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Prevalence of Malaria Among Symptomatic Children Presumptively Treated with Anti-Malarial Medications in Edo State Nigeria

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ABSTRACT

Malaria remains a major threat to public health, therefore the objective of this study was to assess the prevalence of malaria parasites among children presumptively diagnosed and treated for malaria in two healthcare facilities in Edo State, Nigeria. A cross-sectional study involving 595 symptomatic children less than 12 years old who attended two healthcare facilities was conducted. Informed consent was obtained from parents/guardians of each child after which the child's clinical and demographic information were collected. Venous blood sample was taken from each child for determination of haemoglobin concentration, and thick and/or thin blood films for microscopic examination of malaria parasites, and histidine-rich protein 2 (HRP2) immunochromatographic rapid diagnostic tests (RDT). Male patients were 51%, and about 56 % (335/595) of the study participants were below five years old. Clinical diagnosis of malaria was made in 80.3% (478/595) of the children. Overall, malaria parasites rates, obtained by microscopy and RDT were 56.1% (334/595) and 59.3% (353/595), respectively. Out of the 478 clinically diagnosed malaria cases, parasite rates were obtained by microscopy and RDT in 62.8 % and 64.4 % cases, respectively. There was comparative performance between diagnostic capacity of microscopy and RDT, with RDTs exhibiting a sensitivity of 96.7% and specificity of 88.5% when compared to microscopy. The mean duration of fever, respiratory and gastrointestinal symptoms were significantly longer among children with microscopically confirmed malaria than those with negative slides. More than 50% of children who took a particular anti-malarial drug within 2 weeks prior to hospital visit had malaria parasites. The prevalence of malaria was high, presumptive diagnosis resulted in overtreatment. Prior anti-malarial drug use was common, and this practice may undermine chemotherapy as malaria preventive measure in the study locality.

KEYWORDS: Anti-malarial medication; Prevalence; Presumptive treatment, and Symptomatic children

INTRODUCTION

Malaria remains a major threat to public health. The World Health Organization in 2006 reported an estimate of around 350 – 500 million clinical malaria episodes per year [1]. Malaria is the leading cause of mortality among children less than 5 years of age in Africa [2]. A recent WHO publication reported that malaria disease claimed an estimated 627 000 lives in 2012, of which children under five years of age in Africa were most affected [3]. An estimated 1300 young lives are lost every day due to malaria disease [3], even though the disease is preventable and curable. Malaria is highly prevalent in Nigeria; indeed, 2012 World Malaria Report stated that Nigeria and Democratic Republic of Congo account for over 40% of the global total estimate of malaria deaths [4]. Furthermore, available records show that at least 50% of the population of Nigeria experience at least one episode of clinical malaria each year [5] and it accounts for an estimated 250, 000 deaths/year among children under the age of five years [6]. Malaria is characterized by nonspecific signs and symptoms, which are indistinguishable from those of other febrile diseases. Therefore, detection of presence of plasmodium parasites, as well as, quality-assured treatment is essential for effective case management. Currently, the World Health Organization has recommended prompt parasite-based diagnosis of malaria by light microscopy or rapid diagnostic tests (RDTs) in all patients with suspected malaria before initiation of treatment, except when parasitological diagnosis is not accessible [3]. The recommendation for parasitological confirmation will minimize over-diagnosis and treatment with anti-malarial drugs, with consequent reduction of selection pressure for

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drug resistance [3]. Despite this recommendation, several case management of malaria are still based on clinical suspicion [7, 8]. The objectives of this study was to assess the prevalence of malaria parasites among children presumptively diagnosed and treated for malaria in two healthcare facilities in Edo State, Nigeria.

MATERIALS AND METHODS

The study design was cross-sectional, which was carried out at the General Hospital Igarra and Primary Healthcare Referral Centre, Afuze, Edo State, Nigeria. The geographical region has perennial malaria transmission and rain forest vegetation. Prior to patient recruitment, ethical approval was sought and obtained from the Ethical Review Committee of the University of Benin Teaching Hospital, Benin City. In addition, administrative approvals were obtained from the heads of health facilities where the study was carried out.

