International Journal of Tropical Medicine 7 (4): 121-129, 2012
ISSN: 1816-3319

Unusually High Prevalence of Malaria Infection in a Tertiary Institution Setting in South-Western Nigeria

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Abstract: The study determined the prevalence of malaria in Obafemi Awolowo University community, factors that predispose them to malaria and the rate of drug resistance among subjects in a tertiary institution setting in Ile-Ife, South-Western Nigeria. Blood samples obtained from 316 subjects with febrile condition were screened for malarial parasites using thick and thin films blood smear and thereafter stained with Giemsa and Leishman stains. Microscopy of each slide was also done to determine the degree of parasitemia and types of *Plasmodium* species. Well structured questionnaires were administered to all subjects. In addition, case files of subjects were examined and reviewed to determine case series of spontaneous report of treatment failures. Subjects were followed-up for 28 days. Treatment outcome was measured by clinical and parasitological recovery after taking the prescribed drug (artesunate + sulfadoxine/pyrimethamine) combination. The subjects' age range was between 1-63 years mean age of 27.09 (SD = 15.3). The overall prevalence of detection of malaria parasite in the study population was 98.4%. Prevalence rate of malaria in both sexes was insignificant 50.2% in female and 49.8% in male. The prevalence of malaria was highest at age range 16-25 years (54.6%). Symptoms of malaria observed in subjects screened besides fever were headache (68.7%), body pain (40.8%), chills (20%) and vomiting (21.5%). The symptoms resolved proportionally with time and chills and vomiting completely resolved by day 6 in all the subjects and there was total remission of body pain by day 14. Different *Plasmodium* species namely *Plasmodium falciparum*, *Plasmodium malariae* and *Plasmodium ovale* were observed in the blood samples of the subjects screened. *Plasmodium falciparum* accounted for the highest prevalence (82.3%) and predominated in the blood samples obtained from children <5 years. Mixed infection with *P. falciparum* and *P. ovale* (10.6%), *Plasmodium malariae* (5.2%) and *Plasmodium ovale* (1.9%) were prominent in blood samples of adults >15 years of age subjects. Eighty-six subjects fulfilled the follow up criteria as follows: 67.4% (n = 58) of subjects had Adequate Clinical and Parasitological Response (ACPR) of 14-28 days after taking artesunate and antimal (sulfadoxine/pyrimethamine) while treatment failure occurred in 32.6% (n = 22) of subjects. The 7% (n = 6) of the total treatment failure recorded in this study was classified as resistance to the drug used since they returned 4-7 days after treatment with fever and presence of parasitaemia in their blood which indicated Early Treatment Failure (ETF). The remaining 25.6% returned between 7-28 days suggesting recrudescence or re-infection. The high rate of artesunate + sulfadoxine/ pyrimethamine resistance (32.6%) recorded in this study suggests its in-effectiveness in the treatment of uncomplicated malaria infection which is of epidemiological importance in the management of malaria in this community.

Key words: Prevalence rate, malaria, *Plasmodium* species, artesunate, sulfadoxine/pyrimethamine, resistance

INTRODUCTION

Malaria is a vector-borne infectious disease caused by protozoan parasites of the genus *Plasmodium*. It accounts for an estimated 500 million infections and 2.5 million deaths annually (Stauffer and Kamat, 2003). The majority of deaths are in Africa and >90% of life-threatening malaria occurs among African children (WHO/AFRO, 2001). It is reported to account for 30-50% of all out-patient care and 50% of hospital admissions in Sub-Saharan Africa (WHO/AFRO, 2001). In Nigeria it is one of the leading causes of morbidity and mortality accounting for 25-30% of infant and childhood deaths, respectively (FMH, 2002). Deaths due to malaria may be under-estimated. Until recently, there has been a reliance on the cheap antimalarial drugs like chloroquine and

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Sulfadoxine/Pyrimethamine. In 2001, the World Health Organization (WHO) recommended Artemisinin Combination Therapies (ACTs) as the first line of treatment for uncomplicated malaria (WHO/AFRO, 2001). There is now clear evidence that combining them can improve their efficacy without increasing their toxicity and with the development of highly effective artemisinin derivatives, there is renewed hope for the treatment of malaria in the form of Artemisinin-Based Combination Therapy (ACT).

