Original Article

Trends in Pediatric Tuberculosis Diagnosis Utilizing Xpert *Mycobacterium tuberculosis*/Rifampicin in a Poor-Resource, High-Burden Region: A Retrospective, Multicenter Study

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Abstract

Background: The burden of tuberculosis (TB) in Nigeria remains high, and diagnosis in children, a challenge. We aimed to document yield from Xpert *Mycobacterium tuberculosis*/rifampicin (MTB/RIF) as a mode of diagnosis for children and the variables associated with a positive result. **Methods:** This was a retrospective review of TB treatment cards of children aged 0–15 years managed from January 2017 to December 2021 across six public tertiary institutions in Nigeria. The data obtained were analyzed using the descriptive and inferential statistics. Statistical significance was set at $P < 0.05$. **Results:** Of 1489 children commenced on TB treatment, 1463 (97.9%) had sufficient data for analysis the median age of study participants was 60 months (interquartile range [IQR]: 24, 120), and 814 (55.6%) were males. Xpert MTB/RIF test was performed in 862 (59%) participants and MTB was detected in 171 (19.8%) participants, of which 6.4% (11/171) had RIF resistance reported. The use of Xpert MTB/RIF rose from 56.5% in 2017 to 64% in 2020 but fell to 60.9% in 2021. We found that older age (> 10 years), the presence of pulmonary TB (PTB), and a negative human immunodeficiency virus (HIV) status were associated with positive Xpert MTB/RIF tests ($P = 0.002$, 0.001, and 0.012, respectively). **Conclusion:** The utilization of Xpert MTB/RIF in children increased in the years before the COVID-19 pandemic. Factors associated with MTB detection by Xpert MTB/RIF include older age, the presence of PTB, and a negative HIV status. Clinical and radiological evaluation continues to play vital roles in the diagnosis of childhood TB in Nigeria.

Keywords: Childhood tuberculosis, human immunodeficiency virus, multidrug-resistant-tuberculosis, Nigeria, tuberculosis, Xpert *Mycobacterium tuberculosis*/rifampicin

Submitted: 04-Dec-2022 **Revised:** 26-Jan-2023 **Accepted:** 16-Feb-2023 **Published:** 14-Mar-2023

Introduction

Tuberculosis (TB) is a significant cause of morbidity and mortality globally, with vulnerable populations such as the poor, malnourished, and immunosuppressed being at particularly high risk.[1,2] Although efficacious drugs are now available for prevention, treatment, and cure, TB still affects millions of people worldwide, especially in developing countries.[1,2]

Over 9.9 million new cases of TB were reported worldwide in 2020, of which 80% were in 22 high-burden countries, including Nigeria.[1] Of the 450,000 cases reported in Nigeria in 2020, 6% occurred in children aged 0–14 years, although this number is likely an underestimate as a large proportion of cases is missed due to underdiagnosis and underreporting.[1,2]

Access this article online

Quick Response Code:

Website: www.ijmyco.org

DOI: 10.4103/ijmy.ijmy_1_23

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How to cite this article: Garba MA, Ogunbosi BO, Musa A, Ibraheem RM, Alao MA, Jiya-Chitumu EN, *et al*. Trends in pediatric tuberculosis diagnosis utilizing Xpert *Mycobacterium tuberculosis*/rifampicin in a poor-resource, high-burden region: A retrospective, multicenter study. Int J Mycobacteriol 2023;12:77-81.

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Correct reporting of TB depends on a correct diagnosis. Unfortunately, this is difficult in children in whom signs and symptoms of TB often overlap with other tropical diseases such as malnutrition, human immunodeficiency virus (HIV) infection, and lower respiratory tract infections.[2,3] Children also have difficulties in expectorating sputum samples and are more prone to paucibacillary and extrapulmonary TB (EPTB).[2,3] Traditional diagnostic methods of smear microscopy have low sensitivity of only 40% under optimal conditions, whereas mycobacterial culture expends much time and resources[4,5] Thus, better diagnostic tests are needed for TB control programs such as the "End TB Strategy" of the World Health Organization (WHO).[6]

Molecular detection of Mycobacterium tuberculosis (MTB) using MTB /RIF can be performed in 2 h, is more sensitive, and also limits the wrong use of anti-TB drugs in patients with multidrug-resistant TB (MDR-TB).[2,7] Xpert MTB/rifampicin (RIF) (Cepheid, Sunnyvale, USA) is a real-time polymerase chain reaction nucleic acid amplification test which detects the *rpoB* gene of MTB and also detects RIF resistance as a marker for MDR-TB.[8] The WHO recommended the use of Xpert MTB/RIF as a point-of-care test for children with suspected TB in 2013 following the results of a meta-analysis of several studies indicating a sensitivity of 62%–66% and specificity of 98% in diagnostic accuracy.[8] The Xpert MTB/RIF Ultra, which works on the same principle but with greater specificity, is also available and in wide use since 2017.[6] Recent validation studies have shown both methods can also detect MTB in stool samples, thereby increasing diagnostic yield in childhood TB.[9-11]

