1.0)	2.0	5.0	2.08, 3.92	3.8 (1.8)	1.0	5.0	1.90, 5.76	-0.97	0.18
	Armed forces occupations	3.0 (0.00)	3.0	3.0	-	-	-	-	-	3.0 (0.0)	3.0	3.0	-	-	-
	Student	2.6 (1.10)	1.0	5.0	2.22, 3.04	2.6 (1.1)	1.0	5.0	1.69, 3.42	2.7 (1.1)	1.0	5.0	2.16, 3.17	-0.23	0.41
	Housewife	2.0 (0.81)	1.0	3.0	0.70, 3.30	0.0 (0.0)	0.0	0.0	-	2.0 (0.8)	1.0	3.0	0.70, 3.30	-	-
	No response	2.1 (0.64)	1.0	3.0	1.69, 2.46	2.1 (0.7)	1.0	3.0	1.66, 2.51	2.0 (0.0)	2.0	2.0	-	-	-

Table 3: Concurrent medication taken simultaneous in each arm of the study.

Other medication taken concurrently with antimalarial given		Antimalaria taken for current diagnosed malaria illness				Total that took or did not take other medication (n=252, 100%)		χ^2	P-value	Odd ratio	95% CI
		Artemether Lumefantrin (n = 133, 52.8%)		Artesunate Amodiaquine (n =119, 47.2%)							
		Freq.	%	Freq.	%	Freq.	%				
Did not take other medication		80	60.1	47	39.5	127	50.4	10.68	0.001	2.31	1.39, 3.83
Took other medication		53	39.8	72	60.5	125	49.6				
Other medication taken concurrently	Analgesic	26	49.1	42	58.3	68	54.4	1.05	0.31	1.45	0.71, 2.97
	Antibiotics	3	5.7	0	0.0	3	2.4	2.11*	0.15	0.00	undefined
	Anti inflammatory	9	17.0	14	19.4	23	18.4	0.12	0.73	1.18	0.47, 2.97
	Hematinics	11	20.8	16	22.2	27	21.6	0.04	0.84	1.09	0.46, 2.59
	Stimulant	1	1.9	0	0.0	1	0.8	0.02*	0.88	0.00	undefined
	Antihypertensive	2	3.8	0	0.0	2	1.6	0.88*	0.10	0.00	undefined
	Antipruritus	1	1.9	0	0.0	1	0.8	0.02*	0.88	0.00	undefined

* Fisher's exact

Table 4: Dynamics of antimalarial medication.

Variable	Response	All	Artemether Lumefantrin	Artesunate Amodiaquine	χ^2	P-value	OR	95% CI
		Freq (%)	Freq (%)	Freq (%)				
Completed full dose	Yes	243 (96.4)	130 (97.7)	113 (95.0)	0.72*	0.40	2.30	0.56, 9.41
	No	9 (3.6)	3 (2.3)	6 (5.0)			0.43	0.11, 1.78
Ate fatty meal	Yes	170 (67.5)	94 (70.7)	76 (63.9)	1.32	0.25	1.36	0.80, 2.31
	No	82 (32.5)	39 (29.3)	43 (36.1)			0.73	0.43, 1.24
Had ADR after eating fatty meal	Yes	76 (44.7)	25 (26.6)	51 (67.1)	27.73	<<0.00001	0.18	0.09, 0.34
	No	94 (55.3)	69 (73.4)	25 (32.9)			5.63	2.90, 10.92
Had ADR after not eating fatty mean	Yes	44 (53.7)	12 (30.8)	32 (74.4)	15.48	0.00008	0.15	0.06, 0.40
	No	38 (46.3)	27 (69.2)	11 (25.6)			6.55	2.49, 17.18
Had ADR after taking the medicine	Yes	120 (47.6)	37 (27.8)	83 (69.8)	44.09	<<0.00001	0.17	0.10, 0.29
	No	132 (52.4)	96 (72.2)	36 (30.2)			5.98	3.47, 10.31
Outcome of reaction	Recovered fully	116 (96.7)	35 (94.6)	81 (97.6)	0.09*	0.77	0.43 (2.31)	0.06, 3.19 (0.31, 17.10)
	Recovered with disability	0 (0.0)	0 (0.0)	0 (0.0)	-	-	-	-
	Life threatening	4 (3.3)	2 (5.4)	2 (2.4)	0.09*	0.77	2.31 (0.43)	0.31, 17.10 (0.06, 3.19)

