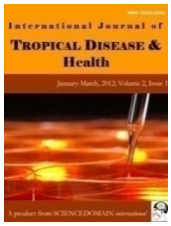

International Journal of TROPICAL DISEASE & Health
5(4): 269-275, 2015, Article no.IJTDH.2015.030
ISSN: 2278–1005

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Challenges of Malaria Diagnosis in Paediatric Patients at a Nigerian Hospital

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Authors' contributions

This work was carried out in collaboration between all authors. Author REO conceived the study and drafted part of the manuscript, author OKI analysed the data and drafted the manuscript, author BO participated in the design of the study and coordination of data collection, author BB helped to draft the manuscript. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJTDH/2015/9965
Editor(s):
(1) Thomas I Nathaniel, Department of Biomedical Sciences, School of Medicine -Greenville, University of South Carolina, Greenville, USA.
Reviewers:
(1) Soumya Mishra, Department of Physiology, KIMS, KIIT University, Bhubaneswar, Odisha, India.
(2) Anonymous, National Institute for Medical Research, Tanzania.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=850&id=19&aid=7310

Original Research Article

Received 10th March 2014
Accepted 30th May 2014
Published 15th December 2014

ABSTRACT

Aims: This study compares the performance of routine malaria diagnostic tests, and explores the challenges of malaria diagnosis in paediatric patients in an endemic setting in South West Nigeria.
Study Design: Cross sectional study
Place and Duration of the Study: The study was conducted at the children's outpatient and emergency units of the University College Hospital, Ibadan, Nigeria. Patients seen between May and August, 2013 were enrolled in the study.
Methodology: The records of all 532 children aged six months to12 years who received treatment for an acute febrile illness at the hospital during the study period were reviewed. The proportion of children classified as having malaria by clinical diagnosis, Rapid Diagnostic Test (RDT) and blood smear microscopy were compared. Factors associated with test positivity were explored using multivariate analysis.
Results: By clinical diagnosis 45.2% of children were diagnosed as having malaria, 37.6% tested

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positive to malaria parasite on RDT and 19.3% had positive blood smears on microscopy. Logistic regression showed that with RDTs, younger children were less often found to be positive than older children [OR: 0.594 (0.401-0.879)]. A similar lower probability of positivity was found for younger children on microscopy [OR0.624 (0.391-0.996)]. Positive smears were however recorded 3.9 times more often for those who gave a history of fever compared to those who did not [OR: 3.882 (1.154-13.057)].

Conclusion: The true malaria morbidity among these paediatric patients remains questionable due to the differences in the results produced by the different diagnostic methods. The clinical implication of RDT-positive but microscopy-negative samples may be grave if microscopy results are erroneous. Quality control systems and surveillance of routine malaria diagnostics are imperative to limit misdiagnosis of malaria in this endemic setting.

Keywords: Malaria; rapid diagnostic tests; microscopy; paediatric; Nigeria.

1. INTRODUCTION

Malaria morbidity and mortality among Nigerian children is one of the highest in the world [1]. Prompt diagnosis and treatment have been identified as critical factors to reducing this burden [2]. A diagnostic challenge in malaria endemic areas has been the non-specific clinical symptoms of malaria which makes laboratory confirmation necessary in any febrile child [2]. Microscopy has long been the standard of malaria diagnosis, but newer diagnostic tests have now been introduced particularly in peripheral health care settings [3]. Many of the new rapid diagnostic tests for malaria are usually compared with microscopy as the gold standard. However, in the absence of expert microscopists, errors in microscopy make it difficult to assess the reliability of these new diagnostic techniques in routine settings [4]. Lack of adherence to malaria test results has led to concerns about the capacity of African health systems to implement the policy of laboratory-confirmed malaria in children [5]. In many places endemic areas clinical diagnosis of malaria has continued and this has been attributed to several factors [5]. Nigeria like other malaria endemic countries in sub-Saharan Africa has had a challenge reaching the goal of universal testing in line with the WHO's recommendation [6]. In implementing this policy, it is important to also identify how to do so effectively and efficiently, while avoiding potential problems associated with malaria diagnosis [7]. In the era of evidence based medicine, it is often necessary to provide additional context specific evidence from routine clinical settings to assess the challenges with implementing confirmatory diagnostics in the management of malaria in endemic settings in Nigeria. This study compares the performance of available malaria diagnostic tests, and explores the challenges of malaria diagnosis among paediatric patients in an endemic setting in South West Nigeria.

