IJPSR (2020), Volume 11, Issue 9 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 05 October 2019; received in revised form, 23 January 2020; accepted, 11 March 2020; published 01 September 2020

UTILITY AND EFFECTIVENESS OF GENEXPERT OVER CONVENTIONAL METHODS FOR DIAGNOSIS OF PULMONARY TUBERCULOSIS

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Keywords:

TB (Tuberculosis), PTB (Pulmonary tuberculosis), MTBC (Mycobacterium tuberculosis complex), MDR-TB (Multidrug-resistant tuberculosis), RIF (Rifampicin)

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ABSTRACT: Background: Tuberculosis (TB) is a global health burden and can cause potential infection in any system of the body. Pulmonary tuberculosis (PTB) is most common presentation, but the diagnosis of TB remains elusive because of none of biochemical or serological test is invalid. During the development of END TB strategy, the gene expert (CBNAAT) test was first endorsed by WHO. **Materials and Methods:** This was a prospective observational study; conducted in the Department of Microbiology, Baba Raghav Das Medical College, Gorakhpur Uttar Pradesh, India. All patients suspect of PTB fulfilling, inclusive criteria were enrolled for PTB confirmation. All kind of clinical samples pertaining to PTB were processed in TB laboratory for Ziehl-Neelsen stain microscopy, solid culture (Lowenstein-Jensen (L. J.) and gene expert. All data were collected and analyzed using SPSS ver. 2017. **Results:** During the study period, a total of 542 clinical PTB cases were enrolled. Among which distribution of clinical samples was (404/74.53% sputum, 104/19.18% gastric aspirate, 34/6.27% broncho-alveolar lavage: BAL). Among 542 total samples enrolled, 102 (18.81%) positive for AFB, 166 (30.64%) culture-positive, but after using 28 kDa antigens based MPT-64 test only 124 (74.69%) culture-positive were confirmed as MTBC. Among 542 samples, 146 (26.93%) samples were confirmed as positive for MTB by gene expert (CBNAAT). **Conclusion:** The gene expert MTB/RIF assay is efficient, reliable, and confirmatory technique for MTB. Its sensitivity and specificity make this technique a very reliable tool for diagnosis of *Mycobacterium tuberculosis* from cases of TB suspects. Simultaneously, it has an advantage of the detection of multidrug-resistant cases.

INTRODUCTION: Tuberculosis (TB) is a global burden for both developing and developed countries. It is one of the oldest diseases known to a human being, still causing a large number of mortality and morbidity and has recently become more complex due to persistence in aging and immune-compromised populations with an incidence of 10.4 million new TB cases worldwide and annually 4,80,000 deaths and 1,400 every day.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(9).4629-36

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(9).4629-36

More than 1 million missing TB cases every year are not notified due to undiagnosed or may be due to the use of less sensitive diagnostic facilities [1, 2, 3]. According to the world health organization (WHO), 1.78 million new incidences recorded in the year 2017 in India, out of which approximately 40% new cases are confirmed by rapid diagnostic tests for positive acid-fast bacilli (AFB) and the vast majority of them have latent rather than active tuberculosis.

Out of the total registered cases in 2017, 84% suspected TB patients registered with symptomatic pulmonary infections, and 60% cases confirmed bacteriologically for tuberculosis [4]. The death rate due to TB in India is nearly 28/100,000 population, which is the highest among all other communicable

diseases and accounts for 26% of all avoidable mortality in adults [5]. Tuberculosis can potentially cause infection in any system or organ of the body. Pulmonary tuberculosis (PTB) is the most common presentation, but even today, the diagnosis of TB remains elusive because of no biochemical or serological test is valid and acceptable for diagnosis of PTB. In this continuation, the microscopic demonstration of *Mycobacterium tuberculosis* bacilli in sputum samples is the only rapid method for confirmatory diagnosis of PTB in small laboratories. Still, its limitation is low sensitivity and specificity [6]. However, the conventional solid culture method (Lowenstein-Jensen medium) has a better sensitivity to detect TB, but it takes about 6-8 weeks. The other liquid culture methods like BACTEC or mycobacterium growth indicator tube (MGIT) gives relatively rapid results, but it is too costly and cannot be possible to place at the district microscopy center (DMC) or in remote settings with less resources [3].

