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ORIGINAL ARTICLE

RESULTS OF THE PERFORMANCE OF AUTOMATED GENEXPERT IN CHILDHOOD TUBERCULOSIS IN ADDIS ABABA, ETHIOPIA: A RETROSPECTIVE CROSS-SECTIONAL STUDY

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Abstract

Background: *Approximately 81% of all childhood tuberculosis cases occur among 22 high-burden countries and Ethiopia ranks eighth among these high burden countries. The GeneXpert Mycobacterium tuberculosis DNA and resistance to rifampicin (MTB/RIF) test can detect pediatric tuberculosis and its multidrug-resistant form with very high sensitivity and specificity, but limited data exists on its use in our country. We aimed to evaluate the effectiveness of the GeneXpert assay in comparison to children with a clinical diagnosis of Tuberculosis.*

Methods: *A descriptive retrospective study on 144 TB-diagnosed children younger than 15 years was conducted at Tikur-Anbessa specialized hospital and Yekatit 12-referral hospital, pediatrics departments, Addis Ababa, Ethiopia. The performace of the GeneXpert test was evaluated by revising the charts of patients who have begun anti-tuberculosis treatment. We extracted information from the chart review of 144 eligible children who were diagnosed with tuberculosis and began anti-TB treatment from February 2014 to July 2016.*

Result*: In the study, 144 patients with clinical diagnosis of tuberculosis were included, and 23% of them also had concurrent HIV infection. Equal numbers of male and female were present; 48.6% were from Addis Ababa. Thirty-four patients (23.6%) were missing their childhood vaccinations. The GeneXpert assay detected disease in only 24 (16.7%) of clinically diagnosed pediatric tuberculosis patients.*

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Conclusion: *Although the GeneXpert assay is helpful in the diagnosis of pediatric tuberculosis, most patients were still receiving treatment even after a negative GeneXpert test, necessitating the need for a more sensitive test.*

Keywords: GeneXpert MTB/RIF assay, Childhood Tuberculosis, Tuberculosis Diagnosis, Pediatrics, Addis Ababa

Background

Tuberculosis remains a significant health problem in developing countries. Ethiopia is one of the world's 30 countries with the highest Tuberculosis (TB) burdens, with an estimated TB incidence rate of 132/per 100,000 people (151,000 people annually) and 21,500 TB deaths (19/per 100,000 people) in 2020. In 2019, it was projected that 1.1% of newly diagnosed TB cases and 7.5% of previously treated TB cases had multidrug resistant (MDR-TB) (1-3). The WHO 2022 report states children make up at least 11.3% of tuberculosis cases worldwide, but this figure may be understated given how challenging it is to diagnose childhood tuberculosis, emphasizing the need for better diagnosis (4-6). In Sub-Saharan Africa, where tuberculosis is endemic, children under the age of 15 make up 15% to 20% of the disease burden. The 22 countries with the highest-burden account for approximately 81% of all childhood cases. Ethiopia ranks eighth among these high-burden countries (7).

Clinical, radiological, and tuberculin skin-test results have been primarily used to diagnose pulmonary tuberculosis in children. The tuberculin skin test, however, is a marker of exposure rather than disease; clinical diagnosis has low specificity; radiological interpretation is subject to inter-observer variability. The growing drug-resistant tuberculosis epidemic makes microbiological confirmation with drug resistance detection increasingly crucial. This is challenging due to the difficulty in collecting sputum samples, the paucibacillary nature of the illness, and the low sensitivity of AFB microscopy (8). To stop the spread of the disease in the community, it is crucial to diagnose and find active TB and multi-drug-resistant strains of TB. Due to the disease's nonspecific signs and symptoms, paucibacillary nature, challenges in obtaining sufficient sputum samples, and lack of an adequate sensitive diagnostic test, pulmonary tuberculosis (TB) in children remains a diagnostic challenge (9).

