Review Article

Cost-Effectiveness of Currently Available Diagnostic Tools for Diagnosis of Pediatric Tuberculosis Under National Tuberculosis Elimination Program

Ragini Bhatia, Anil Chauhan[1], Kulbir Kaur, Monika Rana, Meenu Singh
Departments of Pediatrics and [1]Telemedicine, PGIMER, Chandigarh, India

Abstract

In India, children do not get diagnosed with tuberculosis (TB) for reasons such as lack of screening modality at the health-care settings, inadequate sputum sample, and low detection rate. This study aims to assess various modalities for diagnosis of pediatric TB and their cost-effectiveness. Cost-effectiveness was found for various diagnostic modalities for TB diagnosis in children of India below 15 years of age. TrueNat MTB was the intervention being compared to GeneXpert MTB and sputum microscopy. Evidence pertinent to effectiveness and cost per test, and health benefits in terms of disability adjusted life years were researched and documented. Modeling a cohort of children through a decision tree and assimilating costs and disability-adjusted life years (DALYs) at each step gave results in the form of cost-effectiveness. Interventions were compared by calculating the cost-effectiveness ratio. The results revealed that TrueNat is more cost effective (Rs. 9450/DALY averted) compared to GeneXpert MTB/RIF (Rs. 9750/DALY averted). The incremental cost effectiveness ratio of TrueNat with respect to GeneXpert was found to be Rs. 5925 per DALY averted. Diagnosis through TrueNat point of care (POC) will avert 962 more DALYs compared to GeneXpert. As is evident from the results, TrueNat does alleviate disability caused by TB in children as more DALYs are averted. At an additional cost of Rs. 5925 to avert one DALY, which is below the gross domestic product (GDP) per capita for India (for 2021, it was $2277), TrueNat can have significant health benefits.

Keywords: Children, GeneXpert MTB, TrueNat MTB, tuberculosis

Introduction

There was a global drop in the number of people newly diagnosed with tuberculosis (TB) during coronavirus disease 2019 (COVID-19) pandemic. The reporting decreased from 7.1 million in 2019 to 5.8 million in 2020, and India was among the worst affected countries. Thus, reduced access to TB diagnosis and treatment has resulted in an increase in TB deaths. Estimates for 2020 have shown that 1.3 million TB deaths occurred among human immunodeficiency virus (HIV)-negative people and India accounted for 38% of these global TB deaths. In India, of the deaths among HIV-negative people, 53% were men, 32% were women, and 16% were children.[1] Also, 96% of pediatric TB deaths among 60,000 in the year 2015 were reported to have occurred in children who did not receive treatment for the disease.[2] India notified 2.4 million TB patients in the year 2019. Out of the total TB cases notified in India, children (0–14 years) accounted for 5.65% of total TB cases. Although pediatric TB is estimated to be 10% of total incident cases in India, only 5.6% are reported in the National Tuberculosis Elimination Program (NTEP). There is an estimated 56% gap in pediatric TB notification under the NTEP, with only 1.5 lakh pediatric cases notified in 2019.[3] As per the global estimates of 2019, 5586 children out of 12 lakh children under the age of 15 have drug-resistant TB.[4] Case fatality ratio due to TB in India was 6.5% in pediatric cases.[5]

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Address for correspondence: Prof. Meenu Singh, Department of Pediatrics, PGIMER, Chandigarh - 160 014, Punjab, India.
E-mail: ebm2012apc@gmail.com

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The diagnosis of childhood TB is based on clinical history, radiological findings, and medical examinations.[3] Young children face the greatest risk and the most rapid disease progression. Phase 2 of the disease occurs 1–3 months after primary infection and follows occult hematogenous spread. The risk for the development of tuberculous meningitis (TBM) and disseminated (miliary) TB is highest in phase 2 of the disease.[6] Children have better prognosis compared to adults if initiated on treatment.[7] But there is a lack of high-quality diagnostic tests, sample handling, and point of clinical care. Culture of *Mycobacterium tuberculosis* is considered to be the "gold standard" in diagnosing the disease, but has limitations of 4–8 weeks' time period for detection and need of sophisticated laboratory facilities.[8]

