Rapid Health Technology Assessment for incorporating TrueNat as a diagnostic tool for tuberculosis under RNTCP in India

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ABBREVIATIONS

TB	- Tuberculosis
MDR-TB	-Multi-drug resistant tuberculosis
WHO	- World Health Organization
NTP	- National TB Program
RNTCP	- Revised National TB Control Program
SIDA	- Swedish International Development Agency
DOTS	- Directly Observed Treatment – Short course
NRL	- National Reference Laboratories
IRL	- Intermediate Reference Laboratory
C & DST	- Culture and DST Laboratories
CB-NAAT	- Cartridges Based Nucleic Acid Amplification Test
DMC	- Designated Microscopy Centre
LPA	- Line probe Assay
RIF	- Rifampicin
PCR	- Polymerase Chain Reaction
ICER	- Incremental Cost Effectiveness Ratio
QALY	– Quality Adjusted Life Years
SSM	- Sputum Smear Microscopy
CET	- Cost-effectiveness Thresholds
GDP	– Gross Domestics Products
NHB	- Net Health Benefit
PSA	- Probabilistic Sensitivity Analysis

Introduction

India has world's highest tuberculosis (TB) and multi-drug resistant tuberculosis (MDR-TB) burden with the incidence rate of approximately 2.8 million annually[i]. Due to the poor diagnostics tool at the health care facilities with low sensitivity and low linkage-to-care rates, over 25% of patients who prefer public sector are neither diagnosed nor started on treatment[ii]. Hence there is an urgent need for an affordable and high-sensitivity screening or diagnostic test which could be installed in peripheral health facilities with minimal infrastructure and training.

Table 1: Estimates of TB Burden (2015)

	Global (in Lakh)	India (in Lakh)
Incidence TB cases	104	28
Mortality of TB	14	4.8
Incidence HIV	11.7	1.1
Mortality of HIV	3.9	0.37
MDR-TB	4.8	1.3

Source: TB India 2017, RNTCP Annual Report.[iii]

National TB Program (NTP) and Revised National TB Control Program (RNTCP)

Initially National TB Program (NTP) was launched by the Government of India in 1962 at District level which included BCG vaccination and TB treatment. In 1978, BCG vaccination was incorporated in the Expanded Program on Immunization. Based on the assessment done by Government of India, World Health Organization (WHO) and the Swedish International Development Agency (SIDA) on NTP in 1992, it was observed that there are some shortcomings exist with NTP which are managerial weaknesses, inadequate funding, over-reliance on x-ray, non-standard treatment regimens, low rates of treatment completion and lack of systematic information on treatment outcomes. At the same time TB was declared as global emergency by WHO and recommended DOTS (Directly Observed Treatment – Short course) to all the countries. The basic concepts that underpin the globally implemented DOTS strategy were evolved in India at ICMR – NIRT through a series of trials.

The Government of India revitalized NTP as Revised National TB Control Program (RNTCP) in 1992. DOTS was officially launched as the RNTCP strategy in 1997 and by the end of 2005 the entire country was covered under the program. As a result of RNTCP, during 2006 to 2011 the quality and reach of services, case detection and cure targets had been improved. However still the TB epidemic exist in various part of the country due to undiagnosed and mistreated cases. There are also challenge persist in diagnosing and treating multidrug resistant TB (MDR-TB) cases which are reported every year.

Diagnosis and Case Finding are the most crucial factors which are highlighted in RNTCP and the program recommends installation of various laboratory facilities throughout the nation for effective detection of TB and MDR-TB cases. The laboratories installed by the RNTCP program include National Reference Laboratories (NRL), Intermediate Reference Laboratory (IRL), Culture and DST Laboratories (C & DST), CB-NAAT (Cartridges Based Nucleic Acid Amplification Test) Laboratories, Designated Microscopy Centre (DMC), Line probe Assay (LPA) and Solid Culture and Liquid Culture Certified laboratories.

There has been considerable interest in the miniaturization of the PCR platform as this would confer advantages such as reduction in cost of instruments and tests, faster turnaround times and enhancement in the availability and accessibility of PCR tests in resource-poor geographies. With the combined advantages of affordability, simplicity in operations, diagnostic sensitivity and portability, micro-PCR devices are strong candidates for widescale use among the peripheral laboratories of India and other countries of South-East Asia which account for 50% of the global burden of MTB [iv v].

The GeneXpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) is the only WHO endorsed CB-NAAT assay able to rapidly detect both TB and rifampicin (RIF)-resistance[1]. Decentralization of GeneXpert MTB/RIF assay may be limited by infrastructure requirements such as continuous power supply and air-conditioning [vi , vii] . TrueNat (Molbio Diagnostics/Bigtec Labs, Goa/Bengaluru, India), is an indigenous new chip-based, CB-NAAT or micro real-time polymerase chain reaction (PCR) test developed together by Molbio Diagnostics and Bigtec Labs based in Goa and Bengaluru respectively in India. TrueNat detects *Mycobacterium tuberculosis* in sputum samples and upon positive result, it also detect RIF-resistant *M. tuberculosis* [viii ix].

The test requires the user to add 5 ml of extracted DNA to a pre-loaded microchip [5] containing room temperature stabilized reagents and start the PCR run on a handheld battery operated device, Truelab UnoTM, which is a fully portable standalone thermal cycler [6]. Briefly, the Truelab platform consists of a PDA (personal digital assistant) running the software application, a handheld unit housing the control electronics and optical detection system for real-time monitoring and a microchip with integrated temperature control elements. The Truenat MTB test involves sputum processing using a battery-operated sample preparation device, Trueprep-MAGTM, which extracts nucleic acids by a simple menu driven process using a nanoparticle-based protocol optimized for sputum. The device integrates all operations (heating, fluid mixing, magnet control, step timing) using on a programmed micro-controller, and easy to follow screen instructions, thereby enabling nucleic acid isolation without the need for any additional equipment. The chip-based test has been designed to simplify the process of real-time PCR from 'sample to result' so that laboratories with minimal infrastructure can easily perform these tests routinely in their facilities and report PCR results in less than an hour.

Due to the portability and less turnaround test time, TrueNat will be more valuable in peripheral healthcare settings, such as designated microscopy centers (DMCs) and primary healthcare facilities in India. With the above advantage, TrueNat would be more suitable for resource-constrained settings in India and could increase treatment initiation without further delay due to laboratory referrals. [x-xi]

Based on above preliminary search of literature and available evidences, this study aims to compare clinical effectiveness of smear microscopy, GeneXpert and TrueNat with reference to culture as gold standard. We also analysed the cost-effectiveness study conducted by *Lee et. al.*, 2019. The study also looked in to operational feasibility and challenges of implementing TrueNat under RNTCP.

If used as a point-of-care (POC) test within primary healthcare facilities, Truenat could increase treatment initiation by reducing turnaround time for test results and decreasing the need for laboratory referrals [2,11]. However, uncertainties in parameter values, such as test characteristics and linkage-to-care, must be investigated. In resource-constrained settings, the potential benefits of Truenat must also be weighed against its costs. Using a mathematical model, therefore, we projected the clinical impact, costs, and cost-effectiveness of Truenat, as a replacement for smear microscopy or Xpert. We also evaluated the budget impact of deploying Truenat widely in India's public sector.

Policy Question

Which is most appropriate diagnostic tool for Tuberculosis and Multi Drug Resistant Tuberculosis in India under Revised National Tuberculosis Control Program?

Objectives

1) To explore various technology options available for the diagnosis of TB/MDR-TB.
2) To explore existing evidence regarding specificity and sensitivity of various technology options available for the diagnosis of TB/MDR-TB.
3) To ascertain the cost of TB diagnosis per patient using various technology options available for the diagnosis of TB/MDR-TB.
4) To explore the perception of healthcare providers about technology under assessment feasibility aspects and operational challenges of implementing TrueNat and GeneXpert in field settings.

PICOT

Population: Individuals aged ≥15 years with ≥2 weeks of cough

Intervention: TrueNat (latest and indigenous product for the diagnosis of TB/MDR-TB)

Comparator: GeneXpert, Smear Microscopy, Culture and any other technologies if available.