A total of 595 children less than 12 years who presented with febrile related illness were recruited into the study. A short data collection form was used to collect demographic (age, body weight), clinical (signs, symptoms and duration at presentation), medication information. In addition, laboratory investigations, including haemoglobin concentration/haematocrit, microscopy, and rapid diagnostic test (RDT) were carried out on a sample of venous blood collected via venupuncture into EDTA tube. With regard to RDT, about 5 µl blood was collected by finger prick and tested with histidine rich protein-2 based immunochromatographic RDT (Paracheck-pf) following manufacturer's instructions. Microscopy was done using Giemsa stain, and examined by experienced microscopists using 100 high power light microscopy. Parasites were counted on immersion oil placed on blood film, and parasitaemia determined using assumed 8000 white blood cell per microliter. Anaemia was categorized according to WHO classification of anaemia [9], and sensitivity and specificity of RDT against microscopy were calculated using the equation below.

$$\text{Sensitivity \%} = \frac{\text{Number of true positive (TP)}}{\text{Number of TP + False negatives (FN)}} \text{ X } 100$$

$$\text{Specificity \%} = \frac{\text{Number of true negatives (TN)}}{\text{TN + false positives (FP)}} \text{ X } 100$$

Data were analysed using Graph Pad Instat, version 5.01, and results presented in percentage frequencies, means ± s.d, confidence intervals and odds ratio. Differences between parameters were assessed using Chi-squared tests and Student *t*-test, p-values less than 0.05 were considered significant.

RESUTLS

Out of the 595 children recruited for the study, 302 (50.8%) and 293 (49.2%) were males and females, respectively. About 56 % (335) of the study participants were children under 5 years of age. 478 out of 595 (80%) of study participants were presumptively diagnosed of malaria by the clinicians, based on patient clinical presentations. However, based on microscopy and RDT result, malaria diagnoses were made in 334 (56.1%) and 353 (59.3%) children, respectively. The true positive value (positive by both peripheral microscopy and RDT) and true negative value (negative by both peripheral microscopy and RDT) were 323 and 231, respectively (Table 1). When children who were clinically diagnosed of malaria (478) were assessed for malaria parasites, using microscopy and RDT, parasites rates of 63% (300/478) and 64% (308/478) were obtained, respectively. On the other hand, among children not clinically diagnosed of malaria (n = 117), malaria parasite rates by microscopy and RDT were 29% (34/117) and 39% (45/478), respectively. With peripheral microscopy as the standard, the sensitivity and specificity of RDT in diagnosing *Plasmodium falciparum* malaria were 96.7% and 88.5%, respectively.

The mean parasite count (mean count ± s.d) of microscopically confirmed positive slides was 49,043 ± 182,072 (range 40 – 974,257). Children less than 5 years of age constituted more than 50% of those with malaria parasites. Also, the mean parasite count was highest among children below 5 years of age, while the mean hematocrit was found to be least among same age group (Table 2).

A total of 366 children were reported to have received anti-malarial medications prior to hospital visit. Of this number, the caregivers were able to remember the names of medications taken by 300 children. Despite the use of anti-malarial drugs within two weeks prior to presentations at the study sites, more than 50 % of the users were found to have malaria parasites, either by microscopy or RDT. The most frequently used anti-malarial medications prior to hospital visits by the children were quinine 45% (134/300) and chloroquine 37% (111/300) montherapies. Table 3 shows the varying proportions of the symptomatic children who took various anti-malarial medications within 2 weeks before hospital visit and were still positive for

malaria parasites. The artemisinin combination therapies reportedly taken by the children were artemether/lumefantrine, artesunate/sulphadoxine-pyrimethamine, and artesunate/amodiaquine. The laboratory investigations for malaria parasites using microscopy and RDT showed that more than 70 % of all the children who took chloroquine alone and about 60 % of those who took quinine alone tested positive for malaria parasites 2 weeks after use of the antimalarial medications. With the exception of artemether, which was given intramuscularly, all the antimalarial drugs were reported to have been orally administered to the children.