To fill the diagnostic gaps, the World Health Organization (WHO) recommended the use of a rapid diagnostic test, GeneXpert MTB/RIF (Cepheid Inc, Sunnyvale, CA, USA) as the initial diagnostic test in children suspected of having TB and drug-resistant TB. The GeneXpert MTB/RIF Ultra, an updated technology, has higher sensitivity compared to the Xpert MTB/RIF assay.[9] TrueNat (Molbio Diagnostics/Bigtec Labs, Goa/Bengaluru, India) is a new chip-based test that uses micro real-time polymerase chain reaction (PCR) technology to detect *Mycobacterium* bacilli.[6] It takes 1 h to detect TB and if the test is positive, an add-on chip is used to detect Rifampicin (RIF) resistance, which takes an additional hour. The system is battery operated with capability of testing four samples at a time. It is portable and can be used as a point-of-care (POC) test within primary health-care facilities.[10,11] The results of accuracy studies done by the Foundation for Innovative New Diagnostics (FIND) also indicate that the TrueNat tests have accuracy comparable to Xpert MTB/Ultra and Xpert MTB/RIF, and can be performed at temperatures up to 40°C and in the absence of reliable electricity.[12] TrueNat can increase disease detection rate without the need for laboratory referrals.[13] Another variant of TrueNat is the TrueNat MTB Plus, which has more sensitivity (29 cfu/ml); therefore, it is recommended for TB diagnosis in children.

In this study, using a decision analytical model, we projected the clinical impact, costs, and cost-effectiveness of TrueNat as a replacement for smear microscopy or GeneXpert. Based on the above preliminary search of literature and available evidence, this study aims to compare the clinical effectiveness of GeneXpert and TrueNat with reference to culture as the gold standard. This study also looked into the operational feasibility and challenges of implementing TrueNat under Revised National Tuberculosis Control Program (RNTCP).

Materials and Methods

In this cost-effectiveness study, the existing evidence from related literature was evaluated, which included studies and systematic reviews, and annual or technical reports from different departments of the country. The literature review was targeted to find evidence about the use and effectiveness (in terms of sensitivity and specificity) of smear microscopy, TrueNat MTB, and GeneXpert MTB for the diagnosis of TB in children. Ethical clearance was not required for this study.

From available resources, evidence pertinent to cost per test including all direct and indirect resources was also reviewed. We do not have sufficient data to conduct a formal meta-analysis as studies with children as subjects were limited. The evidence from the literature was incorporated in the decision analytical model, taking into consideration the costs, treatment costs, and disability-adjusted life years (DALYs) averted. The calculations were done by using analytical decision tree model in Microsoft Excel (advanced).

Comparison of the clinical and economic outcomes of three TB diagnostic strategies was done: (1) sputum smear microscopy in Designated Microscopy Centre (DMCs) (SSM), (2) GeneXpert in DMCs, and (3) TrueNat POC. Model-generated outcomes included life expectancy, DALYs, lifetime TB-related health-care costs, and incremental cost-effectiveness ratio (ICER; the difference between two strategies in costs [US dollars] divided by the difference in DALYs averted). We considered a strategy cost-effective if its ICER was less than 50% of India's current gross domestic product (GDP) per capita per DALY averted.[14]

Literature search

Results of the literature review showed that the GeneXpert has 0.66 sensitivity and 0.98 specificity for the diagnosis of TB in children.[15] Due to dearth of studies done with children as subjects, available studies in adults were reviewed to document evidence of effectiveness of TrueNat in children less than 18 years. Thus, a ratio factor of 1.2. was derived by considering the ratio between the sensitivities of adult and pediatric populations for other diagnostic tests such as GeneXpert and sputum microscopy. Taking into consideration the systematic reviews, the sensitivities of TrueNat and GeneXpert were taken as 0.69 and 0.65, respectively, in case of children. The details of the studies considered are given in Table 1.

Model overview

A decision analytical model was built to simulate a cohort of 100,000 children who report to public health facilities in India with signs and symptoms suggestive of TB. They undergo a TB diagnostic protocol as per the national guidelines. We estimated the total costs (in 2020 US dollars) of diagnosing and treating TB and rifampicin-resistant TB for the cohort, as well as the average costs per presumptive TB patient tested, per true TB case, and per rifampicin-resistant TB case detected and initiated on treatment. As individuals move through the states of TB progression, detection, treatment, retreatment, and relapse, the model tracks the clinical outcomes of successful treatment resulting in DALYs averted.

