

## Accuracy of Fever and Fraction of Fevers Attributable to Malaria among Under-fives under Reduced Malaria Infection Prevalence in District

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### Abstract

A decline in malaria transmission is evident in malaria endemic areas of sub-Saharan Africa and is likely to reduce the proportion of fevers due to malaria. Fever has been used as a predictor of malaria, however, the proportion of fevers due to malaria vary with prevalence such that low malaria infection prevalence might alter the accuracy of fever as a marker of malaria. This study examined the diagnostic accuracy and proportion of fevers attributable to malaria among under-fives in a cross-sectional survey carried out in Bagamoyo district, Tanzania from April–May 2012 during peak malaria transmission. Consecutive under-fives with and without history of fever were recruited; for each, fever was measured by digital thermometer, and two Giemsa stained thick and thin blood films taken for parasite count and species identification. Accuracy of fever for prediction of malaria was assessed by performance indices, microscopy as gold standard. Proportion of fevers attributable to malaria was computed by the odds ratio technique at 0.05 significance level. {Formatting Citation}

Only 98 out of 925 (10.6%) under-fives had parasitaemia. Among under-fives with a history of fever, the fraction attributable to malaria was 71.4% [95%CI: 54.8–81.9]; in those with measured fever  $\geq 37.5^{\circ}\text{C}$ , the fraction was 74.3% [95%CI: 61.8–82.7]. In bivariate and multivariate analyses, at 1001–10000 parasites/ $\mu\text{l}$  the attributable fraction was 66%, and 93% for parasitaemia  $>10000/\mu\text{l}$ . Fever was more likely to be due to malaria among infants  $<12$  months than subsequent months. Despite the recorded decline in malaria infection prevalence, fever is highly likely to be due to malaria among under-fives with fever and malaria infection in peripheral blood. This observation highlights the need to scale up and maintain parasitological confirmation of malaria; and to look for other causes of fever.

**Keywords:** Under-fives; Fever; Malaria; Diagnostic accuracy; Attributable proportion; Tanzania

### Background

For decades fever has been the entry point for the management of malaria in African children in endemic settings. Prior to the adoption of Artemisinin based combination therapy (ACTs), presumptive treatment of all fevers with antimalarial drugs was the approach for the management of malaria across sub-Saharan Africa and was in the recommendations proposed by the Integrated Management of Childhood Illnesses (IMCI) [1-6]. However, there are many causes of childhood fevers, *Plasmodium falciparum malaria* being one of them [7-12].

Although fever usually has a high sensitivity for the diagnosis of malaria, it suffers from poor specificity and critically depends on the prevalence of both asymptomatic infection and the overall prevalence of fever. There is a growing evidence indicating that the intensity of *P. falciparum* transmission is declining across many parts of Africa as reflected in reduction of childhood morbidity and mortality resulting from the wide scale use of different malaria interventions [13-15]. Recent demographic and health surveys (DHS) in malaria endemic

countries of sub-Saharan Africa show similar trends whereby 11 of the 12 national surveys conducted since 2004 showed declines in under-fives mortality estimates over the previous five years (declines of 5% to 30%, median 23%) [16]. Thus, a decline in *P. falciparum* prevalence from 37.0% before the year 2000 to 17.0% after the year 2000 onwards has been observed in African children aged 2-10 years as a result of wide scale use of ACTs and ITNs [17,18]. A decline in malaria infection prevalence may conceivably alter the sensitivity and specificity (diagnostic accuracy) of fever as a marker of malaria as well as a reduction in the proportion of fevers attributable to malaria [4,5,19,20].

Following the roll out of ACT and ITNs in Tanzania, a survey in 21 districts covering about 8,000 under-fives found that malaria infection prevalence declined from 20.0% in 2006 to 14.0% in 2008—a relative reduction of approximately 30.0% [21]. This decline has continued in subsequent surveys such that a decline from 18.1% (2007/08) to 4.2% (2011/12) malaria infection prevalence was recorded in under-fives representing a relative reduction of approximately 77.0% [22,23]. However, it is not known how much the reduction of malaria infection prevalence, has translated itself into a reduction in the proportion of fever cases attributable to malaria. These observations are of practical

relevance for the estimation of burden of disease due to malaria and for tracking malaria control progress [24].

