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Evaluation of stool GeneXpert MTB/RIF for the diagnosis of pulmonary tuberculosis among presumptive patients in Tanzania

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ABSTRACT

Background: Diagnosis of pulmonary tuberculosis remains grim, especially in resource-limited settings. Low quality of sputum, particularly among seriously ill, HIV/AIDS, and pediatric patients might result in missing the diagnosis. This study evaluated the performance of GeneXpert MTB/RIF for the detection of pulmonary tuberculosis on stool specimens as an alternative to respiratory specimens.

Methods: A cross-sectional study design was used to evaluate the performance of GeneXpert MTB/RIF to detect TB in stool specimens from presumptive TB patients. Sputum culture on Lowenstein-Jensen media was used as the gold standard. Recruitment of patients into the study was conducted in 12 selected health facilities in Tanzania. Two sputa and a stool specimen were collected from each study participant. Both sputa and stool samples were tested at their respective study sites of collection using GeneXpert, and their respective portions shipped to the Central Tuberculosis Reference Laboratory for testing by stool GeneXpert and sputum culture in the LJ media. Statistical analysis was performed using STATA software version 14.1.

Results: A total of 590 presumptive tuberculosis patients were enrolled in this study. Their median age was 35 years (IQR = 21–47 years). More than half (57.5%, n = 339) of the study participants, were males. Children aged below 15 years constituted 17.6% (n = 104) of the study participants. A total of 75 tuberculosis cases were detected by sputum culture. The sensitivity and specificity of Stool GeneXpert conducted at CTRL was 84% (95% CI: 81.0–87.0%), and 93.4% (CI: 98.5–99.9%) respectively. The overall sensitivity and specificity of stool GeneXpert at the peripheral laboratories was 63.0% (95% CI: 47.8–76.1) and 76.7% (95% CI: 72.1–81.4), respectively.

Conclusion: Findings from this study suggest that stool is a potential alternative to respiratory specimen for use in routine diagnosis of tuberculosis, especially when obtaining a respiratory specimen is challenging.

1. Background

Tuberculosis (TB) is still one of the major causes of morbidity and mortality in both adults and children, especially in developing countries. The number of notified TB cases continues to rise every year especially in low income countries. Globally, about 10 million TB cases were notified in 2017 of which 16% died [1]. Among those notified, 1 million were children and 5.8 million males. Tanzania is one of the 30 high TB burden countries which contribute about 87% of all the TB cases notified globally [1]. In Tanzania, a total of 69,623 cases were notified in 2017, and 13% of them were children [2]. Pulmonary TB accounts for the majority of the cases.

To halt the morbidity and mortality due to TB, the need for timely diagnosis and hence treatment cannot be overemphasized. Currently,

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the diagnosis of pulmonary TB is faced with significant difficulties that are associated with limitations of the widely used diagnostic tests. Although GeneXpert has revolutionized the diagnosis of TB, difficulties in getting good quality respiratory specimens especially in critically ill, HIV/AIDS, and pediatric patients undermine its performance and utility [3–6]. Available techniques for collecting respiratory specimens in patients who cannot expectorate are invasive. Recently, studies have shown that it is possible to recover the tubercle bacilli's DNA in the stool specimen of pulmonary TB patients from swallowed sputum. As such, GeneXpert offers a promising way forward for its capacity to detect *Mycobacterium tuberculosis* DNA in stool specimen.

Several studies evaluating the GeneXpert for detection of pulmonary TB in stool specimen have been published, with highly variable sensitivity and specificity. For example, studies among children with presumptive TB in South Africa, Uganda, and Egypt reported a sensitivity of 31.9%, 55.6% and 83.3% respectively [7–9]. One study conducted in Kenya among HIV-infected presumptive TB children reported a sensitivity of 63% [10], while a study by Kokuto et al., (2015) among adults with presumptive TB reported a sensitivity of 87% [11]. Different factors, such as study population, settings, and study designs can be attributed to such variability. Data on the diagnostic accuracy of GeneXpert to detect TB in stool specimens in Tanzania, a high TB and HIV burden country with limited resources is scarce. This study, therefore, intended to evaluate the diagnostic performance of GeneXpert to detect TB in stool specimen among presumptive TB patients in Tanzania to inform policy and programs.