DALY measures overall disease burden in terms of mortality and morbidity. It is expressed in terms of number of years lost due to ill health, disability or early death, taking into account disutility weight and years lost due to the disease as well as

Table 1: Summary of available literature in context to effectiveness of diagnostic tests

Study title	Publication year	Population	Diagnosis through test	Sensitivity	Specificity	Total number of studies included
Global TB Report 2013, WHO	WHO, 2013[23]	Children (0-14 years)	Xpert MTB/ RIF	66% (52-77)	98%	16 studies (13 studies with 2603 children)
Xpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis in children: A systematic review and meta-analysis	Detjen *et al*., 2015[24]	Children	Xpert MTB/ RIF	62% (51-73)	98% (97-99)	15 studies with 3640 children
Xpert MTB/RIF and Xpert MTB/RIF ultra assays for active tuberculosis and rifampicin resistance in children	Alexander W Kay, 2020[25]	Children	Xpert MTB/ RIF	64.6% (55.3-72.9)	99% (98.1-99.5)	Studies with 68,544 participants
Xpert MTB/RIF ultra improved the diagnosis of paucibacillary tuberculosis: A prospective cohort study	Wang *et al*., 2019[26]	Adults	Xpert MTB/ RIF	65% (61-69)	99% (98-99)	11 studies with 3801 patients
ICMR study: Operational feasibility and performance of TrueNat MTB RiF assays in field settings under the Revised National Tuberculosis Control Program	Tripathi *et al*., 2019[6]	Adults	TrueNat Xpert MTB	84.1% 81.0%		10,878 adults
Evaluation of the Indian TrueNat micro RT-PCR device with GeneXpert for case detection of pulmonary tuberculosis	Nikam *et al*., 2014[27]	Adults	TrueNat Xpert MTB	99% 100%		247
Rapid diagnosis of *Mycobacterium tuberculosis* with TrueNat MTB: A near-care approach	Nikam *et al*., 2014[27]	Adults	TrueNat Xpert MTB	91.1% 90.58%		266
Diagnosis of childhood tuberculosis	ToyinTogun *et al*., 2017[28]	Children	Smear microscopy	15%		Literature review
New specimens and laboratory diagnostics for childhood pulmonary TB: Progress and prospects	Mark P Nicol *et al*., 2011[29]	Children	Smear microscopy	15%		Literature review
Diagnostic accuracy of same-day microscopy versus standard microscopy for pulmonary tuberculosis: A systematic review and meta-analysis	J Lucian Davis *et al*., 2013[30]	Adults	Smear microscopy	64%		Eight studies, 7771 patients

years lived with disability. For the individuals who could not follow up, refused treatment, not provided treatment and in whom death was the outcome, DALYs averted were not calculated. The DALYs were calculated by taking the disability weights (3.3) according to the Global burden of disease report 2019 for TB-related disability for all ages in India.[16] Life expectancy was taken as 69 years for India. The model simultaneously tracks the prevalence of pediatric TB and its sequelae, associates it with the TB-related health-care costs, and calculates the cost-effectiveness of different diagnostic strategies. The details of the model are shown in Figure 1.

Statistical analysis

The decision tree analytical model incorporates the number of patients detected (true positives), which will be in congruence to the sensitivity of the diagnostic tool. In case of children, the detection rate is low and many will be counted as false negative and will go undiagnosed until other tests are performed. False positives will be low as the specificity of the diagnostic tool is higher. The patients detected positive will have either pulmonary TB or extrapulmonary TB. In each category, there will be cases with rifampicin resistance and rifampicin sensitivity.

The cases that are rifampicin resistant will progress toward four sequelae as follows:

1. Treatment (second-line regimen)
2. Loss to follow-up
3. Noninitiation on treatment
4. Death.

The costs will be attached to each sequelae, including the cost of screening. The cases that are rifampicin sensitive will either be on previous treatment or not on previous treatment. If the case is on previous treatment, the case can recover or take retreatment. This could result in success or failure of the treatment. The cases not on treatment will receive first-line treatment, which will eventually lead to success or failure of TB treatment. In this scenario, the cases may be lost to follow-up or may die. The same will apply for patients with extrapulmonary TB. This model will track the prevalence (as given by Kalra *et al.*'s[17] study) of all the consequences resulting in DALYs averted, along with the costs, and will finally give the cost-effectiveness of the diagnostic modality.