A systematic review and meta-analysis of the GeneXpert MTB/RIF assay for pediatric pulmonary tuberculosis showed that culture tests were positive for tuberculosis in 12% and 11% were positive by GeneXpert, showed a sensitivity of 62% for expectorated or induced samples and for samples from gastric lavage, a sensitivity of 66%. Both samples had 98% of their specifications met. GeneXpert sensitivity was 36–44% higher than was sensitivity for microscopy. For the purpose of identifying

rifampicin resistance, GeneXpert's pooled sensitivity and specificity were 86% and 98%, respectively (10). Studies from Ethiopia and other countries have also shown that the GeneXpert MTB/RIF has a sensitivity range of 65–77.3% and a specificity range of 95–99% (11-15).

As Ethiopia is one of the countries with a high TB-burden, early diagnosis and treatment of TB-cases are required. Since 2014, GeneXpert MTB/RIF has been used as the screening test for children with clinical TB. The diagnosis of TB and the beginning of anti-TB treatment primarily depend on clinical presentation, despite the introduction of the GeneXpert MTB/RIF test in various health facilities in Ethiopia. Thus, we aimed to assess this test's performance in identifying and treating pediatric tuberculosis, and the socio-demographic, hematologic and radiologic characteristics of patients with positive GeneXpert MTB/RIF test results.

Method and materials

Study area and period

The study was conducted at Tikur Anbessa Specialized Hospital (TASH) and Yekatit 12 Referral Hospital, Addis Ababa, Ethiopia. TASH is the largest referral hospital in the country, with 800 beds. The TASH pediatrics and child health department was launched in 1964. Children aged 0 to 15 years are treated at the pediatrics unit. It has about 187 beds, excluding the neonatal ward. This includes 42 beds at the emergency inpatient ward (causes ward), 5 beds in the PICU, 32 beds in the orthopedic unit, 26 beds in the oncology ward, and the rest, 68 beds, for surgical and medical admission.

Yekatit-12 referral hospital's pediatric department has both inpatient and outpatient units where children younger than 15 years of age are treated. It has a severe acute malnutrition rehabilitation unit, a burn treatment center, a neonatal ICU, wards, and emergency departments. There is also a TB clinic unit for the follow-up of patients on anti-TB treatment. Data collection from the eligible patients' charts was conducted from July 1 through September 30, 2016.

Study design

Institution based retrospective descriptive study design was employed.

Population

All children under 15 years old with clinical diagnosis of pulmonary or extrapulmonary TB who have been seen as outpatients or inpatients at TASH and Yekatit-12 hospitals over the past 2.5 years from February 2014 to July 2016 (since GeneXpert began in use in these hospitals to the time data collection).

Inclusion and exclusion criteria

Inclusion criteria

- Children < 15 years
- Clinical diagnosis of tuberculosis
- Investigated with GeneXpert MTB/RIF system
- Initiated on anti-TB treatment

Exclusion criteria

- Unknown GeneXpert MTB/RIF status
- Clinical response to treatment of an alternative diagnosis

Sample size determination and sampling technique

A sample size of 139 children was calculated using incidence rate of 132/per 100,000 with a 95% CI. The sample size obtained using the Epitools sample size calculator. The population was drawn from all children who had been diagnosed with TB and had a GeneXpert assay performed within the previous 2.5 years of data collection (from February 2014 to July 2016), where the GeneXpert MTB/RIF assay was performed from pulmonary and extrapulmonary samples.. A total of 144 patients with clinical diagnosis of TB in the age group of 0-15 years were included in the studyè99 patients from Tikur Anbessa Specialized Hospital and 45 patients from Yekatit-12 Hospital were included in the study.