2. Methods

2.1. Study design and settings

A cross-sectional study design was used to evaluate the performance of GeneXpert MTB/RIF to detect TB in stool specimens from presumptive TB patients. Sputum culture on Lowenstein-Jensen (LJ) media was used as the gold standard. The study was part of the East Africa Public Health Laboratory Network (EAPHLN) project whose aim was to strengthen laboratory capacities in the East African member states. The current study was implemented in 12 health facilities (7 primary health facilities, and 5 tertiary health facilities) in Tanzania. These facilities were: Mawenzi regional hospital and Usangi health center in Kilimanjaro region, Mount Meru hospital and Levolosi health center (Arusha region), Mbagala Rangi Tatu hospital, Mbagala Kizuiani hospital, Mwananyamala hospital, and Tandale health center in Dar es Salaam region, St Vicent health center (Pwani region), St Benedict Ndanda referral hospital (Mtwara region), Morogoro regional hospital, and Kilosa health center in Morogoro region. The tests were performed at study sites, and at the Central TB Reference Laboratory (CTRL). The CTRL is the highest level of laboratory hierarchy within the TB laboratory network in Tanzania, located in Dar es salaam city. The CTRL receives 25% of positive and negative TB specimens from all regions in the country for quality control and routine surveillance of drug-resistant TB.

2.2. Sample size estimation

A sample size of 519 was obtained using the Buderer formula for sensitivity and specificity [12]. Previously reported stool GeneXpert sensitivity of 83% [9] and the prevalence of pulmonary TB of 23.7% among presumptive TB patients [13], were used to compute this sample size at 5% precision and 10% attrition.

2.3. Recruitment of participants

Presumptive TB patients were consecutively recruited at the outpatient department, HIV and RCH clinics between January 2017 and July 2017. Tuberculosis screening was done as per standard of care, which mainly relies on self-reporting of symptoms suggestive of TB (cough or fever, night sweats, and weight loss for children). Before enrollment, every participant or parent/legal guardian of children below 18 years provided a written informed consent/assent. Children younger than a year were excluded from the study.

2.4. Specimen and data collection

Socio-demographic characteristics were collected. Participants were asked to provide two spot sputa specimens and a stool specimen in separate sputum and stool containers. Immediately after collection, two aliquots were made from stool specimens. Specimen collection were done as per standard of care. One sputum specimen and one aliquot of stool specimen were tested at the study site laboratory (peripheral laboratory) using GeneXpert, and the others were stored at 4 °C before transportation to CTRL. Specimens were transported in leakage-proof triple compartments and received at CTRL within two days. At CTRL, stool specimens were tested by both GeneXpert and culture, while sputum specimens were tested by culture only. The results were immediately communicated to clinicians, and sputum GeneXpert positive patients were started on anti-TB treatment according to the National Tuberculosis and Leprosy Program (NTLP) guidelines.

2.5. Laboratory procedures

The stool specimens were processed by adding 10 mL of distilled water into 2 cm^3 of thawed stool specimen and the mixture was homogenized by vortexing. The mixture was left undisturbed at room temperature for 15 min. Thereafter, the supernatant was centrifuged at 3000 xg for 20 min. In 1 mL of the supernatant, 2 mL of GeneXpert reagent was added (2:1 reagent to sample) and incubated for 15 min at room temperature. The mixture was then transferred to the GeneXpert cartridge and analyzed using GeneXpert (Cepheid, Sunnyvale, CA, USA) following the manufacturer's instructions. Sputum specimens were processed and tested by GeneXpert following the manufacturer's instructions.

The resulting stool sediments were decontaminated by incubating with 10 mL of 3% N- Acetyl-L- cysteine Sodium Hydroxide (NALC-NaOH) solution for 15 min at room temperature. This was followed by the addition of 40 mL phosphate buffer (pH 6.8) and then centrifuged at 3000 × g for 20 min. The sediments were then re-suspended in 3 mL phosphate buffer and used (0.1 mL of each sample) to inoculate 2% Lowenstein-Jensen (LJ) medium. The inoculated media slants were incubated at 37 °C and observed at least once a week until growth was observed or discarded as negative if no growth was seen after 8 weeks. A culture was reported contaminated following observation of overgrowth of microorganisms that were lacking characteristics of mycobacteria. For sputum specimens, culture was performed according to the standard operating procedures.