did not take fatty meal in AA arm was even higher (χ^2 =0.69, P-value= 0.41, RR=1.26, 95% CI=0.72, 2.21) compared to those in the AL arm while the RR among those who took fatty meal was lower (χ^2 =0.69, P-value= 0.41, RR=0.88, 95% CI=0.67, 1.17) than that in the AL arm. Those in the AL arm, were 1.10 more at risk of ADRs compared to those in the AA arm (χ^2 =0.41, P-value= 0.52, RR=1.10, 95% CI=0.83, 1.46). In general, the relative risks of various ADRs to AL and to AA are as illustrated in Table 5.

Quantity, severity, and mean duration of ADR in each study arm (Table 6).

Although 120 (47.6%) patients reported ADRs, there were a total of 168 mild, moderate and severe ADRs, 58 (34.5%) in the AL arm and 110 (65.5%) in the AA arm. Of the 58 ADR in AL arm, 38 (65.5%), 16 (27.6%) and in 4 (6.9%) were mild, moderate and severe and of the 168 ADR in AA arm, 69 (62.7%), 29 (26.4%) and 12 (10.9%) were mild, moderate and severe, respectively. Of the 38 mild ADR in the AL arm, 10 (26.3%), 26 (68.4%) and 2 (5.3%) started on the day AL was consumed (Day 1), the following day the AL was consumed (Day 2) and the next day (Day 3) respectively. Of the 16 moderately severe ADR in AL arm, 3 (18.7%) started on the same day AL was taken (Day 1) while 13 (81.3%) started the following day (Day 2). Only 1 (25.0%) of the 4 severe ADR in erupted on same day AL was consumed while the remaining 3 (75.0%) broke out the following Day (Day 2). Of the 69 mild ADR in the AA arm, 18 (26.1%), 50 (72.5%) and 1 (1.4%) broke out the same day (Day 1), the following day (Day 2) and the next day (Day 3) the antimalarial was taken while 29 moderately severe ADR, 4 (13.8%) and 25 (86.2%) erupted on the same day (Day 1) and on the following day (Day 2) respectively. Of the 12 severe ADR in the AA arm, 5 (41.7%) broke out on the same day (Day 1) of treatment and 7 (58.3%) on the next day of treatment. The longest mean (± sd) duration of any ADR in the AL arm occurred among those reported loss of appetite (5.0 ± 1.4) and the only patient that reported body pain (5.0 ± 0.0). Mild weakness/fatigue started significantly earlier (t-test=1.84, P-value=0.04) in the AA arm (2.5 ± 0.9 days) compared to the AL arm (3.1 ± 0.9 days) and moderate weakness/fatigue appeared even much earlier (t-test=3.62, P-value=0.0009) in AA arm (2.7 ± 0.7 days) compared to AL arm (4.0 ± 0.7 days). Also, mild (2.5 ± 0.5 days) and moderate (2.5 ± 0.6 days) headache erupted earlier in AA arm compared to in AL arm (3.0 ±1.3 days and 4.0 ± 0.0

Table 5: Risk ratio assessment of fatty meal consumption and development of ADR to AL and AA.

