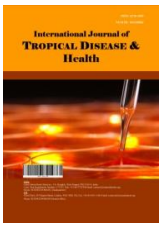

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Fever Cases Associated with *Plasmodium falciparum* Malaria Infection among Children Attending a Tertiary Health Facility in Imo State, Nigeria

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Authors' contributions

This work was carried out in collaboration among all authors. Author CIO designed the study, wrote the protocol and wrote the first draft of the manuscript. Author FCI performed the statistical analysis. Authors KED, KA and FCI managed the analyses of the study. Authors CCO, KKO, ESA and KA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Malaria is a major cause of fever in endemic countries, although the prevalence of malaria has been declining across Sub-Saharan Africa, the proportion of clinical presentation attributable to febrile illness due to malaria to febrile illnesses have remained high. It is therefore important to determine the proportion of fever cases attributable to malaria.
Methods: A descriptive cross sectional study was conducted among children aged 1-72 months presenting at a tertiary facility in Imo state Nigeria from 1st March, 2014 to 31st October, 2015.

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Children between 1-72 months of age with documented fever at presentation or history of fever in the last 24 hours without signs of severe malaria and those without any history of anti-malarial drugs administration were considered eligible. Fever was regarded as axillary temperature of ≥37.5°C. For all subjects (febrile and afebrile), the presence of *Plasmodium falciparum* was assessed microscopically by a WHO Certified malaria microscopist. Malaria parasite density was grouped as 1-1000, 1001–10000, and >10,000 parasites/µl respectively according to World Health Organization guidelines for grouping malaria parasitamae while data was analysed using SPSS 20.1v.

Results: Overall malaria prevalence of both febrile and afebrile at point of assessment but with history of fever in the last 24 hours was 24.3%. Prevalence by microscopy was 26% among the 289 children who were febrile as at point of examination. There was no significant difference (p>0.05) between malaria prevalence in males as against females.

Age group 49-72 months had the highest prevalence (42.6%), while age groups 25-48 and 1-24 months recorded prevalence of 35.7% and 25%, respectively (P<0.05). About 22.5% of afebrile patients had positive *Plasmodium parasitaemia.* The Geo-mean (range) of parasitaemia was 1427(8-180,000) parasite/µl while mean body temperature ± SD was 37.0±0.9°C. About 8% of the children had high parasite density.

Conclusion: *Plasmodium falciparum* although linked with majority of fever is not the cause of fever in all instances. Healthcare providers should make more effort to correctly diagnose non-malaria febrile cases so as to optimize clinical outcomes for the patients and minimize possible over diagnosis and overtreatment of malaria.

Keywords: Plasmodium falciparum; fever; afebrile; febrile; malaria; children.

1. INTRODUCTION

Malaria is endemic in Nigeria and remains a major public health problem, taking its greatest toll on children under age 5 and pregnant women, although it is preventable, treatable, and curable [1]. Nigeria is ranked as one of the high malaria-burdened countries in Africa. Prompt diagnosis and treatment is the most effective means of preventing a mild case of malaria from developing into severe disease and death [2]. Fever is the most common symptom of malaria though it may be absent in congenital and neonatal malaria. Classically, it is described as paroxymal high fever with varying intervals in between episodes [3]. Fever reduces appetite, and exacerbates malnutrition. Furthermore, clinical features of malaria ranges from mild to more severe disease sometimes manifesting as prostration, coma or acidosis. Severity is not necessarily associated with higher parasitaemia but often relates to the immune status of the host [4].

In the first attack of *P. falciparum*, fever is usually irregular rather than occurring with a regular repeating pattern as seen with a tertian fever in subsequent attacks and there are usually no relapses unlike with *P. ovale* and *P. vivax* where hypnozoites are formed [5]. Fever is not always present and rigors may or may not be present. The temperature may rise above 41^{o}C, over several days, and the fever is produced as the schizonts mature, at 48hours intervals usually for *P. falciparum*. The different malarias produce fevers of different frequency depending on how long it takes to complete schizogony in erythrocytes [5].

