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Safety of Artemisinin-Based Combination Therapies in Nigeria: A Cohort Event Monitoring Study

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Abstract

Background A pilot programme of Cohort Event Monitoring (CEM) was conducted across the six geopolitical zones of Nigeria on patients treated for uncomplicated malaria with artemisinin-based combination therapy (ACT). The emergence and spread of malaria parasites resistant to commonly available antimalarial drugs necessitated a shift in policy for malaria treatment by the Federal Government from the use of chloroquine and sulphadoxine-pyrimethamine (SP) as first-line treatments to ACTs. Initial reports following deployment of ACTs in clinical settings raised safety concerns regarding their use. Although artemisinin and its derivatives are generally thought to be safe, there are currently few or no data on their safety among populations in Nigeria.

Objectives The main objectives of the CEM programme were to proactively determine the adverse event (AE) profile of artesunate/amodiaquine (AA) and artemether/lumefantrine (AL) in real-life settings and to find out the factors predisposing to AEs.

Methods The CEM study was observational, longitudinal, prospective, and inceptional. Patients were observed in real-life situations. It was conducted in six public health facilities in Nigeria on patients with a clinical diagnosis of uncomplicated malaria treated with ACTs. Patients were prescribed one of the ACTs on an alternate basis as they enrolled into the programme. Follow-up reviews were undertaken on days 3 and 7 following commencement of ACT treatment. At follow-up, patients were evaluated for any clinical event that they might have experienced

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following the use of the ACTs. We report the result of this initial pilot in which 3,010 patients treated for uncomplicated malaria with AA or AL were enrolled.

Results The seven most common AEs seen were general body weakness 25.0/36.6 % (AL/AA); dizziness 11.9/17.2 % (AL/AA); vomiting 8.0/10.2 % (AL/AA); abdominal pain 8.5/7.2 % (AL/AA); insomnia 6.3/5.9 % (AL/AA); body pains 3.4/5.2 (AL/AA) %; anorexia 8.5/4.6 % (AL/AA). Most adverse events occurred from day 1 and peaked by day 2 and 3 of medication with the mean duration of events being 3 days. By the end of the follow-up visit on day 7, the AEs had resolved in the majority of patients. Adverse events were more common in the AA group than AL revealing a better safety profile for AL ($p < 0.001$). Both ACTs demonstrated good ability to resolve the clinical symptoms of uncomplicated malaria.

Conclusion In conclusion, this pilot CEM programme suggests that adverse events with ACTs were common. However, serious life-threatening events were not common. It appears that ACTs have a tolerable safety profile among Nigerians.

1 Background

Malaria is highly endemic in sub-Saharan Africa and is a major public health hazard. It remains a major cause of morbidity and mortality, especially among the most vulnerable groups, which are children under 5, pregnant women, and populations with low immunity [1–4]. In Nigeria, malaria is endemic with minimal seasonal fluctuations but peak transmission occurs during the rainy seasons. It accounted for 63 % of the diseases reported in healthcare facilities across the six geopolitical zones [5, 6]. It accounts for 25 % of infant mortality, 30 % of childhood mortality, and is associated with 11 % of maternal deaths [1, 7, 8]. It is estimated that "at least 50 % of the population suffer from at least one episode of malaria each year" and children under the age of 5 years have two to four attacks of uncomplicated malaria annually [8]. Malaria is understood to be both a disease of poverty and a cause of poverty and underdevelopment. It accounts for 10 % of Africa's disease burden [9].

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Although malaria is preventable, easily treated, and curable, it still remains one of the leading causes of morbidity and mortality in Nigeria. Chloroquine (CQ), which has been used in Africa since the 1940s as the drug of choice in the treatment of uncomplicated malaria, has become ineffective because of the development of widespread resistance of the *Plasmodium falciparum* parasite [10–14]. In response to growing evidence on the lack of efficacy of CQ, artemisinin-based combination therapy (ACT) replaced CQ as the first-line treatment of uncomplicated falciparum malaria in Nigeria in 2005 [1, 15].