Outcome:

a. Sensitivity and specificity of various technology options available for the diagnosis of TB/MDR-TB.
b. Cost per test with various technology options available for the diagnosis of TB/MDR-TB.
c. Feasibility and operational issues of incorporating TrueNat versus RNTCP.

Methodology

In this HTA, we evaluated the existing evidence from literature including peer review studies and systematic reviews published online, printed material from manufacturers, annual or technical reports from user departments and development partners or agencies from country and abroad.

The literature review was targeted to find evidence about availability of various technologies for the diagnosis of TB and MDR-TB, appropriateness of these technologies in context to Indian healthcare settings in terms of resources required to implement in these diagnosis options in the field.

The literature was also searched for effectiveness of these technology options in terms of their specificity and sensitivity or negative predictive value and positive predictive value. Comparison, wherever available between two or more technologies, was also reviewed and included in our HTA.

From available resources, evidence pertaining cost per test including all direct and indirect resources required was also reviewed. After cost comparison of these technologies, similar technologies based on Real Time PCR were also compared on the basis of their overall cost-effectiveness. Full economic evaluations available in the literature were reviewed and included in this report. The economic evaluation was evaluated for the methodology and input parameters used to ascertain their appropriateness and robustness. All results (regarding cost and cost-effectiveness) from past were indexed to their value in year 2019.

This HTA also includes informal interviews and telephonic interviews of manufacturers, healthcare professionals, program management and first hand users of these technologies (Medical Officers and Lab Technicians) about current status of availability, future plans to scale-up the diagnostic set-up along with its feasibility and operational aspects in field.

Based on evidence available, most appropriate technologies viz.- TrueNat and GeneXpert were considered for budget impact analysis on implementation at national level including both opex as well as capex model which includes all their capital costs, maintenance and other recurrent costs.

Literature Review:

Upon conducting background search, we found 4 studies enlisted in table 1. Four studies were considered for the literature review, out of which two have been explained later in this report.

Table 1: Summary table of studies conducted on TrueNat

Study Title	**Author/year**	**Place of study**	**Sample size**	**Type of study**	**Data reported** (Sensitivity/ specificity)
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	India	10878	Sensitivity/ Specificity analysis	TrueNat: 84.1% (Sensitivity) GeneXpert: 81.0% (Sensitivity)
Rapid, point-of-care diagnosis of tuberculosis with novel TrueNat assay: Cost-effectiveness analysis for India's public sector	Lee *et al*, 2019	Indian setting	-	Cost-effectiveness analysis	-
Evaluation of the Indian TrueNat micro RT-PCR device with GeneXpert for case detection of pulmonary tuberculosis	Nikam *et al*,2014	Mumbai	247	Observational	TrueNat: 99% (Sensitivity) GeneXpert: 100% (Sensitivity)
Rapid Diagnosis of Mycobacterium tuberculosis with TrueNat MTB: A Near-Care Approach	Nikam *et al*,2013	Mumbai	266	Validation	TrueNat: 91.1% & 100% GeneXpert: 90.58% & 91.43%

Operational feasibility and performance of TrueNat MTB RiF assays in field settings under the Revised National Tuberculosis Control Program

The study was conducted in over 100 DMCs. The analysis included 10878 samples. Positivity rates of each test along with pooled positivity in each of the 10 States and the overall total is given in Table 1. Smear, TrueNat and GeneXpert yielded overall positivity rates of 13.29%, 18.80% and 18.11% respectively. Sensitivity of Smear, TrueNat and GeneXpert were found to be 59.4%, 84.1% and 81.0% respectively when compared to the Pooled TB results.

The difference in the sensitivity for detection of MTB between TrueNat and GeneXpert was statistically significant. (p Value - <0.001).

Table 2: MTB detection overall in 10 states

	TB Detection (no. of samples)
TrueNat	2045
GeneXpert	1970
Smear	1446
Pooled TB	2433
No TB	8445
Total	**10878**

Table 2 shows the statewise and overall distribution of positivity rates and sensitivity of smear, TrueNat and GeneXpert. The study also analysed the colony forming units - yielded by TrueNat whenever MTB was detected using the quantification factor. The mean and median of values for GeneXpert positive and negative samples.