Cohort characteristics and TB prevalence

Cohort characteristics were derived from an implementation study of GeneXpert for children (0–14 years) with presumptive TB in 10 cities of India chosen for being geographically and demographically representative of the national population of India.[17] Their mean age was 8 years, 46% were females, and 54% were males. The prevalence of TB in the study population

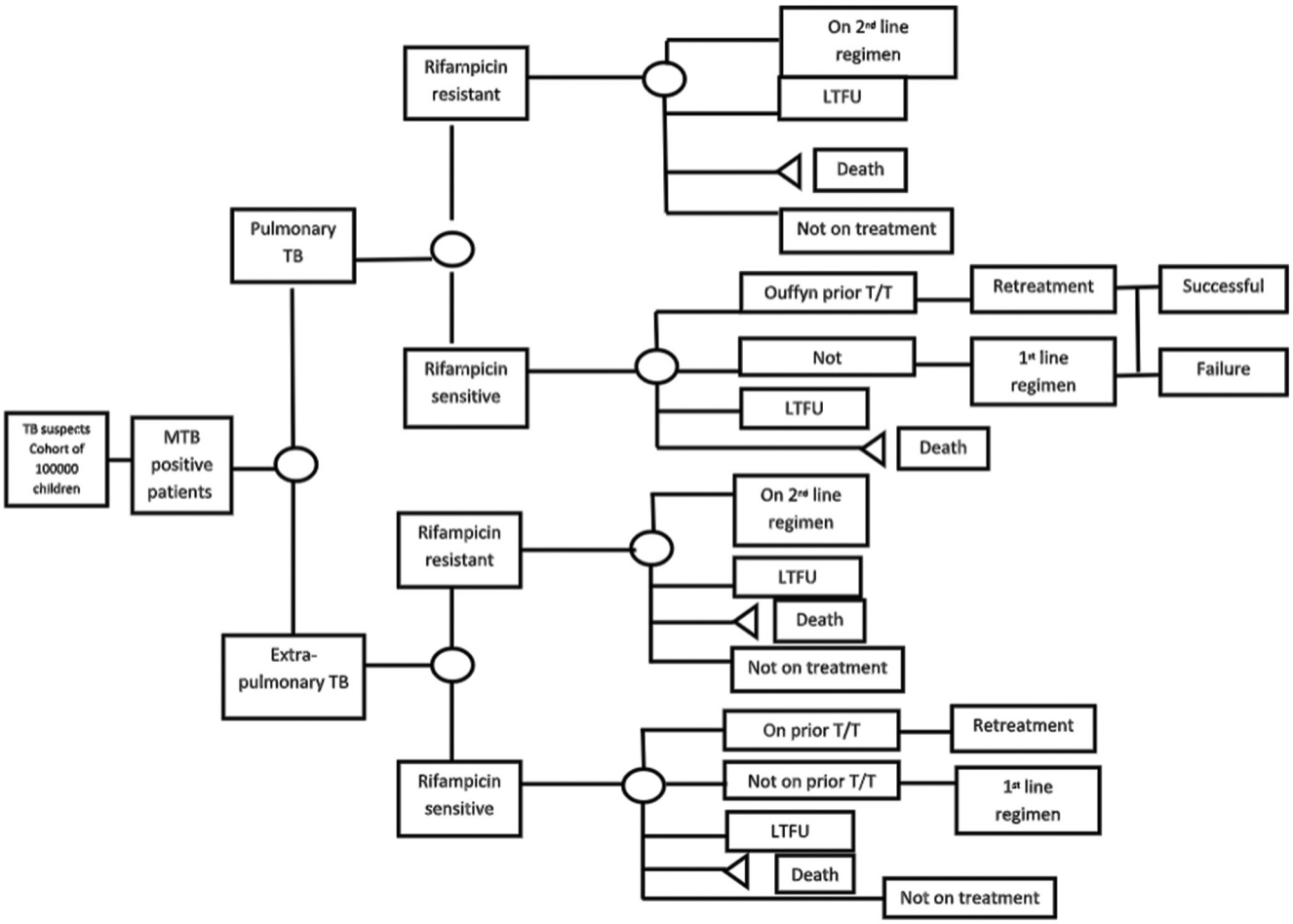

Figure 1: Conceptual framework of the model for cohort of children undergoing diagnosis of tuberculosis in health-care facilities

and other model parameters are presented in Table 2. Also, 6.6% of presumptive TB cases were diagnosed positive for Mycobacterium Tuberculosis (MTB) on Xpert MTB/RIF. Among MTB positives, 8.7% cases were rifampicin resistant. In this study, approximately 50% of the total specimens tested for GeneXpert MTB/RIF were non-sputum. Non-sputum specimens had similar overall positivity rate (10.6%) as sputum specimens (11.7%).[17]

