Original Article

Diagnostic Accuracy of Rapid Antigen Test for Malaria and Determinants of Heavy Malaria Parasitaemia in Children at the Nnamdi Azikiwe University Teaching Hospital, Nnewi, Nigeria

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ABSTRACT

Background: According to the United Nations Children's Fund, malaria kills a child every 30 s and about 3000 every year. Ninety per cent of the global burden of malaria occurs in sub-Saharan Africa. To reduce this burden, prompt recognition of risk factor, rapid diagnosis and immediate treatment are crucial.

Objective: This study evaluated the diagnostic accuracy of rapid diagnostic test (RDT) used in the diagnosis of malaria. It secondarily sought to determine factors that are associated with heavy malaria parasitaemia in children.

Methodology: This cross-sectional and descriptive study was conducted over a 5-month period. Children aged 6 months to 17 years, who had axillary temperature >37.4°C or history of fever in the past 48 h and who had not received a full course of artemisinin combination therapy were included. The patients were enrolled consecutively using purposive sampling methods. Blood samples for malaria parasite were collected from all participants using microscopy and RDT.

Results: Of the 246 participants enrolled, 58 and 188 tested positive and negative for malaria parasite using blood film microscopy (BFM). Of the 58 positive and 188 negative blood samples, 49 and 157 participants, respectively, were reactive and non-reactive for malarial antigen when the RDT was done. This gave RDT sensitivity of 84.5% (95% confidence interval [CI]: 80.3–88.7), specificity of 83.5% (95% CI: 81.1–85.9), false-positive rate of 16.5% (95% CI: 3.8–29.2), false-negative rate of 15.5% (95% CI: 11.9–42.9), positive predictive value of 61.3% (95% CI: 52.4–70.2) and negative predictive value of 94.6% (95% CI: 93.8–95.4). The overall diagnostic accuracy of the RDT was 83.8% (95% CI: 81.7–85.9). None of the respondent's clinicodemographic factors such as age, place of residence, socio-economic status, degree and duration of fever were significantly associated with heavy malaria parasitaemia in surveyed children.

Conclusion: The RDT is a good diagnostic tool and can be conveniently used in situation where rapid diagnosis of malaria parasitaemia is needed and/or where BFM is unavailable.

Key words: Children, malaria, microscopy, Nnewi, rapid diagnostic test

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INTRODUCTION

Malaria is a serious disease of childhood and is one of the top five causes of childhood mortality in many countries, especially in tropical Africa where transmission is stable.[1] Of the 35 countries that account globally for nearly 98% of malarial deaths, 30 are located in sub-Saharan Africa.[1] According to the 2017 World Malaria report, Nigeria bears more than 25% of the global malaria burden and 24% of malarial deaths.[2] Malaria accounts for 30% of under-five mortality and 25% of infant mortality in the country.[3] Malaria is holoendemic although studies have identified holoendemicity in the rural areas and mesoendemicity in the urban areas of the country.[4,5] In Nigeria, *Plasmodium falciparum* accounts for 94.1% of cases, *Plasmodium*

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malariae 1.6%, *Plasmodium ovale* 0.2% and mixed infections in 4.1% of cases.[4]

With global and regional efforts to control malaria and reduce this burden, early diagnosis and prompt treatment play very important roles.[3] To prevent irrational use of antimalarials which worsen the occurrence of drug resistance, it is absolutely necessary to make accurate diagnosis. Laboratory confirmation of malaria is currently recommended before treatment;[6] Giemsa microscopy and rapid diagnostic tests (RDT) are the two most commonly used. This involves identifying malaria parasites or antigens/products in the patient's blood. The identification and interpretation of malaria parasitaemia in a diagnostic test are influenced by many factors such as the parasite species involved, different stages of erythrocytic schizogony, the endemicity of different species, drug resistance, persisting viable and non-viable parasitaemia, sequestration of parasites in the deeper tissues and the use of chemoprophylaxis.[7,8]

The gold standard for the detection of parasites in peripheral blood is light microscopy of thick and thin peripheral blood smears.[9] This technique is largely accepted because of its simplicity, low cost, its ability to identify the presence of parasites, the infecting species and assess parasite density.[8] However, the staining and interpretation processes are labour intensive, time-consuming, require considerable expertise and have low sensitivity particularly at low parasite levels.[8] Hence, an expert microscopist and quality assurance are required to reduce errors and this is widely lacking in many malaria-endemic regions.[9]