The care providers of children reported varying symptoms, which were mentioned to be suggestive of malaria among the children. Commonly reported symptoms among the children were fever, cough, diarrhea, vomiting, loss of appetite, and chills/rigors. There were significant differences in duration of fever, respiratory symptoms (cough, catarrh and difficult breathing) and gastrointestinal symptoms (abdominal pain, diarrhea, vomiting and loss of appetite) between microscopically confirmed malaria-positive and malaria-negative children. Similarly, the mean value of auxiliary temperature was significantly different between the two groups (Table 4).

Complete data on age and haematocrit concentration level of the study participants were obtained for 562 children. Only about 14 % (77/562) of them were non-anaemic. The remaining 86 % of the children had varying degrees of anaemia. Table 5 shows the age distribution of the haemoglobin concentration among the symptomatic children involved in the study. The mean haemoglobin concentrations among children that had mild, moderate and severe anaemia were 10.61± 0.56g/dL, 8.977 ± 1.002g/dL and 6.09 ± 0.937g/dL, respectively.

DISCUSSION

A recent WHO report showed a decline in global estimate of malaria rate by 29 % and malaria mortality rate by 45 % between 2000 and 2012 [3]. However, the improvement in the outcome of malaria control is not distributed evenly across regions of the world. Results of the present study showed that there was high prevalence rate of confirmed malaria parasites among the study participants. As previously shown [10, 11], results of our study support earlier findings that children under 5 years old are still largely affected by malaria. Children are a vulnerable group to malaria as such the caregivers should be educated on the preventive and treatment measures for effective control of the disease in the locality. There was high occurrence of presumed malaria cases among children at the study sites, which is similar to the findings of a recent study done in southeastern part of the country [11]. In an earlier study, 50% of patients clinically diagnosed of malaria had illnesses attributed to some other causes [12]. Therefore, this finding buttresses the need for laboratory-based diagnosis of malaria in order to rule out other febrile related diseases. In some scenarios, the laboratory investigations for malaria might be requested by the clinicians, but parents/guardians will fail to comply [11]. In the recent WHO malaria report, only three countries (Liberia, Sierra Leone and Gambia) out of 17 western African countries where malaria is considered a public health problem achieved > 20 % annual blood examination rate (ABER), defined as the number of slide and RDT examinations carried out between 2007 and 2012, divided by the population at risk for malaria within the same time period [3]. In this regard, Nigeria was reckoned with < 3 % ABER. This goes further to reveal that much effort is required to improve on the practice of laboratory-based malaria diagnosis before instituting treatment. Although malaria commonly manifests with minor symptoms such as fever and vomiting in children, it must be distinguished from other febrile illnesses. In their study, Ughasoro *et al*. (2013) [11] reported that differential diagnoses were made in only 32 % of 1,012 presumed malaria cases, while antimalarial medications were prescribed without prior review of malaria laboratory investigation results in 98 % of the cases, a finding which portrays clinicians' satisfaction with clinical diagnosis of malaria.

Similar to a previous study among children in southwestern Nigeria [13], malaria diagnosis based solely on symptoms resulted in over-diagnosis of the disease and eventually, over-treatment. Presumptive treatment of malaria among children as observed in the present study resulted in over-diagnosis of malaria, unnecessary exposure of children to medications and a delay in the initiation of appropriate treatment for the underlying causes of the symptoms. Despite the over-diagnosis associated with presumed malaria cases, the diagnostic method failed to identify all the children that were confirmed malaria-positive either by microscopy or RDT. In the present study, clinical diagnosis of malaria included subsets of children that were actually malaria-positive and malaria-negative. Undoubtedly, reliance on clinical