Table 3: Sensitivity of Test to Diagnose TB by any Method

Technique	**Senstivity**
TrueNat	**84.1%**
GeneXpert	**81.0%**
Smear	**59.4%**

Additional yield in identifying positive patients if smear is replaced 100% by TrueNat and GeneXpert will be 4,95,587 (41.42%) and 4,33,535 (36.23%) respectively. However, the smear can be replaced completely by TrueNat only at DMC level because it does not require an airconditioned laboratory, whereas the GeneXpert cannot be placed at PHC level without an AC lab.

Table 4: Percentage detection of rifampicin resistance by both tests

	Resistant	**Sensitive**	**Total**
TrueNat	**83 (6.4%)**	**1215 (93.6%)**	**1298**
GeneXpert	**72 (5.5%)**	**1226 (94.5%)**	**1298**

As 70% patients are diagnosed at the Block and District level health facilities and if these 6000 DMCs are replaced by the molecular tests additional 2 to 2.5 lakhs of patients will be diagnosed (2.48 lakhs by TrueNat and 2.16 lakhs by GeneXpert). (As per Table 3, with 100% implementation in 13000 DMCs all over the country, the number of patients diagnosed additionally by TrueNat will be 4.95 lakhs and 4.33 lakhs by GeneXpert). However as per the feasibility and testing requirements, the replacement at PHC is possible only by TrueNat and not by GeneXpert. T Also the detection of TB as well as MDR-TB (Rif Resistance) at DMC level would eliminate need for GeneXpert.

Based on the results of the feasibility study of TB and MDR-TB detection at DMC level using TrueNat in comparison to GeneXpert in State level laboratories, the Replacement of smear microscopy and Gene GeneXpert by TrueNat would be beneficial to achieve NSP targets in view of the following observations:

1. Significantly Incremental detection by TrueNat over microbiologically confirmed TB diagnosis.

2. Higher rate of rifampicin resistance detection by TrueNat as compared to Gene GeneXpert. TrueNat is also a sensitive test for detection of MTB in sputum samples as TrueNat can detect M.TB in samples with lower CFU while GeneXpert detects MTB in samples with higher CFU but not in samples with low CFU/ml. Hence,

3. Similarly, sensitivity of TrueNat (Rif.) for detection of Rifampicin resistance in samples positive for TB is higher as compared to Gene GeneXpert.

4. The PCR results of discrepant cases showed that 74 out of 94 test results resolved in favour of TrueNat (78.7%) indicating that the TrueNat is superior to GeneXpert in detection of M.TB in Indian settings.

5. The feasibility aspects reveal that TrueNat can be implemented in the PHCs which is the first point of contact for TB patients and higher. It also has additional benefit of its ease of use.

6. Use of TrueNat at Primary Health Care (PHC) level Eliminates the need for sample transport as is done in case of GeneXpert thus adding cost benefit besides detecting TB /MDR-TB during the first visit of the patient.

7. Operational requirements of TrueNat – Portable, Battery Operated, Direct Connectivity with mobile interface for data sharing, whereas GeneXpert requires continuous power supply, air-conditioning and connectivity is only through a computer system

8. Time taken for assay – Design of the TrueNat assay is such that MTB detection is completed in 35 minutes and Rifampicin assay is done only as an add on test. Hence samples with negative results can be reported much earlier whereas with GeneXpert, even negative results require 120 minutes as both MTB detection and rifampicin resistance assays are done simultaneously. However, in positive cases, since rifampicin test is done as an add-on assay by TrueNat, the possibility of human error is greater and

9. Availability of DNA – With TrueNat, DNA is available for repeat or any further investigation and QC, whereas with GeneXpert, the cartridge is discarded after the completion of the assay and no DNA is available.

10. The cost of equipment and the test is much lower than Gene GeneXpert and the machine is battery operated which also has option of solar battery.

Cost-Effectiveness of TB diagnostic technologies in Indian Settings

A recent cost-effectiveness analysis entitled, 'Rapid, point-of-care diagnosis of tuberculosis with novel TrueNat assay: Cost-effectiveness analysis for India's public sector' was found from online literature and was reviewed.