Xpert MTB/RIF testing was adopted for use as the first line diagnostic tool in Nigeria in 2016. Nigeria currently has 398, four-module Xpert MTB/RIF platforms (total, 1560 modules) installed at secondary and tertiary hospitals in all 36 states and the Federal Capital Territory.[12]

This study aimed to assess the use of Xpert MTB/RIF test as a modality for diagnosis of childhood TB across Tertiary Health Institutions in Nigeria in compliance with the WHO recommendations. The study also aimed to identify any variables associated with a positive Xpert MTB/RIF test. Results from this study could help inform decisions to bridge the gaps in TB diagnosis and reporting in children and also lay the groundwork for further research on childhood TB.

Methods

Study setting

TB treatment services are offered in both private and public hospitals in Nigeria through directly observed therapy (DOTS) centers. A majority of TB cases are managed at the levels of primary and secondary health care, whereas tertiary hospitals tend to manage more complex cases and provide the best available standards of care. Cases of drug-resistant TB are referred to designated MDR treatment centers. All 36 states of Nigeria have State TB, Leprosy and Buruli Ulcer Control Programs jointly coordinated under a national control program which provides equipment, anti-TB medication, consumables, and data management tools.

Using purposive sampling, six tertiary hospitals with DOTS centers in Nigeria were selected for this study.

Study design

This was a retrospective review of all available TB treatment cards of children managed at the six study centers from January 1, 2017, to December 31, 2021. Reference was made to the presumptive TB register for more information where required.

Study size determination

The minimum sample size was calculated using the formula for determining proportion by Cochran,[13] $N = (Z^2pq)/d^2$, where

N = Minimum sample size

Z = Standard normal deviate set at 1.96 corresponding to the 95% confidence interval

P = Proportion of worldwide new TB cases accounted for by childhood (<15 years)

TB = 0.11 (11%)

$q = (1 - p) = 1 - 0.11 = 0.89$

d = Precision level set at (5%) =0.05

Therefore, the minimum sample size $N = ([1.96]^2 \times 0.11 \times 0.89)/(0.05) = 150$

Inclusion criteria

We included all cases of clinically diagnosed TB (pulmonary TB [PTB] and EPTB) among children aged 0–15 years; cases of TB commenced on treatment with entries in the TB treatment cards/register from January 2017 to December 2021; and all cases diagnosed using acid-fast bacilli microscopy, histology, culture, chest X-ray, and/or Xpert MTB/RIF test.

Definitions of terms

PTB was defined as bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree, including tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar). Miliary TB with lung lesions on chest X-ray was always classified as PTB. EPTB encompassed any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs (e.g., pleura, peripheral lymph nodes, abdomen, genitourinary tract, skin, joints and bones, and the meninges).[3] A person with both PTB and EPTB was classified as having PTB.[3] A successful treatment included both cure and completed treatment, whereas unsuccessful treatment included death and treatment failure.

Outcome measures

The primary outcome was a positive or negative Xpert MTB/RIF test, and variables tested for potential association included age, sex, site of TB, type of TB, HIV status, alternative method of diagnosis, and treatment outcome (successful vs. unsuccessful treatment).

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Data collection and analysis

Data were collected by research assistants who had undergone 2-day training by principal investigators. Data were copied onto a Microsoft Excel® sheet (2010) where they were coded, cleaned, and then imported to IBM Statistical Package for the Social Sciences (SPSS) for Windows, Version 23.0. (Armonk, NY: IBM Corp.) for analysis. Continuous variables were analyzed using the Student's *t*-test, whereas categorical variables were analyzed with the Chi-square tests. Results were presented in tables and figures.

Results

A total of 1489 children were enrolled in the TB treatment program at the study sites, of whom 1463 had sufficient data for analysis (97.9%). The median age of study participants was 60 months (interquartile range; 24, 120), but girls were significantly older than boys (mean ± standard deviation, SD: 74.5 ± 50.2 months vs. 67.9 ± 52.3 months, respectively; $P = 0.015$). The male–female ratio was 1.25:1, which was generally consistent across all age groups [Table 1].