RDTs, on the other hand, are tests that detect malarial antigen in a small amount of blood, usually 5–15 µl by immunochromatographic assay with monoclonal antibodies directed against the target parasite antigen.[7,8] It is simple to perform, easy to interpret and aids quick diagnosis that facilitates prompt treatment. Available ones target parasite antigens such as histidine-rich protein 2 (HRP2) specific for *P. falciparum*, aldolase (genus specific), lactate dehydrogenase (LDH) pan-specific, *P. falciparum*-specific *and Plasmodium vivax* specific.[7,8] Recently, a new RDT method has been developed for detecting *Plasmodium knowlesi* using monoclonal antibodies targeted against *P. knowlesi* LDH.[10] RDT performance for the diagnosis of malaria has been reported as excellent, and some reports from remote malaria-endemic areas have shown wide variations in sensitivity.[8] False-positive results are obtained due to the persistence of HRP2 antigen in the blood for several weeks following clearance of the infection.[8] Furthermore, some *P. falciparum* isolates have been found to lack the HRP2 gene, making HRP2-specific RDTs are unreliable.[9] Hence, it is recommended that RDT be used currently in conjunction with other methods to confirm the results, characterise infection and monitor treatment.[8]

Due to the occasional inaccessibility of microscopy for malaria diagnosis in resource-limited settings like ours, we sought to evaluate the diagnostic accuracy of the RDT and determine factors that are associated with severe malaria parasitaemia in children attending the children emergency and outpatient unit of the Nnamdi Azikiwe University Teaching Hospital (NAUTH) in Nnewi, Southeast Nigeria.

METHODOLOGY

Study area and design

This is a hospital-based, cross-sectional descriptive study carried out between 2nd June and 28th October 2016 at the NAUTH, Nnewi, one of the two tertiary institutions in Anambra state. Nnewi is a commercial city located in Nnewi North Local Government Area. Its population is 391,227 based on 2006 census estimate.[11] The people are predominantly Igbo speaking and mainly traders and civil servants. Nnewi is located on latitude 6°01' N of the equator and longitude 6°55' E of the Greenwich meridian.[12] It has a mean daily temperature of 30.4°C and mean annual rainfall of about 2000 cm.[12] It falls within the tropical rain forest region of Nigeria.[12] It has two main seasons: the rainy season spanning from April to October and the dry season spanning from November to March.[12] The Children Outpatient (CHOP) clinic of the NAUTH is not part of the general outpatient clinic of the Hospital but under the Paediatric Department. Even though NAUTH is a tertiary institution which is supposed to be a referral centre, the CHOP clinic functions as a primary, secondary and tertiary care facility as many patients from the community present there for the first time without any referral.

Study population

The study population consisted of children aged 6 months to 17 years who presented with fever at the CHOP clinic and children emergency room (CHER) of the hospital. Inclusion criteria included children aged 6 months to 17 years with axillary temperature >37.4°C or history of fever in the preceding 48 h[13] and children (<6 years) whose parents/caregivers gave consent or participants (≥6 years) who gave assent for the study. Excluded from the study are children whose caregivers refused to give consent for the study and children who were treated for malaria at a tertiary centre in the past 2 weeks. This is because the shortest incubation period of the malaria parasite is about 2 weeks,[13] and tertiary hospitals are most likely to comply with the national guidelines on the treatment of malaria.[14,15] Other included children on malaria prophylaxis before the onset of the extant illness and those ≥6 years who declined assent for the study.

Subjects' recruitment

The number of respondents enrolled in this study was calculated using the Cochran formula for calculation of sample size based on a confidence interval of 95% which is equivalent to a confidence coefficient of 1.96, malaria prevalence of 20% in febrile children[16] and a non-response rate of 5%. This gave a minimum sample size of 245. The sick children attending the CHOP and CHER were recruited consecutively using purposive sampling method. A resident doctor was trained as a research assistant by the investigators on the administration of the questionnaire.

Once consent/assent was given, the participant was screened by the investigator and/or the research assistant. The screening determined who was recruited into the study. Participants who fulfilled the inclusion criteria were recruited into the study. Information obtained included biodata of the participant such as age, sex, parental occupation and the highest educational level of either parent and place of residence. Socioeconomic class of the participants was grouped into low, middle and high class using Oyedeji social classification indices.[17] Other information obtained included the duration of fever before presentation, use of antimalarials and type of antimalarial taken.