Antimalarial drug resistance has emerged as one of the greatest challenges facing malaria control worldwide and has also been implicated in the spread of malaria to new areas and re-emergence of malaria in areas where the disease had been eradicated (Bloland, 2001). The emergence and spread of *P. falciparum* resistance to antimalarial drugs is now one of the greatest challenges facing the global effort to control malaria in Africa (WHO, 2003). Moreover, in recent years the situation has worsened due to the malaria parasite becoming resistant to several antimalarial drugs in circulation (Hyde, 2002; McCollum *et al*., 2006; Noedl *et al*., 2008). Resistance to antimalarial drugs can be determined *in vivo* and also *in vitro* by parasite susceptibility assays or by the use of molecular techniques including Polymerase Chain Reaction (PCR) Methods to detect genetic markers (WHO, 1996). In the absence of effective and practical preventive measures, the only current options for reducing the morbidity and mortality of malaria especially in Africa are chemoprophylaxis and chemotherapy. For this reason, the increasing prevalence of strains of *P. falciparum* resistant to antimalarial drugs poses a serious problem for the control of malaria.

Despite recent advances in malaria prevention, diagnosis and treatment, the emergence of drug resistance and changes in epidemiology of the disease present new challenges (Stauffer and Kamat, 2003). Recent studies in Kenya and Zanzibar suggest that in countries where there is a high coverage of combined effective malaria interventions, a reduction in the burden of malaria is achievable (Bhattarai *et al*., 2007; Okiro *et al*., 2007). The epidemiology of the disease varies greatly from region to region (Pasvol, 2005) hence, its relevance has become imperative.

In Nigeria, the majority of students in tertiary institutions live in overcrowded hostels and dormitories and in close proximity with one another where they are exposed to environmental factors that make them vulnerable to develop infections including malaria. This scenario therefore creates a useful and efficient opportunity to determine prevalence of malaria and development of resistance to recently developed anti-malaria drugs such as artesunate combination drug therapy hence this study.

The study therefore determined the prevalence of malaria in a tertiary institution setting and the resistance of subjects to recently introduced anti-malarials which have not been reported in this environment.

MATERIALS AND METHODS

Study area: The study was undertaken at the Obafemi Awolowo University Campus Community Ile-Ife, a semi-urban city in Osun State, South-Western Nigeria from June 2008 to February 2009 among students, staff and their dependants. The university is a home to over forty thousand people. The study was carried out at the university health centre where a significant number of the employees and students received their primary health care.

Study population: The subjects that participated in the study include students, staff and staff dependants. Subjects were selected randomly over a period of 9 months starting from June 2008 to February 2009. Only subjects who were sent to the laboratory with febrile condition for a malaria tests were selected for this study. Permission for participation was sought on voluntary basis from parents, guardians, wards of subjects as directed by ethic committee of the university.

Subject inclusion criteria: The inclusion criteria for subjects were the presence of detectable parasite in blood, absence of danger signs or signs of severe and complicated malaria, absence of other concomitant infections like pneumonia which can cause fever, no use of antimalarial 2 weeks prior to this study. The subjects were also requested to agree to compliance for successive visits. However, subjects were withdrawn from this study if they vomited the drug, unable to complete the dosage or unable to comply with the follow up visit.

Sample collection: Peripheral blood was collected from each subject by finger pricking employing a sterile lancet. The blood was either collected on the glass slide directly as the finger was pricked or collected in a numbered and labeled sequestrene tube and later examined for malaria parasite. Two different blood smears were employed. Each subject was screened for thick and thin films blood smear and thereafter stained with Giemsa and Leishman stains, respectively.

A well structured questionnaire was administered to each subject containing the following; age, packed cell volume, genotype, body temperature whether he or she has taken medication before presentation and frequency of occurrence of malaria. Patients were requested by the physicians to report back at the hospital within 4 weeks if

symptoms persisted after using the prescribed drugs. The case files of all the subjects were also examined and reviewed to determine case series of spontaneous report of the treatment failures.

Classification of response for the measurement of resistance: This was done according to standard guidelines of WHO (2003). Adequate clinical and Parasitological Response (ACPR) was recorded as the absence of detectable parasite on day 14 and 28, irrespective of axillary temperature without previously meeting any of the criteria of early treatment failure or late treatment failure.

Early Treatment Failure (ETF) was regarded as the development of danger signs or severe malaria on day 1, 2 or 3 and persistence of parasitaemia on day 4 with measured fever.