The urgent need for accurate, feasible, rapid, and affordable TB diagnostic tests for use in resource-limited settings push WHO to reform the new guidelines and diagnostic methods for TB. During the development of END TB strategy to control TB in 2010, which was followed by India as national strategic plan to achieve END TB goal, the gene expert (CBNAAT) test was first endorsed by WHO as diagnostic tool for diagnosis of pulmonary and extrapulmonary tuberculosis (EPTB), which has the capacity to detect 131 bacilli/ml of sample [7].

The working of gene expertise based on semi-quantitative nested real-time PCR technique *in-vitro* diagnostic test with two uses; detection of *Mycobacterium tuberculosis* complex (MTBC) and rifampicin (RIF) resistance-related mutations of the rpoB gene in suspected samples for PTB. This is not only the first fully automated benchtop cartridge-based nucleic acid amplification (CB-NAAT) assay for TB detection but it also has the capability to give results within 2-3 h. In India, sensitivity (98.8%) and specificity (97.2%) of gene expert have been reported for the detection of MTB and for RIF resistance, it is 96% and 95% respectively [8]. The quality of rapid detection of MTB and its resistance to rifampicin allows the physician to make an early decision to start the treatment therapy during the first visit of suspected TB patients. For few years, the appearance of new forms of resistant TB bacilli has become a significant obstacle to maintain effective TB control globally, and it is all because of the continuous change in the trend of drug resistance TB DR-TB [9, 10, 11].

The aim of this study was to evaluate the diagnostic utility and effectiveness of gene expert (CBNAAT) assay in suspected pulmonary tuberculosis patients for the diagnosis of tuberculosis and rapid detection of rifampicin resistance in smear-positive, smear-negative pulmonary clinical specimens and also for the comparison with solid TB culture.

MATERIALS AND METHODS: This was a prospective observational study; conducted in the Department of Microbiology, Baba Raghav Das Medical College, Gorakhpur, Uttar Pradesh, India from December 2018 to May 2019.

Inclusion Criteria: Patients with any age from any socioeconomic group, irrespective of gender and suspect of PTB based on clinical or radiological findings like cough, hemoptysis, loss of appetite, weight loss breathlessness, multiple nodules, thick wall, opacities *etc.* Associated cases of HIV-TB co-infection were enrolled for this study were also excluded.

Exclusion Criteria: Patients with extrapulmonary tuberculosis based on clinical findings and co-morbidities with chronic inflammatory diseases [12]. Samples received without clinical history or received without consent and requisition form.

Ethical Approval: This study was approved by IEC, BRD Medical College Gorakhpur vide-IEC/BRDMC GKP/637/2018.

Specimen Collection, Storage and Transportation: All kinds of clinical samples for the diagnosis of PTB were collected under the standard conditions in the department of Microbiology or RNTCP unit (TB and chest department) after taking informed consent and transferred the same day to the CBNAAT lab and TB lab. However, if necessary, the specimens can be stored at 2-8 °C. After proper labeling the sample was divided into three parts, first part of sample is used for gene xpert, the second part used to prepare a smear and third part of sample was used to perform cultured

on Lowenstein-Jensen (L. J.) media using standard protocol as provided by RNTCP, government of India [11, 13].

Smear Microscopy: For microscopy examination, an oval or round-shaped direct smear was fixed on a clean grease-free slide and stained by using Ziehl-Neelsen Stain (ZN-Stain). Now, stained smear focused under oil immersion objective (100x) [12]. The minimum number of acid-fast bacilli present in a smear after observing a minimum 100 fields was an indication of the severity of pulmonary tuberculosis infection of the patient. Positive AFB smears results were reported in grading [14].