Since medicines play a very important role in public health programmes, especially in malaria control, it is imperative that their safety and efficacy are known. The change in malaria treatment policy in Nigeria from CQ to ACTs has raised concerns about their safety among Nigerians, including their use in combination with other medicines, as there is little or no information on the safety of ACTs in Nigeria and Africa [1, 13]. The other ACT combinations available in the hospital clinics during the programme were artesunate + mefloquine, artesunate + sulphadoxine/pyrimethamine, dihydroartemisinin + piperaquine + trimethoprim, etc.

The safety of artemether/lumefantrine (AL) in the first trimester of pregnancy and in children less than 10 kg body weight is still being debated, and these groups may be exposed to this medicine. These concerns underscore the need for intensive and active monitoring of patients treated with the newly recommended ACTs.

Since the global antimalarial policy change to ACT in the early 2000s, safety data have been limited and mainly derived from clinical research information from Southeast Asia [16]. In general, safety information can be collected through two main pharmacovigilance channels: (1) spontaneous reporting and (2) systems using pharmacoepidemiological methods through phase IV clinical trials or cohorts [17, 18]. While spontaneous reporting is essential for signal detection of rare events, the pharmaco-epidemiological methods provide additional information on both the utilisation and the extent of consumption, which will permit determination of rates of adverse drug reactions (ADR) in the studied population or safety comparison between two or more products [18]. Although ACTs are generally considered safe, there is still little structured information about their use in real-life settings, and the published data are mainly from clinical trials [19]. Lack of resources, infrastructure and expertise are the main reasons for the slow development of pharmacovigilance systems in developing countries, particularly in sub-Saharan Africa [20, 21].

Also, spontaneous reporting, which is presently the mainstay of safety monitoring of medicines in Nigeria, may not provide adequate information or an accurate risk profile

of ACTs because of underreporting of ADRs by healthcare providers, potential reporting biases, and lack of comprehensive information on utilisation of medicines in the population, making it difficult to accurately assess risks, determine risk factors, and compare different medicines. Hence, the decision was made to actively monitor patients treated with ACTs using CEM, which offers considerable advantages over spontaneous reporting by providing early, comprehensive, nearly complete data on drug utilisation and risk identification and measurement [22].

1.1 Aim and Objectives

The broad objective of this programme is to evaluate CEM in the safety monitoring of ACTs among populations in Nigeria and concurrently develop the safety profile of the ACTs recommended for use in Nigeria, namely AL and AA.

The specific objectives are to:

(1) systematically obtain information on the majority of adverse events occurring in patients using ACTs for the treatment of malaria in the six health facilities by actively monitoring patients being treated under normal clinical conditions;
(2) identify early the adverse event profiles of AL and AA in samples of the Nigerian population;
(3) identify signals of possible interactions between ACTs and other medicines, herbal medicines, and concomitant diseases;
(4) identify risk factors for adverse drug reactions (ADRs) among populations in Nigeria and thus provide evidence for active prevention;
(5) generate data to assist decision making by policy makers on safety issues, establish a cohort for future studies if needed, and evaluate the CEM methodology under Nigerian conditions with a view to expanding the CEM programme to 10,000 patients

1.2 Methodology

A pilot cohort event monitoring (CEM) programme [23] was undertaken to evaluate and document adverse events that could result from the use of two combinations of artemisinin derivatives: AL and AA, both approved by the Federal Ministry of Health for treatment of uncomplicated malaria in Nigeria.

1.2.1 Setting

The programme was carried out in the general outpatient (GOPD) clinics of six health facilities, one in each of the six geopolitical zones of the country: Ahmed Bello University Teaching Hospital (ABUTH) Zaria, Northwest zone; Federal Medical Centre (FMC), Gombe, Northeast zone; Nigerian Institute for Pharmaceutical Research and Development (NIPRD), Federal Capital Territory (FCT) Abuja, North central zone; University of Nigeria Teaching Hospital (UNTH), Enugu, Southeast zone; University of Uyo Teaching Hospital (UUTH), Uyo, South-south zone; University College Hospital (UCH), Ibadan, Southwest zone. It was hoped that this spread of the study sites would give an adequate representation of the Nigerian population based on cultural, ethnic, and religious considerations.