2.6. Statistical analysis

Data was double entered and validated using EpiData software version 3.1. After validation, data was exported to STATA software version 14.1 (STATA Corp Inc., TX, USA) for analysis. Variables were summarized as frequencies, percentages and interquartile ranges as appropriate. The diagnostic performance of stool GeneXpert was analyzed as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with their respective confidence intervals using sputum culture as a reference standard. Ninety-five percent confidence intervals (95% CI) were subsequently calculated.

3. Results

3.1. Demographic information of the study participants

A total of 590 presumptive TB patients were enrolled in the study.

Table 1
Demographic characteristics of the study participants.

Age	Total n (%)	Sex n (%)		
		Male	Female	Missing
1–5	42(7.1)	18(5.3)	24(9.7)	0 (0)
6–14	62(10.5)	25(7.4)	36(14.5)	1(33.3)
15–95	442(74.9)	269(79.4)	172(69.4)	1(33.3)
Missing	44(7.5)	27(8.0)	16(6.4)	1(33.3)
Total	590 (100)	339(57.5)	248(42.0)	3(0.5)

Table 1 reports on their sociodemographic characteristics. The median age of the study participants was 35 years (IQR = 21–47 years); 17.6% of all participants were aged below 15 years. Males constituted 57.5% of the study participants.

3.2. Prevalence of pulmonary TB

M. tuberculosis was detected in 75 (12.7%) out of 590 specimens by sputum culture. Stool GeneXpert was able to detect 97 (16.4%) cases, and sputum GeneXpert detected 173 (29.3%) cases. Stool culture detected only 12 (2%) cases. Table 2 shows the prevalence of pulmonary TB by age group as detected by different tests.

3.3. Performance of stool GeneXpert, sputum GeneXpert, and stool culture

Out of 75 cases detected by sputum culture, stool GeneXpert conducted at CTRL was able to detect 63 cases, with the sensitivity and specificity of 84% (95% CI: 81.0–87.0%) and 93.4% (CI: 91.4–95.4) respectively, and corresponding PPV and NPV of 65% and 98.1%. While stool culture detected only 8/75 (10.7%) cases (Fig. 1), sputum GeneXpert conducted at peripheral laboratories detected 47/75 (62.7%) cases. At the study sites, the sensitivity of stool GeneXpert was 63.0% (95% CI: 47.8–76.1) and the specificity was 76.7% (95% CI: 72.1–81.4) (Table 3).

Analysis of the performance of stool GeneXpert in a subset of participants (children below 15 years), showed lower sensitivity compared to that observed for overall participants. In this age group, the sensitivity and specificity of stool GeneXpert at CTRL were 66.7% (Cl: 57.8–75.6%) and 99.1% (Cl: 97.2–100%) respectively. While at the study sites, the sensitivity of stool GeneXert was 33.3% (Table 4).

4. Discussion

The inability to promptly provide good quality respiratory specimens for the diagnosis of pulmonary TB contributes significantly to missed or delayed detection of TB, especially among pediatric, HIV/AIDS, and severely ill patients. In 2016, for example, about 580,000 children with pulmonary TB were either not diagnosed, treated, and/or reported; and of all reported pulmonary TB cases worldwide, only 57% were bacteriologically-confirmed [14]. In this study, the sensitivity of stool

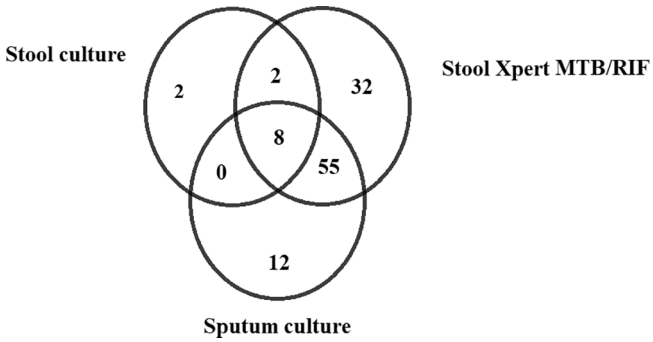

Fig. 1. Venn diagram showing the distribution of positive cases (N = 111) between the three tests performed at CTRL.