TABLE 1: GRADING OF AFB SMEARS

No of acid-fast bacilli (AFB)	Fields	Report
No AFB	In 100 immersion fields	Negative
1-9 AFB	In 100 immersion fields	Positive scanty Record exact figure
10 to 99 AFB	In 100 immersion fields	1+
1 to 10 AFB	Per field (examine 50 fields)	2+
More than 10 AFB	Per field (examine 20 fields)	3+

GeneXpert (CBNAAT): GeneXpert (CBNAAT) is a novel rapid automated machine for the rapid diagnosis of TB. This is the cartridge-based nucleic acid amplification test (CBNAAT) that can detect TB along with RIF's resistance directly from the pulmonary samples within 2 h of collection [1]. Test performed by using disposable cartridges that hold the PCR reagents and host the PCR process because the cartridges are self-contained, so there is no chance of cross-contamination between samples. Its principle based on the detection of the target sequences and nucleic acid amplification by real-time PCR and reverse transcriptase PCR [8, 10]. Approximately 2 ml of sample reagent added in conical tube containing 1ml of a sample (Sputum, BAL, and gastric aspirate) and shake it vigorously. This mixture Incubated for 10 to 15 minutes at room temperature, after that2 -3 ml treated sample transferred into the sample cartridge chamber by using a sterile graduated pipette and then manually load the cartridge into the GeneXpert machine after scanning cartridge barcode for sample identification. GeneXpert Dx System software used to interpret the result, which measured fluorescent signals algorithm [8].

Culture using Lowenstein-Jensen (L. J.) Media:
Preparation of Media it has done: in a clean, dust-free environment. A total of 600 ml of autoclaved mineral salt solution (Potassium dehydrogenate phosphate anhydrous, magnesium sulphate, magnesium citrate, asparagine, glycerol, and malachite green solution) was added into 1000 ml of homogenized egg solution (Fresh hen's egg was used to maintain quality of media). Approximately 1600 ml of solution thoroughly mixed by gentle agitation till the solution becomes uniform pale green in color. Then 400 ml of solution is transferred into another flask, used as plain L. J. media. Sterile McCartney bottles is used to transfer 5-6 ml of L. J. media and sloped on the inspissator racks at 85 °C for 85 min [13, 15].

Culture Processing and Reporting: All the sputum samples were firstly decontaminated by using the N-acetyl-L-cysteine-sodium hydroxide method and then inoculated with 50 µl of sample into plain L. J. Tubes were incubated at 37 °C for a maximum of 8 weeks and observed daily until the appearance of growth and if growth were present, smears were prepared from isolated colonies and identified by Ziehl-Neelsen'sstaining method. Cultures showing no growth after 8 weeks of incubation were reported as negative for MTBC. Any growth other than AFB was considered as contaminants [16].

Detection of MPT-64 Ag: To confirm the presence of MPT-64 Ag in culture-positive isolates, few colonies were emulsified from L. J. media into 200 µl of extraction buffer with sterile glass beads. 100 µl of this inoculation was transferred after vortex into the sample well of immune chromatographic test cassette. The inoculated ICT cassettes were placed for 20 min at room temperature 250 to 35 °C. Test validation and interpretation done by the appearance of pink band in the 'C (control)' region and another pink band in the 'T (test)' region was considered as positive for MPT 64 Ag [17, 18].

Statistical Analysis: Different parameters were tabulated in the form of master chart and analyzed using SPSS ver. 2017. The categorical variables were expressed as frequencies and percentages.

Continuous variables expressed as means with standard deviation when the distribution was gaussian and medicans with interquartile range when the distribution was non-parametric. The socioeconomic or demographic data were analyzed by using modified Kuppuswamy scale [19].

RESULTS: During the study period a total of 542 clinical pulmonary tuberculosis (PTB) cases were enrolled. Among which distribution of clinical samples were (404/74.53% sputum, 104/19.18% gastric aspirate and 34/6.27% broncho-alveolar lavage: BAL) **Table 2**.

