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FEVER SENSITIVITY AND ITS ATTRIBUTABLE FRACTION IN MALARIA DIADGNOSIS AMONG CHILDREN IN MAKURDI NIGERIA

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ABSTRACT
Fever (axillary temperature ≥ 37.5 ºC) is no more recommended for clinical diagnosis of malaria for treatment, but in practice, the use of fever to diagnose malaria is not completely abandoned. This study investigated the sensitivity of fever in malaria diagnosis and its attributable fractions in children. Some 1738 children aged 0-14 years, half with fever and another half without fever were enrolled in a case control study in Makurdi. Fever, Giemsa stained thick blood films, and expert microscopy were used to diagnose malaria, and determine the sensitivity of fever, and its attributable fractions among the children. The sensitivity of fever, specificity, and positive predictive values decreased as the children's age rose, while the negative predictive value increased across the age groups. Sensitivity of 71.3 %, (95 % CI: 64.4 % - 78.2 %) in < 5 years old children decreased to 50.0 %, (95 % CI: 57.1 % - 77.1 %) in 10 – 14 years old, while specificity of 58.5 %, (95 % CI: 53,7 % - 63.3 %) declined to 52.9 %, (95 % CI: 48.5 % –59.3 %). Malaria attributable fraction of fever (MAFF) and population attributable fraction (PAF) also declined from 70.5 % to 56.3 %; and 29.3 % to 11.0 % respectively. These results suggest that the continuous use of fever for malaria diagnosis may identify some cases of the disease among children, but a large proportion of fevers seen in children may not be due to malaria.

Key words: Fever, Malaria, Diagnosis, Attributable Fraction

INTRODUCTION

One of the most recognizable symptom of malaria is fever (Bartoloni and Zammarchi, 2012), defined as the axillary temperature of ≥ 37.5 ºC (Mabunda *et al*., 2009). Infection with human *Plasmodium* species produces varying degrees of fever, but *Plasmodium falciparum* in particular produces very high fevers that are accompanied by chills and other clinical features (Senn *et al*., 2014). The association of fever with malaria made it possible, the presumptive diagnosis of malaria using fever as a marker for malaria diagnosis in the past (Rougemont *et al*., 1991; Okiro and Snow 2010). The use of fever as a marker in the presumptive diagnosis of malaria for the management of the disease was recommended in the integrated management of childhood illness (IMCI) in malaria endemic countries (WHO/UNICEF 1999). Although it is no longer recommended in recent times, areas with deficient resources in the management of malaria still depend on it. However, not all fevers can be attributed to malaria, since many infectious agents that cause fevers are also prevalent in malaria endemic settings (Prasad *et al*., 2015; Hildenwall *et al*., 2016; Asante *et al*., 2016). Consequently, it may be difficult to distinguish fevers of malaria origin from those of other infectious agents even when it is *Plasmodium falciparum* that is causing the fever. The malaria attributable fraction of fever (MAFF) is usually estimated in order to determine which proportions of fever can be deemed to be due to malaria in the presence of many possible agents that can induce similar fevers (Bisoffi *et al*., 2012). It is defined as the proportion of fevers among malaria infected patients that would not have occurred in the absence of malaria infection (Bisoffi *et al*. 2010). Estimates MAFF are important in providing information on the burden of malaria in an area. Moreover, its dynamics over time can indicate the successes or failures of malaria interventions in a given locality (Koram and Molyneux, 2007; Mabunda *et al*., 2009).

The diagnosis of malaria for treatment has traditionally relied on microscopic analysis for confirmation of the presence of malaria parasites (WHO 2009). Microscopy is still the gold standard for malaria diagnosis albeit the challenges associated with its use for the purpose of malaria diagnosis in malaria endemic countries (Kahama-Maro *et al*., 2011, Oladokun *et al*., 2015, Ikpa *et al*., 2017). In many rural areas where the burden of malaria was and still remains very high, lack of access to quality laboratory facilities for reliable malaria diagnosis, has led to persistent reliance on presumptive diagnosis of malaria using fever as a marker (Okeke *et al*., 2006). In recent period in Nigeria, hospitals and clinics located in the cities and urban centres, have rapidly adopted the use of malaria rapid diagnostic tests (RDTs). The RDTs are commonly used nowadays for diagnosis and treatment of suspected cases of malaria fevers in line with current recommendations (WHO 2010). However, in the rural areas, and even in some urban areas, both mix of malaria RDT testing of fevers, and presumptive diagnosis of malaria using fever as a marker for malaria infection is still common. To many people who believe in self-treatment of fevers as malaria, it does not matter whether they reside in an area where it is possible to carry out proper diagnosis of the fever or not. Every case of fever prompts the purchase and consumption of antimalarial drugs to alleviate the fever (Ladner *et al*., 2017).