Late Treatment Failure (LTF) LTF was determined by the presence of parasitaemia and axillary temperature 37.5°C (or history of fever) on any day from day 4-28 without previously meeting any of the criteria of early treatment failure. Presence of parasitemia on any day from day 7-28 and axillary temperature <37.5°C without previously meeting any of the criteria of early treatment failure.

Treatment allocation: Subjects were treated according to their body weight. Antimal (Sulphadoxine/Pyrimethamine) 25 mg kg^{-1} in a single dose on day zero and Artesunate 4 mg kg^{-1} for 3 days.

Statistical analysis of data: The data obtained was analyzed with Statistical Package of the Social Sciences (SPSS) and reported as frequencies and percentages. Cross tabulation was used to determine the association between two variables and Chi-square was used to test the significant association between two measured values. $p \leq 0.05$ were accepted to imply significant differences between sets of data.

RESULTS AND DISCUSSION

Three hundred and sixteen subjects were recruited for this study. Table 1 shows the age distribution of the 316 subjects, 157 (49.7%) was male and 159 (50.3%) was female. Only 29 of the subjects made the records of their genotype available. About 3 (10.3%) were AA, 22 (76.0%) were SS, 3 (10.3%) were SC and 1 (3.4%) were AS. The symptoms of malaria experienced by the subjects is showed that a total of 217 experienced headaches, 129 had body pain, 68 experienced vomiting and 38 chilling.

Table 1: Treatment outcome during subjects' follow-up visit

Parasitaemia (cells/100 thick fields)	Day 0	Treatment failure ETF (4-7 days)	Treatment failure LTF (7-28 days)	Cure ACPR (Day 14-28)	p-values
1-10 (+)	40	4	6	30	0.0001
11-100 (+++)	46	2	16	28	0.0001
Total	86	6 (7%)	22 (25.6%)	58 (67.4%)	-

Rate of drug resistance: The post-treatment follow-up on days 4, 7, 14 and 28 showed that out of the 316 subjects screened, only 86 of the subjects fulfilled the follow-up criteria. The subjects were treated with a standard dose of combination of artesunate and Antimal (sulphadoxine/ pyrimethamine) (Table 1).

During the follow-up period, 6 revisited the clinic within 1 week (ETF), 22 revisited within 7-28 days (LTF) with parasitaemia and fever while 58 subjects had adequate clinical and parasitological clearance when screened 14-28 days after using the prescribed drug. Out of the total of 316 subjects, only 304 subjects' PCV status was checked. A total of 275 (90.5%) had PCV of 30 and above, 18 (5.9%) had PCV >20 while 11 (3.6%) had PCV <20 (Table 2).

Table 3 shows the profile of drugs taken by subjects. A combination of Artesunate and Antimal was administered to 211 subjects, 18 were treated with only Fansidar, 13 with Amodiaquine while 69 were treated with other drugs (including Coartem, Amalar, Lonart and others).

This study was undertaken to determine prevalence of malaria in a campus setting and the resistance of students, staff and their dependants to antimalarials used in this environment. Altogether 316 subjects whose age ranged between 1-63 years with mean age of 27.09 (SD = 15.3) participated in this study. The overall prevalence of malaria parasite in the study population was 98.4%. This value is unusually high and comparatively higher than most cases reported in this environment but similar to the high prevalence rate of 76% reported in Azia, Anambra State (Aribodor *et al*., 2003). It is however >40%

Table 2: Profile of PCV of some of the subjects screened

PCV status	Total no of subjects	No. of subjects screened (%)
≥30	304	275 (90.5)
20-30	304	18 (5.9)
<20	304	11 (3.6)
Total	304	304 (100.0)

Table 3: Profile of the drugs taken subjects

Drugs	Frequency	Percentage
Artesunate and Antimal	211	68.35
Fansidar	18	5.70
Amodiaquine	13	4.10
Others (Coartem, Amalar and Lonart)	69	21.80
Total	311	100.00

annual rate reported in Nigeria (FMH, 2005) suggesting that the prevalence of malaria in Nigeria varies in different locations. Some investigators have also reported lower values: Okonko *et al.* (2010) in Ibadan reported a rate of 50% while 59.9% rate was reported by Ojo and Mafiana (2005) in a study among children under 15 years in Abeokuta both cities located in Southwestern Nigeria Epidi *et al.* (2008) reported 51.5% among blood donors in Abakaliki, Southeastern Nigeria underscoring the variation in malaria occurrence from location to location.