1.2.2 Design

The study was prospective and observational with patients being observed under real-life conditions. Patients were given a standard course of one of the ACTs, which was taken over 3 days according to the National policy for the treatment of malaria [5] (Table 1).

On an alternate basis, one of the study drugs (artemether + lumefantrine (AL) or artesunate + amodiaquine (AA) was given to each patient as they were enrolled in the programme. Clients were informed about the availability of the following assistance and incentive to return for follow-up: (1) transport subsidy to assist return to the clinic (provided at the follow-up visit) and (2) long-acting medicated mosquito nets at the second follow-up visit. On each of the follow-up days, the study doctor at each site assessed the patients for adverse events that may have occurred. Patients who did not return were followed up at home or contacted by telephone.

1.2.3 Population

The study population were all consecutive patients presenting to the GOPDs of each study site who had a complaint of fever and in whom the attending physician had made a presumptive diagnosis of malaria and were enrolled consecutively irrespective of age, sex, presence of other disease conditions, and use of other medicines, until a total of 500 patients was obtained at each site. Enrolment of patients was performed by trained personnel at each facility from January–April 2009. Each patient was given either AA or AL according to local clinical practice without pre-allocation of respective numbers.

1.2.4 Approvals and Ethical Clearance

Advocacy visits were undertaken to various stakeholders including the Federal Ministry of Health and heads of the health institutions involved in patient recruitment to obtain their approval and cooperation. Ethical clearance (waivers) was obtained from the National Health Research Ethics Committee (NHREC) at enrolment. Verbal consent was

Table 1 Recommended dosing regimens for artemisinin combination therapies (from the National Malaria Treatment Policy Booklet [5])

Weight	Dosage regimen	
Artemether–lumefantrine (20 mg/120 mg) (AL)		
5–<15 kg	1 tablet twice daily for 3 days	
15–<25 kg	2 tablets twice daily for 3 days	
25–<35 kg	3 tablets twice daily for 3 days	
≥35 kg	4 tablets twice daily for 3 days	
Weight/age	**Tablet strength**	**Dosage regimen**
Artesunate + Amodiaquine (50 mg/150 mg) (AA)		
≥4.5 kg–<9 kg 2–11 months	25 mg/67.5 mg	1 tablet once daily for 3 days
≥9 kg–<18 kg 1–5 years	50 mg/135 mg	1 tablet once daily for 3 days
≥18 kg–<36 kg 6–13 years	100 mg/270 mg	1 tablet once daily for 3 days
≥36 kg or 14 years and above	100 mg/270 mg	2 tablets once daily for 3 days

The first day dosage should be taken 8–12 h apart

The co-formulated *Artesunate-Amodiaquine* combination tablets exist in various strengths at the ratio of 1:2.7

White tablets = artemether; yellow tablets = amodiaquine

Weight is the primary criterion for dose. In the absence of weight, age is used

[FMOH, Abuja. National Guidelines for Diagnosis and Treatment of Malaria (June 2011)]

obtained from each patient for permission to be included in the programme after they had been given detailed information on the study in the language best understood by the patient.

1.2.5 Personnel

Each site had a team made up of the site coordinator and at least one of the following professionals: doctor, nurse, pharmacist, and a records assistant.

A principal investigator was responsible for overall coordination of activities at all sites. Periodic support supervision of the sites was undertaken by four supervisors who were also responsible for collecting filled questionnaires and forwarding them to the National Pharmacovigilance Centre, the coordinating organisation for the CEM programme.

A data entry clerk and data analyst were also engaged.

1.3 Data Collection and Statistical Analysis

1.3.1 Identification of Adverse Events

Data were collected by trained personnel using specially designed pre- and post-treatment questionnaires (see Supplementary Digital Content). The pre-treatment questionnaire was used at the treatment initiation visit to collect patient-related information such as name, age, sex, weight, and any medicine(s) and disease-related information prior to use of ACTs. At follow-up assessment visits, the post-treatment questionnaire was used to collect additional information including the presence or absence of any adverse events since taking the prescribed ACT. Programme personnel were asked to record and describe new events since the commencement of treatment or previously existing events that had become worse. The WHO definition of adverse events was used: *Any untoward medical occurrence that may present during treatment with a pharmaceutical product but that does not necessarily have a causal relationship with this treatment.* As a way of determining if they had used the prescribed medicine and in the right dose, patients were asked to report how they had taken the medicine.