GeneXpert when evaluated against sputum culture was as high as 84%. In comparison, its specificity was 93.4%, suggesting that the technique can be used in a routine clinical setting, especially when obtaining respiratory specimen is difficult. These findings are in agreement with previous studies that reported that stool samples can be a good alternative for the diagnosis of pulmonary TB [8,10,11,15].

For analysis purposes, paired-samples, i.e. stool and sputum were required from each participant. Since many children could not produce sputum, about three-quarters of participants were adults (≥15 years). Thus, it is difficult to precisely determine the performance of the test in children, however findings from this study showed that stool GeneXpert performed less in children compared to adults (66.7% vs 84%). Other studies that evaluated the performance of GeneXpert on stool specimens from children with presumptive TB, have also reported promising findings. For example, a study by Walters et al., in 2012 and 2017 reported a sensitivity of 75% and 32% respectively [7,16]. Nicol et al., reported a sensitivity of 41.7% [17], a systematic review by MacLean and colleagues reported a pooled sensitivity of 67% [18], while Banada et al (2016), reported a sensitivity of 85% [19]. Specificity, on the other hand, was consistently above 90% across all studies.

Children less than five years of age, malnourished, and immune-compromised are at greater risk for contracting TB infection, and TB is more difficult to diagnose in this age group compared to older children or adults [20]. Due to the very small number of participants below 5 years, we were unable to assess the performance of stool GeneXpert among this particular age group. Since in this age group collection of respiratory specimens for pulmonary TB testing is mostly invasive, and the disease progresses faster to fatal milliary TB or TB meningitis, the benefit of using stool specimens for diagnosis of TB among patients who cannot expectorate outweighs the risks of a missed or delayed diagnosis.

In the present study, the diagnostic accuracy of stool GeneXpert was better at CTRL compared to the peripheral laboratories. CTRL is the highest level of laboratory hierarchy within the TB laboratory network in Tanzania; therefore, the difference in performance can be attributed to technological know-how and laboratory practices. Regular training and supportive supervision to peripheral laboratories can improve

Table 2
Prevalence of pulmonary TB per age group as detected by different diagnostic tests.

Age Group	Stool Xpert at CTRL* N = 590		Stool culture* N = 590		Sputum culture* N = 590		Peripheral labs** sputum Xpert N = 590		Peripheral labs** stool Xpert N = 321	
	Pos (%)	Neg (%)	Pos(%)	Neg (%)	Pos (%)	Neg (&)	Pos (%)	Neg(%)	Pos (%)	Neg(%)
1–5	1 (2.4)	41 (97.6)	1 (2.4)	41(97.6)	1 (2.4)	41 (97.6)	3(7.1)	39(92.9)	0(0)	21(100)
6–14	2 (3.0)	64 (97.0)	1 (1.5)	65(98.5)	2 (3.0)	64 (97.0)	10(16.1)	52(83.9)	4(10.8)	33(89.2)
15–95	81(18.5)	357(81.5)	8(1.8)	430(98.2)	65 (14.8)	373 (85.2)	147(33.3)	291(66.7)	84(33.6)	166(66.4)
Missing	13(29.6)	31 (70.4)	2(4.6)	42(95.4)	7(15.9)	37(84.1)	13(29.6)	31(70.4)	5(38.5)	8(61.5)
Total	97(16.4)	493(83.6)	12(2.0)	578(98.0)	75(12.7)	515(87.3)	173(29.3)	417(70.7)	93(29.0)	228(71.0)

*Tests performed at Central TB Reference Laboratory.
**Tests performed at study sites (peripheral laboratories).