A quarter of the children (25%) enrolled in care had TB-HIV coinfection, a third (33.2%) had EPTB and 66.8% had PTB. Xpert MTB/RIF testing was performed in 862 (59%) cases, which detected MTB in 171 (19.8%) cases. RIF resistance was reported in 6.4% (11/171) of those with a positive Xpert MTB/RIF test. Treatment outcomes were documented in 792 (91.5%) cases, of which 84.6% had a successful treatment outcome.

Treatment for childhood TB relied solely on clinical or radiological diagnosis, or both, in 1139 cases, or 79% [Figure 1]. Bacteriologic diagnosis in general increased gradually from 2017 to 2020 and then declined sharply in 2021 [Figure 1], whereas histologic diagnosis (mainly Ziehl-Neelsen staining and microscopy of lymph node biopsy specimens) was made in 2.3% (34/1463) of the participants and remained relatively steady during that period. Xpert MTB/RIF testing also rose steadily from 56.65% in 2017 to reach a peak of 64% in 2020, which then declined to 60.9% in 2021 [Figure 2]. Using the Chi-square tests of association, we found that age older than 10 years, a negative HIV status, and the presence of PTB were all significantly associated with detection of MTB with Xpert MTB/RIF testing in the study population [Table 2].

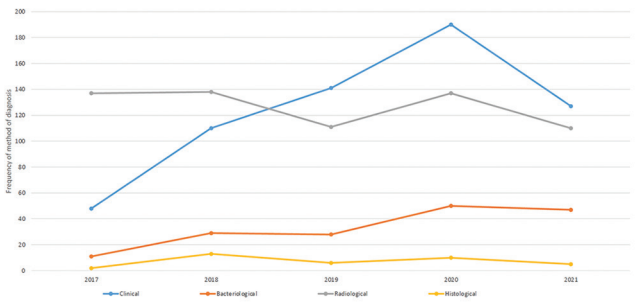

Figure 1: Annual trends in methods of diagnosing childhood tuberculosis during 2017–2021

Discussion

The older age of girls in this study is similar to findings by Fernandes *et al*. in Brazil,[14] but contrary to findings in other studies reporting no gender differences until adolescence when childhood TB becomes higher in boys.[15,16] We have no clear explanations for the gender difference across studies but it could reflect differences in gender distribution in different populations.

About three-fifths (59%) of participants with suspected TB in our study had an Xpert MTB/RIF test during the study period. This suggests that access to Xpert MTB/RIF testing is still limited in Nigeria 6 years after the country implemented the WHO recommendation to use Xpert MTB/RIF as the diagnostic method of choice for suspected TB.

Almost half of all TB cases in our study were diagnosed solely on the basis of radiological and clinical algorithms, which was higher than the 43% global rate reported by the WHO.[3] At the same time, Xpert MTB/RIF testing rose steadily from 56.7% in 2017 to 64.9% in 2020, which then fell to 60.9% in 2021. The slow rise was likely due to the phased introduction of Xpert MTB/RIF testing in Nigeria, and the fall in 2021 was probably due to the COVID-19 pandemic, which caused the closure of hospitals and also limited transportation of TB patients to primary health centers.[17,18] Other contributing factors proposed by Gidado *et al*., include poor maintenance of diagnostic facilities, problems with sample collection and interpretation, and difficulties with cold storage of samples due to poor supply of electricity.[12]

The WHO also integrated COVID-19 testing within Nigeria's national TB control program, especially at tertiary health centers. To compound it further, some symptoms and signs of COVID-19 resembled those of PTB, which may have resulted in misdiagnosis of the two conditions. How COVID-19 testing impacted on the

Table 1: Demographic characteristics of study population

Age (years)	Female, *n* (%)	Male, *n* (%)	Total, *n* (%)
<1	55 (8.5)	75 (9.2)	130 (8.9)
1-5	226 (34.8)	325 (39.9)	551 (37.7)
6-10	193 (23.7)	215 (26.4)	408 (27.9)
11-14	175 (30.0)	199 (24.5)	374 (25.7)
Total	649 (100.0)	814 (100.0)	1463 (100.0)

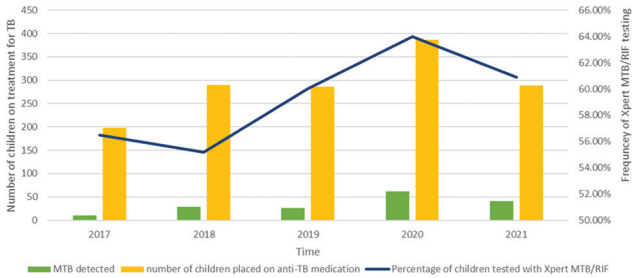

Figure 2: Bar chart showing yearly rates of childhood tuberculosis diagnosed with and without a positive Xpert test. TB: Tuberculosis, MTB/RIF: *Mycobacterium tuberculosis*/rifampicin

