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Original article

Knowledge of artemisinin combination therapy and malaria status among residents of a malaria endemic community North-Central Nigeria

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Abstract
This study investigated the knowledge of Artemisinin Combination Therapy (ACT) and malaria status of inhabitants of a malaria endemic region and also determined if ACT use confers a reduction in malaria outcome. A cross-sectional study was conducted in Ilorin metropolis, North-Central Nigeria. Quantification of malaria parasite in venous blood was carried out using Giemsa-stained thick blood film. Respondent's bio-data, socio-demographic factors, knowledge of malaria and ACTs were obtained using a pre-tested questionnaire. Two hundred and nine participants (68; 32.5% males and 141; 67.5% females) were recruited for the study. Malaria prevalence increased with increasing age; viz; 35-45 years (70.4%) with a remarkable decline (51.0%) at age-group >45years. Educational status significantly correlated with infection rate ($p=0.09$). Large family size and resting together at night were determinants of disease occurrence ($p>0.05$). Knowledge of malaria and ACTs among respondents was 96.7% and 65.6% respectively. Knowledge of ACT significantly differed with knowledge of malaria and its mode of transmission ($p<0.05$). Knowledge of ACT was not dependent on gender, age-group, ethnicity, occupation, family size and resting at night together. However, this was comparable among those with complete secondary education (67.1%), primary education (65.2%) and illiterates (56.8%) ($p<0.05$). Malaria prevalence among respondents who had knowledge of ACT was higher (57.7%) compared to those who do not (54.2%; $p>0.05$). Knowledge of ACTs and infection intensities revealed that more respondents with adequate knowledge of ACT were moderately infected (54.4%), likewise for participants with dearth of ACT knowledge (41.0%; $p=0.223$). Prevalence of infection based on the choice of ACT indicated a least prevalence (42.9%) among those that used a combination of artemether-mefloquine and artemether-lumefantrine, compared to artemether-mefloquine (60.4%) and artemether-lumefantrine (57.4%; $p=0.714$). Despite the vague knowledge of ACT use and its importance in malaria therapy, the disease still persists in this region. The perceived knowledge is insignificant, mass awareness is encouraged and self-medication should be discouraged.
Keywords: Malaria, Knowledge, Artemisinin Combination Therapy, North Central, Nigeria.

Introduction

Malaria remains a life-threatening parasitic disease responsible for approximately 429 000 deaths (range 235 000–639 000) worldwide. The disease is primarily transmitted to man by the bite of an infected female *Anopheles* mosquito

during the insects' blood meal. It may also be spread by transfusion of blood from *Plasmodium*-infected people or by the use of contaminated needles or syringes. People with untreated or inadequately treated malaria are sources of infection to mosquitoes that bite them (WHO, 2016). The national Malaria Control Program (MCP) has identified three main strategies viz; the development of vaccine, vector control and drug therapy. Early diagnosis and prompt treatment of confirmed cases with effective drugs remains a priority and part of a worldwide comprehensive malaria control and elimination strategy (Douglas *et al.*, 2010; WHO, 2010, 2012, 2016).

Over the years, malaria treatment has changed substantially (Achan *et al.*, 2011). Resistance to chloroquine (CQ) and anti-folate combination therapy which utilized sulfadoxine and pyrimethamine (SP) combination, have paved way for more efficacious artemisinin combination treatments (ACTs), as first-line therapy for uncomplicated falciparum malaria (Beer *et al.*, 2009; Yeka *et al.*, 2009; Phyo *et al.*, 2012). ACTs are safe and remarkably well tolerated. However, problems of affordability, limited knowledge and public awareness on the concept of combination therapy (CT) and safety of use in pregnancy are still major challenges mitigating its use in malaria control (Mutabingwa, 2005; Johnbull and Ume, 2013; Yakasai *et al.*, 2015). By 2010, 84 countries had adopted ACT, with 60 countries providing ACT free-of-charge to all ages in the public sector and eight have piloted the provision of subsidized ACT in the private sector through the Affordable Medicines Facility-malaria (AMFm) (Matowe and Adeyi, 2010; Amzat, 2011; WHO, 2012).

