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Prevalence of *Plasmodium falciparum* in symptomatic and asymptomatic children in Minna, North Central Nigeria

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ABSTRACT: The prevalence of *Plasmodium falciparum* in asymptomatic children and its association with symptomatic malaria cases was assessed in a cohort of children from Minna, Nigeria. A total of 220 children aged 6 months to 17 years were recruited from the community and healthcare facilities. Thick and thin films of the blood samples were prepared and the parasite density was determined using the thick film while the parasite species was identified using thin film. Overall, the prevalence of *Plasmodium falciparum* was 70% (153/220) out of which 28% (43/153) was observed in apparently healthy children from the community (asymptomatic) and 72% (110/148) from children with fever (symptomatic). The highest parasite prevalence was observed in children 6 to 11 years 30% (22/72) for asymptomatic infection; while symptomatic infection recorded 44% (65/110) from 6 months to 5 years of age. Females tends to show a greater prevalence of *Plasmodium falciparum* infection with 77% (20/26) and 78% (49/63) for both asymptomatic and symptomatic infections respectively. Parasitemia was, however, not significantly associated with fever ($p>0.05$). This study confirms that malaria remains a major cause of febrile illness during the early stages of childhood (<5 years). This may however, guide case definition for clinical trials of preventive tools, as well as provide definitions that may improve the precision of measurement of the burden of malaria.

Keywords: Fever, malaria, parasite density, parasitemia.

INTRODUCTION

In 2016, an estimated 216 million cases of malaria occurred worldwide, compared with 237 million cases in 2010 and 211 million cases in 2015 (WHO, 2017). In high-transmission areas of the world, children under five years of age (including infants) are the most vulnerable group. In 2015, over 69% of malaria deaths worldwide occurred in children under five years of age. Asymptomatic parasitemia for malaria infection can be defined as the detection of parasites in the blood of human (which does not include dormant liver stages) while in the absence of clinical symptoms characterized to the infection during a specified time frame. It is widespread in highly endemic areas of Africa, with only a small percentage of individuals exhibiting clinical symptoms. Abundant evidences show that asymptomatic malaria infection contributes to mortality and morbidity, the underlying pathologies associated with this remain obscured (Chen et al., 2016). Numerous reports from previous study indicate dysregulated immune responses in individuals with malaria—at any density of infection (Scholzen and Sauerwein, 2013; Riley and Stewart, 2013)—but these have rarely been linked directly to specific disease outcomes (Chen et al., 2016). The clinical consequences of asymptomatic malaria may vary across different epidemiological settings and are not fully understood. Asymptomatic parasitemia provides a pool for the transmi-

ssion of the parasite and may be a precursor in the progression to symptomatic disease (Denise et al., 2004). Use of antimalarial drugs to target the reservoir of malaria infection is an option to reduce the transmission of malaria between humans and mosquito vectors. However, a large proportion of human malaria infections are asymptomatic, requiring treatment that is not triggered by care-seeking for clinical illness (Kim et al., 2014). Some malaria infections are asymptomatic because the partial immunity to malaria infections can lead to a reduction in the acute clinical symptoms of disease. The immunity is a prime factor that most strongly determines whether a malaria infection produces symptoms. A person's level of immunity to infection is determined by past exposure history and age. An increased level of immunity leads to improved control over parasite multiplication and a decreased parasite density, which in turn lessens the severity of symptoms.

Immunity against malaria is acquired from exposure to malaria infection and develops more quickly with frequent exposure; most children in areas with moderate-to-high levels of malaria transmission gain protection from severe disease by a very young age, usually by 2 to 5 years of age, followed by a decrease in the rate of symptomatic illness at the onset of adolescence (Filipe et al., 2007). On the contrary, immunity increases with maturation of the immune system and appears to be somewhat independent of exposure frequency in areas of moderate-to-high transmission. By adulthood, parasite densities following infection often remain at very low levels, frequently undetectable by microscopy, and most infected adults do not exhibit clinical symptoms. However, asymptomatic parasitemia can occur at any age (Kim et al., 2014).

In malaria-endemic regions, one of the most susceptible populations that suffered severe and complicated malaria are children less than five years of age (Quintero et al., 2011), and the vast majority of deaths due to malaria parasite could be caused by *Plasmodium falciparum* which is the most virulent species of the malaria parasites (Abdel Hamid et al., 2013). This study was carried out to establish detailed baseline data on the prevalence and distribution of *P. falciparum* for both symptomatic and asymptomatic cases in a cohort of children from Minna, Nigeria.