1.3.2 Statistical Analysis

Statistical analyses were carried out using simple frequency distribution, percentages and chi-square analysis to study relationships. Graphs and tables were employed to present the results.

We subjected some potential risk factors for adverse events, e.g., age, gender, pregnancy, use of traditional medications, and presence of comorbid conditions (e.g. respiratory tract infections, epilepsy, diabetes, HIV, and diarrhea) to the statistical analysis using multinomial logistic regression.

2 Results

2.1 General Characteristics

A total of 3,010 patients (Table 2) were enrolled in the programme. A total of 2,904 (96.5 %) returned for the first

follow-up visit, while 59 (2.0 %) returned for the second follow-up visit only. Twenty-four (0.8 %) were lost to follow-up. The total number of patients seen at follow-up was 2,963 (98.4 %). A total of 1,919 (63.7 %) patients received AA while 1,068 (35.5 %) received AL. A further 23 (0.8 %) patients attended follow-up clinics, but were not included in the analysis because of missing values.

Patients in the AL group were significantly younger in the $0 < 5$ year ($p < 0.0001$) and $5 < 15$ year ($p = 0.0005$) age groups. Weights were higher in the 15 to <25 year age group ($p < 0.001$) for AA compared with AL. The mean weight overall for AL was lower than AA at a statistically significant level ($p = 0.0230$). The % distribution of male and female who received AL as medication was 42.9 and 59.1 as against 43.8 and 56.2 respectively for those who received AA.

2.2 Pregnancy

As at the time of enrolment, 96 (3.2 %) participants were pregnant women. The distribution across the two groups was 57 (5.3 %) and 39 (2.0 %) for AL and AA, respectively.

2.3 Clinical Characteristics at Presentation

Table 3 shows the symptoms and signs at presentation, with the five most common being, respectively for AL and AA, fever 914/1,580 (26/24.5 %), headache 506/1,131 (14.4/17.5 %), loss of appetite 382/463 (10.9/7.2 %), bitter taste in the mouth 262/549 (7.4/8.5 %), and joint pain 154/450 (4.4/7.0 %). The mean number of clinical symptoms and signs per patient was 3.3 for AL and 3.4 for AA.

2.4 Comorbid Conditions

The comorbidities observed during the study are as shown in the figure. Respiratory infection, hypertension, HIV/AIDS, and chronic diarrhoea were the most common (Fig. 1).

2.5 Adverse Events

Overall 1,482 events were recorded, of which 176 were recorded among the AL group and 1,306 among the AA group, giving event rates for AL and AA of 16.6 and 68.7 % respectively.

Table 4 compares the rates of events for AL and AA. There was a much higher event rate for AA. Mann-Whitney non-parametric tests for the two samples show a significant difference ($p < 0.0001$).

The most common types of events were neurological and alimentary. Neurological events were more common in the AA group. Body weakness was the predominant event in both groups. The nature of this event is uncertain. It has been included under the musculoskeletal events, though it could be neurological. Bleeding events were more frequent among the AL group (epistaxis 2, haematuria 1).

Of the events reported at the second follow-up visit, there were 31 recorded among the AL group and 323 among the AA group, which constituted 17.8 and 24.9 % of the total events for each ACT respectively. One event (sleeplessness) showed a trend to later onset. This occurred in both the AL and AA groups in a ratio of 2:1 approximately between the first and second follow-up visits.

2.6 Outcome of Events

Eighty-seven percent (1,278) of all the events had either cleared or subsided in both groups of patients by the second follow-up. Three (0.16 %) patients in the AA group had serious life-threatening adverse events with one (0.05 %) of them requiring hospital admission. They were all recorded in children. Two of these children had twitching/foaming in the mouth (in keeping with convulsive disorders), while the third child had severe anaemia that had to be transfused during ACT therapy. It was not clear whether this was due to the malaria or an ADR.