Fever or a recent history of fever (usually above 38°C) is almost always present, but rarely in the classic tertian (occurring every 48 hours) or quartan (every 72 hours) pattern [6]. Fever and splenomegaly are the most frequent physical findings in a study of malaria presentation. Less often, hepatomegaly, jaundice and abdominal tenderness are noted [7]. In a study in Niamey, Niger, the prevalence of fever was 91% among children diagnosed with malaria [7]. Fever and malaria episodes were frequently accompanied by diarrhoea, vomiting and cough. In another finding, fever was shown to be the main clinical presentation for malaria in endemic areas [8]. Fever is caused by the action of parasitic molecules in host cells particularly monocytes and macrophages which release Tumor Necrosis factor (TNF) and other endogenous pyrogens. These pyrogens will in turn act on the hypothalamus to increase body temperature [9]. The onset of fever coincides with schizogony when hemozoins and other parasitic molecules are released during schizont rupture [9,10]. In areas of intense malaria transmission for instance Nigeria, malaria diagnosis and

treatment is often dispensed on the basis of "fever" and other malaria associated symptoms rather than on the basis of parasitologically confirmed diagnosis [11]. The clinical features of uncomplicated malaria irrespective of the parasite species responsible include; fever, headache, muscle ache, lethargy, vomiting, convulsion, poor feeding, diarrheoa, cough, sweating and shivering among others; in its most typical form, the malaria paroxysm has a characteristic periodicity [11,12]. Young children however manifest this disease in many different ways and the classic picture of malaria with periodic fever, shivering and sweating is usually not observed [11]. Malaria infection symptoms can mimic any febrile illness and should be suspected in any febrile child in any malarious area in view of the fact that *Plasmodium* specie is not the only etiology of fever but just one of the pathogens that can cause identical pyrogenic response that leads to fever in young African children [13]. Over the decades, there has been a growing evidence of a decline in malaria transmission, morbidity and mortality especially in East Africa [14]. However there is still doubt whether this decline is reflected in the proportion of fever due to malaria parasitaemia. Theoretically, a reduction of malaria transmission and hence parasitaemia should translate to a decline in the degree of fever due to malaria but the relationship between the two parameters is not straight forward [14]. Although fever usually has a high sensitivity for the diagnosis of malaria, it lacks specificity and it is of low reliability [10]. Hence microscopic confirmation of malaria parasitaemia is highly necessary. The study therefore was carried out to evaluate the actual fever cases that were attributable to malaria in a tertiary health institution.

2. MATERIALS AND METHODS

2.1 Study Area

This hospital based cross sectional descriptive study was carried out in Imo State, South Eastern Nigeria, between the months of March 2014 to October, 2015. The climate of Imo State is essentially tropical with very high temperature within the months of November to March and seasonal rainfall. Two seasons are prominent in the State, namely rainy and dry seasons. The dry season starts in November and lasts until March while rainy season starts in April and ends in October. The mean monthly temperature of Imo State during the dry season is 34°C while it is 30°C in rainy season. It has relative humidity of about 60% to 80% throughout the year. Its mean annual rainfall is between 2000 and 2500 millimeters [15]. The Federal Medical Center (FMC) Owerriis a tertiary health institution which receives patients from localities with environmental conditions which most likely contribute to human-mosquito contact and which may invariably influence urban malaria transmission. The parasitology unit of the hospital is a reference laboratory for malaria microscopy with WHO Certified microscopists [16]. Children for the study were randomly recruited.

2.2 Enrolment of Study Participants

Seven hundred and forty six (746) children aged 1-72 months who presented to the study facility between March to October 2015 with history of fever in the past 24 hours but with or without fever (febrile and/or afebrile) at time of presentation were enrolled. Children were excluded if they have taken any anti-malarial medicine in the past 7 days prior to their presentation, those with signs of complicated/severe malaria such as convulsions/coma, prostration, severe vomiting etc were also excluded .Fever was regarded as axillary body temperature of ≥37.5^{o}C. For all subjects who met the selection criteria, the presence of *Plasmodium falciparum* was assessed microscopically while history of fever attack, age, sex were documented using a standard questionnaire.

2.3 Sample Collection and Parasitological Diagnosis of Malaria Parasitaemia

Peripheral Blood samples were obtained from deep finger pricks of all 746 eligible participants that gave consent. Thin and thick smears were prepared for each participant following standard procedures for malaria microscopy. Examination of 3% Geimsa stained blood film was done using x100 objective. Malaria parasite density was grouped as 1-1000parasites/µl, 1001–10000 parasites/µl and >10,000 parasites/µl respectively [17]. The parasite density was measured as the number of parasites per 500 leucocytes on a thick film and this was calculated as parasites per microlitre of blood assuming an average white blood-cell count of 8000 per µl of blood [18]. The parasite density of blood was expressed as:

Parasite density per µl of blood = (No of Parasite Count X 8000/ No of Leucocytes Count/ WBC count)

The thin films were used to speciate the *Plasmodium* parasite. Stained slides were examined under the light microscope using the x100 objective lens (immersion oil). A slide was considered negative after 100 high power fields (HPF) have been examined. As part of the Standard Operating Procedures (SOPs) for slide reading in this study two competent microscopists read each slide, and when there was discordance in reading, a third (WHO certified) Malaria microscopist re-reads the slide and breaks the tie. Essentially, the discordance level for the acceptance of any two parasite counts was set at less than 20%.