The reason for the exceptionally high prevalence rate of malaria parasite in the study population may be due to the selectivity of the sample population in which only febrile subjects that were sent to the laboratory for a malaria test were selected for this study. The high prevalence rate (98.4%) obtained in this study among subjects screened suggests a large proportion of subjects that reported at the hospital had malaria infection indicated by high parasitaemia in their blood.

Malaria parasites infect humans of all age groups and of both sexes. Studies have also shown seasonal variations in the rate of infection and differences in the types of parasites depending upon the climatic conditions (Ghulam *et al.*, 2004). The current study further revealed presence of malaria parasite in both sexes even though there was a marginal difference in prevalence rate among both sexes; 50.2% in females and 49.8% in males.

Some studies have shown predominance of malaria infection in male subjects (Askling *et al.*, 2005; WHO, 2005; WHS, 2006; Atif *et al.*, 2009; Abdullahi *et al.*, 2009). However, Ibekwe *et al.* (2009) and Okonko *et al.* (2009) corroborated the finding of marginal difference of malaria infection among both sexes underscoring the fact that malaria infection vary among people in different locations. However, there does not appear to be scientific evidence linking malaria prevalence to gender.

The study also showed that malaria infection was common in all age groups screened in this environment. The highest prevalence rate occurred among subjects age range 16-25 years (54.6%) followed by the age group 36 years and above (23.8%). This finding correlated well with those reported Atif *et al.* (2009) who reported infection rate to be higher among ages 12-35 and 35-60 years of age in Pakistan but at variance with Okonko *et al.* (2010) that showed that the highest prevalence of malaria was in age group 45 years and above followed by age group 16-30 years.

Generally, there is slow acquisition of active immunity to malaria (Perlmann and Troye-Blomberg, 2002). The high rate of malaria infection in adults in this study suggests that these individuals may have lost some degree of immunity as a result of lifelong exposure. Children born to immune mothers are known to be protected against the disease (malaria) during their first half year of life by maternal antibodies primarily IgG and IgA. Plebanski and Hill (2000) have shown as children they grow older after continued exposure from multiple malaria infection over time, they build up an acquired immunity and become relatively protected against the disease. People residing in malaria-endemic regions have been reported to acquire immunity to malaria through natural exposure to malaria parasites. It has been observed that naturally acquired malarial immunity that is protective against parasites and clinical disease, results only after continued exposure to multiple infections with malaria parasites over time.

Doolan *et al.* (2009) have argued that clinical immunity generally provides protection against severe effects of malaria but fails to provide strong protection against infection with malaria parasites which generally develops first. After several years of continued exposure individuals develop immunity that limits high-density parasitaemia however, this phenomenon does not lead to sterile protection.

In this study headache and body pain produced the highest frequency 68.7 and 40.8%, respectively. Anumudu *et al.* (2006) reported that symptoms experienced during malaria episodes were loss of appetite, joint pains, dizziness, vomiting and nausea with headache being 80% in subjects followed by nausea 53%. However, Khan *et al.* (2006) reported that symptoms apart from fever were headache 79.57%, chills 52.1%, body pain 47.96% and vomiting 45.92%.

The study further revealed that all known *Plasmodium* species responsible for malaria existed in this environment with *P. falciparum* predominating (82.3%) followed by mixed infection with *P. falciparum* and *P. ovale* (10.6%), *P. malariae* (5.2%) and *Plasmodium ovale* (1.9%). The findings are at variance with report by Khan *et al.* (2006) that recorded *P. falciparum* was 58.1% among subjects screened and *P. vivax* 40.8%, *P. malariae* 1% in an adult population in their study and that by Sheikh in Quetta where 30.72 and 66.87%, respectively had *P. falciparum* and *P. vivax* among the adult population. Mockenhaupt *et al.* (2000) who examined malaria parasites in blood of Nigerian children found *P. falciparum* 62%, 16% *P. malariae,* 9% *P. ovale* with mixed infection of *P. falciparum* with other species seen in 18% of the children as diagnosed by nested PCR assay.