diagnosis alone would deprive some children of immediate treatment for malaria and or other infectious disease that manifest like malaria. Either situation will result in progression of the infection to severe disease condition with its attendant consequences. Thus, strict adherence to parasite-based diagnosis of malaria by microscopy or RDTs prior to treatment in all suspected malaria cases, which is considered cost-effective and a safer approach [14], should be practiced. RDTs is time-saving and do not require expertise for its performance. However, histidine receptor protein 2 (HRP-2)-based RDTs may give false positive result as the HRP-2 has been shown to persist in the blood even after the malaria parasites have been cleared [15]. There was high occurrence of malaria parasites among the children despite anti-malarial drug use in the previous two weeks. This could have been due to use of wrong drug, administration of wrong dose, incomplete doses, use of substandard drugs or re-infection. More than 50 % of the children who reported antimalarial drug use were found to be positive for falciparum malaria, either by microscopy or RDTs. Of note is the occurrence of malaria in some of the children that were administered artemether/lumetantrine, an artemisinin combination therapy (ACT) that is recommended as the first-line anti-malarial drug in the management of acute uncomplicated malaria in Nigeria [5]. Possibly, the anti-malarial drug may not have been taken for the recommended duration of time or inadequate doses were taken, or the absorption of the orally administered drug was incomplete, especially when lumefantrine based ACT is not taken with fatty meals.

Although the mean haematocrit was least among the children below the age of five, there was no significant association between the mean haematocrit and parasitaemia. This can be explained by the fact that anaemia in children may involve other factors as well. Thus, interpretation of anaemia as an outcome among malaria-positive children should be done with caution. In the present study, while some malaria-positive children had high-leveled parasitaemia and PCV values appropriate for the age, a significant number of the malaria-negative children had varying degrees of anaemia. This is consistent with findings from southern Ghana, where more than 80 % of severely anaemic children demonstrated no malaria parasitaemia but had detectable plasma levels of soluble malaria antigens [16]. Our finding may indicate repeated malaria infections among the children over a long period of time that eventually resulted in low haemoglobin levels. This explanation is supported by the data presented in Table 5, which shows low heamoglobin levels among a significant number of the study participants.

Table 1.0: Comparison of malaria diagnostic performance of both microscopy and RDT

	Microscopy		
RDT	**Positive**	**Negative**	**Total**
Positive	323	30	353
Negative	11	231	242
Total	334	261	595

Table 2.0: Distribution of mean parasite count and PCV by age group of the symptomatic children with positive slides who attended two rural health care facilities in Edo state

Age (years)	N	%	Mean count ± SD (Range)	Mean PCV (%) (Range)	P value
< 5	174	52.1	68,181± 217,198 (40 – 974,257)	23.5 (10-40)	0.4998
5 – 11	140	41.9	32,008 ±140,612 (76 – 956,097)	26.1 (14-49)	0.4995
> 11	20	6	3,807 ±3,679 (79 – 11,862)	28.3 (18-34)	0.4953

N = number; % = percentage; SD = Standard deviation

Table 3.0: Parasite-based diagnosis in symptomatic children following the intake of antimalarial medications within 2 weeks prior to hospital visits