Globally, the prevalence and incidence of malaria has significantly declined (WHO, 2015; WHO, 2016) such that most fevers may not be due to malaria. In Nigeria which is a top malaria endemic country, there is very little data on the estimates of MAFF (Owolabi *et al*. 2016). The aim of this study was to determine the sensitivity and specificity of fever as a marker for malaria diagnosis in an area of endemic malaria, using microscopy as a reference standard. In addition, the malaria attributable fraction of fever and the population attributable fraction (PAF) were also determined among children 0 - 14 years old stratified by age. This was to ascertain how the reliance on fever as a marker for malaria diagnosis and treatment in recent period may impact the management of malaria among children in Nigeria. Moreover, the study also aimed to demonstrate the level of the burden of malaria that could be reduced among the children using estimates of malaria attributable fraction of feverOne of the most recognizable symptom of malaria is fever (Bartoloni and Zammarchi, 2012), defined as the axillary temperature of ≥ 37.5

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MATERIALS AND METHODS

Study area: the study was conducted in Makurdi the Benue State capital. Makurdi is located at latitude 7 ^{0}44'27"N and longitude 8^{0}30'43"E. Sample collection lasted from April 2016 to March 2017.

Study design and sample size: the design was a case control study. A sample size of 869 fever cases and 869 controls were enrolled. Both cases and controls were grouped according to three age classification among the subjects. The number of subjects who consented to the study were consecutively enrolled in to each of the three age categories of < 5 years old, 5-9 years old, 10-14 years old. The number of cases versus controls enrolled into each of the age categories were: 290 versus 289; 288 versus 289 and 291 versus 291 respectively.

Study subjects: these were children aged between 0-14 years old, drawn from a longitudinal population of those with fever, and without fever whose parents brought them for medical care at the Epidemiological Centre in Makurdi. The inclusion criteria were the presence of fever experienced by the child at the time of reporting to epidemiological centre with axillary temperature ≥ 37.5 °C. Also recruited as controls subjects were children who reported to the epidemiological centre for other purposes, but had no evidence or fever. The exclusion criteria were children whose conditions for reporting to the unit needed urgent medical attention. Parents who presented with their children were informed of the study, and informed consent to enrol the child was sought. Those who gave oral or written informed consent had their children enrolled in the study. Prior to blood sample collection, parents were asked to indicate if there had been any evidence of fever experienced by the child within in the last 48 hours. The axillary temperature of the child was obtained with a digital thermometer before blood sample collection.

Blood sample collection: blood was collected using a sterile disposable lancet to prick the left thumb after cleaning the thumb with methylated spirit. A few drops of blood were collected on a grease free microscopy slide, which was used to prepare a thick blood film and allowed to air dry for 1 hour. The thick blood film was stained with 10% Giemsa stain for 10 minutes, washed in distilled water and allowed to air dry before screening for the presence of malaria parasites. on a microscope using the 100 (s) oil immersion objective at a total magnification of 1000×.

Microscopy examination of thick blood films for malaria parasites and quantification of parasite load: Two independent expert microscopists examined the thick blood films using 200 fields of the oil immersion objective. A few of the thick blood films with discordant results were collected and examined by a third microcopist whose decision was considered to be final. In order to estimate the parasitaemia, a tally counter was used to count the

number of parasites seen per 200 white blood cells. The total counts were multiplied by 40 to yield the asexual blood parasites per micro litre (µl) of blood (WHO, 2009). To determine the effect of asexual parasite load on the presence or absence of fever, the asexual parasite load was grouped two fold ranging from 1-200 - >12800 parasites/µl of blood, and the number of children with fever, or without fever, bearing asexual parasites were tallied in each group and analysed.