Measures

The investigator performed a general examination on each participant assessing for pallor on the palpebral conjunctiva, buccal mucosa, palms and soles. Axillary temperature was taken using a digital thermometer (Domotherm® Germany, 0.2°C sensitivity). The tip of the thermometer was placed at the apex of the axilla and held in place with upper limb adducted till a beep was heard. The displayed reading, in centigrade to one decimal place, was taken as the participant's temperature.

Laboratory procedure

Two laboratory scientists trained and certified in malaria microscopy by the WHO assisted in preparation and reading of the thick and thin blood film for malaria microscopy. All the laboratory scientists who assisted in this study were blinded to the history and examination findings of the participants. Two millilitres of blood were collected from each participant and put in an ethylenediaminetetraacetic acid (EDTA) bottle, maintaining aseptic and universal safety precautions all through. A code number was assigned to each EDTA bottle. The blood collected was subjected to tests within 24 h of collection. Thin and thick malaria microscopy was done, and malaria parasite density was calculated using the following formula:[8]

$$\frac{\text{Number of parasites counted} \times \text{Total leukocyte count}}{\text{Number of leukocytes counted}} = \text{Parasite density}$$

The malaria parasite density was classified into the different parasite classes[18] as: (i) Class 1: 0 -< 50 (ii) Class 2: 50–<500. (iii) Class 3: 500–<5000 (iv) Class 4: 5000–<50,000 and (v) Class 5: ≥50,000. Parasite classes 1–3 were further recategorised to light parasitaemia while classes 4–5 were classified as heavy parasitaemia. The diagnosis of malaria was made by demonstrating the presence of plasmodium parasites in the peripheral blood by microscopy which is the gold standard.[9] RDT for malarial antigen was done for all participants using Bioline SD® from SD Diagnostics USA. This is an immunochromatographic test coated with monoclonal antibody that recognises specific HRP2 found in *P. falciparum*. The test uses 5–15 µl of blood and readable after 15 min following the manufacturer's instruction.

Ethical clearance

Ethical clearance was obtained from the Health Research and Ethics Committee of NAUTH, Nnewi, with reference number NAUTH/CS/66/VOL. 7/44. Informed consent was obtained from each caregiver and assent from children who were 6 years and above.

Data analysis

Data was analyzed using IBM® SPSS version 23.0 (SPSS Inc, Chicago, IL). The predictor and outcome variables were categorised accordingly, and association was compared using contingency tables such as the Chi-square or Fischer's exact analysis where appropriate. *P* value was considered statistically significant at <0.05.

RESULTS

Characteristics of children enrolled in the study

Three hundred and twenty-four children presented to the institution with complaints of fever and 246 (75.9%) met the inclusion criteria. Among the 78 (24.1%) children excluded, 22 (28.2%) had received a full course of Artemisinin-based combination therapy (ACT), 18 (23.1) had been treated in a tertiary centre for malaria in the past 2 weeks, 18 (23.1%) refused to give written consent/assent, 10 (12.8%) were on malaria prophylaxis and 10 (12.8%) did not have axillary temperature >37.4°C on presentation or history of fever in the past 48 h. Slightly over half (55%) of the recruited children were under 5 years old while the remainder were 5–10 years (23%) and over 10 years old (22%). The median age with interquartile range (IQR) was 4.3 years (IQR: 1.8–9.2) and the male-to-female ratio was approximately 1.45:1. One hundred and thirty-five (55%) of the respondents are resident in an urban setting and the other 111 (45%) lives in rural areas. Sixty-seven (27%), 95 (39%) and 84 (34%) were from the low-, middle- and high-socio-economic class, respectively. Majority of the respondents had mothers with tertiary or higher education (62%) while 26% and 12% had secondary and primary or no education [Table I].

Malaria prevalence and clinical characteristics in respondents

On the clinical parameters, 156 (63%) of the 246 respondents presented with fever and 55% (86/156) of these recorded temperature >38°C. Duration of fever was ≤1 day (29%), 2 days (22%), 3 days (16%), 4 days (19%) and ≥5 days in 14% of respondents with a median fever duration of 2 days (IQR: 1.0–4.0). Malaria parasite density on thick film was light (i.e., <5000 parasites per µL of blood) in 38 (66%) of the 58 films examined and heavy (i.e., ≥5000 per µL) in the remaining 34% of blood films. The median parasite density was 24,996 per µL (IQR: 2937–81,324). Finally, 77 (31%) of respondents had used antimalarial medication before presentation to the hospital. Of this number, 69% took artemisinin-based antimalarial drugs, 21% took quinine-based and 10% took sulphur-based antimalarial drugs [Tables I and II].