2.4 Data Analysis

Data was entered, cleaned and analyzed with SPSS software version 20.1. Descriptive statistics were summarized as mean ±2SD and range were appropriate and categorical variables presented as frequencies and percentages. Appropriate tests for statistical significance were performed as necessary at 5% alpha.

3. RESULTS

A total of 746 children were enrolled in the study. The mean age ± 2SD of the patients was 40.3 ± 18.4 months. Also the mean body temperature ±2 SD was 37.0 ± 0.9. *Plasmodium falciparum* was the dominant species (100%). The geometric mean parasite density of the children was 1427 parasites/µl of blood with a range of (8-180,000parsites/µl of blood). Plasmodium parasite density was categorized as: group I (1-1000 parasites /µL), group II (1001-10000 parasites /µL) and group III (>10,000 parasites /µL) [18] with the following distribution: 89(49.7%), 63(35.2%), 27(15.1%) prevalence respectively (Table 1).

Table 1. Profile of study participants aged 1-72 months

Character	Test
Number of participants	**746**
Sex	
Male	389 (52.1%)
Female	357 (47.9%)
Age (months)	
Mean ±SD	40.3±18.4
1-24	179 (24.0%)
25-48	233(31.2%)
49-72	334 (44.8%)
Temperature (^{o}C)	
Mean±SD	37.0±0.9
<37.5	457 (61.3%)
≥37.5	289 (38.7%)
Microscopy Test result	
Positive	179 (24.0%)
Negative	567 (76.0%)
Parasitaemia (p/µL)	
Geomean (range)	1427(8-180,000)
Group I(1-1,000)	89 (49.7%)
Group II (1,001-10,000)	63 (35.2%)
Group III(>10,000)	27 (15.1%)

Table 2. Prevalence and intensity of *Plasmodium parasitaemia* in the different age groups

Age (months)	No of examined	No of positive (%)	Parasitaemia range	Mean parasitaemia (p/μ L)	P value
1-24	179	15 (8.4)	15–161,269	19,903.6	(p=0.045)
25-48	233	61 (26.2)	16–176,077	20,678.2	
49-72	334	103 (30.8)	12–180,269	26,141.2	

Malaria positivity by fever status showed that only 25.3% of the children who had fever (febrile) at presentation and 22.7% of children who had no fever at presentation (afebrile) but they all had history of fever in the past 24 hours actually had malaria and there was significant (p=0.0345) difference between the variables. The proportion of fever cases attributable to malaria is 24% (Table 3).

Children 25-48 months had significant (p=0.0045) more fever (60.5%) episodes than other age groups while children aged 49-72 had more malaria infection 30.8%. This suggests that higher fever episodes seen in younger children may not all be due to malaria. There was significant difference between age and fever (temperature status).

4. DISCUSSION

Promptly identifying the aetiology of fevers in malaria endemic areas has been the subject of concern among health care givers and public health researchers for many years.

The present study shows 24.0% prevalence of malaria parasites by microscopy in peripheral blood samples of children 72months and below in a malaria-holoendemic area of south eastern Nigeria. Prior to scale up of malaria prevention strategies, malaria prevalence reports in Nigerian children varied widely across the various zones ranging from 20.8% to 87.2% [19,20]. There has been a divergent report of parasitaemia levels in Nigeria, South East in particular. Prevalence of 60.7% reported among preschool children [21], 80.3% was reported by Iloh et al. [22] in Imo state while 20.8% was reported among 1,296 afebrile school children in Enugu and 7.7% of 2000 children case notes reviewed in Enugu State were diagnosed for malaria [18,21]. This variation in malaria prevalence could be due to the season when the study was done, the population of children and the quality of methods employed. The issue of methodology is significant due to the employment of poor malaria microscopy processes and competency of the microscopist. This has been seen as a challenge in the report of malaria both in routine diagnosis in the health facilities and in research where microscopists have low malaria microscopy skills required for accurate detection, staging, speciation and quantifying the parasites. The highly quoted burden of malaria among the under-five children in south east Nigeria is of great concern considering the level of malaria intervention strategies employed in the state. More so there is need to ensure that competency of malaria microscopists and or equipment is assured while embarking on malaria prevalence studies.