Characteristics	MS Pos. n (%)	MS Neg. n (%)	RDT Pos. n (%)	RDT Neg. n (%)
Used anti-malarial drugs within two weeks prior to presentation at the clinics (n = 366)	222 (60.7)	144 (39.3)	230 (62.8)	136 (37.2)
Did not use anti-malarial drugs within two weeks prior to presentation at the clinics (n = 229)	112 (48.9)	117 (51.1)	123 (53.7)	106 (46.3)
Type of anti-malarial medication used by patients				
Chloroquine (n = 111)	79 (71.2)	32 (28.8)	83 (74.8)	28 (25.2)
Artesunate (n = 8)	4 (50)	4 (50)	3 (37.5)	5 (62.5)
SP (n = 21)	14 (66.7)	7 (33.3)	16 (76.2)	5 (23.8)
Artemether (n = 3)	3 (100)	-	3 (100)	-
Artemeter / Lumefantrine (n = 13)	7 (53.8)	6 (46.2)	7 (53.8)	6 (46.2)
Quinine (n = 134)	80 (59.7)	54 (40.3)	83 (61.9)	51 (38.1)
Artemether / lumefantrine + Quinine (n = 5)	5 (100)	-	5 (100)	-
Artesunate / amodiaquine (n = 1)	1 (100)	-	1 (100)	-
Artesunate / SP (n = 2)	1 (50)	1 (50)	1 (50)	1 (50)
Artemether / Quinine (n = 1)	1 (100)	-	1 (100)	-
Artesunate / Quinine (n = 1)	1 (100)	-	1 (100)	-

n = number of children; % = percentage; MS = microscopy; Pos. = positive; Neg. = negative; SP = sulphadoxine-pyrimethamine

Table 4.0: Comparison of the signs and symptoms between malaria-positive and negative children, identified by microscopy

Symptom / Sign	Mean (level/duration) ± SD		P-value
	Children with MP+	Children with MP–	
Fever (days)	9.26± 11.07	9.76 ± 7.467	0.0167
Axl. temperature (°C)	36.98 ± 2.291	37.92 ± 3.437	0.0080
Chills / rigor (days)	2.07±2.253	3.287±3.848	0.1425
Sweating (days)	2.966±2.796	4.397±3.763	0.1220
Vomiting (days)	1.809±1.311	1.903±1.547	0.0154
Catarrh (days)	3.629±9.391	3.392±2.937	0.0208
Abdominal pains (days)	4.787±4.443	5.353±4.830	0.0351
Diarrhoea (days)	3.522±3.028	3.944±3.115	0.0358
Cough (days)	4.792±9.820	4.710±18.67	0.0171
Loss of appetite(days)	2.137±2.217	2.417±2.822	0.0390
Difficult breathing (days)	1.771±1.750	1.869±1.533	0.015

$P < 0.05$ is considered significant; axl. =auxiliary; MP + = malaria parasite positive; MP – = malaria parasite negative

Table 5.0: Distribution of haemoglobin concentrations by age groups of the symptomatic children that were presented at the two health care facilities in Edo State

Classification	Number of cases (%)	Hb conc. (g/dL) ± SD	
		Mean value	Range
Non-anaemic	77 (13.7)	12.21 ± 1.129	11.00 – 18.67
< 5yrs	52 (9.3)	12.07 ± 1.193	11.00 – 18.67
5 – 12 yrs	25 (4.4)	12.45 ± 1.082	11.67 – 16.33
Anaemic	485 (86.3)	8.036 ± 1.876	3.330 – 11.33
Mild	53 (9.4)	10.61 ±0.5605	10.00 – 11.33
< 5yrs	30 (5.3)	10.14 ± 0.1663	10.00 – 10.33
5 – 12 yrs	23 (4.1)	11.20 ± 0.1642	11.00 – 11.33
Moderate	244 (43.4)	8.977 ± 1.002	7.000 – 10.67
< 5yrs	112 (19.9)	8.836 ± 0.8868	7.000 – 9.670
5 – 12 yrs	132 (23.5)	9.448 ± 0.8001	8.000 – 10.67
Severe	188 (33.5)	6.090 ± 0.9378	3.330 – 7.670
< 5yrs	78 (13.9)	5.923 ± 0.7013	3.330 – 6.670
5 – 12 yrs	110 (19.6)	6.228 ± 1.021	3.330 – 7.670

CONCLUSION

In conclusion, there is need for clinicians to imbibe the practice of laboratory based diagnosis before initiating antimalarial treatment, particularly among children in whom data on safety profile of antimalarial medications are limited.

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