Table I: Characteristics of study respondents

Characteristics	Variables	*n* (%)
Sociodemographic parameters		
Age (*n*=246) (days)	<5	137 (55)
	5-10	56 (23)
	>10	53 (22)
Gender (*n*=246)	Male	145 (59)
	Female	101 (41)
Place of residence (*n*=246)	Urban	135 (55)
	Rural	111 (45)
Maternal education (*n*=246)	Primary or less	28 (12)
	Secondary	65 (26)
	Tertiary	153 (62)
Socioeconomic class (*n*=246)	Lower	67 (27)
	Middle	95 (39)
	Upper	84 (34)
Clinical parameters		
Degree of fever (*n*=246) (°C)	≤37.4	90 (31)
	>37.4-≤38	70 (28)
	>38	86 (35)
Fever duration (*n*=156) (days)	≤1	45 (29)
	2	34 (22)
	3	25 (16)
	4	30 (19)
	≥5	22 (14)
Malaria density (*n*=58) (per µL)	<5000	38 (66)
	≥5000	20 (34)
Prior use of antimalarial (*n*=246)	No	169 (69)
	Yes	77 (31)
Type of antimalarial used (*n*=77)	Artemether based	53 (69)
	Quinine based	16 (21)
	Sulphur based	8 (10)

Diagnostic performance of the rapid antigen test against the blood film microscopy

Table III shows the accuracy algorithm of the RDT used in this study against the blood film microscopy (BFM). A total of 58 of the 246 respondents tested for malaria were confirmed to have malaria parasite using the BFM under direct vision. Of these, 49 were reactive (i.e., positive test) for malarial antigen when tested with the RDT kit, while 9 were non-reactive (i.e., negative test). Similarly, of the 188 respondents that tested negative on BFM, 31 and 157 respondents, respectively, were reactive and non-reactive on RDT. This gives an RDT sensitivity of 84.5% (95% confidence interval [CI]: 80.3–88.7) and specificity of 83.5% (95% CI: 81.1–85.9). Correspondingly, the false-positive rate and false-negative rate (FNR) of the RDT was 16.5% (95% CI: 3.8–29.2) and 15.5% (95% CI: 11.9–42.9), while the positive predictive value (PPV) and negative predictive value of the RDT was 61.3% (95% CI: 52.4–70.2) and 94.6% (95% CI: 93.8–95.4). The sensitivity of the RDT was 33.3% at malaria parasite density of 50 to <500 per µL, 59.3% at density of 500–<5000 per µL and 95.5% and 100% at parasite density of 5000–<50,000 and ≥50,000, respectively [Table IV]. The overall diagnostic accuracy of the RDT was 83.8% (95% CI: 81.7–85.9). Figure 1 shows the receiver operating characteristics (ROC) of the RDT with reference to the BFM. The area under the curve on the ROC for the RDT was 0.840 (95% CI: 0.778–0.902).

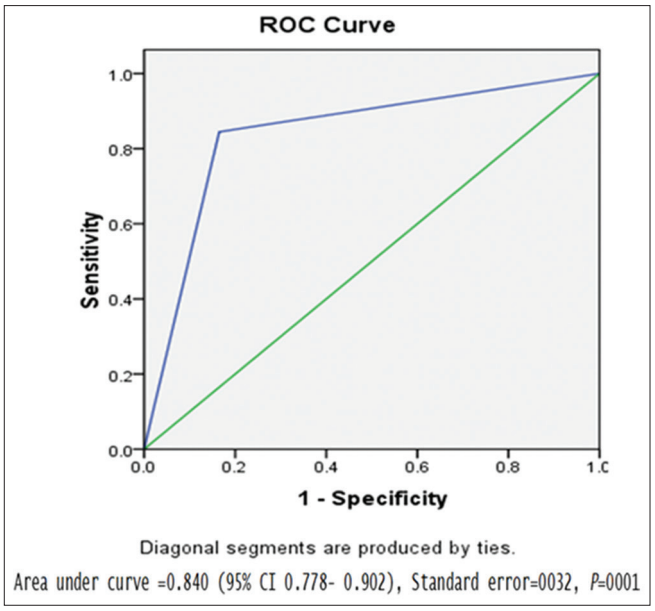

Figure 1: Receiver operating characteristic curve of the rapid diagnostic test used in the current study