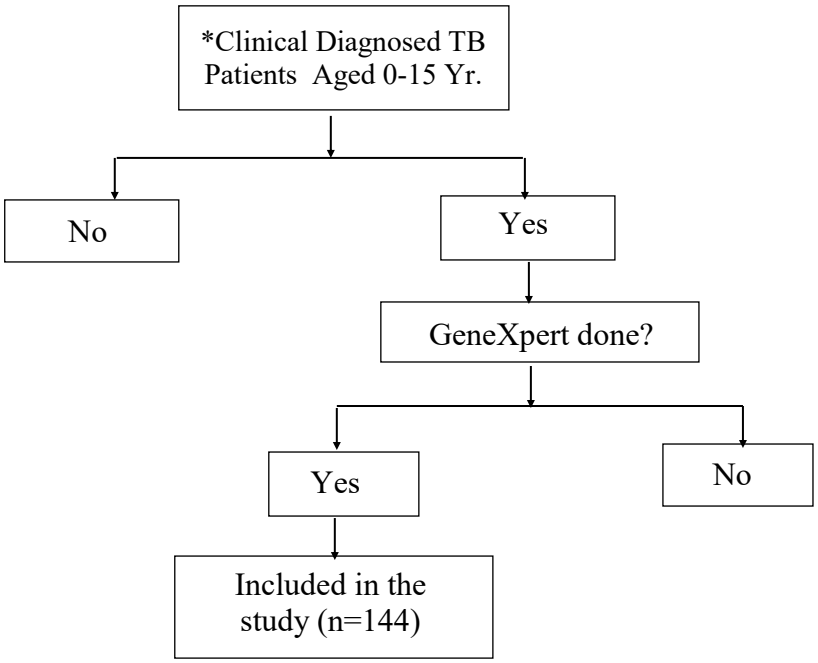

Figure 1: Diagram showing Inclusion criteria of patients with presumptive tuberculosis seen at Tikur-Anbessa specialized hospital and Yekatit-12 referral Hospital from February 2014 to July 2016

* The study collected the retrospective GeneXpert results from patients who were clinically diagnosed with TB and already initiated on anti TB

Study Variables

The study variables are diagnosis by GeneXpert MTB/RIF assay, socio-demographic factors; age, sex, address, contact history, clinical presentation, previous history of tuberculosis, comorbid conditions; HIV infection, immunodeficiency, type of TB and nutritional assessment interpreted based on WHO.

Operational definitions

Contact history with TB patient: contact with a person who has active tuberculosis, particularly sputum smear-positive (open) pulmonary tuberculosis.

Pulmonary TB: is an active mycobacterial infection of the lungs and includes miliary TB.

Extrapulmonary TB: infection of any other organ; this includes the meninges, brain, joints, bones, lymph nodes, kidneys, liver, gastrointestinal (GI) tract, and spleen.

Disseminated TB: is a mycobacterial infection involving both the lungs and other systems.

Severe acute malnutrition: extreme thinness is diagnosed by a weight-for-length (or height) below -3 SD of the WHO Child Growth Standards. In children ages 6–59 months, a mid-upper arm circumference <115 mm or bilateral pitting edema.

Moderate acute malnutrition: is diagnosed by a weight-for-length (or height) between -2 SD and -3 SD of the WHO Child Growth Standards.

Clinical diagnosis of tuberculosis: clinical suspicion of tuberculosis by a health practitioner based on the classic symptoms.

Presumptive diagnosis of TB: a patient who presents with symptoms or signs suggestive of TB (previously known as a TB suspect)

Primary tuberculosis: active tuberculosis infection in an immunologically naive patient.

Post-primary (secondary) tuberculosis is active tuberculosis infection in patients who have been previously exposed to tuberculosis infection.

Data collection procedures, and quality assurance

Structured questionnaires were used in this study to extract data from medical records. First, physician identified the medical records of every child who had been given a TB diagnosis at the two hospitals in the previous two and half years of data collection (form February 2014 to July 2016). A structured questionnaire prepared for the study was used to abstract the data from the cases that met the inclusion criteria. The data abstraction process was under the principal investigator's supervision. Before starting the actual data abstraction to determine the final questionnaires, pretest on 10% of the sample. The pretested surveys were not included.

Before data abstraction, data collectors received a one-day training to ensure data quality. The primary investigator was maintaining a close eye on the accuracy with which all data was being gathered and recorded. The principal investigator verifies the validity, accuracy, and clarity of all collected data at the end of each day.