Estimation of Sensitivity, specificity, positive predictive value and negative predictive values of fever as a marker for malaria diagnosis: the total number of subjects enrolled for blood collection were classified into four mutually exclusive categories based on the results of microscopy examination of each individuals thick blood film for the presence or absence of malaria parasites as a reference standard. The classifications were: presence of fever/microscopy positive as true positives (TP) and presence of fever/microscopy negative as false positive (FP), absence of fever/microscopy positive as false negative (FN) and absence of fever microscopy negative as true negative (TN). Sensitivity was estimated as TP/(TP+FN), specificity as TN/(TN+FP), positive predictive value as TP/(TP+FP), negative predictive value as TN/(TN+FN) (Banoo *et al*., 2010). The estimated parameter in each case was multiplied by 100% to determine the percentage value.

Estimation of malaria attributable fractions of fever (MAFF) and population attributable fractions of fever (PAF): the malaria attributable fractions of fever in each age category was estimated using the odd ratio (OR) method for a case control study where patients with fever were classified as cases, while those without fever as controls. The formula was AF= OR-1/OR, while the population attributable fraction was estimated as the prevalence of parasitaemia in the febrile group multiplied by the attributable fraction in each age category (Bisoffi *et al*., 2010).

Statistical Analysis

A 2 by 2 contingency table was used to analyse the data on sensitivity, specificity, positive predictive, and negative predictive values using the Clinical Research Calculator 3 online, available at http://www.vassarStats.net. The estimated values of the Chi-square (χ^2) and its associated probability as well as the odd ratio (OR) value for each age group was obtained.

RESULTS

The median ages of children examine in the different age groups both with and without fever at the time of enrolment were 3 years in the < 5 years old group, 8 years in the 5-9 years old, and 11 years in the 10-14 years old category. Out of 1738 children that were examined, the overall prevalence of malaria parasites among the children enrolled in the study was 20.4 % (355/1738). When partitioned between febrile cases (study group) and the non-febrile cases (control) group, the prevalence was 27.7 % (241/869) and 12.0 % (104/869) respectively. Among the children less than 5 years old which had fever that were examined by microscopy, 41.0 % (119/290) had malaria parasites. The comparable cases of positive parasitaemia in the other age groups with fever were 22.7 % (65/288) and 19.6 % (57/291) in the age groups 5-9 years and 10-14 years respectively. Among the group of children without fevers, parasitaemia ranging from 1-3200 asexual parasites/µl of blood was also detected in 16.6 % (48/289), 9.7 % (28/289) and 9.6% (28/291) of the children, corresponding to age groups < 5 years old, 5-9 years old, and 10-14 years old (Tables 1 and 3).

Table 1. Diagnosis of malaria in children with or without a fever.

Age category	Fever diagnosis	Microscopy diagnosis		Total (%)	Odd ratio (95% CI)	χ^2 (P – values)
		Positive (%)	Negative (%)			
< 5 years n = 579	Positive	119 (41.0)	171 (59.0)	290 (100)	3.49 (2.37 - 5.15)	42.08 (<0.001)
	Negative	48 (16.6)	241 (83.4)	289 (100)		
	Total	167	412	579		
5-9 years n = 577	Positive	65 (22.6)	223 (77.4)	288 (100)	2.72 (1.69 – 4.38)	17.7 (<0.001)
	Negative	28 (9.7)	261 (90.3)	289 (100)		
	Total	93	484	577		
10-14 years n = 582	Positive	57 (19.6)	234 (80.4)	291 (100)	2.29 (1.41 – 3.72)	11.59 (= 0.001)
	Negative	28 (9.6)	263 (90.4)	291 (100)		
	Total	85	497	582		

The sensitivity of fever in malaria diagnosis, using microscopy as a gold standard was 71.3 % in children < 5 years old but decreased in the remaining age groups to 69.9 % and 50.0 %. Specificity also decreased consecutively from 58.4 % in children < 5 years old to 52.9 % in the oldest age group. A similar decreasing trend was also observed with the positive predictive value among the age groups. In contrast, the negative predictive value increased from 83.4 % in children < 5 years old to 90.4 % in the oldest age group. The MAFF and PAF both decreased as age increased with the highest value of each parameter recorded in the children < 5 years old, while the smallest value of each parameter was obtained among children aged 10-14 years (Table 2).