The basic use of ACTs is to combine any long half-life drug such as mefloquine, amodiaquine, piperaquine, pyrimethamine/sulfadoxine or lumefantrine with fast acting drug (artemisinin), to achieve effective and rapid eradication of malaria parasite (Egunsola and Oshikoya, 2013; Jadhav and Shinde, 2014). Studies on efficacy of currently available ACTs in the treatment of uncomplicated malaria in some endemic countries of sub-Saharan Africa indicated that amodiaquine-artesunate (ASAQ), dihydroartemisinin-piperaquine (DHAPQ) and artemether-lumefantrine (AL) had excellent efficacy due to low risk of recurrent infections (Karunajeewa *et al.*, 2008; Group, 2011). In recent times, resistance to ACTs is also emerging since the malaria parasites began exhibiting acquired resistance towards the long half-life drugs used in combination therapy (Phyo *et al.*, 2012).

A study on knowledge and perception of patent medicine dealers on ACT and compliance with current antimalarial therapy in rural Nigeria identified that most of the dealers had proper understanding of the drug, adequate drug regimen but poor understanding of the recommended time of administration (Chukwuocha *et al.*, 2013; Nduka *et al.*, 2013). Recent studies have suggested that mass advocacy and enlightenment campaign will certainly contribute to knowledge, therapy and reduce ACT abuse among inhabitants of endemic communities (Vundule and Mharakurwa, 1996; UM *et al.*, 2007; Suleiman, 2014). The use of artemether-lumefantrine at home and community level was found feasible with adequate training of community medicine distributors and caregivers (Ajayi *et al.*, 2008). Documented literatures on the association between knowledge of ACT and malaria outcome in our settings is scarce. It becomes exigent to verify current knowledge and perception of the populace. Therefore, we assessed the knowledge, attitude and practice about artemisinin combination therapy as well as determined if ACT use confers reduction in malaria episodes among residents in a malarious zone, Ilorin, North Central Nigeria.

Materials and methods

Study area

Ilorin, the capital of Kwara state is an urban area found in the North Central zone of Nigeria. It is located on longitude 4º35'E and latitude 8º 35'N. It covers an area of about 150 km^2 with an estimated population of 766,000 people (NPC, 2009). The region is associated with intense rainfall which spans from April to October, while dry season last from October to March. Daily temperature ranges between 23ºC and 37ºC. Inhabitants are predominantly civil servants, traders, farmers and students.

Study design and Data collection

A cross-sectional study involving four randomly selected public and private hospitals was conducted. The target populations were patients suspected of symptomatic malaria. A structured questionnaire comprising of two parts was developed. The first part was used to obtain socio-demographic details (age, sex, ethnic group, educational status, occupation and family size) while the second part was used to assess knowledge about malaria and its treatment practices as regards ACTs and its use. Three millilitres of blood was collected from each participant via venipuncture into an Ethylene Diamine Tetracetic Acid (EDTA) bottle using a 5ml syringe.

Inclusion criteria: Participants were out-patients not less than 16 years of age.

Screening for malaria parasite

Blood samples were screened for the presence of malaria parasites. Thick blood films were made on clean microscope slides and allowed to air-dry. Each slide was stained with 10% Giemsa solution for 45minutes, rinsed with clean water and air-dried. They were then examined under oil immersion microscope. A blood film is regarded as positive if it indicates the presence of asexual blood stage of *Plasmodium* species. Any film with no parasite after examining at least 200 fields was considered negative. The number of parasite per microliter of blood was estimated following the recommendations of Greenwood and Armstrong (Greenwood and Armstrong, 1991). Parasite density was classified into light, moderate and heavy following the guidelines of WHO (WHO, 2010).