TABLE 2: DEMOGRAPHICAL DISTRIBUTION OF SUSPECTED TB PATIENTS

Variable		Number of suspected cases		Positive for TB (CBNAAT) n=146	
		Male	**Female**	**Male**	**Female**
Age wise distribution (n=542)	0-15 years	76	70	3	7
	16-40 years	122	114	48	42
	41-60 years	86	40	26	8
	61 and above	32	2	12	0
Total	**312**	**230**	**88**	**58**	
Area wise distribution	Gorakhpur	304	88		
	Basti	10	3		
	Santkabirnagar	16	2		
	Deoria	54	15		
	Kushinagar	70	12		
	Siddhartnagar	32	7		
	Maharazganj	24	7		
	Bihar	22	8		
	Others (Nepal etc.)	10	4		
Sample distribution	Sputum	404	127		
	Gastric aspirate	104	8		
	BAL	34	11		
Cases (n=146)	New	111			
	Previously treated	32			
	Treatment history not available	03			
	HIV-positive cases	28			
	Diabetic	31			
Key population (n=542)	Contact of TB/DR-TB cases	179			
	Tobacco chewer	50			
	Migrants	43			
	Others	270			
Socio-economic status (n=542)	Upper class	33			
	Upper middle class	138			
	Lower middle class	177			
	Upper lower	150			
	Lower	44			

All the samples underwent for smear microscopy in which 102 (18.81%) found positive for AFB while, 166 (30.64%) samples were detected as culture positive but after confirmation by using 28 kDa antigen based MPT-64 rapid diagnostic test which is specific for MTBC and not found in BCG strains, only 124 (74.69%) culture positive growth were confirmed as MTBC strain, while 34(20.48%) were non-tubercular bacteria and 8(4.81%) found as contaminants **Fig. 1**. Among 542 samples which were suspected for MTB, 146 (26.93%) samples were confirmed appositive for MTB by GeneXpert (CBNAAT) as summarized in **Table 4**. The average age of clinical presentation was 30 years. Majority of the patients were in the age group 16-40 years (43.54%), minimum age was4months and the maximum 82 years **Table 2**. Out of 146 positive TB cases, 32 (21.91%) had past history of tuberculosis and 111(76.02%) were newly registered cases had family history of contact with TB/DR-TB cases and only in 3(2.05%) cases treatment history was not available. The socioeconomic status defines as per modified Kuppuswamy scale **Table 2**.

Clinical presentation at the time of patient enrollment and radiological abnormality found in chest X-ray of positive CBNAAT cases is summarized in **Table 3**.

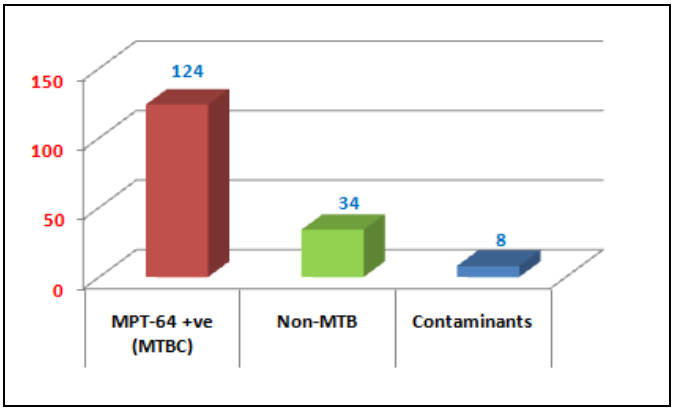

FIG. 1: MYCOBACTERIUM TUBERCULOSIS COMPLEX (MTBC) SPECIES CONFIRMATION OF POSITIVE CULTURE USING MPT-64 TEST (N=166)

Out of 146 positive TB cases through GeneXpert, only 24(16.44%) patients were resistant against rifampicin and diagnosed as drug resistance tuberculosis (DR-TB) as a surrogate marker for MDR-TB, while 122 (83.56%) cases which were confirmed with drug susceptibility **Fig. 2**.

We found that among 146 positive TB patients, 31 (21.23%) were diabetic, 28 (19.17%) were people living with human immunodeficiency virus (PLHIV) **Table 2**.

Among 542 cases, 304 (56.08%) population belongs to district Gorakhpur in which 88 (28.94%) were confirmed as TB positive and few cases were visited from Bihar (22) and Nepal as described in **Table 2**.