In malaria endemic countries, including Tanzania; the national policy is to administer ACTs on the basis of parasitological confirmation of malaria either by microscopy or RDT. However in spite of the roll out rapid diagnostic tests (RDTs), malaria was found to be over-diagnosed with equal frequency whether parasitological confirmation was carried out using RDT or conventional microscopy [25-27]. It is not known in the case of non-adherence to laboratory results or when tests are out of stock, what proportion of patients receiving ACT has fever that is not attributable to malaria.

This study aimed to examine how accurately fever (reported and measured) predicts malaria following the reduction in malaria infection prevalence and determine the proportion of the fevers attributable to malaria among under-fives. The main steps are outlined below:

Prevalence of malaria infection was assessed among under-fives with and without fever (reported or measured).

The accuracy of fever for the diagnosis of malaria was determined.

The proportion of fevers attributable to malaria infection was then computed.

## Materials and Methods

The study was carried out in Bagamoyo district, one of the 6 administrative districts of the Coast region with a hot and humid climate, resulting in excellent breeding opportunities for *Anopheles* mosquitoes, the main species being *Anopheles gambiae* and *Anopheles funestus* as the main malaria vectors [28]. According to the new world malaria map of *P. falciparum* endemicity in Tanzania, the Bagmoyo district is located in a stable malaria transmission whereby *P. falciparum* annual parasite incidence (PfAPI) greater than or equal to 0.1 per thousand per annum [29]. Malaria is thus one of the leading causes of morbidity and mortality in the population, especially among under-fives and pregnant women.

A facility based comparative cross-sectional survey was carried out in April, 2012, in Chalinze and Mlandizi health centres of the Bagamoyo district. The WHO recommendation for the clinical diagnosis/suspicion of uncomplicated malaria among under-fives is based on the history of fever in the previous 48 hours or measured fever (axillary temperature  $\geq 37.5^{\circ}\text{C}$ ) which should be confirmed with a parasitological diagnosis [30]. Children under five years of age with reported fever (history of fever in the previous 48 hours) or measured fever (axillary temperature  $\geq 37.5^{\circ}\text{C}$ ) were regarded as cases; those without as controls. Participation required individuals who have been resident in the study area for a minimum period of four weeks prior to the survey and provision of parental informed consent. The study had two primary end points: the diagnostic accuracy of fever and fraction of fevers attributable to malaria. The fraction of fevers attributable to malaria was defined as the proportion of fevers that would not have occurred in the absence of malaria infection i.e the excess risk of fever associated with malaria infection [31].

A power based sample size calculation was computed [32] using the formula:

$$N=[P_1(1-P_1) + P_2(1-P_2)]/(P_2-P_1)^2 \times f(\alpha, \beta)$$

Assuming the prevalence of malaria infection among under-fives with fever ( $P_1$ ) to be 14% [24], the prevalence of malaria infection ( $P_2$ ) among under-fives without fever to be 8%; at the power of 80% ( $\beta=0.2$ ) and 95% confidence interval ( $\alpha=0.05$ ), a minimum sample of 920 under-fives was required. For this study a total of 925 under-fives were recruited: 460 with a history of fever in the last 48 hours and 465 without a history of fever.

Upon informed parental/caregiver consent, data were collected using structured questionnaire to obtain socio-demographic and clinical characteristics. Consecutive under-fives were recruited into the study until the sample size of 925 was reached. History of fever was obtained from each participant and axillary body temperature measured using a digital thermometer.

Finger prick blood samples were obtained from each participant for establishing presence of malaria infection by thick and thin blood films. Two blood smears were obtained from each participant; these were stained with 4% Giemsa for 20 minutes. One of the blood smears was read in the field by microscopist who was blind to the results of clinical diagnosis and mRDT results; the other was sent to the Parasitological Laboratory at Muhimbili University of Health and Allied Sciences for another microscopic examination by two expert laboratory technologist who were blind to the results of clinical diagnosis and mRDT results. Each smear required approximately 20 minutes reading; parasite species was identified in the film and count made on the thick film. A minimum of 200 consecutive fields were counted in the thick blood film before a slide was classified as negative. Parasites in thick blood films were counted against 200 white blood cells, and the parasite density was estimated assuming 8,000 white blood cells/L of blood.