Table 2. Estimated parameters using fever as a marker for malaria diagnosis in children

Parameters	Age category		
	< 5 years old	5-9 years old	10-14 years old
% Sensitivity (95 % CI)	71.3 (64.4 – 78.2)	69.9 (60.6 - 79.2)	50.0 (57.1 - 77.1)
% Specificity (95 % CI)	58.5 (53.7 – 63.3)	53.9 (49.5 – 58.3)	52.9 (48.5 – 57.3)
% PPV (95 % CI)	41.0 (35.3 – 46.7)	22.6 (17.8 – 27.4)	19.6 (15.0 – 24.2)
% NPV (95 % CI)	83.4 (79.1- 87.7)	90.3 (86.9 – 98.7)	90.4 (87.0 – 93.8)
% MAFF	70.5	63.2	56.3
% PAF	29.3	14.3	11.0

PPV: positive predictive value, NPV: negative predictive value, CI: confidence interval,
MAFF: malaria attributable fraction of fever, PAF: population attributable fraction.

The median range of asexual blood parasites/µl of blood among the febrile group of children was 401-800 in children < 5 years old, and 1601-3200 in the latter two groups. In the children without fever, the median parasite range was 1-200 asexual parasites/µl of blood in the two groups of children < 5 years old and 10-14 years old. In the children aged 5-9 years however, the median range of parasitaemia was 201-400 parasites/µl of blood (Table 3).

Table 3. Malaria parasite load in children of different ages

Parasite load/µl of blood	Children < 5 years		Children 5-9 years		Children 10-14 years	
	Fever n (%)	No fever n (%)	Fever n (%)	No fever n (%)	Fever n (%)	No fever n (%)
1-200	4 (3.4)	45 (93.8)	3 (4.6)	12 (42.9)	5 (8.8)	22 (78.6)
201-400	10 (8.4)	3 (6.2)	2 (3.1)	5 (17.9)	8 (14.0)	4 (14.3)
401-800	49 (41.2)	-	3 (4.6)	8 (28.6)	2 (3.5)	1 (3.6)
801-1600	17 (14.3)	-	1 (1.5)	2 (7.1)	13 (22.8)	1 (3.6)
1601-3200	25 (21.0)	-	26 (40.0)	1 (3.4)	4 (7.0)	-
3201-6400	7 (5.9)	-	8 (12.3)	-	2 (3.5)	-
6401-12800	1 (0.8)	-	17 (26.2)	-	21 (36.8)	-
>12800	6 (5.0)	-	5 (7.7)	-	2 (3.5)	-
Total	119 (100)	48 (100)	65 (100)	28(100)	57 (100)	28 (100)

DISCUSSION

Malaria is still prevalent in sub Saharan Africa where the local environment permits the transmission of the disease. In Nigeria, *P. falciparum*, the most virulent species of the malaria causative agent is also the most prevalent (National Population Commission *et al.,* 2010). Infection with *P. falciparum* is commonly associated with high fevers (Antinori *et al*., 2012). This feature has been used on many occasion as a clinical sign to diagnose malaria and initiate treatment without confirmation that the fever was due to malaria (WHO/UNICEF, 2009). There is existence of an association between the cause of fevers, and infection with *P. falciparum* in malaria endemic areas where *P. falciparum* is prevalent especially among children (Abellana *et al*., 2008; Okiro and Snow, 2010). However, fevers may be due to malaria, as well as other pathogens that initiate them (Akpede *et al.,* 1992; O'Dempsey *et al*., 1993; Asante *et al*., 2016). Thus sensitive diagnostic tools are needed in the diagnosis of fevers, so that appropriate treatments can be given to patients experiencing fevers with malaria, while excluding those whose fevers may not be due to malaria from needless exposure to antimalarial drugs.

The present study examined the sensitivity of fever in malaria diagnosis among children of malaria in children which was higher in children < 5 years old compared to the older age groups. Yet, the percentage sensitivity of approximately 71% clearly fell short of the 95% sensitivity requirement that is currently recommended for malaria RDTs in the diagnosis of malaria (WHO, 2015). The specificity of fever as a diagnostic parameter was even lower, across the different strata of age classification among the children examined. These findings suggest that although fever is a common symptom of malaria in the study area, relying on fever for malaria diagnosis and treatment as it is done in many instances may lead to over treatment of febrile non-malaria cases with antimalarial drugs. The reduction in the fever sensitivity in the older groups of children in particular may be due to further exposure to fever causing infectious agents that are not malaria (Hildenwall *et al*., 2016). This evidence is further supported by the MAFF estimate in the present study. The estimated values of MAFF indicated that nearly 29 %, 37 % and 44 % of the fevers harboured among the age categories of children < 5 years old, 5-9 years old, and 10-14 years old respectively were probably fevers of different etiologies other than malaria. These cases would be erroneously treated as malaria if fever diagnosis alone were used as a diagnostic tool to treat suspected malaria cases, thus denying the child the appropriate treatment which may prove fatal in some cases (Bartolini and Zammarch , 2012).