MATERIALS AND METHODS

Description of the study area

From the months of February to March, 2018, a cross sectional study was conducted on children in Minna, the capital city of Niger State, North Central Nigeria. Minna is located at 9.62 latitude and 6.55 longitude and situated at elevation 243 meters above sea level, covering a land area of 88 km^2 with an estimated population of 1.2 million. The city has a tropical climate with two seasons, the rainy and the dry seasons, which start from May to October and December to March respectively. However, there is a transitional period of April and November. The rainy seasons in Minna have a good deal of rainfall, while the dry seasons have very little or no rainfall. The average annual temperature is 27.5°C in Minna, the rainfall averages 1229 mm and the relative humidity is 61%. The least amount of rainfall occurs in January with an average 1 mm. Most of the precipitation falls in September, averaging 260 mm. The temperatures are highest on average in March, at around 30.5°C. August is the coldest month, with temperatures averaging 25.3°C.

Study population

The study subjects included children of both sex from 6 months to 5 years, 6 to 11 years and 12 to 17 years. Blood samples were collected from apparently healthy children from the community and also children who visited the outpatient department of healthcare facilities within the period of the study. The healthcare facilities visited were: General Hospital, Minna; Primary Health Care, Old Airport Road; Primary Health Care, Gwari Road; Family Support Programme; Primary Health Care, Tunga and Primary Health Care, Kpakungu.

Assessment of asymptomatic infection

At enrolment, blood samples of children with no history of fever in the past 48 hours was taken, thus asymptomatic infection was defined as no measured fever at the time of the study.

Assessment of symptomatic infection

Blood samples of children with new history of fever or temperature ≥37.5°C attending the outpatients department of the healthcare facilities were taken. Patients were diagnosed with malaria if they fulfilled any of these criteria: complicated malaria [presence of severe malaria (Warrell et al., 1990) or danger signs as described by (WHO, 1996); and any parasitemia; and/or temperature ≥37.5°C; and ≥500 asexual parasites/μl blood.

Parasitological examination

Thick and thin films of the blood samples were prepared for each sample using standard procedures with 3% Giemsa stain pH 7.0 for 45 minutes. The blood films were then examined microscopically using 100x (oil immersion) objectives as described by WHO (2010). The parasite density was determined using the thick film while the parasite species was identified using thin film. Parasite density per microliter of blood was estimated from the thick film according to the method of counting parasites

described by Trape (1985). Parasite was obtained by counting the number of asexual parasites per 200 WBCs and calculating parasites/μl assuming a WBC count of 8000/μl. A smear was considered negative if no parasites were seen after review of 100 high-powered fields. Parasitemia was categorized as low (<1000parasite/μl), moderate (1001-10,000parasite/μl), high (>10,001/μl) and hyper parasitemia (≥100,000) (Omalu et al., 2012; Sumbele et al., 2016).

Ethical permission

Ethical clearance was obtained from the Niger State Ministry of Health after a research protocol and an application letter to that effect was tendered. Following administrative clearance from the ministry, clearance was also sought from the coordinator, Primary Healthcare, Chanchaga Local Government. Furthermore, informed consent of parents and guardians was sought for.

Data analysis

Data analysis was performed using SPSS version 23.0 statistical software programs. Descriptive statistics was used for calculation of mean and standard deviation values. Comparison between the prevalence of asymptomatic and symptomatic parasitemia by using bivariate correlation/associations. Differences in proportions of age, sex and parasite densities were evaluated using Pearman's chi square. The *p* value less than 0.05 was considered statistically significant.

RESULTS

Characteristics of the study population

A total of 220 subjects participated in the cross-sectional survey and blood samples were collected from each. A vast majority of the children showed signs of fever 63.30% (148) while 32.70% (72) were asymptomatic. As highlighted in Table 1, majority of the study participants were males 59.50% (131), and the females were only 40.50% (89). Most of the children were from 6 months to 5 years, 40.00% (88) of the participants were between 6 years to 11 years and the remaining 11.80% (26) were from 11 years to 17 years. More than half of the populations were infected with *P. falciparum* 70.00% (153) and the remaining 30.00% (67) were negative.

Prevalence of *P. falciparum* in asymptomatic and symptomatic infections

Children with fever (symptomatic infections) had a higher prevalence of *P. falciparum* infections than children with no signs of fever (asymptomatic) as seen in Table 2. By contrast, asymptomatic children showed a higher negative prevalence of 40.27% (29/72) than children with symptomatic infection with 25.67% (38/148). It was also revealed that, though, 38 participants had febrile illness, there was no clinical evidence of *P. falciparum* infection. Thus, parasite was however, significantly associated with fever ($r = 0.149$, $p = 0.027$).

