

## Short Report: Assessment of Fever in African Children: Implication for Malaria Trials

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**Abstract.** We evaluated methods for assessing body temperature by comparing subjective assessment of fever by parents and doctors with objective axillary, tympanic, and rectal measurements of body temperature in 1000 children ≤ 10-years-old who presented at outpatient clinics with recent history of fever. Sensitivity of subjective assessment of fever were higher at thresholds of  $\geq 38.3^{\circ}\text{C}$  with specificity as low as 60%. Axillary methods showed better specificity at fever thresholds of  $> 38.0^{\circ}\text{C}$  with maximum sensitivity of 63% at thresholds of  $\geq 37.5^{\circ}\text{C}$ . Bland-Altman analysis showed wide limits of agreement between objective methods of measurements:  $-1^{\circ}\text{C}$  to  $3^{\circ}\text{C}$  for comparison of rectal and axillary,  $-1^{\circ}\text{C}$  to  $2^{\circ}\text{C}$  for rectal and tympanic, and  $-1^{\circ}\text{C}$  to  $2^{\circ}\text{C}$  for tympanic and axillary measurements. A choice of method to measure body temperature for diagnosis of fever in African children should be informed by a trade off between its specificity and sensitivity that considers thresholds  $> 38.0^{\circ}\text{C}$ .

### INTRODUCTION

The core temperature of the human body lies between  $36.4$  and  $37.4^{\circ}\text{C}$ , depending on the time and measurement.<sup>1,2</sup> A universally accepted definition for fever is still elusive,<sup>3,4</sup> and there are problems in measuring “true” body temperature in clinical situations, which include variations in body temperature of children with level of activity, meals, time of day, environmental conditions, even improper positioning of thermometers, and hurried measurements, amongst others.<sup>5–14</sup> These factors are difficult and almost impossible to control or standardize, making the use of a single temperature measurement an unreliable indicator.

However, the Brighton Collaboration Fever Working Group recommends a body temperature  $\geq 38^{\circ}\text{C}$  as fever irrespective of device, anatomic site, age, or environmental conditions<sup>4</sup> and a World Health Organization expert study group accepts fever as an axillary temperature measurement of  $\geq 37.5^{\circ}\text{C}$ .<sup>5</sup> Apparently the choices of fever threshold in malarial trials are determined by intention to increase the sensitivity and specificity of primary study endpoints. We have evaluated by comparison subjective and objective methods of determining fever in African children.

### METHOD

We carried out a study in Lambaréné, Gabon from March 2007 to March 2008, and we enrolled 1000 children aged 10 years and younger who presented at the outpatient department of the private hospital (HAS) and government hospital (HG), which serve Lambaréné community and its neighboring area. Every morning,<sup>15</sup> irrespective of any other associated complaint, children presenting with complaints of fever within the past 14 days were recruited after obtaining an oral consent from their parents or guardians. Their age, sex, and brief medical history including drug intake in the preceding 6 hours were recorded. For each child, an investigator (SO or KP) asked parents/guardians if the child had a “fever” presently, noting their impression or the part(s) of the child’s body palpated. The investigators also subjectively determined if the child had

a “fever”. Parents were asked if they objectively measured the body temperature of their children at home because health care practice in this community encourage mothers to objectively measure body temperature whenever they felt their children had a fever. They were then asked to go ahead and measure the body temperature of their children in their usual or preferred manner. The parents read the mercury thermometers immediately after measuring and the doctors (SO or KP) verified their readings. Thereafter, the doctors measured the body temperature of eligible children in the following order: tympanic temperature with infrared tympanic thermometers (ThermoScan: BRAUN type: 6022, Kronberg, Germany) and axillary and rectal temperature with electronic thermometers (Thermoval Basic: Paul Hartmann AG, 89522, Heidenheim, Germany). SO and KP assessed equal number of children during this study, the above sequence of objective measurements was followed for every eligible child aged 6 years or younger and completed within 5 minutes. Children older than 6 years of age did not have a rectal temperature taken by the investigators. Microscopic parasitemia was the only parameter for diagnosis of malaria in this study, therefore  $10\ \mu\text{L}$  of capillary blood was taken to quantify malaria parasite.<sup>16</sup> Ethical clearance for this study was obtained from the local ethics committee (Comité d’Ethique Regional Independent de Lambaréné).

Data was analyzed with Stata 10 for Mac OS X (Stata Corp., College Station, TX) using Spearman correlation and Bland-Altman bias methods.<sup>17</sup> Sensitivity, specificity and predictive values were performed with rectal temperature as “gold standard”.

