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Diagnosis of Malaria among Children in Sokoto: A Comparison of Microscopy and Rapid Diagnostic Tests

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Abstract

Malaria is a life-threatening disease primarily found in tropical countries, and it is the leading cause of morbidity and mortality among children. Diagnosis of malaria depends largely on clinical presentations and laboratory diagnosis. Microscopy is the gold standard for laboratory malaria diagnosis but requires adequate training and time compared to Rapid Diagnostic Tests (RDTs). The study compared the utility, sensitivity, specificity, and predictive values between microscopy and RDTs in diagnosing malaria among children accessing care in Specialist Hospital Sokoto. A total of 367 blood samples of consented children who met the study inclusion criteria were examined. All samples were screened for malaria using RDT thin and thick blood films. Of the 367 samples assessed, RDT was positive for 202 (55.0%) and negative for 165 (45.0%), while microscopy was positive for 235 (64.1%) and negative for 132 (35.9%), a non-statistically significant (x^2 = 0.090, P = 0.922) difference was observed when both positive tests were compared. The Rapid diagnostic tests (RDTs) showed a sensitivity of 85.95% and a specificity of 83.33%. This study confirms the higher positivity rate of microscopy to RDTs in diagnosing malaria. As such, RDTs are useful for rapid malaria diagnosis, especially in resource-limited settings; microscopy should be encouraged as much as possible for children to avoid missing any positive cases.

Keywords: Children, Malaria, Microscopy, Rapid Diagnostic Tests

INTRODUCTION

Malaria is a life-threatening parasitic disease and continues to be a disease of public health concern in tropical Nations; an infected female Anopheles mosquito transmits it. The mosquito bite introduces the parasite from the mosquito`s saliva into the bloodstream (WHO, 2014). Malaria diagnosis in endemic regions depends largely on clinical findings, microscopy, or Rapid Diagnostic Tests (RDTs) (Wongsrichanalai *et al.*, 2007). Microscopy is considered the gold standard for malaria diagnosis because of its affordability, sensitivity, and identification of *plasmodium* species, alongside the determination of parasite density (Amexo *et al.*, 2004). However, some of the biggest obstacles associated with microscopy are unpredictable power supply, significant turnaround times, and the requirement for technical competence (Amexo *et al.*, 2004). In view of these challenges, RDTs were designed to improve the sensitivity, objectivity, and turnaround time of malaria diagnosis through less dependence on microscopy.RDT is a rapid lateral flow immune-chromatographic technique designed to capture and target antigens abundant in all malaria parasite stages. It specifically detects *Plasmodium* Aldolase, an enzyme found in all *Plasmodium* species, Histidine-Rich Protein 2 (HRP2), a protein present only in *Plasmodium falciparum* and Parasite-Specific Lactate Dehydrogenase (pLDH) found in all *Plasmodium* species (Abanyie *et al.*, 2011). RDTs are recommended by the World Health Organisation to enhance early diagnosis, management of cases, prevention of complications due to delayed treatment, and monitoring of treatment, especially in children (WHO, 2014). Moreover, studies have shown that it is acceptable to both practicing physicians and patients (Reyburn *et al.*, 2007). It is timely for case management of malaria and avoids the drawbacks of defective microscopes and erratic power supply (Reyburn *et al.*, 2007).

The proportions of malaria cases confirmed by laboratory diagnosis in Nigeria are few. Diagnosis of malaria is often clinical-based (Faucher *et al.*, 2010).

In endemic countries, the most commonly used methods are clinical signs and symptoms which are nonspecific and not sufficient (Weber *et al.*, 1999; WHO, 2010). This can lead to misdiagnosis, overdiagnosis, inappropriate treatment, and potential development of drug resistance. However, the accuracy of clinical diagnosis varies with the extent of endemicity and malaria season, so RDTs evolved for objective malaria diagnosis (Wongsrichanalai *et al.*, 2007).

MATERIALS AND METHODS

Study Area

The research was conducted at Specialist Hospital Sokoto (SHS), Sokoto state, North Western Nigeria. SHS is a tertiary institution located within the Sokoto metropolis. Sokoto is the capital city of Sokoto State. The rainy season starts from June to November, during which showers are daily. The major Indigenous inhabitants of the area are Hausa, Fulani, and Yoruba. SHS is located within the Sokoto metropolis, specifically in Sokoto south Local Government area. The hospital receives referrals from neighbouring states. It has a bed capacity 448, with approximately 11,000 to 13,000 monthly patient flow (NPC, 2012; Taofiq *et al.*, 2017).