## Data processing and statistical methods

All data were entered into Social Science (SPSS) computer software version 17. Data were entered twice and cross-checked for errors before they were conflated. All data analyses were performed using WINPEPI (PEPI-for-Windows) statistical program. The primary aim of the analysis was to determine the diagnostic accuracy of fever and the proportion of fever (reported or measured) attributable to malaria.

To examine the diagnostic accuracy of fever for the prediction of malaria infection, prevalence of malaria infection was computed among under-fives with reported or measured fever and those without. Then true and false positives as well as true and false negatives were computed. This was followed by the computation of sensitivity and specificity, positive and negative predictive values and the overall diagnostic accuracy.

The proportion of reported or measured fever attributable to malaria was estimated from the odds-ratios according to the methods described for case-control studies [33] where under-fives with reported or measured fever were defined as cases and those without as controls. The proportion of reported or measured fevers attributable to malaria was estimated at any parasite density then stratified by parasite density class and age group. Odds ratios and corresponding 95% confidence intervals were computed. Logistic regression analysis was used to examine the relationship between parasite density and fever. In a multivariate model, age-adjusted odds ratios were estimated.

### Ethical considerations

Informed written consent was obtained from each parent/guardian on behalf of the under-fives by reading the consent statements from the consent form using the local language (SWAHILI). The study protocol was approved by the Muhimbili University of Health & Allied Sciences ethical review board. Administrative permission to carry out the study was obtained from the Regional Medical Officer (RMO) and District Medical Officer (DMO).

### Results

#### Socio-demographic characteristics

A total of 925 under-fives attending in the health facilities were recruited into the study. The median age was 14 month (interquartile range 7-33 month); 43.2% was infants (age ≤ 12 months). Of the 460 under-fives with reported fever (history of fever in the past 48 hours), 311 (67.6%) had measured fever (axillary temperature ≥ 37.5°C).

#### Diagnostic performance of fever for the prediction of malaria infection among under-fives

Among under-fives with reported fever, the prevalence of malaria infection was 16.5% while in asymptomatic under-fives, the prevalence was 4.7%. Reported or measured fever had a high sensitivity (77.6% versus 66.3%) for correctly identifying under-fives with malaria, however measured fever was significantly more specific than reported fever (70.3% versus 53.6%; P<0.05) for correctly identifying under-fives without malaria (Table 1). As expected, both history of fever in the last 48 hours & measured fever had very low positive predictive values (16.5% [95%CI: 13.3–20.3] & 21.0% [95%CI: 16.6–25.9] respectfully) but very high negative predictive values (95.3% [95%CI: 92.8–96.9] & 94.6% [95%CI: 92.5–96.2]). Measured fever had a significantly higher overall diagnostic accuracy than reported fever (69.8% versus 56.1%; P<0.05).

Performance	Reported fever (history of fever in the last 48 hours)	Measured fever (axillary temperature ≥ 37.5°C)
True positives (a)	76	65
False negatives (b)	22	33
False positives (c)	384	246
True negatives (d)	443	581
Sensitivity (a/(a+b))	77.6% [95%CI: 67.8–85.1]	66.3% [95%CI: 56.0–75.4]
Specificity (d/(c+d))	53.6% [95%CI: 50.1–57.0]	70.3% [95%CI: 67.0–73.3]
Predictive value positive (a/(a+c))	16.5% [95%CI: 13.3–20.3]	21.0% [95%CI: 16.6–25.9]
Predictive value negative (d/(b+d))	95.3% [95%CI: 92.8–96.9]	94.6% [95%CI: 92.5–96.2]
Overall diagnostic accuracy (a+d)/N	56.1% [95%CI: 52.9–59.3]	69.8% [95%CI: 66.9–72.8]

Table 1: Performance of fever for the diagnosis of malaria in under-fives (N=925).