Table 2 Patient follow-up

Patients	AL (%)	AA (%)	Total (%)
Total numbers of patients enrolled	1,068 (35.5)	1,919 (63.8)	3,010 (100)
Numbers of patients who returned for 1st FUV	1,049 (98.2)	1,855 (96.7)	2,904 (96.5)
	(% of AL)	(% of AA)	(% of total)
Numbers of patients who returned for the 2nd FUV only (Missed 1st FUV, but returned at 2nd FUV appointment)	12 (1.1)	47 (2.5)	59 (2.0)
	(% of AL)	(% of AA)	(% of total)
Total numbers of patients seen at follow-up	1,061 (99.3)	1,902 (99.1)	2,963 (98.4)
	(% of AL)	(% of AA)	(% of total)
Numbers of patients who were lost to follow up	9 (0.8)	15 (0.8)	24 (0.8)
	(% of AL)	(% of AA)	(% of total)
Patients where type of ACT was not recorded			23 (0.8)
			(% of total)

FUV first follow-up visit, *AL* artemether–lumefantrine, *AA* artesunate-amodiaquine, *ACT* artemisinin-based combination therapy

Table 3 Clinical characteristics at presentation[a]

	Symptoms at presentation	AL $n = 3,517$		AA $n = 6,456$	
		No.	%	No.	%
1	Fever	914	26.0	1,580	24.5
2	Headache	506	14.4	1,131	17.5
3	Bitter taste/sore Mouth	262	7.4	549	8.5
4	Loss of appetite	382	10.9	463	7.2
5	Joint pain	154	4.4	450	7.0
6	Body weakness	157	4.5	412	6.4
7	Body pains	133	3.4	310	4.8
8	Abdominal pain	147	4.2	286	4.4
9	Cough	233	6.6	250	3.9
10	Vomiting	160	4.5	210	3.2
11	Dizziness[b]	67	1.9	149	2.3
12	Chills and rigours	86	2.4	138	2.1
13	Nausea	65	1.8	116	1.8
14	Diarrhoea	75	2.1	107	1.7
15	Any other	176	5.0	305	4.7

% = % of total number of symptoms for each ACT

AL artemether-lumefantrine, *AA* artesunate + amodiaquine

[a] Listed in order for patients receiving AA

[b] Dizziness refers to lightheadedness, unsteadiness, or vertigo

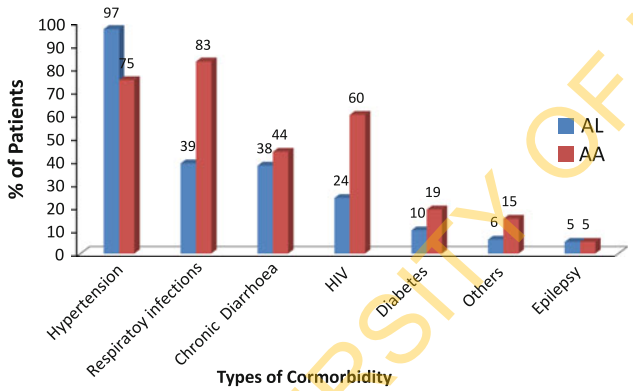

Fig. 1 Proportions of patients with comorbidities at presentation in the artemether/lumefantrine (AL) and artesunate/amodiaquine (AA) treated groups

2.7 Clinical Effectiveness of the ACTs

Although parasitological clearance was not assessed in this study, clinically, by day 7, 1,800 (94.6 %) of the patients followed up in the AA group recovered from the presenting symptoms of malaria completely, as well as 1,009 (95.1 %) of the patients in the AL group. These symptoms presumably were those of malaria even though no microscopy or rapid diagnostic tests were used to confirm the diagnoses. It is possible that a proportion of these patients may not have had malaria at all.

2.8 Risk Factors

Some potential risk factors were subjected to regression analysis (Table 5). Age group 15 to <25 years, the use of AA, and pregnancy showed statistical significance for AEs (p-values 0.041, <0.001 and 0.040 respectively). The use of AA had the strongest association.