Data management and analysis

The statistical package for social sciences (SPSS) for Windows version 20 was used to enter, clean, and analyze data. The categorical variables were shown in frequencies and proportions (%) for the description, as well as the appropriate graphs and charts that were also used to summarize the data.

Result

The study consisted of 144 patients with clinical diagnosis of TB who were between the ages of 0 and 15 years. Majority of the children were in the age 6-9 years with mean, and SD of 9.38 and 1.62 respectively. In 24 (16.7%) of the patients with clinically

diagnosed tuberculosis, the GeneXpert MTB/ RIF assay found mycobacteria. The male to female ratio was 1:1, with 70 (48.6%) of them hailing from Addis Ababa, 41 (28.5%) from Oromia, 14 (9.7%) from Amhara, 13 (9.7%) from SNNPR, and 5 (3.5%) from Tigray. Thirty-four patients (23.6%) did not receive their childhood vaccinations. (Table 1)

Table 1: Socio-demographic characteristics of the children on anti-tuberculosis, Tikur Anbessa Specialized and Yekatit 12 Hospital, Addis Ababa, Ethiopia

Variables	**Category**	**n (%)**
Age in years	0-5 year	42 (29.2)
	6-9 year	49 (34.0)
	10-14 years	53 (36.8)
Sex	Male	72 (50.0)
	Female	72 (50.0)
Family size	1-4	39 (27.1)
	5-9	47 (32.6)
	≥10	28 (19.4)
	Unknown	30 (20.8)
Vaccination*	Yes	110 (76.4)
	No	34 (23.6)
Address	Addis Ababa	70 (48.6)
	Oromia	41 (28.5)
	Amhara	14 (9.7)
	Tigray	5 (3.5)
	SNNPR	13 (9.0)
	Others	1 (0.7)

* BCG Vaccine

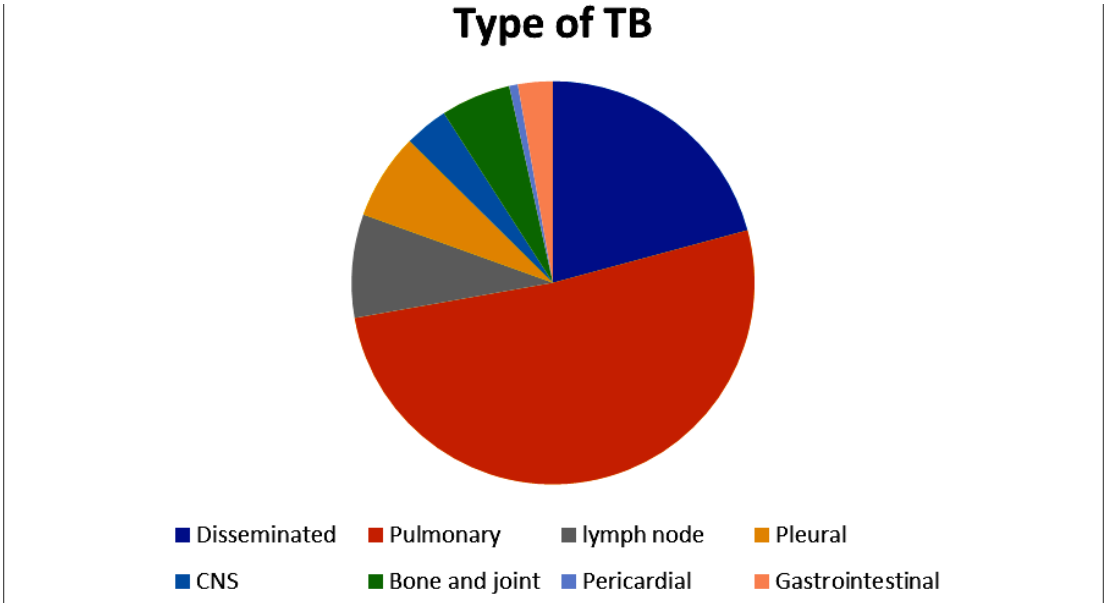

Figure 2: Pie chart depicting the type clinical diagnosis of TB, Tikur Anbessa Specialized and Yekatit 12 Hospital, Addis Ababa, Ethiopia.