A micro simulation model was run to assess the cost effectiveness of four Tuberculosis (TB) Diagnostics that include Sputum Smear microscopy (SSM) in designated microscopy centers (DMCs), GeneXpert MTB/RIF in DMCs (GeneXpert), TrueNat in DMCs (TrueNat DMC), TrueNat for point-of-care testing in Primary health care facilities (TrueNat POC). The Cost-Effectiveness of Preventing AIDS Complications-International (CEPAC-I) model, individual-based Monte Carlo state-transition model by considering TB natural history, diagnosis, and treatment. This study simulated a cohort of adult, HIV-negative patients with presumptive pulmonary TB, who were being tested for TB testing at DMCs and their attached primary healthcare facilities under Revised National Tuberculosis Control Program (RNTCP).

This study projected clinical and economic outcomes over patient's life times. 3% of discount was considered for cost effective analysis whereas, for clinical and budget evaluations, outcomes were undiscounted. Model included individuals TB progression through various states and treatment for estimating clinical and monthly cost related to TB. This study projected life expectancy, costs, incremental cost-effectiveness ratios (ICERs), and budget impact analysis of deploying TrueNat POC for 5 years in public sector of India. This study stated cost-effective if ICER < US$990/year-of-life saved (YLS). Model inputs included were, TB prevalence of 15% among those without prior treatment history for TB and of 27% for past history of TB treatment. Mean age taken was 41 years. Sensitivity values for TB detection in comparison to culture were 89% for GeneXpert and 86% for TrueNat. In relation to linkage to care and treatment is concerned, it was 84% for patients diagnosed at DMCs and 95% for those diagnosed by TrueNat POC alone.

Loss to followup (LTFU) with reference to treatment were obtained from Indian TB surveillance data. Cost per test were $12.63 for GeneXpert and $13.20 for TrueNat and $0.86 for SSM, obtained by considering costs of overhead and building space, labor, reagents. Monthly costs were calculated using cost of drugs, monitoring tests, clinic visits and hospitalization during treatment as $28.13 for first line treatment, $32.25 for retreatment and $104.23 for second-line drug treatment. This study considered 4-module PCR analyzer device which is capable of testing four specimens simultaneously, whose price was reported as $14,150.

This particular cost was used in the base case for comparison with the 4-module GeneXpert system. This cost was annualized over the expected lifespan of the TrueNat device under study considering 3% discount per year, and divided by the expected number of tests it would perform annually. This study reported that they conducted both one way and two way sensitivity analysis. Besides, the authors also performed scenario analysis for various assumption that they made in this study.

The most effective strategy reported were TrueNat POC showing an increase in life expectancy by 0.39 years compared to SSM and by 0.08 years compared to GeneXpert. Whereas life expectancy was increased by 0.30 years for TrueNat DMC compared to SSM and decrease by 0.01 compared to GeneXpert. It was also reported that TrueNat POC increased the number of TB cases correctly detected and linked to care by 590 and 140, respectively, per 10,000 individuals with presumptive TB.

Compared to SSM, TrueNat DMC and TrueNat POC strategies both increased discounted per patient lifetime costs by ~$40. Compared to GeneXpert, TrueNat DMC decreased discounted per-patient lifetime costs by $1 and TrueNat POC increased costs by $5.

While TrueNat DMC was cost-effective compared to SSM (ICER $240/YLS), it resulted in lower life expectancy and higher ICER than GeneXpert and was, therefore, “weakly dominated” (i.e., economically inefficient). TrueNat POC was cost-effective compared to both SSM (ICER $210/YLS) and GeneXpert (ICER $120/YLS). When viewed over different time horizons, TrueNat POC became cost-effective compared to GeneXpert and SSM after 4 and 6 years, and GeneXpert became cost-effective compared to SSM after 6 years. The respective ICERs continued to decrease beyond these time horizons.

One-way sensitivity analyses also revealed that TrueNat POC was cost-effective when compared to SSM across all parameters analyzed at a lifetime horizon. It was also stated that variation of prevalence in TB and MDR-TB had little influence on the ICER value of TrueNat POC. A change in the specificity of TrueNat within the range of 80-100% had little influence on the ICER value of TrueNat POC. It was found that for RIF-resistance detection, TrueNat’s ICER ($350/YLS) that resulted from decreasing the specificity by 10% remained well below the cost effectiveness threshold of $990/YLS. In the scenario analysis it was revealed that TrueNat POC remained cost-effective compared to SSM (ICER $240/YLS) and compared to GeneXpert($240/YLS).