All the pregnant patients were in their second or third trimester. The study follow-up period was not long enough to allow assessment of the outcome of pregnancy.

3 Discussion

Medicines are used all over the world and in all continents for prevention, diagnosis, or treatment of disease, or for palliative care. These medicines may have adverse reactions and therefore need to be monitored in order to reduce their potential for harm and increase their benefits.

Artemisinin and its derivatives are remarkably well tolerated. Large-scale safety monitoring or pharmacovigilance is often talked about in the context of antimalarial drugs, but it is difficult, and it is not often done [24]. Most antimalarial safety data therefore have been gathered in clinical trials evaluating treatment of single episodes of malaria. However, in practice, African children are treated for malaria repeatedly, raising concern for toxicity resulting from repeated short-term exposures [25]. The relatively small sample size of clinical trials may also limit the ability to detect uncommon events [17]. As deployment increases the ACTs will be used with increasing frequency in individuals. More information on safety with frequent dosing is needed. Cohort event monitoring is an active form of pharmacovigilance that is particularly concerned with the post-marketing surveillance of adverse events, with the main objectives being to determine the adverse event profile of monitored medicines and early detection of previously unrecognised ADRs [26].

Though artemisinin derivatives appear to be remarkably safe in clinical practice and have been used to treat millions of malaria patients worldwide without serious problems being identified [27, 28], in many countries these drugs are being deployed in large quantities and most often as over the counter (OTC). Post-marketing surveillance is therefore important to determine their use and safety in the particular user population. This pilot CEM programme had a very high follow-up rate. We looked at the pattern of adverse events reported by patients who were treated with AA and AL for a presumptive diagnosis of malaria. The events observed and their rates are listed in Table 4. Most patients begin to experience adverse events by day 1 after medication, and this worsens and peaks by day 2. Thereafter, the symptoms tend to subside or completely resolve.

Table 4 Adverse events recorded at 1st and 2nd visits. Figures are numbers (%)

Patients	AL $n = 1,061$	AA $n = 1,902$
Total no. of events	176 (16.6)	1,306 (68.7)
Neurological		
Dizziness	21 (11.9)	224 (17.2)
Insomnia	11 (6.3)	77 (5.9)
Headache	20 (11.4)	47 (3.6)
Blurred vision	0	7 (0.5)
Twitching/mouth foaming	1 (0.6)	4 (0.3)
Burning sensation	2 (1.1)	2 (0.2)
Tinnitus	2 (1.1)	0
Alimentary		
Abdominal pain	15 (8.5)	93 (7.1)
Anorexia	15 (8.5)	60 (4.6)
Vomiting	14 (8.0)	133 (10.2)
Nausea	7 (4.0)	28 (2.1)
Diarrhoea	4 (2.2)	34 (2.6)
Bitter taste/sore mouth	2 (1.1)	6 (0.5)
Dyspepsia	0	4 (0.3)
Musculoskeletal		
Body weakness	44 (25)	478 (36.6)
Body pains	6 (3.4)	69 (5.2)
Joint pain	1 (0.6)	9 (0.7)
Other		
Fever	8 (4.5)	20 (1.5)
Rashes/itching	6 (3.4)	17 (1.3)
Weight gain	11 (6.3)	12 (0.9)
Palpitations	0	4 (0.3)
Anaemia	0	2 (0.2)
Bleeding (epistaxis, haematuria, gums)	3 (1.7)	0

AL artemether–lumefantrine, *AA* artesunate + amodiaquine

This finding suggests that patients should always be counseled and encouraged to complete their medications as the expected reactions are most often short-lived and not severe. A few had paracetamol prescribed to alleviate their symptoms; otherwise, they might have changed therapy. Adverse events were the reasons given by some of the patients for failing to return for follow-up and so they had to be visited at home. It is possible that adverse events have been reasons for changed or inadequate therapy when using ACTs in Nigeria.