Ethical Consideration

Ethical approval for the study was obtained from the University of Ilorin ethical review committee as part of a previous study protocol on 10th December, 2012 with protocol approval number: UERC/ASN/2012/221. The management/head of each hospital was duly notified about the study protocol. Likewise, consent of volunteer patients was sought before enrolment in the study.

Statistical Analysis

Data was analysed using the Statistical Package for Social Sciences (SPSS) version 16 software program. Relative frequency and percentage of variables was measured using descriptive statistics. Chi-squared (χ^2) test was used to determine the statistical significance of the variations in relative frequencies. The level of statistical significance was set at $P<0.05$.

Results

A total of two hundred and nine (209) participants comprising of 68(32.5%) males and 141(67.5%) females were recruited for this study. Of these, 39(57.4%) males and 79(56.0%) females were infected with malaria parasite. Stratification into age-group showed an increased prevalence with increasing age with a decline at age group >45years. Age group 36-45years had the highest prevalence (70.4%) while >45years had the lowest (51.0%). According to ethnicity, significantly higher prevalence of infection was observed among the Hausas (69.2%) and Igbos (65.0%) than Yoruba (48.5%) $p<0.05$. The level of education was a determinant of infection as least prevalence was recorded among those who completed secondary school (52.3%), $p=0.09$. Farmers had the higher prevalence (64.3%) than wage earners (58.6%) and unemployed (54.2%), although not comparable $p=0.529$. Respondents from Large families (size >6) had a higher malaria occurrence (60.5%), although not significantly correlated. In like manner, resting together at night was a determinant of disease occurrence. However, it was not statistically significant.

In Table 2, 202 (96.7%) participants acknowledged that they have heard of malaria. Only 193(92.3%) knew the cause while 16(7.7%) ascribed it on other sources. Interestingly, 15(7.2%) claimed they have never had malaria while 194(92.8%) admitted to have experienced the disease. One hundred and thirty five (66.8%) participants have heard of malaria and knew ACT, but only one subject (14.3%) who claimed to know ACT had never heard of malaria. Knowledge of ACT significantly differed among those who have heard of malaria and those who have not, $p=0.015$. Likewise, knowledge of ACT among those who knew the cause of malaria significantly differed from

those who do not, p=0.011. Of the 194(92.8%) who had experienced malaria, only 130(67.0%) knew about ACT while 63(32.5%) were found to be deficient. A higher proportion (73.0%) of those that treated malaria in less than 1 month had more knowledge of ACT compared to those who treated <3months (63.3%) and >6months (59.3%).

Knowledge of ACT was not dependent on gender, age-group, ethnicity, occupation, family size and resting at night together (Table 3). However, it significantly differed with the educational status of respondents as those who completed secondary school had more knowledge of ACT (67.1%) compared to those who completed primary school (65.2%) and the illiterates (56.8%), p=0.047.