Malaria parasite density and selected characteristics of respondents

Malaria parasite density was done for all patients who had a positive test for malaria using thick blood film. Table V shows malaria parasitaemia stratified by selected parameters of respondents. The median parasite density was 24,996 (IQR: 2937–81,324) per µL with a range of 494–3,938,534 parasites per µL of blood. Further analysis showed that more children under the age of 5 years (60%) had heavy parasitaemia compared to children 5–10 (20%) and >10 years (20%), $P = 0.069$. Similarly, higher proportion of male participants (65%) compared to females (35%) had higher parasite density ($P = 0.739$).

Furthermore, more respondents living in urban area (55% vs. 45% rural, $P = 0.258$) and those in the low (40%) and middle (40%) had heavy parasitaemia compared to those in the high socioeconomic class (20%), $P = 0.531$. Finally, it was noted that patients who presented to the hospital with fever duration of 48 h or less (55%) versus >48 h (45%), $P = 0.985$, those with fever level of >38°C (50%) versus <37.4°C (35%) and 37.4°C–38°C (15%), $P = 0.738$ and those who had not used antimalarial medication before presentation, 65% versus 35%, $P = 0.359$ had heavy malaria parasite density on thick film microscopy. None of these, however, attained statistical significance [Table V].

DISCUSSION

This study sought to evaluate the diagnostic accuracy of the malarial antigen test using the rapid diagnostic kits and to

Table II: Summary statistics of some respondents' clinicolaboratory parameters

Parameters	Age (years) (n=246)	Fever (°C) (n=246)	Fever duration (days) (n=246)	Malaria density (per μL) (n=58)
Median (IQR)	4.3 (1.8-9.2)	37.8 (36.9-38.4)	2.0 (1.0-4.0)	24,996 (2937-81,324)
Mean±SD	5.9±4.9	37.7±1.1	3.5±3.3	155,703±53,202
SE	0.31	0.07	0.21	69,857
Minimum	0.5	35.7	0.0	494
Maximum	17.9	40.3	21.0	3,938,534
Range	17.4	4.6	21.0	3,938,040

IQR: Interquartile range, SD: Standard deviation, SE: Standard error

Table III: Diagnostic accuracy of the malaria rapid diagnostic test

Parameters-RDT	Blood film		Sensitivity	Specificity	FPR	FNR	PPV	NPV
	Positive	Negative						
Reactive	49	31	49/58	157/188	31/188	9/58	49/80	157/166
Non-reactive	9	157	85%	84%	17%	16%	61%	95%
Total (95% CI)	58	188	80.3-88.7	81.1-85.9	3.8-29.2	11.9-42.9	52.4-70.2	93.8-95.4

FPR: False-positive rate, FNR: False-negative rate, PPV: Positive predictive value, NPV: Negative predictive value, CI: Confidence interval, RDT: Rapid diagnostic test

Table IV: Sensitivity of the rapid diagnostic test at different classes of malaria parasite density

Parameters	Malaria parasite density			Positive on BFM	Reactive on RDT	Sensitivity (%)
	Mean±SD	Minimum	Maximum			
Class 1	-	-	-	0	-	-
Class 2	494±0.00	494	494	3	1	33
Class 3	1795±1186	623	4847	13	7	54
Class 4	20,774±10,822	5735	42,091	22	21	96
Class 5	427,318±854,576	52,681	3,938,534	20	20	100.0