Study design

This cross sectional study involved the recruitment of children between the ages of 1 to 15 years. The research was conducted between June to December 2021. A consecutive sampling technique was applied, and participants were recruited as they presented to the Paediatric Outpatient Clinic (POPC). An interviewer-administered questionnaire was designed to collect information like age, sex, tribe, area of residence, and parent educational background. Malaria tests (RDT and microscopy for thick and thin blood film) were performed concurrently on all samples collected from the study subjects.

Ethical Approval and Informed Consent

Following submitting the research proposal, this study was approved by the Ethics and Research Committee of Specialist Hospital Sokoto with Ref. No: SHS/SUB/133/VOL. 1. Before recruitment of the study participants, written informed consent was obtained from parents or guardians, and assent was obtained from the children

Sample Size Determination

The sample size was calculated using the previous prevalence of 60.4%, reported by Mohammad *et al.* (2017) in Sokoto. It was determined according to the statistical formula: $n = Z^2PQ/d^2$ Where, n = Minimum sample size required, Z = Confidence level set at 95% (standard error from the mean 1.96), P = 60.4% is the prevalence of malaria among children in Sokoto (Mohammad *et al.*, 2017), Q = 1-P, 1-0.604 = 0.396, d = Margin of error at 5% (standard value of 0.05).

$$n = \frac{(1.96)^2 \times (0.604) \times (1 - 0.604)}{(0.05)^2}$$

n = 367. As such, 367 participants were recruited for this study

Sample Collection and Processing

Three (3) ml of venous blood was aseptically collected from each participant. The blood was placed in an EDTA container, and an aliquot of the sample was used to screen for malaria parasites using a Rapid Diagnostic Test (RDT) kit. Thin and Thick smears were also made, stained, and examined for the presence of malaria parasite.

Rapid Diagnostic Test (RDT)

The rapid Diagnostic Test was carried out using a pan-specific kit that contains Histidine-rich protein 2 (HRP-2), Parasite *Plasmodium* lactate dehydrogenase (pLDH), and Aldolase (pan-specific). Pan-specific means that the RDT detects all four types of plasmodia that infect humans. This kit was obtained from LabACON® Company. Ref. No.: IMPN-C52. Storage temperature 2°C to 30°C. Lot No.: MAL21030010, Mfg Date: 2021-03-26 Exp. 2023-03-25. The kit detects antigens to *P. falciparum* malaria and non- *P. falciparum malaria,* which infect humans with P. vivax, P. ovale, or P. malariae. The procedure was carried out according to the manufacturer's instructions.

Procedure of Rapid Diagnostic Tests (RDTs)

The kit was allowed to attain room temperature (18-25°C), the pouch was opened at the notch, and the cassette was removed. The Cassettes were placed on a clean, flat surface and labeled with the participant's identification number. From each participant, Five (5) µl of whole blood from each participant was dropped into the "S" (Sample) well. Three drops of assay buffer were immediately added into the "B" well, and the timer was switched on. The result was read within 10 minutes after adding the buffer.

Interpretation of Rapid Diagnostic Test Results

In the Kit, the 'T1' test line is specific for *P. f*, 'T2'test line is Pan-specific, and 'C' is the control line.

1. A line in 'T1 ' and a line in 'C' means the participant is positive for *P. falciparum* malaria. The test is POSITIVE even if the line in 'T1 ' is faint.
2. A line in 'T2'and a line in 'C' means the participant is positive for the non- *P. falciparum* malaria that is *P. vivax*, *P. ovale*, or *P. malariae*.

3. Lines in 'T1'and 'T2' and a line in 'C' mean the participant is positive for P. falciparum malaria mono and/or mixed infection of *P. vivax, P. ovale,* and *P. malariae*.
4. No line in 'T1' or 'T2' and a line in 'C' means the participant does not have either *P. falciparum* malaria nor mixed infection of *P. vivax, P. ovale,* and *P. malariae*.
5. No line in 'T1' or 'T2' and No line in 'C' means the test is damaged. The results are Invalid.
6. A line in 'T1' or 'T2' and No line in 'C' means the test is damaged. The results are Invalid.

Microscopy

Smears of thick and thin blood films were duplicated from each child's fresh whole blood. Before staining, thin blood films were fixed with absolute methanol for 1 second and stained with 3% Giemsa for 45 minutes (PH 7.2). The slides were examined using× 100 oil immersion objectives lens. Before declaring a slide as malaria positive or negative, a total of not less than70 microscopic fields were examined. Three (3) Medical Laboratory Scientists guide the microscopy and interpret the results (Cheesbrough, 2006).