The events recorded among Nigerians are similar to those seen in the literature and controlled studies. The most common AEs seen were general body weakness, dizziness, vomiting, abdominal pain, insomnia, body pains, and anorexia [29–33]. Moreover, the side effects from the artemisinin class of medications are similar to the symptoms of malaria: nausea, vomiting, anorexia, and dizziness [16]. Since acute malaria is associated with symptoms of lethargy, nausea, vomiting, abdominal pain, dizziness, headache, muscle pain, and sometimes diarrhoea, it is often difficult in the acute phase of the disease to distinguish disease effects (Table 3) from possible drug effects. In this study, we carefully recorded only new or worsening events so as to help differentiate the malaria symptoms from AEs associated with treatment.

Patients who received AA had a much higher rate of adverse events than those who received AL. If these were largely disease effects, a similar rate for both would be expected. There is no apparent confounding or bias in the collection or recording of events data, which could explain the striking difference, nor in the patient demographics or selection of patients or method of treatment. The only different approach to treatment was that some patients were given a split daily dose of AA in order to try and reduce the possibility of adverse reactions. All events were recorded for both ACTs in the same clinics by the same staff. Some of the reactions could be attributable to the amodiaquine component of AA since documented side effects of 4-aminoquinoline antimalarial agents (including amodiaquine) are dizziness, general body weakness, blurring of vision, abdominal pain, and fatigue [16, 34]. AL has also been shown in the literature to cause abdominal pain [34–38]. Our findings are in keeping with those of Catherine Maiteki-Sebuguzi et al, in which at 14 days of follow-up, AQ (amodiaquine) +SP treatment was associated with a higher risk of anorexia, weakness, and subjective fever than treatment with AL [29]. Recently there has been controversy over extrapyramidal events observed with AA and these are thought to be caused by AQ [39, 40]. There are a small number of reports of 'twitching' in the reported events, which could possibly be dystonic reactions. However, neurological events are prominent and have a much higher rate with AA, with a rate ratio of 5.6. Neurotoxicity in experimental animals has been associated with the use of intramuscular injections of artemether or arteether [16, 41]. Also neurotoxicity has been observed with parenteral doses close to those used in the treatment of malaria and has given rise to concerns that similar effects could occur in humans [16, 42]. In this study, three children had seizure-related episodes after receiving AA, but no other apparent signs of neurotoxicity; as causality assessments were not done, these could be related to the malaria illness or some other cause.

Mild blood abnormalities with AL have been noted in our study. We observed one patient had haematuria, one epistaxis, and one bleeding gum requiring prolonged observations. Two patients on AA had severe anaemia, one requiring referral for blood transfusion. A rare but serious adverse effect such as reticulocytopaenia has been related to artemisinin-based combination therapy [15, 16, 43]. In early Chinese studies, neutropenia was reported [27].

Table 5 Potential risk factors for adverse events assessed by multinomial logistic regression

Effects of risk factors on AEs	ß	SE	*p* value	CI (95 %)
Age (years)				
0–<5	2.165	445.130	0.739	0.175–3.126
5–<15	8.278	443.216	0.375	0.195–1.849
15–<25	−1.575	1.157	0.041*	0.320–0.976
25–<35	−0.072	1.282	0.730	0.642–1.365
>35	−0.00	0.0	–	–
Weight range (kg)				
0–<5	−0.206	4.808	0.966	1.063–6.578
5–<15	−0.473	0.641	0.460	0.177–2.189
15–<25	−0.239	0.516	0.643	0.286–2.166
25–<35	−0.137	0.591	0.817	0.274–2.780
>35	0.00	–	–	–
Gender (male)	0.877	0.30395	0.092	0.625–1.232
Drug				
AA	29.959	4,791.770	0.000*	4.390–2.395
AL	28.696	–	–	2.900–2.900
Pregnancy	0.357	1.229	0.040*	0.032–3.977
Traditional medicines	−8.951	339.336	0.979	1.858–9.039
Diabetes	11.671	1,800.99	0.995	0.000–0.000
Hypertension	7.831	150.177	0.958	3.716–1.704
Respiratory tract infections	7.213	262.231	0.978	8.344–2.207
HIV	6.91	133.233	0.958	4.180–2.633
Epilepsy	9.896	724.269	0.989	0.000–0.000
Diarrhoea	9.875	343.517	0.977	7.705–4.902