2. MATERIALS AND METHODS

The study was conducted at the children's outpatient and emergency units of the University College Hospital, Ibadan. The hospital serves as a referral hospital for South West Nigeria. The hospital is located in Oyo state, South West Nigeria, a region with the highest malaria parasite prevalence of 50.3% among children under 5 years [8]. In Nigeria, peak malaria transmission occurs during the rainy season from April to October each year. Transmission in South West Nigeria is holoendemic and occurs all year round. *Plasmodium falciparum* is responsible for 97.3%, of all malaria infections in South West Nigeria [8].

All 532 children aged six months to 12 years who received treatment for an acute febrile illness at the hospital between May and August, 2013 were recruited for the study. Patients were recruited from the children's out-patient department and the Children's Emergency Ward, of the University College Hospital Ibadan over this four month period.

Using a cross sectional design, the record of patients seen over the study period were reviewed to assess malaria diagnostic practices. Rapid diagnostic tests had been recently introduced at out-patient departments to augment diagnosis with microscopy. Prior to the study all clinicians were informed to request for RDTs in parallel with microscopy for all febrile children presenting at paediatric entry points of the hospital.

The documented clinical diagnosis before laboratory test, malaria rapid diagnostic tests

result and microscopy examination of blood smears results was compared. The RDTs and smears were done independently by personnel in different laboratories.

The SD Bioline[R] kit for the detection of *P. falciparum* specific histidine rich protein-2 (Pf.HRP-2) was used for all tests. SD Bioline RDT is WHO approved with reported sensitivity and specificity of 90.2% and 98.5% for *P. falciparum* under routine conditions [9]. The test uses a rapid antigen capture assay in a lateral flow immunochromatographic test, similar to a pregnancy test, with a visual result in <15 min.

The protocol for malaria diagnosis in the routine malaria laboratory is Giemsa stained thick and thin blood smears. Asexual *Plasmodium falciparum* parasites identified were counted against 200 white blood cells. Smear was declared negative if no parasites were found after examining 100 high power fields. Microscopy was performed by the usual laboratory scientists in the hospital.

The primary outcome measure was the proportion of children classified as having malaria by clinical diagnosis, RDT and blood smear microscopy. Malaria diagnosis was compared for children under five years and those five years and older. Diagnosis was also compared based on records of axillary temperature readings (<37.5°C or ≥37.5°C) at presentation using the Chi-square test.

The dataset was analyzed using appropriate tests in StatsDirect[R] version 2.8.0 software. Binary logistic regression analysis was used to explore factors associated with positive RDT and Microscopy results.

3. RESULTS AND DISCUSSION

3.1 Patient Characteristics

Out of the 532 records of children seen during the study period, only 525 were used as seven had either microscopy or RDT test result missing. There was no difference in the characteristics of children with missing records compared to those used for the study. The median age of children was 2.2 years (IQR: 1.0-5.1 years). The proportion of male children was higher than that of females (57.1%: 42.9%). The common presenting complaints were history of fever (91.4%) and vomiting (42%) (Table 1). Previous drug treatment for malaria was reported by 46.3%.

Table 1. Demographic and clinical characteristics of children

Demographic and clinical characteristics	N=525 (%)
Age group	
<5 years	364 (69.5)
5 years and above	160 (30.5)
Sex	
Male	299 (57.1)
Female	226 (42.9)
***Presenting symptoms**	
Fever or history of fever	479 (91.4)
Vomiting	223 (42.0)
Chills	26 (4.9)
Headache	36 (6.8)
Duration of symptoms before presentation	
≤ one day	101 (19.0)
2-3 days	236 (44.4)
≥4 days	178 (33.5)
Drug history	
Artemisinin –based Combination drugs	182 (34.6)
Chloroquine	15 (2.9)
Quinine	10 (2.0)
Sulphadoxine-Pyrimethamine	4 (0.1)
**Others	35 (6.7)
No drug	279(53.7)

**multiple response **Amodiaquine, herbal medicine, Paludrine, unknown injections*

3.2 Diagnosis of Malaria

The Venn diagram (Fig. 1) displays the distribution of positive malaria test results. Clinical diagnosis had 120 suspected malaria cases not confirmed by RDT or Microscopy. RDT had 99 positive malaria tests which did not agree with microscopy. Of these, 48 (48.5%) had been on malaria treatment prior to presentation.