Data Analysis and Presentation

The results obtained were entered into SPSS software version 22.0 (IBM, USA). A test of normality was carried out to ascertain the distribution pattern of the variables. Data was not normally distributed based on test of normality results. As such, standard non-parametric tests were used. The *P*-value of less than or equal to 0.05 ($P \leq 0.05$) was considered statistically significant. Standard equations were used to calculate sensitivity and specificity and negative and positive predictive values (NPV and PPV).

RESULTS

The result presented in Figure 1 shows the frequency distribution of *Plasmodium* species among study participants using RDT. Of the 367 children studied, 202 (55.0%) were positive for malaria, 165 (45.0%) were negative for malaria, 134 (36.5%) were positive for *P. falciparum* infection, 64 (17.4%) were positive for mixed infection of both *P. falciparum* and *Plasmodium spp* other than *P. falciparum*, while 4 (1.1%) of the study participants were positive for *Plasmodium spp* other than *P. falciparum*.

The frequency distribution of *Plasmodium* species among study participants using microscopy (thin and thick blood film) is shown in Figure 2. Of the 367 children studied, 235 (64.1%) were positive for malaria, while 132 (35.9%) were negative for malaria; 146 (39.8%) were positive for *P. falciparum* infection, 85 (23.2%) had co-infection of both *P. falciparum* and *P vivax* while 4 (1.1%) of the study participants were positive for *P vivax* only.

The result presented in Table 1 shows the frequency distribution of malaria parasitaemia based on the sex of the study participants using the Rapid Diagnostic Test (RDT). Of 367 children studied, 207 (56.4%) were male, while 160 (43.6%) were female. Of the 165 (45.0%) participants that were negative for malaria, 91 (24.8%) were male and 74 (20.2%) were female. Out of 134 (36.5%) participants that were positive for *P. falciparum*, 72 (19.6%) were male and 62 (16.9%) were female. 64 (17.4%) of the children studied were positive for both *P. falciparum* and *P. vivax*, out of which 40 (10.9%) were male and 24 (6.5%) were female. Only four (1.1%) were positive for *P. vivax* and were all male participants. A significant difference was observed when the total positive value for RDT and that of microscopy were analysed using the Mann-Whitney U test, a non-statistically (P= 0.155, U= 15217).

Table 2 depicts the frequency distribution of malaria parasitaemia based on the sex of the study participants using microscopy (thin and thick blood film). Out of 367 children studied, 207 (56.4%) were male, while 160 (43.6%) were female. From the 132 (35.9%) participants that were negative for malaria, 71 (19.3%) were male, and 61 (16.6%) were female. Out of 146 (39.8%) participants that were positive for *P. falciparum*, 79 (21.5%) were male and 67 (18.3%) were female, 85 (23.2%) of the children studied were positive for both *P. falciparum* and *P. vivax*, out of which 53 (14.5%) were male and 32 (8.7%) were female. Only four (1.1%) were positive for *P. vivax* and were all male participants.

The results in Table 3 depict the frequency distribution of malaria based on the age range of the study participants using RDT.

The participants within 1-5 years age group had a total malaria positive participants of 56 (15.3%) and a total negative participants of 36 (9.8%). The participants that are within6-10 years age group had a total malaria negative of 44 (11.9%) and a total malaria positive of 55 (14.9%). The participants within the 11-15 age range had the highest prevalence of malaria parasitaemia, with 91 (24.8%) positive and 85 (23.1%) negative. When the total positive value for RDT and that of microscopy were analysed using the Kruskal-Wallis test, a non statistically (P = 0.63, x^2= 0.89) significant difference was observed.

The result of a frequency distribution of malaria based on the age range of the studied children, using microscopy, is depicted in Table 4.

Out of those in the 1-5 years age group, 43 (11.7%) were positive for *P. falciparum*, 19 (5.2%) were positive for *P. falciparum* and *P. vivax*, while 2 (0.5%) were positive for *P. vivax* and this age group had a total positive participants of 64 (17.4%) and a total negative of 28 (7.6%). The age group 6-10 years had a total negative of 34 (9.3%) and a total positive of 65 (17.8%), which comprises 41 (11.2%) positive for *P. falciparum*, 22 (6.0%) positive for *P. falciparum* and *P vivax*, while 2 (0.5%) were positive for *P vivax*. The age group 11-15 years had the highest malaria with a total of 106 (28.8%) positive and 70 (19.1%) negative, 62 (16.9%) were positive for *P. falciparum*, and 44 (12.0%) were positive for *P. falciparum* and *P vivax*.