In South Western Nigeria, MAFF obtained from children aged 6 months to 12 years old using the classical method of estimating AF was 27 % (95 % CI: 17.84 % – 35.20 %), (Owolabi *et al*., 2016). Compared to the present estimate, it is apparent that malaria childhood fevers in Makurdi are at least more than double those in South West Nigeria. Both studies however demonstrate that a high proportion of fevers experienced by Nigerian children nowadays are still due to malaria. Furthermore, it shows that malaria may be in rapid decline elsewhere in the world but in Nigeria, hospital attendance due to malaria still remains very high. The present estimate of PAF imply that a 29 % reduction in malaria can be achieved with effective malaria burden reduction interventions that target children < 5 years old. Similarly, some 14 % and 11 % reductions can equally be achieved in the age groups 5-9 years old and 10-14 years old as well.

Given the unacceptable high proportions of malaria fever that is still prevalent among Nigerian children, a reasonable proportion of real malaria cases are often correctly treated whenever fever is used to treat malaria in Nigeria. The worry however is those cases whose fever may not be due to malaria, but may not receive appropriate treatment for the cause of their ailment, since other pathogens that produce fevers similar to *P. falciparum* (Prasad *et al*., 2015) are also prevalent in Nigeria, and can inflict unwanted fatalities among their victims. The recommended policy of treating suspected cases of fever as malaria without parasitological evidence has been altered, and might have abated in certain countries with very low malaria prevalence. However, in Nigeria where malaria prevalence is still very high and many people are conversant with the clinical features of the disease, self-treatment of fever is still common. It is often undocumented practice to see households first embark on self-treatment of childhood fevers as malaria, before considering hospital visitations when treatment does not resolve the fever. In non-endemic areas of malaria, treating fever cases as malaria may be reasonable provided that a blood smear prepared from the same febrile child may yield positive parasitaemia by microscopy. However, in a highly endemic area of malaria transmission like Nigeria, cases of asymptomatic malaria are very common (Oladeinde *et al*., 2014; Akinbo *et al*., 2015; Abah and Temple, 2015). Thus, the presence of malaria parasites in the blood without clinical symptoms does not always imply that the person is suffering from malaria (Bisoffi *et al*., 2012). If the source of fever can be attributed to malaria, or other causes, it will reduce ambiguities in the choice of treatment to be administered to the feverish child.

Despite many years of research in malaria related fevers, predicting the levels of asexual blood parasitaemia that results to clinical malaria still remains equivocal. This is because, parasite densities that may be responsible for triggering fever are dependent of many factors. A few examples include individual differences, age of the subjects, seasonality, and the zone of malaria transmission (Delley *et al*., 2000; Afrane *et al*., 2014). The median parasitaemic range among feverish children observed in this study paints a picture which suggests that increasing densities of parasites/µl of blood may be required to cause clinical malaria as children get older. This is consistent with findings in Kenya that observed increasing cut off values of parasite densities responsible for clinical malaria among older groups of children (Afrane *et al.,* 2014)

In the past, the prompt treatment of cases of fever among children as malaria without confirmation saved lives. Despite current recommendations (WHO, 2010), It may still be very relevant to

embark on clinical diagnosis and treatment of fevers in dire situations provided that there are no immediate alternative diagnostic tools to quickly and reliable determine the cause of the fever. Such a scenario still exists in the rural areas with very high impact of malaria still evident today. However, in doing so one should always be mindful of the fact that some other dangerous pathogens that mimic malaria fevers, which may be rather fatal are equally prevalent. Thus, a large proportion of fevers frequently experienced by children in malaria endemic areas may not necessary be due to malaria. Those fevers would need to be correctly diagnosed and given appropriate treatment. It is by this simple practice that children, particularly those living in malaria endemic areas would be better protected from the disease, and other infectious agents that mimic its clinical features.

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