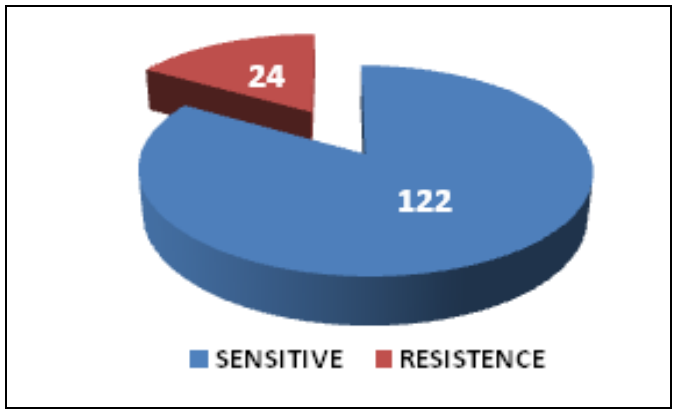

FIG. 2: RIFAMPICIN SENSITIVITY AND RESISTANCE AMONG TB CASES (146)

TABLE 3: CLINICAL AND RADIOLOGICAL CHARACTERISTICS AMONG TOTAL SUSPECTED / CONFIRMED TB CASES

Distribution of different clinical presentation (n=542)		
Symptoms	**Numbers**	**Percentage (%)**
Cough	372	68.63
Hemoptysis	62	11.43
Loss of appetite	298	54.98
Weight loss	214	39.48
Fever	380	70.11
Breathlessness	244	45.01
Night sweat	118	21.77
Distribution of different radiological findings in positive TB cases (n=146)		
Characters	**Numbers**	**Percentage (%)**
Thick wall	19	13.01
Infiltration	105	71.91
Consolidation	44	30.13
Single/multiple nodules	9	6.16
Bronchiectasis	13	8.90
Other opacities	48	32.87

TABLE 4: COMPARISON OF RESULT OF GENEXPERT WITH AFB SMEAR AND CULTURE

Variables (n=542)	Smear	%	Culture	%	GeneXpert	%
Positive	102	18.81	166	30.64	146	26.93
Negative	440	81.19	353	65.12	390	71.97
Contamination/Invalid result	00	00	23	4.24	06	1.10

TABLE 5: SAMPLE WISE COMPARISON OF RESULT OF GENEXPERT WITH AFB SMEAR AND CULTURE

Specimens	Distribution	Culture after confirmed by MPT-64		AFB smear		GeneXpert	
		+ve	-ve	+ve	-ve	+ve	-ve
Sputum	404	108	296	91	313	127	277
Gastric aspirate	104	7	97	5	99	8	96
BAL	34	9	25	6	28	11	23

DISCUSSION: In this observational study, we have assessed the role of GeneXpert over conventional methods for the detection of MTB and rifampicin-resistant in pulmonary specimens (Sputum, Gastric aspirate and BAL) because pulmonary tuberculosis is the leading cause for mortality and morbidity in India. In our study MTB prevalence was high in urban population in comparison with rural population which is similar with the study at Madurai, India in 2015 20 and Madya Pradesh in 2016.12The mean age of PTB patients was 35 years in male and 26 years in

female which was less in comparison with the study done by Subbaraoet.al. In 2018.3 in our study, the majority of the patients belong the age in between 16-40 years. The most common symptoms in our study were fever (70.11%) and cough (68.63%). In a similar study from Avashia *et al.,* in 2016, as they found fever (69.4%) and cough (72.2%) as the main symptom. Among radiological finding infiltration was most common (71.91%) followed by consolidation (30.13%) in positive PTB cases in our study, which was nearly similar with the study done by Avashia *et al.,* in 2016 and Ganesh CM *et al.,* in 2018 found consolidation in 33.3% and infiltration in 79% of cases respectively [6, 12]. In our study, 76% of patients were newly detected for PTB among all positive cases for MTB, which was similar (71%) with other study carried by Subbarao *et al.,* in 2018 3. Among total of 542 registered cases, 32% of patients belong to the lower middle class (category-II) followed by 27.67% as upper lower (category-IV), which was quite similar to the study conducted by Mohamed *et al.,* in 2015. The reason for the higher incidence of PTB reported in the middle and lower class population, especially in males, was attributed due to the social contacts, improper or irregular diet, and mixed infections [20].