ADR developed		AL arm				AA arm				χ^2	P-value	RR	95% CI
		Fatty meal											
		Yes (n=94, 70.7%)		No (n=39, 29.3%)		Yes (n=76, 63.9%)		No (n=43, 36.1%)					
		Freq.	%	Freq.	%	Freq.	%	Freq.	%				
ADR	Yes	25	26.6	12	30.8	51	67.1	32	74.4	0.41	0.52	1.10	0.83, 1.46
	No	69	73.4	27	69.2	25	32.9	11	25.6	0.07	0.78	1.04	0.81, 1.33
χ^2 (P-value)		0.24 (0.63)				0.69 (0.41)						-	
RR (95% CI)		0.94 (0.73, 1.21)		1.15 (0.66, 2.03)		0.88 (0.67, 1.17)		1.26 (0.72, 2.21)					
All perceived ADR													
Weakness/fatigue		12	48.0	4	33.3	36	70.6	19	59.4	0.17*	0.68	1.15	0.81, 1.61
Loss of appetite		3	12.0	0	0.0	1	2.0	0	0.0	5.61*	0.02	undefined	
Sleeplessness		2	8.0	1	8.3	2	3.9	0	0.0	0.00*	1.00	undefined	
Itching		0	0.0	0	0.0	3	5.9	2	6.2	-	-	-	-
Dizziness		6	24.0	2	16.7	6	11.8	5	15.6	0.19*	0.67	1.38	0.70, 2.69
Restlessness		2	8.0	1	8.3	4	7.8	2	6.2	0.00*	1.00	1.00	0.38, 2.66
Rashes		0	0.0	0	0.0	0	0.0	0	0.0	-	-	-	-
Abdominal discomfort		0	0.0	0	0.0	2	3.9	1	3.1	-	-	-	-
Nausea		2	8.0	1	8.3	2	3.9	2	6.2	0.00*	1.00	1.33	0.38, 4.72
Vomiting		1	4.0	0	0.0	0	0.0	0	0.0	-	-	-	-
Headache		5	20.0	4	33.3	9	17.6	9	28.1	0.00*	1.00	1.11	0.53, 2.34
Tremors		0	0.0	0	0.0	0	0.0	0	0.0	-	-	-	-
Profuse sweating		1	4.0	1	8.3	0	0.0	0	0.0	-	-	-	-
Dry throat/Thirst		1	4.0	0	0.0	0	0.0	1	3.1	-	-	-	-
Sedation		2	8.0	3	25.0	2	3.9	0	0.0	0.36*	0.55	0.40	0.14, 1.17
Increased appetite		1	4.0	1	8.3	1	2.0	0	0.0	0.00*	1.00	0.00	undefined
Heartburn		0	0.0	0	0.0	0	0.0	1	3.1	-	-	-	-
Body pains		0	0.0	1	8.3	0	0.0	0	0.0	-	-	-	-
Palpitation		3	12.0	0	0.0	0	0.0	0	0.0	-	-	-	-

days) though the difference in time was not significant. None of the study subjects in the AA arm reported a longer duration of ADR. Percent distribution of quantity of ADR in either arm of the study is as shown in Figure 5.

Discussion

Monitoring and evaluating the safety of drugs and medications in clinical use and patient care, especially among humans, is one of the main reasons for the establishment of pharmacovigilance. Due to resistance of malaria parasites to insecticides and to monotherapies such as Chloroquine, there has been a resurgence of malaria which has become endemic in many parts of the tropical world, including Africa. The resurgence of this disease has contributed in no small measures to high morbidity and mortality, especially among the at-risk groups of children under the age of five and pregnant women, more often those in their first pregnancy. Since the early 2000's, the WHO has been promoting the therapeutic use of ACTs for the management of acute Plasmodium falciparum malaria, after confirmation by microscopy or Rapid Diagnostic Test (RDT) [25].

This study explored and compared the scope and scale of acute ADR among adults who had taken government recommended Artemsinin-based Combination Therapies (ACTs) - Artemether-Lumefantrine (AL) and Artesunate-Amodiaquine (AA) as a curative measure for malaria in a malaria-endemic semi-urban Nigerian community. In this study, AL and AA were administered to the participants in real-time situation, based on which of the two medications was available at any of the health facilities where data were collected. One major finding in this study is that, statistically, patients in AA arm were approximately six times more likely to develop ADR than those on AL, and the number of participants that reported ADR to AA was about three times the number that reported ADR to AL, a report dissimilar to Adisa's findings [26] but proves the high prevalence of ADR to AA than to AL in the community of study. Pre-medication fatty food intake may increase AL absorption in adults with Plasmodium falciparum malaria infection [27] though only a very small amount of dietary fat is necessary to ensure optimal efficacy with AL [28]. Majority of the reported ADRs in both arms of the study were related to weakness/fatigue which occurred more in the AA arm than in the AL arm, and to neurological effect such as headache which also occurred more in the AA arm than in the AL arm.

This is contrary to the findings of Belhekar [29] who reported more of gastrointestinal disorders - nausea, anorexia, vomiting and bitterness in the mouth - in his study of ADR among patients given ACT in India. In contrast to the study of Falade and Manyando [30] that noted 52.9% frequency of headache among AL users, this study found only 15.6% of participants in AL-arm reporting headache. However, it is interesting to note that headache was more prevalent in AA-use than in AL use. Possibly, central bioamines, including histamine and serotonin are responsible for the genesis of headache among participants in this study, especially in the AA arm. In the present study, it was noticed that probable prophylactic co-administration of other medications was more prevalent in the AA arm than in the AL arm, especially with analgesic, followed by hematinics.