While the diagnosis of malaria was significantly higher for older children for all diagnostic modalities, there was no significant difference in diagnosis based on the presence of fever among children of different age groups. Clinical diagnosis estimated 7.6% more children as having malaria than did RDT and 26.1% more than microscopy (See Table 2).

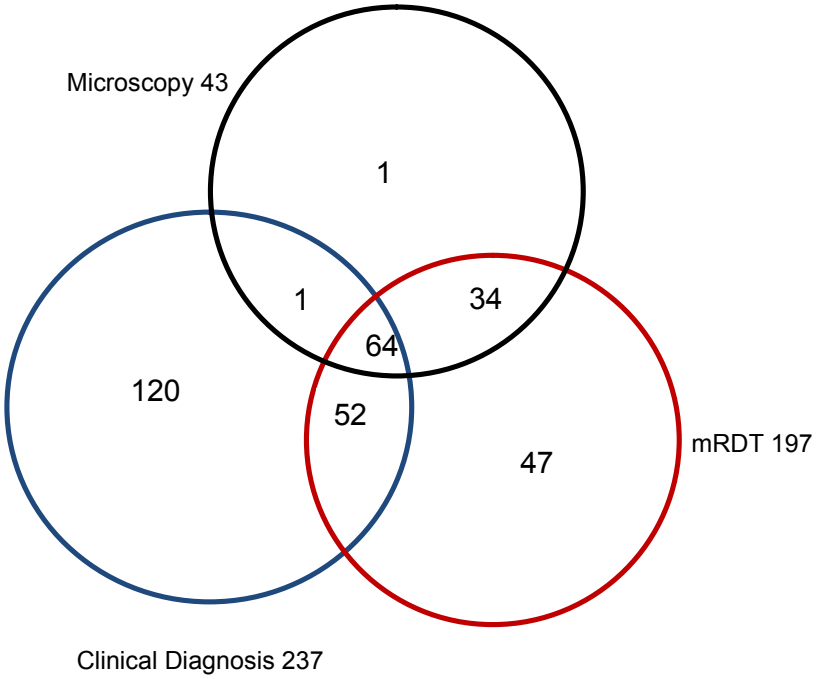

Fig. 1. Malaria diagnosis by treatment modality

Table 2. Proportions of children diagnosed with malaria using different modalities stratified by age and presence of fever

Diagnosis modality	Age <5 years N (%)	Age ≥ 5 years N (%)	Total N (%)	P value
Clinical diagnosis of malaria	153 (42.0)	84 (52.5)	237(45.2)	0.027
Positive RDT	123 (33.8)	74 (46.3)	197 (37.6)	0.007
Positive blood film on microscopy	60 (16.5)	40 (25.0)	100 (19.3)	0.022
Positive to both RDT and microscopy	59 (16.2)	39 (24.4)	98 (18.7)	0.027
Diagnosis modality	**Temperature <37.5**	**Temperature ≥ 37.5**	**Total N (%)**	**P value**
Clinical diagnosis of malaria	105 (46.5)	127 (44.3)	237 (45.2)	0.618
Positive RDT	81 (35.8)	115 (40.1)	197 (37.6)	0.328
Positive blood film on microscopy	39 (17.3)	61 (20.9)	100 (19.3)	0.298
Positive to both RDT and microscopy	38 (16.8)	60 (20.6)	98 (18.7)	0.282

3.3 Predictors of Test Positivity

Tables 3 and 4 indicate the factors associated with RDT positivity and Smear positivity for the patients. With RDTs, younger children were less often found to be positive than older children [OR: 0.594 (0.401-0.879)]. A similar lower probability of positivity was found for younger children on microscopy [OR0.624 (0.391-0.996)]. Positive smears were however recorded 3.9 times more often for those who gave a history of fever compared to those who did not [OR: 3.882 (1.154-13.057)].

4. DISCUSSION

This article reviews daily clinical practice of malaria diagnosis comparing three frequently used diagnostic modalities in a Nigerian tertiary hospital setting. The prevalence of malaria of 19.1% as detected by routine microscopy was lower than the expected 50.3% for a peak transmission period in a high malaria endemic region of Nigeria [8]. In the absence of other superior confirmatory tests microscopy is often used as the gold standard in clinical practice in this setting. Although previous studies show that RDT often overestimate malaria prevalence

relative to microscopy [9], the difference of 18.5% observed in this study was larger than expected and raises the possibility of false negatives on microscopy. Some bias in the microscopy result is apparent as a history of fever significantly affected results but not objective clinical evidence of fever using axillary temperature. This implied microscopy error with possible missed malaria diagnosis would have dire consequences if patients are left untreated. This may be responsible for the often documented practice of clinicians continuing to treat patients with negative microscopy results for malaria [10]. Other studies have also reported limitations in microscopy in routine settings [11,12]. Thus, the possibility of a superior performance of RDT to routine microscopy which has been documented in other studies needs to be considered in this setting as well [13]. This diagnostic challenge with microscopy has serious implications for referral centres tasked with the responsibility of making definitive malaria diagnosis since RDT use in often limited to peripheral health care settings [9].