Costs

The costs were enumerated from Rupert *et al.*'s[18] study which uses bottom-up micro-costing technique to calculate the costs of diagnostic strategies from a health system perspective.[19] The costs per test for SSM, Xpert, and TrueNat were $0.86, $12.63, and $13.20 [as given in Table 1], respectively, which included costs of labor, overhead and building space, reagents (e.g., cartridges for Xpert, chips for TrueNat), and equipment (test instruments). The monthly costs of TB treatment were found to be $28.13 (first line), $104.23 (second line), and $32.25 (retreatment), which included the costs of drugs, clinic visits, monitoring tests, and hospitalizations during treatment.[20,21] It was assumed that overhead, building space, and labor-related costs for TrueNat strategies would be similar to those of Xpert.[18]

Results

When all the model parameters were considered simultaneously, the ICER was calculated as follows:

$$\text{ICER} = \frac{\text{cost of intervention} - \text{cost of comparator}}{\text{effectiveness of intervention} - \text{effectiveness of comparator}}$$

$$\text{ICER of TrueNat} = \frac{\text{Ccost of TrueNat} - \text{Ccost of Ssmear microscopy}}{\text{DALYs averted by TrueNat} - \text{DALYs averted by comparator}}$$

ICER of TrueNat MTB (compared to smear microscopy) = (1,479,589 – 831,029)/(11,788 – 2958)

= $73/DALY averted = Rs. 5475 per DALY averted

ICER of Xpert MTB/RIF (compared to smear microscopy) = (1,406,273 − 831,029)/(10,862 – 2958)

= $72.5/DALY averted = Rs. 5437 per DALY averted

Table 2: Model parameters

Parameter	Point estimate (range)	Source
Baseline cohort characteristics		
Age, years, mean (SD)	0-14 years, mean age 8 years	[17]
Males/females	54%/46%	[17]
Prevalence of TB in children (pulmonary and extrapulmonary combined)	6.6%	[17]
Prevalence of pulmonary TB in children	78%	[17]
Proportion of rifampicin-resistant patients among pulmonary TB cases	8.1%	[17]
Proportion of rifampicin-sensitive patients among pulmonary TB cases	91.9%	[17]
Proportion on treatment among rifampicin-resistant patients	85.9%	[17]
Proportion of lost to follow-up cases among rifampicin-resistant patients	6.8%	[17]
Proportion of deaths among rifampicin-resistant patients	5.1%	[17]
Proportion of patients not on treatment among rifampicin-resistant patients	2.2%	[17]
Proportion of rifampicin-sensitive patients on treatment	89.4%	[17]
Proportion of rifampicin-sensitive patients on retreatment with previous treatment	16%	[17]
Proportion of rifampicin-sensitive patients on treatment without previous treatment	84%	[17]
Proportion of lost to follow-up cases among rifampicin-sensitive patients	7.6%	[17]
Proportion of deaths among rifampicin-sensitive patients	1.9%	[17]
Proportion of patients not on treatment among rifampicin-sensitive cases	1%	[17]
Prevalence of extrapulmonary TB in children	22%	[17]
Proportion of rifampicin-resistant patients among extrapulmonary TB cases	10.5%	[17]
Proportion of rifampicin-sensitive patients among extrapulmonary TB cases	81.5%	[17]
Rate of success among rifampicin-sensitive patients	84%	[3]
Rate of failure among rifampicin-sensitive patients	16%	[3]
Diagnostic test accuracy		
Sensitivity of Xpert MTB/RIF for diagnosing TB in children	66% (52-57)	WHO Global TB report (2013), [1]
Specificity of Xpert MTB/RIF for diagnosing TB in children	98% (94-100)	[1]
Sensitivity of TrueNat for diagnosing TB in children	68.54%	Factorization of result of Xpert in children and adults
Specificity of TrueNat for diagnosing TB in children	98.5%	Factorization of result of Xpert in children
Sensitivity of sputum smear for diagnosing TB in children	15%	Nicol *et al*. (2011)[27], ToyinTogun *et al*. (2017)[28]
Positivity rate of smear microscopy	2%	[17]
Diagnostic test unit costs (in US$ 2013)		
Cost of Xpert testing, per patient tested	$12.63 (11.47-14.84)	[18, 20]
Cost of TrueNat testing, per patient tested	$13.20 (12.75-13.79)	[18, 20]
Cost of sputum smear microscopy	$8.24	[18, 20]
Cost of treatment		
Full first-line regimen, 6 months	$28.13 (24.13-32.49)	[18, 25, 27], Global drug facility report
Retreatment regimen, 8 months	$32.25 (28.30-36.23)	[18, 20]
Second-line regimen, 24 months	$104.23 (96.15-112.13)	[18,20]
Life expectancy in India	69 years	