A study by May *et al.* (1999) observed the prevalence of *P. falciparum*, *P. malariae* and *P. ovale* infection increased with age in their study with *P. ovale* being rare in children younger than 5 years of age. Their observation supports the findings in which only *P.*

falciparum predominated in the blood samples obtained from children <5 years. Other species increased in blood samples of adults older than 15 years of age. In a study in Ibadan South-Western Nigeria, prevalence of *P. falciparum* in children was comparably high in rural area of Abanla 82.2% (n = 189) and Ibadan school children 79.7% (n = 47) and children from health centers had 74.6% (n = 106) in South-Western Nigeria. In contrast, adults have a lower prevalence of *P. falciparum* 38.4% (n = 61) in their study. The reason behind these differences in the type of species identified in different age groups was attributed to age range difference, geographical difference such as climate and topography. It has also been suggested that the course of an infection might be influenced by the simultaneous occurrence of several *plasmodial* species (Snounou *et al*., 1993). Higher than expected prevalence of mixed infections have been explained by immunosuppressive effects caused by chronic *P. falciparum* infection and have also been attributed to differences in the individual exposure. However, animal models studies have demonstrated the presence of a preceding infection with one *Plasmodium* species might be responsible for increased susceptibility to other *Plasmodium* species (Collins *et al*., 1975). Drug resistance in malaria is the ability of the parasite to survive and/or multiply despite administration and absorption of a drug given in equal doses to or higher than those usually recommended but within the tolerance limit of the subject (Bruce-Chwatt *et al*., 1986).

In the study, the subjects' response to anti-malaria drugs was measured by adequate clinical and parasitological response after day 28 of using the drugs. Data from subjects' responses revealed that the associated symptoms resolved proportionally with time (Table). Parasitaemia clearance and complete resolution of symptoms such as fever, chills, vomiting (frequent signs of malaria) and body pain in some of the subjects provided evidence for clinical efficacy of the drug used. Chills and vomiting completely resolved by day 4 in all subjects and there was total remission of body pain by day 7 although many of the subjects still complained of general weaknesses after 14 days of treatment.

There were 7% of the total treatment failure which can be classified as resistance to the drug used. Subjects returned 4-7 days after treatment with fever and presence of parasitaemia in their blood which indicates Early Treatment Failure (ETF). Malaria parasites were recovered from the blood of 25.6% (n = 22) of subjects who returned between 7-28 days (LTF) and this can be said to be recrudescence or re-infection. Since, parasite genotyping (PCR) was not done, re-infection cannot be distinguished from recrudescence.

This observation is at variance with that of other investigators Marquino *et al*. (2005) reported 100% ACPR in Peru where only one (1) out of the 94 subjects treated with combination of Artesunate plus Sulfadoxine/ Pyrimethamine (AS + SP) had a recurrence of parasitaemia on day 21 (late RI resistance) perhaps because of the relatively high efficacy of SP in this area. However, Elamin *et al*. (2005) recorded ACPR of 99.3% in the Sudan. Another two studies of this combination have been reported from the Gambia, West Africa where resistance to SP is uncommon. Both studies showed an efficacy of 100% (Von Seidlein *et al*., 2000; Doherty *et al*., 1999).

The reason for the relatively high failure rate in this study may be attributed to high resistance to sulfadoxine/pyrimethamine in this environment (Sowunmi *et al*., 2004) which could reduce the efficacy of its combination with artesunate. Others (Falade *et al*., 1997; Sowunmi *et al*., 1998; Omar *et al*., 2001) have reported increasing prevalence and intensities of resistant infections to sulfadoxine-pyrimethamine in much of Sub-Sahara Africa and the tendency for the drug to increase gametocyte carriage after its application for the treatment of malaria (Robert *et al*., 2000; Sowunmi and Fateye, 2003)

The 25.6% recrudescence rate recorded in this study within 7-28 days after treatment is comparable to the value obtained by Dorsey *et al*. (2002) in a longitudinal randomized trial in Uganda, East Africa where the efficacy of Sulfadoxine/pyrimethamine alone or with amodiaquine or artesunate for treatment of uncomplicated malaria was assessed.