Table 1: Malaria status of the inhabitants

Factor	*No examined (%)*	*No infected (%)*	*Malaria status*			
			Mild	*Moderate*	*Heavy*	*p-value*
Gender						
Male	68(32.5)	39(57.4)	11(28.2)	15(38.5)	13(33.3)	0.142
Female	141(67.5)	79(56.0)	20(25.3)	44(55.7)	15(19.0)	
Age group						
16-25	85(40.7)	41(48.2)	12(29.3)	16(30.0)	13(31.7)	0.530
26-35	46(22.0)	32(69.6)	8(25.0)	19(59.4)	5(15.6)	
36-45	27(12.9)	19(70.4)	6(31.6)	10(52.6)	3(15.8)	
>45	51(24.4)	26(51.0)	5(19.2)	14(53.8)	7(26.9)	
Ethnic group						
Yoruba	101(48.3)	49(48.5)	8(16.3)	28(57.1)	13(26.5)	0.014
Hausa	13(6.2)	9(69.2)	1(11.1)	7(77.8)	1(11.1)	
Igbo	20(9.6)	13(65.0)	7(53.8)	1(7.7)	5(38.5)	
Others*	75(35.9)	47(62.7)	15(31.9)	23(48.9)	9(19.1)	
Educational status						
Pry sch.	23(11.0)	16(69.6)	0(0.0)	12(75.5)	4(25.0)	0.090
Sec. sch.	149(71.3)	78(52.3)	25(32.1)	34(43.6)	19(24.4)	
Illiterate	37(17.7)	24(64.9)	6(25.0)	13(54.2)	5(20.8)	
Occupation						
Wage Earner	87(41.6)	51(58.6)	12(23.5)	29(56.9)	10(19.6)	0.529
Farming	14(6.7)	9(64.3)	3(33.3)	5(55.6)	1(11.1)	
Unemployed	107(51.2)	58(54.2)	16(27.6)	25(43.1)	17(29.3)	
Family size						
<6	123(58.9)	66(53.7)	16(24.2)	32(48.5)	18(27.3)	0.578
> 6	86(41.1)	52(60.5)	15(28.8)	27(51.9)	10(19.2)	
Rest at night together						
Yes	143(68.4)	89(62.2)	25(28.1)	44(49.4)	20(22.5)	0.698
No	66(31.6)	29(43.9)	6(20.7)	15(51.7)	8(27.6)	

Key: Mild: 1- 499; Moderate: 500- 9,999; Heavy: >10,000 asexual parasites/μL

Table 2: Knowledge of ACT with respect to signs, symptoms and treatment of malaria

Typical questions		*Knowledge of ACT* (%)		
	Frequency (%)	Yes	No	p-value
Have you heard of malaria before				0.015
Yes	202(96.7)	135(66.8)	66(32.7)	
No	7(3.3)	1(14.3)	6(85.7)	
Transmission route				0.011
Mosquitoes	193(92.3)	131(67.9)	61(31.6)	
Others	16(7.7)	5(31.2)	11(68.8)	
Have you had malaria before				0.095
Yes	194(92.8)	130(67.0)	63(32.5)	
No	15(7.2)	6(40.0)	9(60.0)	
Last medication for malaria				0.159
>6months ago	86(41.1)	51(59.3)	35(40.7)	
About 3months ago	49(23.4)	31(63.3)	17(34.7)	
<1month ago	74(35.4)	54(73.0)	20(27.0)	