BFM: Blood film microscopy, RDT: Rapid diagnostic test, SD: Standard deviation

Table V: Malaria parasite density stratified by selected respondents' parameters

Characteristics	Variables	Numbers of children with malaria parasitaemia, n (%)		χ^2	$P^{\dagger}$
		Light (<5000 p/μL)	Heavy (≥5000 p/μL)		
Age (years) (n=58)	<5	11 (29)	12 (60)	5.340	0.069
	5-10	12 (32)	4 (20)		
	>10	15 (39)	4 (20)		
Gender (n=58)	Male	23 (61)	13 (65)	0.111	0.739
	Female	15 (49)	7 (35)		
Place of residence (n=58)	Urban	15 (40)	11 (55)	1.277	0.258
	Rural	23 (60)	9 (45)		
Socioeconomic class (n=58)	Low	17 (44)	8 (40)	1.264	0.531
	Middle	10 (26)	8 (40)		
	High	11 (28)	4 (20)		
Fever duration (n=58) (h)	≤48	21 (55)	11 (55)	0.001	0.985
	>48	17 (45)	9 (45)		
Degree of fever (°C) (n=58)	≤37.4	10 (26)	7 (35)	0.608	0.738
	>37.4-≤38.0	8 (21)	3 (15)		
	>38.0	20 (53)	10 (50)		
Prior use of antimalarial (n=58)	No	29 (76)	13 (65)	0.840	0.359
	Yes	9 (24)	7 (35)		

†Yates correction applied where applicable

ascertain factors associated with heavy malaria parasitaemia in febrile children.

Our study reported high accuracy of the diagnostic kit used in the rapid diagnosis of malaria in these children. It was noted

that compared to BFM, the RDT had a sensitivity, specificity and diagnostic accuracy within the recommended values by the World Health Organization.[19] It specifically noted a sensitivity of 84.5% which indicates that for every 100 children with febrile illness due to malaria, the RDT will be able to correctly diagnose approximately 85 of them. Conversely, with a specificity of 83.5%, the RDT will be able to correctly rule out malaria in approximately 84 of 100 children without malaria. This is quite impressive considering the rapidity and ease of carrying out this test, unlike the BFM which requires more technicality and takes several hours to be ready. Several studies[16,20,21] within and outside Nigeria have documented similar sensitivity and specificity for the RDT for malaria with values within ± 5% range. These small differences in values may be related to the difference in the manufacturers' specifications, storage and handling of the RDT kits in different settings.

In spite of the high sensitivity and specificity of the diagnostic kit noted in this study, the value of the FNR and the PPV calls for caution when using this test. It was found that the RDT had an FNR of 15.5%; in other words, 15 of every 100 febrile children will be falsely diagnosed as negative when they indeed have malaria parasitaemia. Furthermore, with a PPV of 65% seen in our study, this implies that only 65 of 100 febrile children that tested positive using the RDT would actually have malaria. It was similarly noted that the sensitivity of the RDT approached optimal accuracy when the parasite density was above 5000. A similar study in Nnewi reported FNR and PPV of 20.0% and 76.2%.[16] These scenarios could lead to both underdiagnosis and overdiagnosis of malaria in febrile children and consequent over prescription of antimalarial medication that could lead to resistance. It is, therefore, recommended that in places where BFM is not readily available for confirmation, clinical thoughtfulness should be applied in the use of RDT for malaria diagnosis.

Finally, our study reported that children under 5 years old were more prone to heavy parasitaemia compared to older children. Although statistical significance was not attained (probably due to small sample size), this finding is of utmost clinical significance. Based on authors' experiences working in the children emergency and outpatient units of the study centre, children under the age of 5 years more commonly presented with complication of severe malaria (such as anaemia, anaemic heart failure, renal failure and cerebral malaria which is a type of severe malaria with cerebral involvement.) due to heavy malaria parasitaemia. According to the United Nations Children's Fund,[22] in 2016 alone, there were 216 million malarial cases that led to 440,000 deaths. Of these, about two-thirds (290,000) were children under the age of 5. This translates into a daily toll of nearly 800 children under the age of 5 and most of these deaths occurred in sub-Saharan Africa.[22] This finding is also supported by a national wide study in South Sudan which showed that under-five children together with pregnant and people living with HIV were more at risk of mortality from severe forms of malaria parasitaemia.[23]

The strength of our study lies in the fact that children that presented with fever were diagnosed onsite using both microscopy and RDT by the WHO certified laboratory scientists and were prospectively followed up until discharge or death. However, because about a third of children enrolled in this study were self-medicated at home with antimalarial drugs before presentation to the hospital, there may have been some misdiagnosis and misclassification as regard to malaria parasitaemia and density. Consequently, this may have affected some of our study parameters and conclusion. We, therefore, recommend that the findings of this should be interpreted in light of this limitation.

CONCLUSION

This study shows that malaria is still very prevalent among children in Southeast Nigeria, and the use of the RDT for malarial antigen detection is significantly and well correlated to BFM for the diagnosis of malaria, especially in settings where microscopy is unavailable and/or prompt intervention is required. Caution must, however, be applied in its use.

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Conflicts of interest

There are no conflicts of interest.

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