Useful as RDTs are, the tendency for false positive result also raises concern about the possibility of over treatment. In the situation where more than 40% of those having diagnostics done had previously received antimalarial treatment, the line between positives and negatives becomes blurred. Persistent antigenicity for as much as 37 days after malaria treatment has been demonstrated for HRP2-based RDTs [14]. As such, for patients returning with symptoms within two to four weeks of treatment, RDTs may not be the best malaria diagnostic test [14]. The evidence of parasitaemia also needs to be interpreted with caution since finding malaria parasites in an ill person in highly endemic regions does not necessarily mean that the illness is caused by the parasites and other tests may be necessary to explore other causes of fever [15]. Patients testing negative on RDT can however be considered less likely to have malaria as such further testing with routine microscopy may not be required [16].

Table 3. Predictors of RDT positivity

Variable	Odds ratio (95% confidence interval)	*P* value
Sex (male)	0.834 (0.576-1.207)	.34
Sex (female)	referent	
History of fever (yes)	1.598 (0.798-3.201)	.19
History of fever (no)	referent	
Sign/symptom of severe illness (absent)	0.869 (0.5361-0.410)	.57
Sign/symptom of severe illness (present)	referent	
Age group (<5 years)	0.594 (0.401-0.879)	**.009**
Age group (≥5 years)	referent	
Temperature at presentation (<37.5°C)	0.868 (0.5911-0.274)	.47
Temperature at presentation (≥37.5°C)	referent	
Previous use of antimalarial (No)	0.745 (0.5141-0.080)	.12
Previous use of antimalarial (Yes)	referent	
Illness duration (days)	0.994 (0.9531-0.036)	.77

Table 4. Predictors of blood smear positivity on microscopy

Variable	Odds ratio (95% confidence interval)	*P* value
Sex (male)	1.102 (0.6981-0.738)	.68
Sex (female)	referent	
History of fever (yes)	3.882 (1.154-13.057)	**.03**
History of fever (no)	referent	
Sign/symptom of severe illness (absent)	0.961 (0.531-1.739)	.90
Sign/symptom of severe illness (present)	referent	
Age group (<5 years)	0.624 (0.391-0.996)	.048
Age group (≥5 years)	referent	
Temperature at presentation (<37.5°C)	0.951 (0.597-1.516)	.83
Temperature at presentation (≥37.5°C)	referent	
Previous use of antimalarial (No)	0.863(0.548-1.359)	.53
Previous use of antimalarial (Yes)	referent	
Illness duration (days)	0.966(0.906-1.031)	.30

Findings from this study show that clinical diagnosis overestimated malaria among patients relative to RDTs and Microscopy and does not seem very useful in making malaria diagnosis with certainty [17]. This buttresses the need for parasite based diagnosis. However the choice of which malaria test to use needs the clinician to take into consideration the patients' circumstances and the available skill for diagnosis.

5. CONCLUSION

This study highlights the attendant challenges with decision making that clinicians may face in the use of malaria diagnostic tests in clinical practice in a Nigerian hospital. The low confidence in malaria test results which is often reported may be related to the observed performance of malaria tests in routine settings. The true malaria morbidity among these paediatric patients remains questionable due to the differences in the results produced by the different diagnostic methods. RDTs appear to have the potential to improve routine diagnostics, but the clinical implication of the many RDT-positives, Microscopy-negative samples may be grave if microscopy results are erroneous. For the policy of universal testing to be effective in Nigeria, quality-control systems and surveillance of routine malaria diagnostics are imperative.

CONSENT

Not applicable.

ETHICAL APPROVAL

The patient data retrieved from records were anonymous and all information were routine information collected in the course of routine clinical practice. All data analysed were collected as part of routine diagnosis and treatment. Approval to use patient data was given by the head of the paediatrics department.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=850&id=19&aid=7310