Table 6: Adverse drug reaction reported during the survey (multiple answers).

Reported Adverse Drug Reaction	AL Arm													AA Arm											
	Severity			Mild			Mod.			Sev.			Mean (± sd) Duration of reaction (days)				Severity			Mild			Mod.			Sev.			Mean (±sd) Duration of reaction		
	Mild (n=40)	Mod. (n=15)	Sev. (n=3)	Day reaction started									Mild	Mod.	Sev.		Mild (n=69)	Mod. (n=29)	Sev. (n=12)	Day reaction started									Mild	Mod.	Sev.
				1	2	3	1	2	3	1	2	3								1	2	3	1	2	3	1	2	3			
Weakness/ fatigue	10 (25.0)	5 (33.0)	1 (33.0)	1	8	0	1	4	0	0	1	0	3.1 (0.9)	4.0 (0.7)	3.0 (0.0)		32 (46.4)	16 (55.2)	7 (58.3)	6	26	0	1	15	0	4	3	0	2.5 (0.9)	2.7 (0.7)	2.7 (0.5)
Loss of appetite	2 (5.0)	1 (6.7)	0 (0.0)	0	0	0	0	3	0	0	0	0	5.0 (1.4)	4.0 (0.0)	0.0 (0.0)		0 (0.0)	0 (0.0)	1 (8.3)	0	0	0	0	0	0	0	1	0	0.0 (0.0)	0.0 (0.0)	3.0 (0.0)
Sleeplessness	2 (5.0)	1 (6.7)	0 (0.0)	1	1	0	0	0	0	0	1	0	3.5 (2.1)	0.0 (0.0)	3.0 (0.0)		0 (0.0)	0 (0.0)	2 (16.7)	0	0	0	0	0	0	1	1	0	0.0 (0.0)	0.0 (0.0)	2.5 (0.7)
Itching	0 (0.0)	0 (0.0)	0 (0.0)	0	0	0	0	0	0	0	0	0	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)		4 (5.8)	1 (3.4)	0 (0.0)	1	3	0	0	1	0	0	0	0	2.8 (0.5)	3.0 (0.0)	0.0 (0.0)
Dizziness	5 (12.5)	3 (20.0)	0 (0.0)	1	4	0	0	3	0	0	0	0	3.6 (0.9)	3.3 (2.1)	0.0 (0.0)		5 (7.2)	5 (17.2)	1 (8.3)	0	5	0	1	4	0	0	1	0	2.8 (1.1)	3.0 (0.7)	3.0 (0.0)
Restlessness	2 (5.0)	1 (6.7)	0 (0.0)	0	2	0	0	1	0	0	0	0	4.5 (0.7)	3.0 (0.0)	0.0 (0.0)		2 (2.9)	3 (10.3)	1 (8.3)	0	2	0	0	3	0	0	1	0	1.5 (0.7)	2.7 (0.6)	2.0 (0.0)
Abd. discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0	0	0	0	0	0	0	0	0	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)		3 (4.3)	0 (0.0)	0 (0.0)	3	0	0	0	0	0	0	0	0	2.3 (0.6)	0.0 (0.0)	0.0 (0.0)
Nausea	3 (7.5)	0 (0.0)	0 (0.0)	3	0	0	0	0	0	0	0	0	2.7 (0.6)	0.0 (0.0)	0.0 (0.0)		4 (5.8)	0 (0.0)	0 (0.0)	2	2	0	0	0	0	0	0	0	2.8 (0.5)	0.0 (0.0)	0.0 (0.0)
Vomiting	1 (2.5)	0 (0.0)	0 (0.0)	0	2	0	0	0	0	0	0	0	3.0 (0.0)	0.0 (0.0)	0.0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	0	0	0	0	0	0	0	0	0	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Headache	7 (17.5)	1 (6.7)	1 (33.0)	2	5	0	1	0	0	0	1	0	3.0 (1.3)	4.0 (0.0)	3.0 (0.0)		14 (20.3)	4 (13.8)	0 (0.0)	5	9	0	2	2	0	0	0	0	2.5 (0.5)	2.5 (0.6)	0.0 (0.0)
Profuse sweating	1 (2.5)	1 (6.7)	0 (0.0)	0	0	1	0	1	0	0	0	0	3.0 (0.0)	4.0 (0.0)	0.0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	0	0	0	0	0	0	0	0	0	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Dry throat/ Thirst	1 (2.5)	0 (0.0)	(0.0)	0	1	0	0	0	0	0	0	0	2.0 (0.0)	0.0 (0.0)	0.0 (0.0)		1 (1.4)	0 (0.0)	0 (0.0)	0	1	0	0	0	0	0	0	0	3.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Sedation	4 (10.0)	1 (6.7)	0 (0.0)	2	2	0	1	0	0	0	0	0	2.5 (0.6)	2.0 (0.0)	0.0 (0.0)		2 (2.9)	0 (0.0)	0 (0.0)	0	2	0	0	0	0	0	0	0	3.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Increased appetite	1 (2.5)	1 (6.7)	(0.0)	0	1	0	0	1	0	0	0	0	2.0 (0.0)	2.0 (0.0)	0.0 (0.0)		1 (1.4)	0 (0.0)	0 (0.0)	0	0	1	0	0	0	0	0	0	3.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Heartburn	0 (0.0)	0 (0.0)	0 (0.0)	0	0	0	0	0	0	0	0	0	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)		1 (1.4)	0 (0.0)	0 (0.0)	1	0	0	0	0	0	0	0	0	2.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Body pains	1 (2.5)	0 (0.0)	0 (0.0)	0	0	1	0	0	0	0	0	0	5.0 (0.0)	0.0 (0.0)	0.0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	0	0	0	0	0	0	0	0	0	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Palpitation	0 (0.0)	0 (0.0)	1 (33.0)	0	0	0	0	0	0	1	0	0	0.0 (0.0)	0.0 (0.0)	3.0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	0	0	0	0	0	0	0	0	0	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Total	40	15	3	10	26	2	3	13	0	1	3	0	-	-	-		69	29	12	18	50	1	4	25	0	5	7	0	-	-	-