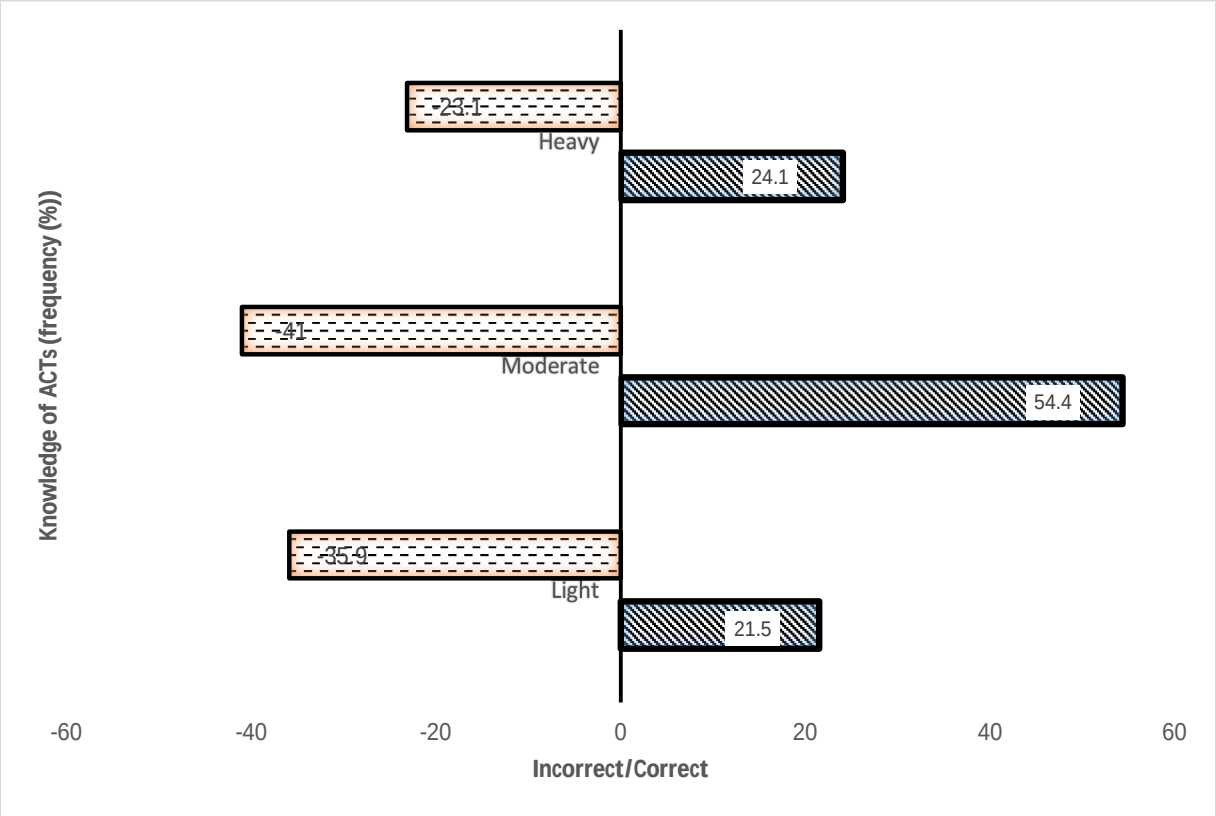


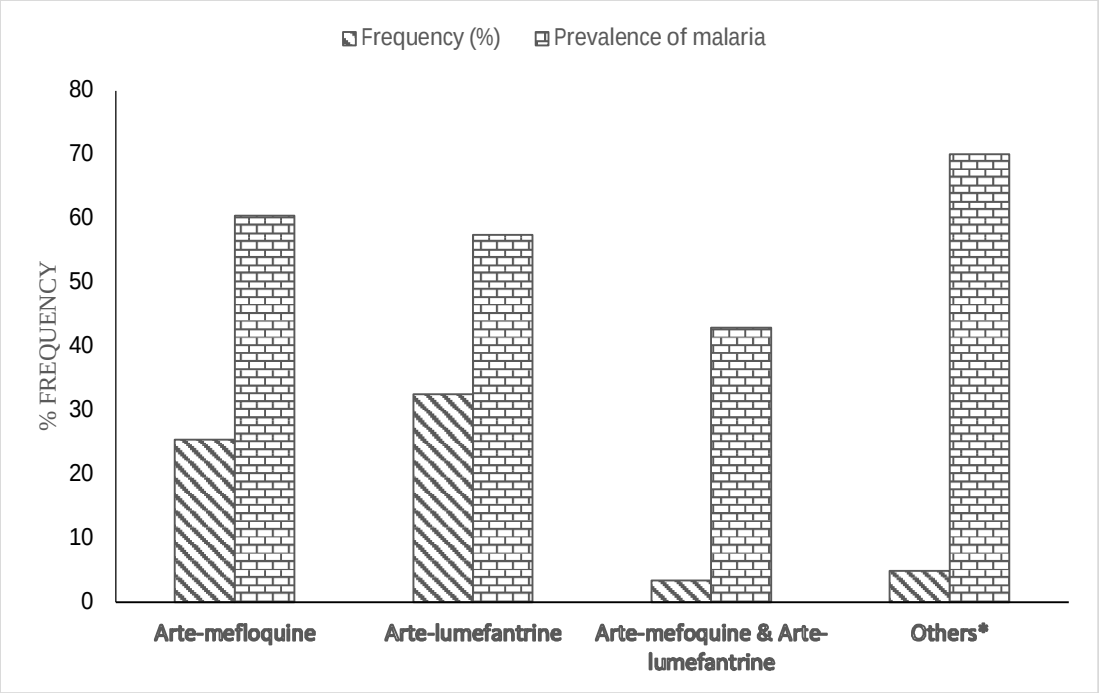
Figure 1: Knowledge of ACTs with respect to current malaria status of the inhabitants (p=0.223)