### RESULTS

We observed 1000 children with median age of 3 years; 51% of them were enrolled at HG and 49% at HAS. Twenty-one children (2.1%) had taken paracetamol within the 6 hours before enrollment and three children had taken amodiaquine plus artesunate combination. Malaria parasites were found in blood slides of 73 children. At presentation, parents of 70% (700 of 1000) of the children enrolled indicated that their children had fever by palpating the head or face and others by body contact, breathing pattern, rate of activity, oral warmth during breast-feeding, or unspecified subjective impressions. Doctors said 60% (596 of 1000) of these children had a fever by palpating their head and/or their face. The sensitivity of subjective assessment of fever by parents and doctors were

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TABLE 1  
Proportions of children with objectively measured "fever" at various temperature thresholds

Thermometry	Doctors			Parents	
	Tympanic	Axillary	Rectal	Axillary	Rectal
Number of children	1000	1000	835	141	611
Temperature thresholds (°C)	n (%)	n (%)	n (%)	n (%)	n (%)
37.5	615 (62)	462 (47)	594 (71)	99 (70)	434 (71)
38.0	428 (42)	315 (32)	449 (54)	75 (53)	348 (57)
38.3	348 (35)	233 (24)	338 (41)	72 (51)	238 (39)
38.7	245 (25)	139 (14)	254 (30)	56 (40)	189 (31)

above 95% at a tympanic and axillary fever threshold above 38.3°C or at a rectal fever threshold above 38.7°C. The specificity of subjective assessment of fever by parents and doctors were lower than 60% and 80%, respectively.

Eighty-six percent (862 of 1000) of the parents said they objectively measured body temperature in their children when they felt their children had fever, and when asked to measure the body temperature of their children at enrollment, majority used a mercury thermometer, of which 81% (611 of 753) measured *per rectum*, 19% (141 of 753) in the axilla, and one child's temperature was measured orally. Only a tenth (109 of 1000) used digital thermometers (not considered in our analysis). We observed that 43% of parents participating from HG and 45% from HAS did not read the mercury thermometer correctly, plus there was another 12% in each group that could not read the mercury thermometer.

Mean  $\pm$  SD of body temperatures of children aged 0–10 years was 37.9  $\pm$  1°C with tympanic thermometers, 37.5  $\pm$  1°C with axillary thermometers, and children 0–6 years was 38.1  $\pm$  1°C with electronic rectal thermometer. The proportions of children with fever at various body temperature thresholds by method of measurement are shown on Table 1. Sensitivity, specificity, and predictive values of axillary and tympanic measurements of body temperature compared with electronic rectal measurements are shown on Table 2.

We found no correlation between age of children and objective measurements of fever using any of the three methods. Linear correlations of paired measurements were excellent, with Spearman rank correlation coefficients of 0.85 for the paired readings of tympanic and axillary temperatures, 0.83 for tympanic and rectal, 0.81 for axillary and rectal, and 0.81 for parents' mercury and doctors' electronic rectal thermometers ( $P < 0.001$  for all pairs). Bland-Altman analysis showed that electronic rectal measurements were systematically higher than tympanic measurements, which were in turn

higher than electronic axillary measurements. The mean differences were 0.9°C (95% confidence interval [CI] 0.7–0.9) with limits of agreement (LOA) of  $-1^\circ\text{C}$  to  $3^\circ\text{C}$  for the comparison of rectal and axillary, 0.3°C (95% CI 0.2, 0.3) with LOA of  $-1^\circ\text{C}$  to  $2^\circ\text{C}$  for rectal and tympanic, and 0.6°C (95% CI 0.5, 0.6) with LOA of  $-1^\circ\text{C}$  to  $2^\circ\text{C}$  for tympanic and axillary measurements (Figure 1). Additionally the prevalence of malaria parasitemia at axillary temperature thresholds of  $\geq 37.5^\circ\text{C}$ ,  $38.0^\circ\text{C}$ ,  $38.3^\circ\text{C}$ , and  $38.7^\circ\text{C}$  were 3.4%, 2.9%, 2.6%, and 2.1%, respectively. Although we observed an association between presence of malaria parasites in blood smears and axillary measured temperature at thresholds of  $38.3^\circ\text{C}$  (odds ratio [OR] = 1.8, 95% CI 1.1–2.8,  $P = 0.02$ ) and  $38.7^\circ\text{C}$  (OR = 2.4, 95% CI 1.5–3.9,  $P < 0.001$ ), half of the children with more than 5000 parasite per microliter had an axillary temperature less than  $37.5^\circ\text{C}$ .<sup>18,19</sup>

## DISCUSSION

Results of this study showed wide limits of agreement between body temperatures measured by axillary, tympanic, or rectal route. Limits of agreement correspond to 95% confidence intervals of the difference between two measurements. The range of these limits was as large as 4°C between rectal and axillary measurement, which implies that fever threshold should be considered specific for the site of measurement used.