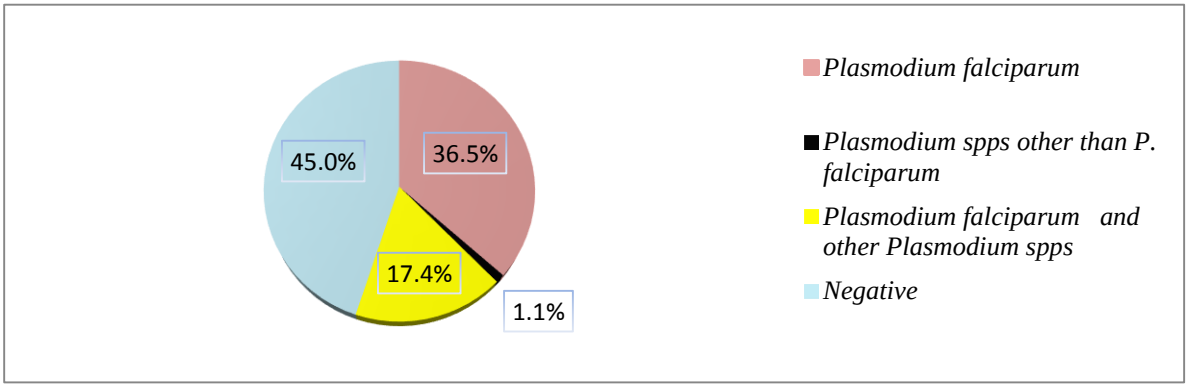

Figure 1: Frequency distribution of *Plasmodium* species among study participants using Rapid Diagnostic Test (RDT)

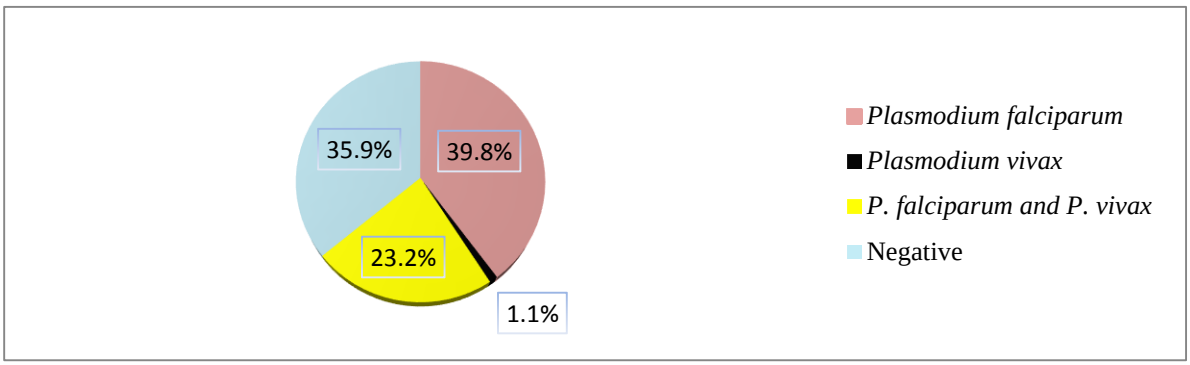

Figure 2: Frequency distribution of *Plasmodium* species among study participants using Microscopy (thin and thick blood film)

Table 1: Frequency distribution of *Plasmodium* species among study participants based on Sex using Rapid Diagnostic Test (RDT)

Sex	Positive for *P. f* N (%)	Positive for *P. f* and other malaria *spp* N (%)	Positive for Other malaria *spp* N (%)	Total positive N (%)	Negative N (%)	Total
Male	79 (21.5)	53 (14.5)	4 (1.1)	136 (37.1)	71 (19.3)	207 (56.4)
Female	67 (18.3)	32 (8.7)	0 (0.0)	99 (27.0)	61 (16.6)	160 (43.6)
Total	146 (39.8)	85 (23.2)	4 (1.1)	235 (64.1)	132 (35.9)	367 (100)

Key: *P.f* = *Plasmodium falciparum*, N=number, % = percentage

Table 2: Frequency distribution of *Plasmodium* species among study participants based on Sex using microscopy

Sex	Positive for *P. f* N (%)	Positive for *P. f* and Other malaria *spp* N (%)	Positive for Other malaria sppN (%)	Total positive N (%)	Total Negative N (%)	Total
Male	72 (19.6)	40 (10.9)	4 (1.1)	116 (31.6)	91 (24.8)	207 (56.4)
Female	62 (16.9)	24 (6.5)	0 (0.0)	86 (23.4)	74 (20.2)	160 (43.6)
Total	134 (36.5)	64 (17.4)	4 (1.1)	202 (55.0)	165 (45.0)	367 (100)