Age and gender related prevalence (%) of *P. falciparum* in asymptomatic and symptomatic infections

From the total of 72 blood samples collected from healthy children from the community, it was pictured that negative cases to *P. falciparum* parasite was lower 40.27% (29/72) than the positive cases with 59.72% (43/72). Asymptomatic malaria occurred most in children within the age of 6 to 11 years with 30.55% (22/72 cases) which was higher than what was observed in children from 6 months to 5 years of age 11.11% (8/72) (Table 3). Children from this category had lower asymptomatic infection due to the fact that their immune system is fragile (especially from 6 months to 2 years) and any appreciable exposure to parasite will show symptoms of febrile illness. In contrast, symptomatic malaria occurred mostly in patients less than 5 years of age and its prevalence decreases with age. There was however, no significant difference between *P. falciparum* infection and the age of the children ($\chi^2 = 0.178$, $p = 0.915$).

Males on the other side, had the highest number of enrolments which translates to a high malaria prevalence for both asymptomatic 23/72 (31.94%), and symptomatic 61/148 (41.21%) infections (Table 3). Females tend to show a greater percentage if considered separately having 20/26 (77%) positive cases whilst the males had 23/46 (50%) positive cases in asymptomatic infection. In contrast, both symptomatic males and females had a fairly comparable *P. falciparum* prevalence of 61/85 (72%) and 49/63 (78%) respectively. Though, fever was not significantly associated with the sex of the children ($r = 0.062$, $p = 0.362$), there was a positive weak correlation between *P. falciparum* infection and sex of children ($r = 0.133$, $p = 0.034$).

Parasite density of *P. falciparum* between symptomatic and asymptomatic infections

Blood samples from children with moderate parasite density had the highest prevalence for both asymptomatic 44.44% (32/72) and symptomatic infections 50.67% (75/148) and only one case (0.67%) was reported with high parasite density and was observed in symptomatic infection (Table 4). This shows the level of parasite load in apparently healthy children which is likely to result in mosquito infections. Numerous studies have demonstrated that mosquitoes can become infected by blood from

Table 1. Characteristics of the study population.

Factors	n (%)	Mean (SD)
P. falciparum parasite		
Negative	67(30.00)	1.70 (0.461)
Positive	153(70.00)	
Age		
6mnths- 5yrs	106(48.20)	4.30 (3.67)
6yrs-11yrs	88(40.00)	
11yrs-17yrs	26(11.8)	
Gender		
Male	131(59.50)	1.40 (0.492)
Female	89(40.50)	
Mean hemoglobin		1.57(0.496)
Children with no symptomatic malaria	72(32.70)	
Children with symptoms of malaria	148(67.30)	

Table 2. Prevalence of *P. falciparum* between symptomatic and asymptomatic infections.

Malaria infection	Malaria parasite		Total n (%)
	Negative n (%)	Positive n (%)	
Asymptomatic infection	29(40.27)	43(59.72)	72(100.00)
Symptomatic infection	38(25.67)	110(74.32)	148(100.00)

Table 3. Age and gender related prevalence (%) of *P. falciparum* in asymptomatic and symptomatic infections.

Parameters	6 mnts-5 yrs n (%)	6-11 yrs n (%)	12-17 yrs n (%)	Total n (%)	Male n (%)	Female n (%)	Total n (%)
Asymptomatic infection							
Negative	7(9.72)	18(25.00)	4(5.55)	29(40.27)	23(31.94)	6(8.33)	29(40.27)
Positive	8(11.11)	22(30.55)	13(18.05)	43(59.72)	23(31.94)	20(27.77)	43(59.72)
Symptomatic infection							
Negative	26(17.56)	9(6.08)	3(2.02)	38(25.67)	24(16.21)	14(9.45)	38(25.67)
Positive	65(43.91)	39(26.35)	6(4.05)	110(74.32)	61(41.21)	49(33.10)	110(74.32)
Total N (%)	106(48.18)	88(40.00)	26(11.81)	220(100)	131(59.54)	89(40.45)	220(100)

Table 4. Parasite density of *P. falciparum* between symptomatic and asymptomatic infections prevalence.