During the course of this study we came across some practical limitations, most of which had previously been reported,<sup>20–27</sup> including the inherent limitations and variations in individual thermometry that are difficult to reconcile, particularly individual techniques of measurement coupled with the environmental influence on body temperature. Moreover, it was cumbersome maintaining a thermometer appropriately in the axilla of very young children, who were also startled with infrared tympanic probes,<sup>28</sup> and older children resented the rectal method.

However, the findings in this study underpin the fact that there are significant inaccuracies in subjective assessment of body temperature,<sup>24,28,29</sup> and using either axillary or tympanic or rectal methods as "benchmark" for the assessment of body temperature for fever diagnosis in all circumstances is misleading.<sup>30–36</sup>

We conclude that when fever is of primary concern especially in large interventional trials, a standard objective measurement of body temperature is required for the diagnosis of fever taking into account possible physiological variations. The choice of method should be informed by a trade off between its specificity and sensitivity that considers thresholds higher than  $38.0^\circ\text{C}$ .

TABLE 2

Sensitivity, specificity, and predictive values of axillary and tympanic temperatures measured by doctors compared with "gold standard" electronic rectal temperatures measured by same doctors

Site	Number of children	Temperature threshold °C	Sensitivity %	Specificity %	PPV* %	NPV† %
Axillary	835	$\geq 37.5$	63	96	97	51
		$\geq 38.0$	56	99	98	66
		$\geq 38.3$	52	98	94	75
		$\geq 38.7$	41	98	90	79
Tympanic	835	$\geq 37.5$	81	86	94	65
		$\geq 38.0$	75	95	94	76
		$\geq 38.3$	75	93	87	84
		$\geq 38.7$	68	95	86	87

\* Positive predictive value.

† Negative predictive value.

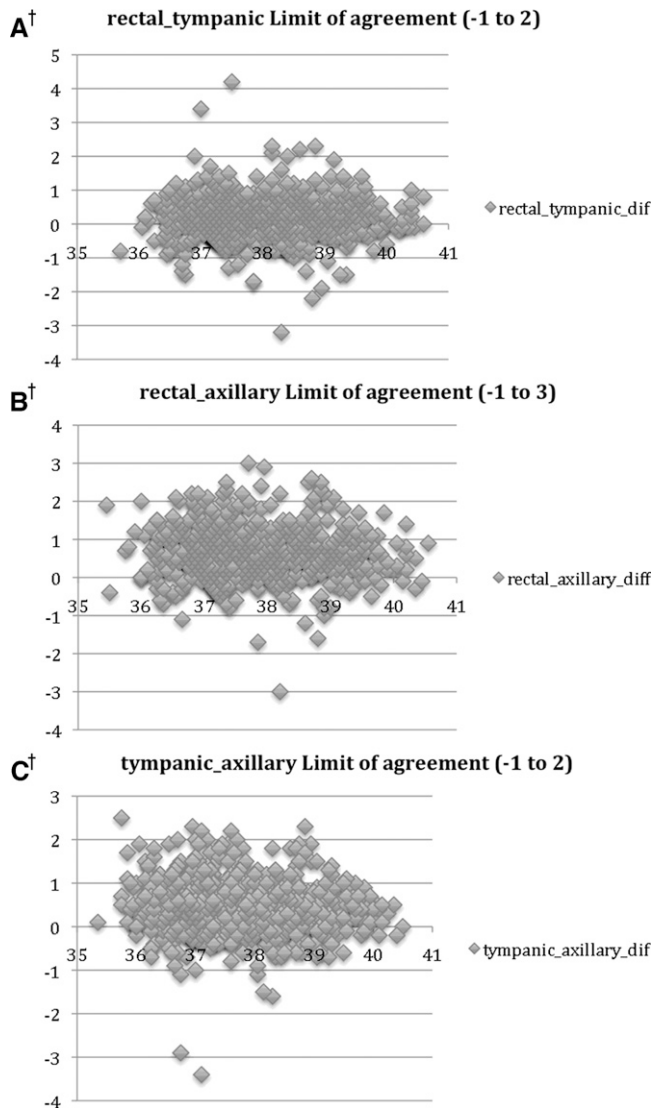


FIGURE 1. Bland-Altman plots of pairwise comparisons between different temperature measurement methods showing differences in means and upper and lower 95% limits of agreement. **A**, agreement of rectal with the tympanic thermometer; **B**, agreement of the rectal with the axillary thermometer; **C**, agreement of the tympanic and the axillary. † The difference between paired temperature measurements on y-axis and the mean of corresponding temperature on x-axis.

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