AL artemether-lumefantrine, *AA* artesunate-amodiaquine, *CI* 95 % confidence interval, *SE* standard error of the mean

* Significance level for $p < 0.05$

Haematuria could be associated with haemoglobinuria or haemolysis from G6PD deficiency, which could not be assessed in our study. However, haemoglobinuria has been reported in clinical trials with artemether and artesunate [44, 45], and a case of significant liver inflammation has been reported in association with prolonged use of a relatively high dose of artemisinin used for an unclear reason (the patient did not have malaria) [46, 47]. These findings were not observed in our study.

The administration of antimalarial treatments in patients with concomitant illness, including HIV/AIDS, tuberculosis, and malnutrition, is a concern as one expects the presence of these illnesses with complex treatments to have the potential to cause drug-drug interactions and perhaps drug-disease interactions. In this study, 26 % of the cohort had comorbidity requiring co-administration of medications other than antimalarials, the common ones being for hypertension (5.7 %), URTI (4.1 %), diarrhoeal illnesses (2.8 %), HIV (2.7 %), and diabetes (1.0 %). Also 2.8 % of patients were pregnant. Of all these factors, only pregnancy was shown to be a statistically significant ($p = 0.040$) risk factor for adverse events. This is rather surprising as studies have shown that ACTs may have lower efficacy in pregnancy because drug concentrations were seen to be reduced during pregnancy [48]. It is also gratifying to note that despite the severity of some of the events, such as dizziness, general body weakness, vomiting, etc., most resolved within the 7-day follow-up period (mean duration of events is 3 days). This is particularly encouraging in a cohort of 3,010 and the different geographical backgrounds of the patients. A cohort of 3,000 patients should have a 95 % chance of identifying an event with an incidence of 1:1,000 [48]. The very small number of serious events indicates that ACTs are well tolerated among Nigerians, and the short duration of the events is reassuring of their safety. Although the CEM programme was observational and based on presumptive diagnosis of uncomplicated malaria rather than a clinical trial with parasitological monitoring, we observed that the clinical response (reduction of body temperature and resolution of malaria symptoms) was high and is comparable to the efficacy of ACT in case-controlled studies [36, 38].

Finally, no standardised system for adverse event monitoring in antimalarial clinical trials currently exists,

and the approach to monitoring may differ between sites. Guidelines for use of laboratory testing in antimalarial drug safety monitoring are also lacking. In this study, events were actively assessed at all follow-up visits with interviews and a standard physical exam at standard intervals. Although time intensive, the system allowed events related to drug tolerability to be captured. Relying on spontaneous reporting by participants or assessing only for serious adverse events and laboratory abnormalities will not produce a complete risk profile and may overlook some important hazards.

3.1 Challenges/Limitations of the Study

Two follow-up visits seem unnecessary and the ongoing programme aimed at a cohort of 10,000 patients will have a single follow-up at 7 days.

The splitting of the dose of AA by some physicians (to twice daily instead of once daily) may possibly have reduced the rate of adverse events with AA. There was incomplete filling of some sections of the questionnaires (e.g., 44 patients have no gender indicated and in some, information on the age and weight of patients were missing), but these missing values are low in number and should not affect the results.

The sample size of the pilot would not have the power to detect uncommon events reliably.

4 Conclusion

We can conclude that this pilot study has demonstrated the power of CEM to provide AE rates. We observed that ACTs produced AEs among the Nigerian population that were similar to the AE profile of ACTs reported in the literature, including general body weaknesses, dizziness, vomiting, loss of appetite, and abdominal pain, etc. These AEs might result in change of therapy among Nigerians. However, these AEs are generally short lived with a mean duration of illness of 3 days in this programme.

Additionally, serious life-threatening events are not common. These suggest that the ACTs monitored in this programme are well tolerated among Nigerians with a presumptive diagnosis of uncomplicated malaria. It is hoped that the ongoing scaling up of the programme aiming at assessing 10,000 patients will produce clearer and more complete information on which to base policy decisions.

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