### Relationship of malaria infection with fever

Compared to under-fives without malaria infection, significantly more under-fives with malaria infection had reported history of fever in the last 48 hours (OR: 3.99 [95%CI: 2.4–6.9] or had actual fever, body temperature ≥ 37.5°C (OR: 4.7 [95%CI: 2.9–7.5]); indicating that presence of malaria infection was suggestive of fever due to malaria infection (Table 2). History of fever in the last 48 hours was attributable to malaria in 74.9% [95%CI: 59.3–84.9] under-fives while measured fever was attributable to malaria in 78.5 [95%CI: 66.5–86.3] representing the excess fever morbidity due to malaria infections indicating that malaria is still a major cause of fever among under-fives presenting with fever and having *P. falciparum* in peripheral blood. At the population level, the excess fever morbidity due to malaria was less than one fifth of all fever cases indicating that only a small fraction of fever was due to malaria.

Attribute	History of fever in the last 48 hours		Measured fever (temperature ≥ 37.5°C)	
	Yes	No	Yes	No
Infected	76	22	65	33
Not infected	384	443	246	581
Odds Ratio	3.99 [95%CI: 2.4–6.9]		4.65 [95%CI: 2.9–7.5]	
Attributable Proportion: (OR-1)/OR	74.9% [95%CI: 59.3–84.9]		78.5 [95%CI: 66.5–86.3]	
Population Attributable Proportion: Attributable Proportion x Prev. of parasitaemia in cases	(0.749 x 0.165) 12.4% [95%CI: not computed]		(0.785 x 0.209) 16.4% [95%CI: not computed]	

Table 2: Proportion of fevers attributable to malaria among under-fives (N=925).

As expected, the risk of having fever significantly increased with fever e ever among the underfives attending the health facilities as shown in the Table 4.istory of malaria w parasite density ( $\chi^2$ trend=20.3 p-value<0.001) (Table 3). In a bivariate and multivariate analysis (Table 4), it was found that at high parasite densities the proportion of fevers attributable to malaria increased steadily, thus at parasite density>10,000/μL of blood almost all fever cases (94.0%) were attributable to malaria. When adjusted for age, still the proportion of fevers attributable to malaria increased steadily to as high as 93% with parasite density>10,000/μL of blood.

Parasite density (count/μL of blood)	Fever(n=76)	No fever(n=22)
1-1,000	9 (45.0%)	11 (55.0%)
1,001-10,000	20 (71.4%)	8 (28.6%)
>10,000	47 (94.0%)	3 (6.0%)

Table 3: The relationship between parasite density and history of fever  $\chi^2$ trend=20.3 p-value<0.001.

Parasite density/ $\mu\text{L}$ of blood	Crude OR (95%CI)	AF	OR adjusted for age	Adjusted AF
0	1		1	
1-1,000	0.9 (0.4-2.3)	Undefined	0.9 (0.4-2.2)	Undefined
1,001-10,000	2.9 (1.3-6.6)	0.66	2.6 (1.1-6.1)	0.62
>10,000	18.1 (5.6-58.5)	0.94	13.8 (4.2-44.9)	0.93

Table 4: Bivariate and multivariate analysis of attributable fraction and parasite density AF: Attributable fraction was calculated as:  $AF=OR-1$ .

## Discussion

This study was carried out during rainy season from April–May 2012 when malaria transmission was peak in the study area. Of the 460 under-fives with a history of fever, 67.6% had raised body temperature ( $\geq 37.5^\circ\text{C}$ ). Although fever is a common cause of seeking care in health facilities in Tanzania and a strong predictor of receiving treatment for malaria [6], only 16.5% of the under-fives with reported fever had malaria infection. The observation that less than one fifth (16.5%) of the under-fives with reported fever had parasitologically confirmed malaria clearly indicates the need to scale up and maintain parasitological confirmation of malaria before prescribing antimalarial drugs in accordance to the national guidelines as more than four fifth (83.5%) of the under-fives with fever would have received an antimalarial drug irrationally [34]. The fact that among under-fives with fever, only a small percentage (16.5%) had malaria infection reflects a major reduction in malaria transmission as prevalence of up to 74.5% has been recorded in the same setting in the past two decades [35]. The changing epidemiology of malaria and the introduction of ACTs have increased the urgency of improving the specificity of malaria diagnosis. A parasitological confirmation of malaria in stable high-transmission settings is recommended as it improves the differential diagnosis of fever, improves fever case management, and reduces unnecessary use of antimalarial drugs [34].