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Table 2: Chi-square tests of Xpert *Mycobacterium tuberculosis*/rifampicin resistance yield and clinical/demographic variables

Clinical/demographic variable	MTB positive (%)	MTB negative (%)	Total	*P*
Age (years)				
<1	5 (6.5)	72 (93.5)	77	0.002
1-5	55 (18)	250 (82)	305	
6-10	52 (21.9)	185 (78.1)	237	
>10	59 (24.3)	184 (75.7)	243	
Sex				
Male	87 (18.2)	390 (81.8)	477	0.198
Female	84 (21.8)	301 (78.2)	385	
Type of TB				
PTB	135 (22.9)	435 (77.1)	570	0.001
EPTB	36 (13.1)	238 (86.9)	274	
HIV status				
Positive	26 (38.7)	169 (86.7)	195	0.012
Negative	139 (21.7)	502 (78.3)	641	
Site of TB				
PTB	150 (21.6)	549 (78.5)	699	0.002
Abdomen	3 (10.3)	26 (89.7)	29	
CNS	4 (33.3)	8 (66.7)	12	
Others***	14 (11.4)	108 (88.6)	122	
Treatment outcome				
Successful	110 (19.6)	452 (80.4)	562	0.685
Unsuccessful	18 (17.6)	84 (82.4)	102	

***TB pericarditis, Pott's disease, renal TB, skin TB, and cold abscess. HIV: Human immunodeficiency virus, CNS: Central nervous system, TB: Tuberculosis, PTB: Pulmonary TB, EPTB: Extra PTB, MTB: *Mycobacterium tuberculosis*

diagnosis and management of pediatric TB patients in Nigeria remains unknown, but studies elsewhere have shown negative impacts of the COVID-19 pandemic on TB services.[17,19]

Although radiologic and clinical diagnosis of childhood, TB was much higher than bacteriologic diagnosis in our study, we have noted a gradual increase in the detection of MTB during the 5-year spanning 2017–2021. We attribute the steady rise to wider access to Xpert MTB/RIF testing and the use of stool samples on that platform.[9,11,20-23] The introduction of Xpert MTB/RIF Ultra may also have improved diagnostic yield in paucibacillary TB, which is more common in children.[8,11,24] Nonetheless, some of these gains were reversed during the COVID-19 pandemic in the years 2020 and 2021.

Xpert MTB/RIF testing detected RIF resistance in 6.4% of cases, with more cases seen in 2021 than in previous years. Whether this was a result of improved case detection or increased household exposure and transmission due to pandemic lockdowns is not clear.

We found that positive Xpert MTB/RIF tests were more common in children older than 10 years compared to younger children. Older children in our study probably had a higher prevalence of adult-type multibacillary disease, rather than paucibacillary and extrapulmonary disease frequently seen in younger children.[3,24] Our finding agrees with Ogbudebe *et al*., who also described a higher yield of Xpert MTB/RIF among older children in Nigeria.[25] On the other hand, Das *et al*. reported equally high yields among both infants and preadolescents in India and Nepal.[10] We also found significant associations between the presence of PTB and the detection of MTB by Xpert MTB/RIF testing among study participants. Conversely, the yield from children with TB/HIV coinfection was significantly less than those without HIV, which was similar to reports from previous studies.[24]

Yet, despite these benefits of Xpert MTB/RIF, including the use of stool samples, the diagnostic yield of Xpert MTB/RIF and Xpert MTB/RIF Ultra in clinically-suspected childhood TB is still marginal in Nigeria.[26]

Conclusion

The use of Xpert MTB/RIF for diagnosis of childhood TB is still limited in Nigeria, with most cases of suspected TB still relying on clinical and radiologic diagnosis. Age older than 10 years, a negative HIV status, and the presence of PTB are all associated with MTB detection by Xpert MTB/RIF among Nigerian children. There is the need for wider access to Xpert MTB/RIF testing for childhood TB in Nigeria. Further studies are needed to understand those barriers limiting Xpert MTB/RIF testing of Nigerian children with suspected TB.

Limitation

A major limitation of our study was the lack of mycobacterial culture in the national TB control program, which prevented a comparative analysis of MTB detection rates with bacterial culture versus molecular detection with Xpert MTB/RIF testing. We also could not analyze the diagnostic yields of different specimens on the Xpert MTB/RIF platform, such as sputum versus stool samples, as this information was not available in the treatment records.

Ethical clearance

Ethical approval was obtained from the National Health Research Ethics Committee of the Federal Ministry of Health (NHREC/01/01/2007-22/08/2022).

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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