SD=Standard deviation, TB=Tuberculosis

ICER of TrueNat in relation to Xpert MTB = (1,479,589 − 1,406,273)/(11,788 − 10,862)

= $79/DALY averted

When calculated, it was found that TrueNat is more cost effective (Rs. 9450/DALY averted) compared to GeneXpert MTB/RIF (Rs. 9750/DALY averted). The ICER of TrueNat with respect to GeneXpert was found to be Rs. 5925 per DALY averted, which is under the willingness to pay threshold. The results for cost-effectiveness were calculated for the time frame of a month without discounting and are shown in Table 3.

Discussion

It is evident that as TrueNat POC will be installed in primary health-care settings, more patients will be diagnosed and linked to the treatment strategies. In this scenario, TrueNat MTB will be more cost-effective averting more DALYs. The ICER of TrueNat when compared to smear microscopy is Rs. 5475 per DALY averted and when compared to GeneXpert MTB/RIF, it is Rs. 5925 per DALY averted. As the sensitivity of TrueNat MTB is higher, it will detect more TB cases and link them to treatment. As a result, more

Table 3: Results for the three diagnostic strategies for a cohort of 100,000 children

Parameter	TrueNat MTB	Xpert MTB/RIF	Smear microscopy
1. Cost of 100,000 tests	1,320,000	1,269,000	800,000
2. Cost of treatments initiated after detection of TB through the diagnostic test	159,589	137,273	31,029
3. Total cost	1,479,589	1,406,273	831,029
4. Total DALYs averted due to the successful treatment after treatment initiation	11,788	10,862	2958
5. Cost-effectiveness=cost/DALY averted	126	130	281
6. Cases detected and linked	4521	4356	990

DALY=Disability-adjusted life year, TB=Tuberculosis

and more patients will be put on treatment, hence leading to an overall increased cost. At a primary health facility, the children will be diagnosed earlier, resulting in reduced transport costs, indirect costs, and opportunity costs. This study was limited to a health system perspective and did not include economic costs or savings to patients. The cost of treatment was not updated as per the latest guidelines for the treatment of TB in children. Dosages of anti-TB drugs for children have been revised upwardly to achieve optimal drug levels, and now, the fixed drug combinations are used to decrease the risk of missing a particular drug from the prescribed regimen. The standard retreatment regimen, better known as category II therapy, has been withdrawn.[22] Our health-care expenditure projections should also be interpreted only for diagnostic test costs, drug costs, and treatment-associated clinical, monitoring, and hospitalization costs. According to the WHO report on TB 2020, 17% of people in India face catastrophic expenditure due to TB. Also, 49% of people living with TB face catastrophic expenditure and 80% of those living with Multi Drug Resistance Tuberculosis (MDR-TB) around the world.[1] But there are some limitations and challenges in the use of TrueNat POC in primary health-care settings. It is evident that it is difficult to collect a good sputum sample in children, which creates a need to collect other samples like Bronchoalveolar lavage (BAL), gastric lavage, and others. This requires special training of human resource involved as well as space and equipment. At a primary health-care level, it is difficult to get such trained personnel or to train them in collecting samples from children. At higher health-care level like a district hospital or a medical college, such facility and trained human resource are possible. Likewise, training regarding these diagnostic equipment at primary health-care facilities will also be challenging, leading to increased costs.

Conclusion and Recommendations

Each year, millions of children with TB miss out on quality care, usually because their infection remains undiagnosed. The WHO endorsement of TrueNat POC will enable molecular diagnosis in less time and in an efficient way. There will be more life years saved and more DALYs averted. TrueNat MTB is the first TB test with capacity comparable to the four-module GeneXpert with operational features suited for primary health-care level. Early diagnosis will lead to better outcomes with improved linkage to care compared to GeneXpert. We recommend its use as it is in congruence with Indian health-care settings.

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Conflicts of interest

There are no conflicts of interest.

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