Table 3: Knowledge of Artemisinin Combination Therapy (ACT)

Factor	*No examined (%)*	*Knowledge about ACT*		
		Correct	*Incorrect*	*p-value*
Gender				0.104
Male	68(32.5)	38(55.9)	30(44.1)	
Female	141(67.5)	98(69.5)	42(29.8)	
Age group				
16-25	85(40.7)	63(74.1)	22(25.9)	0.207
26-35	46(22.0)	29(63.0)	17(37.0)	
36-45	27(12.9)	15(55.6)	12(44.4)	
>45	51(24.4)	29(56.9)	21(41.2)	
Ethnic group				
Yoruba	101(48.3)	71(70.3)	29(28.7)	0.558
Hausa	13(6.2)	8(61.5)	5(38.5)	
Igbo	20(9.6)	10(50.0)	10(50.0)	
Others*	75(35.9)	47(62.7)	28(37.3)	
Educational status				
Pry sch.	23(11.0)	15(65.2)	7(30.4)	0.047
Sec. sch.	149(71.3)	100(67.1)	49(32.9)	
Illiterate	37(17.7)	21(56.8)	16(43.2)	
Occupation				
Wage Earner	87(41.6)	51(58.6)	35(40.2)	0.182
Farming	14(6.7)	7(50.0)	7(50)	
Unemployed	107(51.2)	78(72.9)	29(27.1)	
Family size				
Less than six	123(58.9)	83(67.5)	39(31.7)	0.445
More than six	86(41.1)	53(61.6)	33(38.4)	
Rest at night together				
Yes	143(68.4)	95(66.4)	48(33.6)	0.301
No	66(31.6)	41(62.1)	24(36.4)	

Table 4: Knowledge of ACTs with respect to last malaria medication of the inhabitants

	Malaria status with respect to last malaria medication (%)		
Knowledge of ACTs	*>Six months ago*	*3months ago*	*<1month ago*
Correct	51(37.5)	31(22.8)	54(39.7)
Incorrect	35(48.6)	17(23.6)	20(27.8)
p-value	0.159		



*4-aminoquinolines: Amodiaquine + chloroquine

Figure 2: Choice of ACT Drug use and malaria outcome among the inhabitants

Individuals with knowledge of ACTs had higher disease prevalence (57.7%) compared to those who do not (54.2%), p=0.367. Also, a comparison of knowledge of ACT with intensity of infection among participants showed that 43(54.4%) of those who indicated correct knowledge of ACT had moderate infection. Among those who lack knowledge of ACT, 14(35.9%) had light infection, 16(41.0%) showed moderate infection with only 9(23.1%) severely infected, p=0.223 (Table 4).

The knowledge of ACT among the studied population did not differ significantly with respect to last malaria medication, p=0.159. Fifty four (39.7%) of respondents who treated malaria <1 month ago knew about ACT compared to those who treated 3months (22.8%) and >6months ago (37.5%). Thirty five (48.6%) of those who lack knowledge of ACT treated malaria over 6 months ago.

There were variations in malaria occurrence among respondents, depending on their choice of ACT. The least prevalence (42.9%) was observed among those who used a combination of artesunate-mefloquine and artemether-lumefantrine. Respondents who used artesunate-mefloquine recorded higher prevalence (60.4%) compared to those who used artemether-lumefantrine (57.4%). However, the highest prevalence (70.0%) was perceived among those who utilized other drugs (p=0.714) (Table 6).