Table 3
Performance of diagnostic tests performed at CTRL and study sites

TB diagnostic test	N	Sensitivity (%)	Sensitivity (95%CI)	Specificity (%)	specificity (95%CI)	PPV (%)	PPV (95%CI)	NPV	NPV (95%CI)
Stool culture (CTRL)	590	10.7	8.2–13.2	99.2	98.5–99.9	66.7	32.8–89.1	88.4	85.5–90.8
Stool Xpert (CTRL)	590	84.0	81.0–87.0	93.4	91.4–95.4	65	54.8–73.9	98.1	97.6–98.6
Sputum Xpert (Peripheral labs)	590	62.7	58.8–66.6	75.5	72.1–79.0	27.2	21.0–34.4	93.3	90.4–95.3
Stool Xpert (Peripheral labs)	321*	63.0	47.8–76.1	76.7	72.1–81.4	31.2	22.5–41.5	92.5	88.3–95.3

*Six study sites could not perform stool GeneXpert on site. The specimens were sent to the CTRL where they were tested.

Table 4
Performance of diagnostic tests in children <15 years old performed at both the CTRL and study sites.

TB Diagnostic Test	N	Sensitivity (%)	Sensitivity (95%CI)	Specificity (%)	specificity (95%CI)	PPV (%)	PPV(95%CI)	NPV	NPV(95%CI)
Stool culture (CTRL)	108	33.3	24.4–42.2	99.1	97.2–100	50	–	98.1	92.6–99.5
Stool Xpert (CTRL)	108	66.7	57.8–75.6	99.1	97.2–100	66.7	0.3–100	99.1	93.4–99.9
Sputum Xpert (Peripheral labs)	108	33.3	24.4–42.2	88.6	82.6–94.6	7.7	0.8–46.9	97.9	91.8–99.5
Stool Xpert (Peripheral labs)	60	33.3	21.4–45.3	94.7	89.1–100	25.0	0.5–95.8	96.4	86.3–99.1

diagnostic performance towards better patients' quality of care. In circumstances where the laboratory has the necessary equipment to perform GeneXpert, and availability of good quality clinical specimen by non-invasive methods (in this case stool), the laboratory personnel's expertise remains one of the major determining factors for improving case detection, hence, curbing mortality and transmission of TB.

5. Conclusion

Increasing early detection and treatment among patients with TB is necessary as we race towards the global end TB goal. This study affirms the previous findings that stool is a potential alternative to respiratory specimens in the diagnosis of pulmonary TB using GeneXpert, especially in patients who cannot expectorate.

Declarations of competing interest

Ethics approval and consent to participate

This study was granted ethical clearance by the National Medical Research Coordinating Committee of the National Institute for Medical Research in Tanzania. Gateway permission to conduct this research was obtained from the management of each health facility and local government administrations. Written informed consent was obtained from each participant aged 18 years and above before enrolment into the study. For children aged below 18 years, permission and written informed consent was obtained from parents/legal guardians.

Consent for publication

Not applicable

Availability of data and material

Data sets used and/or analyzed during the current study are available from the corresponding author on a reasonable request.

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Author contributions

EN, GK, ES, and SM conceived, designed and coordinated the study. NM performed culture and GeneXpert. NPM, CL, AW, GK, CM, and EN performed the analysis and drafted the manuscript. The remaining authors NM, FM, DH, and SM reviewed the write-up and all authors approved the submission of the manuscript.

CRediT authorship contribution statement

Esther Ngadaya: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing - review & editing, Supervision, Project administration, Funding acquisition. **Godfather Kimaro:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - review & editing, Supervision, Project administration. **Erica Sandi:** Conceptualization, Methodology, Investigation, Writing - review & editing, Project administration. **Nicholaus P. Mnyambwa:** Formal analysis, Data curation, Writing - original draft, Visualization. **Amani Wilfred:** Formal analysis, Data curation, Writing - original draft, Visualization. **Clara Lubinza:** Formal analysis, Data curation, Writing - original draft, Visualization. **Coline Mahende:** Investigation, Writing - original draft, Writing - review & editing, Visualization. **Nicodem Mgina:** Validation, Investigation, Writing - review & editing. **Fausta Mosha:** Writing - review & editing, Visualization. **Doulla Hassan:** Writing - review & editing, Visualization. **Sayoki Mfinanga:** Conceptualization, Methodology, Validation, Investigation, Resources, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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