Malaria infection	Negative n (%)	Parasite Density			Total n (%)
		Low n (%)	Moderate n (%)	High n (%)	
Asymptomatic infection	29(40.27)	11(15.27)	32(44.44)	0(0.00)	72(100)
Symptomatic infection	38(25.67)	34(22.97)	75(50.67)	1(0.67)	148(100)
Total	67(30.45)	45(20.45)	107(48.63)	1(0.45)	220(100)

individuals with gametocyte densities as low as five gametocytes (g)/µl, and theoretically as low as 1 g/µl (White, 2008). Parasite density was, however, not significantly associated with fever (p>0.05).

DISCUSSION

Asymptomatic parasitemia was fairly common in all the cohort of children. From the total of 15 apparently healthy children less than 5 years recruited for this study, more than half of them (8 cases) were infected with *P. falciparum* with parasite density above 1000 u/l (moderate parasitemia). This suggests evidence of protective immunity in children less than 5 years of age. This trend was also observed in more than half of the population of each cohort (6 to 11 years and 12 to 17 years). In contrast with another study conducted by Starzengruber et al. (2014) on asymptomatic malaria cases in South-eastern Bangladesh, they observed significantly ($p < 0.01$) more asymptomatic cases recorded among participants older than 15 years as compared to younger participants, whereas prevalence and parasite density were significantly ($p < 0.01$) higher in patients younger than 15 years. Though children with no clear symptoms of fever were infected with *P. falciparum*, it was generally evident from this study that only 44% had parasite density above 1000u/l. This also suggests partial immunity to malaria infections which can lead to a reduction in the acute clinical symptoms of disease (Filipe et al., 2007).

Moreover, immunity is acquired from exposure to malaria infection and develops more quickly with frequent exposure; most children in areas with moderate-to-high levels of malaria transmission gain protection from severe malaria at a very young age, usually by 2 to 5 years, followed by a decrease in the rate of symptomatic illness in early adolescence (Filipe et al., 2007). In a similar study conducted by Denise et al. (2004) in a cohort of Ugandan children from Kawempe Division of Kampala, the overall prevalence for asymptomatic parasitemia was lower than what was observed in this study with only 8% (205) and a range of parasite densities 16–592 ×800 parasites/µl. This discrepancy could be ascribed to the fact that malaria is meso-endemic in Kawempe Division and holo-endemic in the study area of this research. Furthermore, it was also observed that females tend to show a greater prevalence of asymptomatic infection with 20 cases out of the 26 healthy females recruited for this study.

Over 25% of children with febrile illness were not infected with *P. falciparum* and interestingly, more than 60% of them comprises of children less than 5 years of age. Though, significant relationship was not observed between infection with *P. falciparum* parasite and the age of the child, the occurrence of parasite was however, significantly associated with fever. This observation was not similar to the results obtained by Denise et al. (2004) which observed the incidence of fever not associated with symptomatic malaria for two dry seasons. Similarly, as observed with asymptomatic infection, females had a greater prevalence of *P. falciparum* with a total of 49 cases (78%) out of the 63 cases of febrile illness.

However, the prevalence of fever associated with *P. falciparum* decreases rapidly with increasing age peaking among children less than five years of age 44% and the lowest was observed from 12 to 17 years of age 4%. This was consistent with the study of Mabunda et al. (2009) who also observed that the prevalence of malaria infection associated with fever peaked among children during the first year of life and thereafter decreased sharply with increasing age.

The risk of being febrile was observed at its peak in blood samples from children with moderate parasite density (1001-10,000 parasite/µl) than those with low parasite density. High parasite density was observed in only one case, hyperparasitemia was not observed in children with febrile illness (symptomatic). This has also been highlighted by Mabunda et al. (2009) who observed that the risk of being febrile increased with increasing parasite density, particularly from parasite density category equal or higher than 5,000 parasites/µl.

A significant limitation of this study was its lack of significant follow up to assess the true impact of asymptomatic infection. However, a strong correlation between asymptomatic and symptomatic infections was observed and there was no significant association between them. Similarly, significant association was not observed between asymptomatic and symptomatic infection with age, and also with sex.

Conclusions

This study confirms that malaria is holo-endemic - the young are more likely to express pathogenic responses, whilst the older hosts will carry the disease asymptomatically, or with reduced damage, due to adaptive immunity- and remains a major cause of febrile illness during the early stages of childhood (<5 years). The outcome of this study also defines the relation between parasite density, the presence of fever and how it varies with age and sex. This may help guide case definition for clinical trials of preventive tools, as well as provide definitions that may improve the precision of measurement of the burden of disease.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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