Out of 166 culture-positive isolates tested by MPT-64 Ag (ICT kit), 124(74.69%) were found positive for MTBC strain, and the remaining 34 (20.48%) were considered as NTM followed by 8(4.81%) as contaminants. These results were similar to the study conducted by Maurya *et al.,* 2012.21. Using the samekit, Chihota *et al.,* reported sensitivity and specificity of almost 100 percent in a total of 108 broth culture, which indicates that advance and molecular method has been found more accurate and reliable for the detection of MTBC strain over conventional culture method. This test is able to differentiate between MTBC and NTM, because diagnostic delay may affect treatment and outcome. With this rapid method identification and it also helps in the early detection, same time more economical than the other two methods [21, 22].

Till now, a wide range of rifampicin resistance was reported by using CBNAAT [23]. In a study by Ikuabe *et al.,* in 201824. Among CBNAAT positive samples had rifampicin resistance in 14.7%, which was nearly similar to our study (16.43%), but in a different study by Lee *et al.,* 201325 reported 5.7% resistance. RIF's resistance by CBNAAT is considered to be a surrogate marker of MDR-TB [26].

Out of 146 CBNAAT positive samples, [24] were resistant to rifampicin, which was comparatively higher as compared with other studies indicated multidrug-resistant tuberculosis (MDR-TB) because prevalence of MDR-TB is variable in literature and it's heterogeneous and depends upon multiple factors; different levels of resistance may be due to variation in mutation, co-infection with HIV and inadequate or inappropriate dosage of anti-TB therapy. Resistance from these medications in mycobacterium strain was accounted for not long after their clinical presentation. As far as the development of new chemical combinations to treat MTB, some new medications in the pipeline, however, these are still in preliminary clinical stages [27].

Limitation of This Study: This study has few limitations: first, it is a prospective study based on only pulmonary samples, which includes sputum, BAL, and gastric aspirate; further studies with more varieties of samples need to be done especially among extrapulmonary cases. Second, the cost of the cartridge was too high, and the number of test failures due to power cut-off needs to be reprocessed again, which created an overburden and increase in expenditure [28]. Third, WHO recommends CBNAAT for diagnosis of pulmonary tuberculosis and detection of RIF's resistance simultaneously, especially in those clients who were already suffering with HIV and re-treatment cases who are at risk of development of MDR-TB. Fourth, the sensitivity and specificity of RIF's resistance were not evaluated in our study by phenotypic method or line probe assay (LPA) [11.]

CONCLUSION: Pulmonary TB constitutes a maximum of all tuberculosis, among which more than half are resembled as smear-negative, and it is very difficult to make a bacteriological diagnosis in negative tuberculosis samples [6]. CBNAAT detects pulmonary TB with greater specificity and sensitivity than culture and sputum microscopy; it also helps in early diagnosis of MTB within 2 h after the collection of samples. It also detects RIF's resistance simultaneously with high efficacy and can be used for screening for MDR-TB, so that

early treatment can be started, thus decreasing the incidence of MDR-TB among new cases [29].

ACKNOWLEDGEMENT: Authors would like to thanks the faculties and all technical staff of the Department of Microbiology, TB and the chest Department and RNTCP unit, Baba Raghav Das Medical College, Gorakhpur and RNTCP program Lucknow, Uttar Pradesh, India for their guidance and support during this research work.

Source of Support: Revised national tuberculosis control program (RNTCP), Govt. of India, State TB cells, Lucknow UP and District health society (DHS), Gorakhpur UP.

CONFLICTS OF INTEREST: None declared.

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How to cite this article:
Gaur V, Singh AK, Kumar A and Mishra AK: Utility and effectiveness of genexpert over conventional methods for diagnosis of pulmonary tuberculosis. Int J Pharm Sci & Res 2020; 11(9): 4629-36. doi: 10.13040/IJPSR.0975-8232.11(9).4629-36.