In a 5-year time horizon, TrueNat POC was cost effective compared to GeneXpert when its sensitivity was ≥ 78%. It also increased life years and costs. The higher cost is due to raise in the number of patients that initiated treatment; however, costs were offset by improved clinical outcomes. This results in decreased ICER value for TrueNat as sensitivity increased. In another scenario where sensitivity of TrueNat POC was below 75%, compared to GeneXpert, it was reported that GeneXpert was cost effective due to fewer life-years and lower cost.

In case of Two-way sensitivity analysis, this study compared TrueNat POC with GeneXpert by varying TrueNat's sensitivity for TB detection between 68-100% and linkage to care between 84-100%. It was found that, at 86% sensitivity, TrueNat POC was cost-effective when linkage to care was 88%, kept GeneXpert's sensitivity at base case values. It was observed that decreasing TrueNat sensitivity resulting an increased linkage threshold for cost effectiveness. Whereas, when sensitivity was ≤ 74%, TrueNat POC was reported as not cost-effective strategy at any linkage value. However, TrueNat POC was cost effective at 90% sensitivity even linkage to care values were as low as 84%.

In the scenario where chip cost of TrueNat is dropped down to 60% of current estimate, TrueNat POC was cost effective or cost saving compared to GeneXpert. When linkage was 95% (as assumed for POC test), TrueNat POC was cost effective with sensitivity > 88%, it is cost-saving with sensitivity 77-87% and decrementally cost-effective at ≤ 76% sensitivity. At 84% linkage (typical of DMC), TrueNat POC was found cost-saving at sensitivity >88% and decrementally cost-effective at sensitivity levels 74-88%.

For Budget impact analysis, this study has assumed 7.9 million adults would be tested for TB annually. Scaling up of GeneXpert usage in India increases cumulative expenditure for TB related health care by $580 million which accounts for 81% increase over 2 years and by $1.58 billion accounting an increase of 80% over 5 years. Over 5 years, difference in the cost was mostly due to increased spending on MDR-TB treatment by 56% and diagnostic test by 37%. Bringing TrueNat POC in place of GeneXpert, the cumulative health care expenditure raised by $100 million showing 7% increase over 2 years and by $270 million accounting an increase of 8% over 5 years. Difference in the cost over 5 years was mostly reported due to raise in MDR-TB treatment by 63% and drug-susceptible TB treatment by 22%.

Information collected through Telephonic interview:

Background:

In India, CB NAAT has been used for diagnosis of TB under RNTCP program. Recently, the Andhra Pradesh State Government adopted TrueNat for TB diagnosis at various health levels like CHCs, PHCs and DMCs. A total of 225 TrueNat Duo modules have been installed so far in the state. Out of these, 200 have been installed at CHC level and 25 at PHC level.

Apart from published literature on these devices telephonic interviews, with eGeneXperts from program, were also conducted. These eGeneXperts had been working with TrueNat and had experience of working with CB NAAT as well. This exercise was done in order to understand operational feasibility of the TrueNat system.

Features of TrueNat:

It is a Portable and battery-operated device.

Cost of TrueNat:

Cost per test for TrueNat is approximately INR 800 (INR 640 + GST). The procurement is done through rate contracts and signed MOUs between manufacturer and the state government.

Requirements to run the test:

One Technician, clean work space and electricity to charge the instrument. It takes an hour to fully charge the instrument. Technicians are required to get a brief training before they can start working on the machine.

Time taken to run the test:

It takes approximately 2 hours to run the test from start to finish which is similar to CB NAAT. In contrast, CB NAAT requires 5-10 minutes of technician time whereas TrueNat takes 25-30 minutes in addition to the 2 hours run time to prepare the sample for processing. Another point that was raised during the interview, was that the manufacturer claimed that the result of rifampicin resistance may be read after 60 minutes whereas, the time actually required to run the complete test and get results is 75 minutes, as observed and reported by technical staff.