Discussion

The overall prevalence of malaria (56.5%) in this study is comparable to 58% reported among children and adults in North Central Nigeria (Kolawole *et al.,* 2014) and 59% in South Western Nigeria (Ojo and Mafiana, 2005). The relatively high prevalence of infection in this study is expected probably because it is a hospital based research and malaria is known to represents a high proportion of hospital visits (Ajayi and Falade, 2006; Igboeli *et al.*, 2010; Builders *et al.*, 2013; Kolawole *et al.*, 2014). The increased prevalence with increasing age, with a marked decline at >45years, observed in this study buttresses other reports of protective immunity in older age-groups (Djimde *et al.*,

2003; Pierce and Miller, 2009; WHO, 2015; Shittu *et al.*, 2017; Tessema *et al.*, 2018).

Our study population showed a relatively high knowledge of malaria and its transmission route. This is similar to reports from some endemic regions of Nigeria (Asante *et al.*, 2010; Babamale *et al.*, 2015). The level of awareness of ACTs was higher among respondents who have heard, experienced and knew how malaria was transmitted. Hence, it can be concluded that the knowledge of malaria and its cause significantly impinge on the level of awareness of ACTs. However, the knowledge of ACT (65.6%) depicted in this study is lower compared to 82.5% reported in South East Nigeria (Chukwuocha *et al.*, 2013) and 86.3% in the Democratic Republic of Congo (Siddiqui *et al.*, 2015). Intriguingly, the individuals with good knowledge of ACTs recorded higher malaria disease prevalence compared to those who do not. The aforementioned might be ascribed to a number of factors, viz; biological and disease related factors such as immunity, age, genetics, pregnancy and interactions with other diseases (Bates *et al.*, 2004). Other supposed reasons may include socio-demographic and socioeconomic status/poverty (De Silva and Marshall, 2012), nutritional status, livelihoods, behaviour, education, and religious belief (Mbacham *et al.*, 2019). Artemisinin is a sesquiterpene lactone peroxide with an endo-peroxide bridge, and it is effective against blood and early gametocyte stages of *P. falciparum* (White, 1997; Rudrapal and Chetia, 2016). The peroxide bridge is broken down by heme or free iron manifesting in the degradation of the molecular structure of artemisinin to form the nucleophilic radical metabolites. Consequently, the free radicals, acting as an alkylating agent, will attack the macromolecular bearing electrophilic groups or centres eventually terminating in the death of the parasite (Olliaro *et al.*, 2001). No association was found between knowledge of ACT and gender, age-group, ethnicity, occupation, family size and resting at night together. Nonetheless, higher educational attainment had tremendous impact on ACT knowledge among respondents. This agrees with findings from Northern Ghana (Chatio *et al.*, 2015), but contrary to the report from Southern Nigeria (Chukwuocha *et al.*, 2013).

A higher proportion of our study population identified Artemether-lumefantrine as the most prefered and frequently used ACT. This may be attributed to increased availability, reduced price, efficacy and minimal side effect as earlier reported (Gelband *et al.*, 2004; Sayang *et al.*, 2009; Chatio *et al.*, 2015). Other ACTs used during the course of the study with insignificant efficacy were 4-aminoquinolines and Amodiaquine + chloroquine. Out of all the ACTs used, Artemether-mefloquine exerted the best antimalarial activity. The choice of ACT by respondents did not significantly confer a reduction in malaria prevalence. In spite of this, malaria outcome was observed to be higher amongst respondents who utilize other drugs outside the conventional combination therapies.

Conclusion

This study depicts that knowledge of ACTs in this locality is still low when compared to other regions of sub-Saharan Africa. We therefore recommend an intensive regular education particularly in health facilities, which will invariably result in reduction in malaria cases.

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