Interestingly, there is increasing evidence that low parasite prevalence is a common feature of most of South Eastern part of Nigeria and fever alone remains a poor discriminator of malaria infection suggesting that all fevers should be tested to confirm or refute the role of malaria in the febrile presentation. Nigeria Malaria Indicator Survey (NMIS) 2015 reported a marked reduction in malaria prevalence by microscopy amongst children 6-59 months in South eastern Nigeria as follows: Imo (5.1%), Enugu (14.3%), Abia (11.1%), Anambra (16.2%) and Ebonyi (21.7%) as when compared with other zones. The percentage of children with malaria in Nigeria as reported in the 2015 National Malaria Indicator survey ranges from 14 percent in South East to 37 percent in North West.

Presumptive treatment of all fevers has been the most risk-adverse approach to managing "malaria" across Africa and is enshrined in the recommendations proposed by the Integrated Management of Childhood Illnesses (IMCI) [23]. In this study, the levels of parasitemia in peripheral blood as estimated by microscopy negatively correlated with the frequency and intensity of fever. This association, however, raises the important question of whether the administration of anti-malaria to every child presenting with fever as practiced by most health care providers should be sustained.

Table 3. Distribution of parasitaemia in children aged 1-72 months by fever status, FMC owerri, 2015

Variable	Frequency (%)	Positive *Plasmodium parasitaemia* (%)	P value
Febrile	376(50.4)	95(25.3)	
Afebrile	370(49.6)	84(22.7)	
Total	746	179(24.0)	(p=0.0345)

Table 4. Distribution of fever in different age groups

Age groups (months)	No of children examined	No of febrile (%)	No of febrile with parasitaemia (%)	No of afebrile (%)	No of afebrile with parasitaemia (%)
1-24	179	98 (54.7)	10 (10.2)	81 (45.3)	5 (6.2)
25-48	233	141 (60.5)	39 (27.7)	92 (39.5)	22 (23.9)
49-72	334	137 (41.0)	45 (32.2)	197 (59.0)	58 (29.4)

This study agrees with the report in Okoro et al. [24] of 27.9% prevalence which also demonstrated significant relationship between children's age and the prevalence of uncomplicated malaria ($p<0.05$). In malaria endemic areas, the main strategy for reducing under-five childhood morbidity and mortality from malaria disease is presumptive treatment of all fevers in under-five children with antimalaria drugs [5]. This Study also observed presumptive suspicion and treatment of Malaria based on the signs and symptoms as was also previously reported [23,24]. In their report, Okiro et al. [23] stated that recognizing the combined needs to mitigate the threats of drug pressure on the emergence of drug resistance, the changing malaria epidemiology in Africa and the need to improve the way febrile children are managed clinically has provided support for calls to move away from presumptive treatment of African children The interplay of epidemiological and immunological factors have been documented to influence the outcomes of malaria in under-five children [25-27]. The study demonstrated high parasitaemia (30.8%) with parasite density Geo – mean of 26,141.2 parasites/ul in older age groups (49-72 months) as against 8.4% with parasite density Geo – mean of 19,903.6 parasites/ul in 1-24 months. This agrees with a report that age group specific prevalence of malaria ranged between 11.2% and 49.0% in different age groups with the highest prevalence of 49.0% in older patients between 37-60 months and lowest prevalence of 11.2% in patients aged 0-12 months in a rural setting Imo state [28]. This study also agrees with NMIS 2015 that reported increase in Malaria prevalence with the age of the child regardless of the test used.

The probability of having poor clinical outcome when children are managed as malaria without parasites is very high because other etiologies of illness will be missed [19-21,29]. It is therefore of necessity that definitive diagnosis be promoted especially among health workers, by use of techniques that readily and easily demonstrates the parasite or its components in other to guide treatment of malaria as an etiology of fever especially in the South Eastern Nigeria where there is evidenced decline in malaria prevalence.

5. CONCLUSION

Effective surveillance of malaria cases is essential for identifying the groups that are most affected by malaria and other etiologies of febrile illness and for proper case management for maximum impact. A strong surveillance system requires high levels of access to care and case detection and complete reporting or documentation by all health sectors especially tertiary Health facilities.

CONSENT

Each eligible child was enrolled after informed consent was obtained from their caregiver/ parents.

ETHICAL APPROVAL

Ethical approval to conduct this study was obtained from the Ethical committee of Federal Medical Center Owerri, Imo State and the protocol was conducted in accordance with Good Clinical Practice (GCP), Good Clinical Laboratory Practices (GCLPs).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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