In the opinion of this paper, self-co-administration of analgesics and hematinics may indicate patient's anticipation of some sort of pain and *"weakening of blood"* which needs strengthening with hematinic. Another key finding is the influence of pre-medication fatty meal on ADR. The proportion of participants in AA arm who did not have a pre-medication fatty meal but developed ADR was significantly higher than those in AL arm. In this study, ADR to AA appeared earlier without pre-medication fatty meal. Nigerian diet is traditionally carbohydrate-based with supplements of red palm-oil or groundnut-oil soup which are fat-based. Pharmacovigilance (PV) activity to identify, record and report ADRs, especially to ACTs in Nigeria has been on-going for about 20 years now and it is expected that some challenges may have affected its proper implementation. Pharmacovigilance received moderate attention in public health programs when ACTs were introduced into the country but over the years, it has received negligible support by donors and national governments. Funding more PV programs is necessary for it to run effectively, especially in developing countries such as Nigeria.

Conclusion

The frequencies of various ADRs in AA arm of the study were observed to be significantly higher than those to AL arm. The commonest ADRs reported were weakness/fatigue, and headache. Less common ADRs reported include dizziness, restlessness, nausea and itching. The study reveals that fatty meal reduces the frequency of ADR to either AL or AA by about 10%. The National Pharmacovigilance Centre (NPC) of the National Agency for Food and Drug Administration and Control (NAFDAC) of Nigeria should strengthen their collaboration with other sub-Saharan African (SSA) countries and with WHO program for international drug monitoring at the Uppsala Monitoring Centre (UMC) to continuously monitor drugs consumed by the public and ascertain early recognition, adequate collation of and prompt response to ADRs to avoid the thalidomide experience.

Recommendation

Considering the fact that a large quantity of medications, both herbal and orthodox are consumed daily in Nigeria and since

no study regularly or periodically provide data on medications that are consumed and their toxicity, there is need for design and implementation of national epidemiological studies [31] on adverse drug reactions to various antimalarials as well as other medications. Such study should be an integral part of the National Demographic Health Survey, or could be a periodic stand-alone study. The National Agency for Food and Drug Administration and Control are in the best position to originate and conduct such study for policy-making. Nigeria should be in the fore-front of drug monitoring which, according to WHO [32], has two objectives (i) to establish the frequency and incidence of adverse reactions and (ii) to detect serious and unexpected adverse reactions as early as possible. These should be regarded as a primary aspect of fundamental human right.

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