Most patients, 74 (51.4%), had pulmonary TB; the remainder had disseminated TB (30.8%); and the rest had extrapulmonary TB (28.7%) (Figure 2). A history of contact with an active tuberculosis patient was reported by 29 individuals (20%). Among all, 33 (23%) had HIV. A prior history of tuberculosis treatment was present in 14 patients (10%). Forty-three (30%) had sever malnutrition and 65 (45%) were moderately malnourished (Table 2)

Table 2: Clinical features of the study population, Tikur Anbessa Specialized and Yekatit 12 Hospital, Addis Ababa, Ethiopia

Contact history			**HIV status**			**Nutritional status /malnutrition**				**Previous TB history**	
No	Yes	N/A	+ve	-ve	Not done	Nor-mal	Mod-erate	Severe	Not Meas-ured	No	Yes
72.2%	20.1%	7.6%	22.9%	54.2%	22.9%	23.6%	45%	29.9%	1.4%	90.3%	9.7%

In terms of the samples sent, 32.6% of the samples came from gastric aspirate, and 48.6% of the samples were taken from sputum. lymph node asp 8 (5.6%), CSF-12 (8.3%), pleural 5 (3.5%), and peritoneal fluid 2 (1.4%) are some additional samples taken from. GeneXpert MTB/RIF assay detected mycobacteria in 24 (16.7%) of patients with clinical diagnosis of tuberculosis (Figure 3). AFB microscopy detected 2 patients with M. Tuberculosis, which were also positive by GeneXpert study. It was not possible to compare the AFB microscopy test with the GeneXpert study because the two tests were not performed simultaneously for all study population.

Laboratory results showed that 14% of patients had leukocytosis, 34.7% of patients had leukopenia, and 50.7% of patients had a normal WBC count. Radiologic TB evidence was present in 72.2% (Table 3).

Table 3: Laboratory findings of the children on anti-tuberculosis, Tikur Anbessa Specialized and Yekatit 12 Hospital, Addis Ababa, Ethiopia.

Variables	**Category**	**n (%)**
WBC count	<4,000 mm3	42 (29.2)
	4,000-12,000 mm3	82 (56.9)
	>12,000 mm3	10 (13.8)
ESR	<20 mm3	24 (16.7)
	20-100 mm3	81 (56.3)
	>100 mm3	38 (26.4)
Lymphocyte %	<25%	50 (34.7)
	25%-33%	73 (50.7)
	>33%	21 (14.6)
Radiologic evidence	Yes	40 (27.8)
	No	104 (72.2