Key: *P. f* = *Plasmodium falciparum*, *P. v* = *Plasmodium vivax*, N = number, % = percentage

Table 3: Frequency distribution of malaria based on the age range of the study participants using RDT

Age range (years)	Positive for *P. f* N (%)	Positive for *P. f* and Other malaria sppN (%)	Positive for Other malaria spp N (%)	Total positive N (%)	Total Negative N (%)	Total
1- 5 years	40 (10.9)	14 (3.8)	2 (0.5)	56 (15.3)	36 (9.8)	92 (25.1)
6- 10 years	37 (10.1)	16 (4.4)	2 (0.5)	55 (14.9)	44 (11.9)	99 (26.9)
11-15years	57 (15.5)	34 (9.3)	0 (0.0)	91 (24.8)	85 (23.1)	176(48.0)
Total	134 (36.5)	64 (17.5)	4 (1.0)	202 (55.0)	165 (45.0)	367 (100)

N= number, *P. f* = *Plasmodium falciparum*, N = number,% = percentage

Table 4: Frequency distribution of malaria based on the age range of the study Participants using microscopy

Age range (years)	Positive for *P. f* N (%)	Positive for *P. f* and *P. v* N (%)	Positive for *P. v* N (%)	Total positive N (%)	Negative N (%)	Total
1- 5 yrs	43 (11.7)	19 (5.2)	2 (0.5)	64 (17.4)	28 (7.6)	92 (25.0)
6- 10 yrs	41 (11.2)	22 (6.0)	2 (0.5)	65 (17.8)	34 (9.3)	99 (27.1)
11-15 yrs	62 (16.9)	44 (12.0)	0 (0.0)	106 (28.8)	70 (19.1)	176 (47.9)
Total	146 (39.8)	85 (23.2)	4 (1)	235 (64.1)	132 (35.9)	367 (100)

N= number, *P. f* = *Plasmodium falciparum*, *P. v* = *Plasmodium vivax*, N = number, % = percentage

DISCUSSION

The prevalence of malaria parasitaemia among study participants using RDT was found to be 55.0%, but with microscopy, a higher prevalence rate of 64.1% was obtained. The specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) were also calculated. There were 202 true positives, 33 false positives, 132 true negatives, and 33 false negatives. There was no significant (x^2 = 0.090, *P* = 0.922) difference when the positivity of both tests was compared. RDT exhibited a sensitivity of 85.95% and specificity of 83.33%.PPV was 85.95% and NPV was 80%. Many studies comparing RDT and microscopy have revealed a very similar high sensitivity and specificity in the diagnosis of malaria (Azikiwe *et al.*, 2012; Ojurongbe *et al.*, 2013). In this research, microscopy was found to be more sensitive and specific than RDT, which is similar to what was obtained by (Uzochukwu *et al.*, 2009; Ojurongbe *et al.* 2013; Sani *et al.* 2013 and Garba *et al.*, 2016). Contrary to our findings, Batwala *et al.* 2011; and Kurup and Marks (2012); reported RDT as sensitive and less time-consuming than microscopy. This may be attributable to differences in methodology, type of RDT kit used and experience of the person that carried out the test. In this study, males had a relatively higher prevalence rate of 37% (n=136) of malaria parasitaemia compared with their female counterparts, with a prevalence rate of 27% (n=99). Similar reports had indicated a higher prevalence in males than females using both RDT and Microscopy (Ocheje and Dogara, 2016), but Gilles and Warrell (1993) reported a non-significant association between the sex of the study participants and test methods. However, this disagrees with later reports by Harchut *et al.* (2013) and Elechi *et al.* (2015), who reported a higher prevalence of malaria parasitaemia among female participants. An increased positivity rate with an increase in the age range of the study participants was observed for both RDT and microscopy. The highest prevalence of malaria was 28.9% (n=106) among the participants aged 11-15 years, while the lowest prevalence 17.5% (n=64) was found among 1-5 years age group, but this was not statistically significant. This is in consonance with what was obtained by Elechi *et al.* (2015), who reported a strong positive correlation between the prevalence and severity of malaria and the age range of the studied school children. Contrary to our findings, Acheampong *et al.* (2011) and Abeku *et al.* (2008) reported a decrease in malaria prevalence with an increase in the age range of the studied children. This may be due to differences in geographical location or related to the immunity status of the studied participants.

CONCLUSION

This study proves that microscopy is more accurate and sensitive in diagnosing malaria. It is important to note that negative malaria RDT results may not necessarily indicate an absence of a malaria parasite. The study recommends the use of microscopy following negative RDT cases.

Conflict of Interest Declaration: The authors hereby declare that they have no conflict of interest.

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