The recorded decline in intensity of *P. falciparum* transmission that supports a reduction in malaria infection prevalence may conceivably alter the diagnostic performance of fever as a marker of malaria disease [19]. The present findings show that reported and measured fever had a high sensitivity for correctly identifying under-fives with malaria; however measured fever was more likely to correctly identify under-fives without malaria that makes it important to take temperature measurements for under-fives with a history of fever. From the epidemiological and clinical view points, the present findings show that fever could predict presence (positive predictive value) of malaria infection in only about one fifth of under-fives with fever (reported or measured fever); however absence of fever could predict absence of malaria infection (negative predictive value) in the large majority (95.0%) of the under-fives. This re-affirms the fact that fever is a poor maker of malaria disease clearly indicating the need to strengthen parasitological confirmation of malaria before prescribing antimalarial drugs as this would also ensure appropriate management of non-malaria fevers and rational use of antimalarial drugs [25-27].

The recorded decline in intensity of *P. falciparum* transmission that supports a reduction in malaria infection prevalence, should plausibly

translate into a decline in the proportion of fevers attributable to malaria, but the relationship might be influenced by the other causes of fever in such areas. In stable malaria transmission areas such as the Bagamoyo district, the entire population is exposed to malaria infection perennially [29]. Of the under-fives with malaria infection, only some are ill because of malaria and in those with fever and malaria infection, not all of them are sick because of malaria; there is a proportion with malaria infection and have fever, but the fever is due to other causes [36]. The malaria attributable fraction (AF) of fevers was defined as the proportion of fevers among under-fives with malaria infection that would not have occurred in the absence of malaria infection [31]. The present findings show that the presence of malaria infection was significantly more likely to be associated with reported fever or measured fever as reflected by the large odds ratios (3.99 [95%CI: 2.4–6.9] versus 4.65 [95%CI: 2.9–7.5]). Thus the proportion of reported or measured fevers attributable to malaria infection was also high (74.9% [95%CI: 59.3–84.9] versus 78.5 [95%CI: 66.5–86.3]), representing the excess fever morbidity that would have been prevented if malaria infections were eliminated among under-fives. This implies that among the under-fives presenting with fever and having *P. falciparum* in peripheral blood, about three quarters (74.9%) have fever that is attributable to malaria

Though population based data from Pwani region of which Bagamoyo district belongs to, show a decline in malaria infection prevalence among under-fives from 20.8% (2007/08) to 10.2% (2011/12) representing a relative reduction of 51.0% [22,23], findings from this study show that the population malaria attributable proportion of fever (reported or measured fever) was less than one fifth indicating that only less than one fifth of fever morbidity would have been prevented if malaria infections were eliminated in the study area. This re-affirms that fever among under-fives has many other causes hence the need for scaling up parasitological diagnosis for the management of fever in under-fives [34]. This study primarily focused on malaria and was carried out in a setting where other causes of fever like viral, bacterial and fungal agents could not be assessed, hence the need for further studies to establish the burden of other causes of fever [37].

As expected, the risk of having fever increased with increasing parasite density, particularly from parasite density category equal or higher than 10,000 parasites/ $\mu\text{L}$ . High *P. falciparum* parasite densities were significantly associated with fever ( $\chi^2_{\text{trend}}=20.3$ ; p-value<0.001). In malaria endemic areas, clinical manifestations of malaria have a very wide spectrum and the parasite density required to trigger fever differs significantly from one individual to another [38]. Despite this variability, at higher parasite densities, fever morbidity is highly likely to be attributable to malaria as reflected by the steady increase in the proportion of fevers attributable to malaria infection with the increase in parasite density, especially when equal or more than 10,000/ $\mu\text{L}$ . This may guide on the development of case definition for clinical trials of malaria interventions, as well as definitions that may improve the precision in the assessment of burden of disease due to malaria. The occurrence of fever cases due to other causes in the presence of parasitaemia, may well result in an over-diagnosis of clinical malaria [36] Thus, estimation of the proportion of fever cases attributable to malaria infection is crucial so as to establish a more concise definition of clinical malaria under the changing malaria epidemiology [31].

## Conclusion

Despite the recorded decline in malaria infection prevalence, fever is highly likely to be due to malaria among under-fives with fever and malaria infection in peripheral blood. This observation highlights the need to scale up and maintain parasitological confirmation of malaria; and to look for other causes of fever.

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