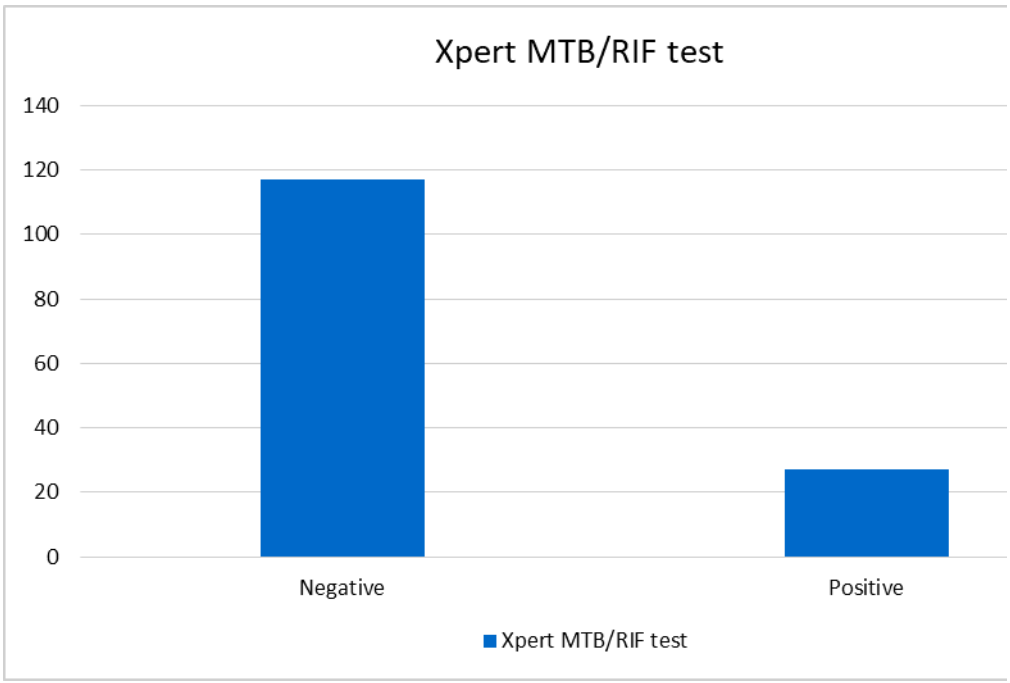

Figure 3. Bar chart showing the number of clinically diagnosed TB patients by GeneXpert MTB/RIF assay, Tikur Anbessa Specialized and Yekatit 12 Hospital, Addis Ababa, Ethiopia.

Discussion

This retrospective study included 144 children ages 0–15 years seen at Tikur Anbessa Specialized Hospital and Yekatit 12 Referral Hospitals, Addis Ababa, Ethiopia, over a period of 2 years and 6 months.. Only 16.7% (24 out of 144) children with a clinical diagnosis were positive for the GeneXpert MTB/RIF assay. The yield of culture in childhood tuberculosis ranges from 20% to 70% depending on factors such as age, disease severity, type and quality of the specimen, and the culture method used. Meta-analysis of the GeneXpert MTB/RIF assay for the diagnosis of pulmonary TB in children showed that 2% of culture-negative children started on anti-TB were detected by the GeneXpert MTB/RIF assay (10). In another meta-analysis, the yield of culture among children with TB diagnoses was found to be 25% (16).

Considering that the GeneXpert MTB/RIF assay has a pooled sensitivity of 62–66% in childhood TB compared with culture, and since culture is positive in only 25% of clinical TB cases, our result of 16.7% falls close to the yield of the previous meta-analysis study (16).

Among children with a positive GeneXpert result, 33.3% are 0–5 years old, 22% are between 6–10 years old, and the remaining 44.4% are between 11–15 years old. Previous studies showed a trend toward increased GeneXpert yield with increasing age (6). In our study, no such trend was present, but compared to younger children, those in the age group of 11–15 years had a higher GeneXpert positivity. This can be due to the difficulty of obtaining proper samples from younger children. There is also a challenge in diagnosing TB in this age group due to a lack of typical presentations, and the risk of overdiagnosis of TB is also high.

Among the children with TB diagnoses, 45% had moderate acute malnutrition, and 30% had severe acute malnutrition. Given that Yekatit 12 Hospital, which is a nutritional rehabilitation facility, provided a third of the sample, the high percentage of severe malnutrition is due to this. In our study, 23% of the children with TB diagnoses also tested HIV-positive. According to the WHO, the HIV prevalence among children with TB ranges from 10 to 60% in nations with moderate to high prevalence, which is comparable to our study. Among the studied children, 51.4% are pulmonary TB cases, 20.8% are disseminated TB cases, and the remaining 27.8% are extrapulmonary TB cases. Sputum from gastric aspirate make up 81.2% of the total samples collected.. This indicates a paucity of GeneXpert MTB/RIF test results from way the sample collected and extrapulmonary samples (lymph node, pleural fluid, peritoneal fluid, CSF, tissue samples), which can lower the yield from GeneXpert MTB/RIF in those patients.