The result of this current study suggests sulfadoxine/pyrimethamine plus artesunate may not be an appropriate regime for the treatment of uncomplicated malaria in this environment where substantial resistance to sulfadoxine/pyrimethamine has been documented. Therefore, there is urgent need to carry out more studies to re-evaluate the efficacy of this combination in this environment. However, as a potential alternative, a combination of artesunate and amodiaquine have proved to be effective in this environment where resistance to amodiaquine monotherapy appears to be low (Sowunmi, 2002). In Nigeria, the efficacy of artesunate plus sulfadoxine/pyrimethamine has not been fully evaluated but the efficacy of artesunate and amodiaquine had been documented and in other African countries. Sowunmi *et al*. (2005) in Ibadan, South-Western, Nigeria recorded 100% cure rate on 21-28 days, respectively accompanied by a significant reduction in gametocyte carriage following treatment. Also in another setting in Ibadan, Falade *et al*. (2008) recorded 98 and 91% cure rate on 14 and 28 days. In another part of Nigeria,

Ogbonnaya *et al.* (2010) reported 95% ACPR to artesunate-amodiaquine combination in 14 days follow-up assessment in Enugu, South-Eastern, Nigeria.

Outside Nigeria studies on Artesunate-Amodiaquine (AA) in other countries using parasitaemia clearance rates on day 14 as the primary endpoint showed 91% cure rate in Kenya, 98% in Senegal, West Africa and 98% in Gabon Central Africa. It must be borne in mind that transmission, acquired immunity, risk of infection leading to clinical disease and treatment practices are generally quite different in African countries (Bloland *et al.*, 2000).

Drug resistant parasites can be selected both when infecting parasites survive beyond the initial treatment period and when new populations of parasites are exposed to suboptimum drug concentrations (White *et al.*, 1999). Besides, the ability of anti-malarial to clear parasites could be affected by the levels of parasitaemia at presentation (White *et al.*, 1999). Therefore, subjects with high initial parasitaemia at presentation are more likely to develop recrudescence within 42 days irrespective of the drug given.

It has been observed that recrudescence in the sulfadoxine/pyrimethamine plus artesunate occurred almost exclusively >14 days after treatment when concentrations of artesunate are expected to be negligible and concentrations of sulfadoxine/pyrimethamine are reduced to those that likely select for parasites resistant to this combination (Dorsey *et al.*, 2002).

The increasing awareness of the important role played by human behavior in the epidemiology of malaria has drawn attention to the need to identify the various social and behavioral risk factors that are related to the disease and their impact not only to occurrence and transmission but also on its severity, the occurrence of drug resistance and more importantly, on its control.

From subjects' responses, relatively poor living conditions on campus such as the existence of stagnant water in blocked drainage systems around the students' hostels, overcrowding living condition, poor sanitation and bushes around the staff quarters which are effective breeding grounds for mosquitoes are undoubtedly factors that may have contributed to subjects' vulnerability to malaria. Also inadequate preventive measures such as torn or non-existence of protective insecticide mosquito nets in students halls of residence and homes of staff and other control measures may also have contributed to high rate of malaria infection in this environment.

One of the most consistent behavioral risk factors that may account for the increased occurrence and transmission of malaria in a campus setting is the periodic population movements of people in and out of the university community especially students. This can largely be attributed to the potential increased probability of exposure of the student population to the mosquito vectors. Studies in Thailand and in the Philippines have provided conclusive evidence of its major contributory role in the spread of the disease among migrant workers (Buttraporn *et al.*, 1986; Saeed and Ahmed, 2003). It is generally perceived that the closer the proximity of the living and/or work place to the vector breeding places, the higher the risk.

CONCLUSION

The results obtained in this study revealed unusually high occurrence of malaria infection among febrile subjects screened, the etiologic agents were however similar to studies reported in South-Western Nigeria and other parts of the Sub-Saharan Africa. Artesunate + Sulfadoxine/Pyrimethamine combination therapy was the drug regime frequently prescribed by the clinicians during this study but resistance to this combination was high (32.5%) suggesting this combination was not effective which portends danger to the community in treating uncomplicated malaria infections. One of the limitations of the study is that it determined only the failure rates of antimalarials among subjects whose illness was unresolved. The study did not associate this drug failure to resistance of any *Plasmodium* species per say. Therefore, further studies are required to definitively identify the plasmodium type (s).

ACKNOWLEDGEMENT

The researchers expressed gratitude to all the Laboratory staffs of the Obafemi Awolowo University Health Centre Ile Ife for materials and technical assistance rendered.

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