Operational Challenges faced during use of TrueNat:

1. Probe related errors were encountered while running the test.
2. Issues with spillage and cross-contamination were also reported. Spillage may lead to cross contamination of samples as well as the machine. To remedy this sodium hypochlorite treatment of the instrument or fumigation of the entire laboratory is required.
3. Issues with coating of chip used in cassette were encountered initially, leading to 10-12% invalid results of the test. After the manufacturer has resolved the issue by changing the chip coating, the invalid results have dropped down to 4-5%. This can be attributed to the hands-on technique of pipetting and handling of reagents by the technician operating the machine. Please note that in CB NAAT the percentage of invalid test results is 2-3%.
4. One particular batch was giving most problems with invalid results and errors in detection. The problem may be with the buffers provided with the kit.
5. For rifampicin detection, the technicians were facing the problem of indeterminate results due to issues with master-mix.
6. Once any test result comes as invalid/indeterminate, another hour is consumed in repeating the test, not to mention the added cost of testing.
7. The manufacturer claimed that one kit can be used to perform 25 tests but practically it was observed that DNA buffer provided in one kit was sufficient only for 20 tests.
9. Between 29/07/19 – 15/08/19 a total of 38 tests were run on TrueNat for TB detection in a district TB control office, out of which 10 samples were detected as positive for TB by TrueNat and 9 by CB NAAT. However, the 10^{th} sample was confirmed to be positive with X-ray examination of the patient. At present, all the sputum samples that are analyzed by TrueNat are also cross checked using CB NAAT.

Other comments:

The device did not require periodic calibration and the service and technical support provided by the manufacturer, in case of any technical issue, was prompt. Once a complaint was filed, the manufacturer sent an engineer to rectify the problem, which took 2-3 days. If the problem was with the contamination of instruments, then it took up to a week before the machine could be used again.

The manufacturer also assigned regional officers to various testing centers to monitor the functioning of the instruments. It was found that using TrueNat, 8-12 samples could be processed in a day. It was concluded that technicians generally preferred to use CB NAAT for TB detection because of its ease in operation.

Budgetary Impact of TrueNat for RNTCP

1. Capex Model (To Install machine in 1 TU):

1. Equipment cost (Quattro) 9, 50,000 (Annualized cost, considering life expectancy of 10 years =118437)

2. Other expenditures (Annual)

- Maintenance cost of equipment = 11843 (10% of annualised cost)
- Annual HR cost (Taking LT salary=20000) = 56,250 (90 mins daily dedicated to work on TrueNat)
- Cost of Reagents = 400/test = 400 X 2144 = 8,57,600
- Electricity consumption per Year = Rs 1608

(Test possible to do in a year = 268 days X 8 tests a day= 2144)

ANNUAL COST FOR 1 TU = 10,45,738

ANNUAL COST FOR 2698 TUs = 10,45,738 X 2698 = 2,82,14,01,124 (282 Crores)

2. Opex Model (To Install machine in 1 TU):

- Annual Cost for contract at same efficiency = 2144 X 8 = 17,15,200
- Annual HR cost (Taking LT salary=20000) = 56,250 (90 mins daily dedicated to work on TrueNat)
- Electricity consumption per Year = Rs 1608

ANNUAL COST FOR 1 TU = 17,72,833

ANNUAL COST FOR 2698 TUs = 17,72,833 X 2698 = 4,78,31,03,434 (478 Crores)

Conclusions and Recommendations

Truenat as compared to GeneXpert is very cost-effective in Indian settings with ICER: INR 8400 per Life Year saved (against threshold of per capita GDP 1,20,000). Sensitivity and Specificity of both equipment are comparable but TrueNat is more sensitive (Difference=3.1%). As per Lee *et al*., 2019 deploying Truenat POC instead of GeneXpert increased 5-year expenditures by $270 million, due mostly to treatment costs. Cost per test for both is also comparable but GeneXpert is cheaper (Difference = Rs. 86 per test).

TrueNat is more cost-effective and feasible option for peripheral healthcare facilities (due to portability and requirement of less sophisticated infrastructure). GeneXpert is almost equally good (in terms of sensitivity as well as cost) and cost-effective as compared to other diagnostic tools like Smear Microscopy and can be used at District level and above due to its ease of use and less chances of error (due to automation) results.

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