The current study had several limitations. Because it was a retrospective study, it was not possible to oversee the specimen collection, processing, and analysis. It was not also possible to take additional specimens for culture and AFB microscopy studies. Because of this,

the increased sensitivity of molecular study over AFB microscopy was not assessed. Since mycobacterial culture is not routinely done for TB-diagnosed patients, it was only possible to compare the efficacy of the GeneXpert MTB/RIF assay with clinical diagnosis of childhood TB.

Conclusion

In conclusion, our study showed the GeneXpert MTB/RIF assay detected only 16.7% of clinically diagnosed tuberculosis in children. The GeneXpert MTB/RIF assay is beneficial in the diagnosis of childhood TB, but a more sensitive test is required.

Declarations

Ethical consideration: Ethical clearance was obtained from Research and Ethics committee of the department of pediatrics and child health, School of medicine, AAU. On the questionnaires, there was no place for personal information, and all data were treated confidentially over the course of the study.

Author's contribution

YG and WA conceived and designed the study. YG involved in the data collection. WA and BB were actively involved in the data interpretation and writing of the final manuscript. All authors approved the final manuscript.

Competing risk: No competing risk to disclose

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References

1. Global tuberculosis report 2019. Geneva: World Health Organization; 2019
2. Guidelines for Clinical and Programmatic Management of TB, TB/HIV, DR-TB and Leprosy in Ethiopia. 2021.
3. WHO. Tuberculosis profile: Ethiopia 2020.
4. Tuberculosis (TB).” Tuberculosis, 27 Oct. 2022, www.who.int/news-room/fact-sheets/detail/tuberculosis.
5. Dodd P, Gardiner E, Coghlan R, Seddon J. Burden of childhood tuberculosis in 22 high-burden countries: A mathematical modelling study. The Lancet Global Health. 2014;2.
6. Jenkins HE, Tolman AW, Yuen CM, Parr JB, Keshavjee S, Pérez-Vélez CM, et al. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. Lancet. 2014;383(9928):1572-9.
7. Kebede A. Implementation Guideline for GeneXpert MTB/RIF Assay in Ethiopia 2014.

8. Nicol MP, Workman L, Isaacs W, Munro J, Black F, Eley B, et al. Accuracy of the Xpert MTB/RIF test for the diagnosis of pulmonary tuberculosis in children admitted to hospital in Cape Town, South Africa: a descriptive study. Lancet Infect Dis. 2011;11(11):819-24.
9. Marais BJ, Schaaf HS. Tuberculosis in children. Cold Spring Harb Perspect Med. 2014;4(9):a017855.
10. Detjen AK, DiNardo AR, Leyden J, Steingart KR, Menzies D, Schiller I, et al. Xpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis in children: a systematic review and meta-analysis. Lancet Respir Med. 2015;3(6):451-61.
11. Tadesse M, Aragaw D, Rigouts L, Abebe G. Increased detection of smear-negative pulmonary tuberculosis by GeneXpert MTB/RIF® assay after bleach concentration. International Journal of Mycobacteriology. 2016;5(2):211-8.
12. Geleta DA, Megerssa YC, Gudeta AN, Akalu GT, Debele MT, Tulu KD. Xpert MTB/RIF assay for diagnosis of pulmonary tuberculosis in sputum specimens in remote health care facility. BMC Microbiol. 2015;15:220.
13. Hillemann D, Rüsch-Gerdes S, Boehme C, Richter E. Rapid molecular detection of extrapulmonary tuberculosis by the automated GeneXpert MTB/RIF system. J Clin Microbiol. 2011;49(4):1202-5.
14. Roberts I. Nelson's textbook of pediatrics (20th edn.), by R. Kliegman, B. Stanton, J. St. Geme, N. Schor (eds). Pediatric Radiology. 2017;47(10):1364-5.
15. Boehme CC, Nicol MP, Nabeta P, Michael JS, Gotuzzo E, Tahirli R, et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. Lancet. 2011;377(9776):1495-505.
16. DiNardo AR, Detjen A, Ustero P, Ngo K, Bacha J, Mandalakas AM. Culture is an imperfect and heterogeneous reference standard in pediatric tuberculosis. Tuberculosis (Edinb). 2016;101s:S105-s8.