

# Increased Notification of Tuberculosis Cases and MDR and XDR Cases Post Introduction of CBNAAT in Rajasthan: A Retrospective Case Study of 4 Years from 2015-2018

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## ABSTRACT

**Context:** Tuberculosis is a major health problem in India. Accurate and also fast diagnosis of tuberculosis has remained a challenge and we determined the impact of CBNAAT on notification of tuberculosis cases in Rajasthan.

**Aims:** The Aim of the present Study was use of CBNAAT in tuberculosis and impact on rate of detection of TB and MDR and XDR TB in Rajasthan.

**Methods and Material:** We did a retrospective study of notified tuberculosis cases registered in government and private hospital from 2015 to 2018. Comparison was done for these 4 years

**Results:** There was a total increase of 57 percent over the period of 4 years from 2015 to 2018 in no of tuberculosis notified cases and during the same time there was a 51 percent and 66 percent increase in the number of MDR and XDR tuberculosis cases respectively.

**Conclusion:** Use of CBNAAT significantly increases the no of notified cases of tuberculosis along with MDR and XDR cases. As we recommend that it should be widely adopted and expanded.

**Keywords:** CBNAAT, MDR, XDR

## INTRODUCTION

Tuberculosis (TB) kills 1.8 million people annually. Aims to get TB under control has remained elusive globally despite increased standard measures of TB control. National TB Control Programmes in most TB and TB/HIV endemic countries continue to rely largely on century old, antiquated and inaccurate tools such as direct smear microscopy, solid culture, chest radiography and tuberculin skin testing<sup>2</sup>.

Conventional sputum based methods to detect pulmonary tuberculosis are sputum microscopy and culture. But there are situations like HIV in which the sputum production is scarce and there is no caseous necrosis leading to a limited number of bacilli in sputum. These confounding factors decrease the sensitivity and specificity of sputum microscopy as a Diagnostic tool.

To overcome the drawbacks, sputum culture for mycobacteria can be used. But it is a slow procedure that usually takes 4 to 8 weeks and not widely standardized and not cost effective for screening purposes. This leads to a delay in starting of antitubercular treatment specially for drug resistant forms of Tuberculosis, increases risk of transmission of drug resistant TB in communities and the risk of spread to extrapulmonary sites within the patient<sup>3</sup>. Cartridge based nucleic acid amplification test (CBNAAT) is the latest type of

Polymerase Chain Reaction (PCR) based method for detecting tuberculosis. It can detect rifampicin Resistance as it targets the rpoB gene of mycobacteria. CBNAAT is a mycobacterium tuberculosis specific automated, cartridge based nucleic acid amplification assay, having fully integrated and automated amplification and detection using real time PCR, providing results within 100 minutes. It is a highly specific test as it uses 3 specific primers and 5 unique molecular probes to target the rpoB gene of mycobacterium Tuberculosis which is the critical gene associated with rifampicin resistance.<sup>4</sup>

Many studies have shown that there is no cross reactions with other bacterial species tested, including exhaustive panel of mycobacteria, thereby excluding non-tuberculous mycobacteria (NTM). Being a PCR based method, clinical validation trials done in four distinctly diverse settings have shown that 92.2 percent of culture positive patients were detected by a single CBNAAT test with the sensitivity of 99% as compared to sensitivity of a single direct sputum smear of 59.5%.<sup>4</sup>

Its role in diagnosis of TB is not widely studied in India. This study was carried out to evaluate the role of CBNAAT in early detection of mycobacterium Tuberculosis in sputum by CBNAAT compared to conventional sputum microscopy in pulmonary tuberculosis of notified cases along with MDR and XDR notified cases.

In 2009 the first technical data was announced from an automated molecular test for TB, the Xpert MTB/RIF assay developed by the foundation for innovative new diagnostics cepheid (Sunnyvale California USA) and University of medicine and dentistry of New Jersey<sup>5</sup>. The assay got CE mark in 2009 and it avoids many of the pitfalls of conventional nucleic acid amplification test and can be performed by the staff with minimal training and used for change detection and MDR screening at that time.

It can be used to specifically detect mtb and rifampicin resistance from one sputum within 2 hours. It is a greatly simplified nucleic acid amplification test which can be performed by any laboratory for clinical personnel after minimal introductory training<sup>5</sup>. The Xpert MTB/RIF is a single-use sample processing cartridge system that holds all required reagents to perform the whole PCR reaction. The assay has recently undergone performance evaluation for respiratory samples as well as non respiratory samples, one of them was a multi-country technical evaluation which showed that Xpert MTB/RIF Assay to have high sensitivity and specificity and capability to result in 2 hrs<sup>6</sup>. From December 2010 WHO recommends the use of Xpert MTB/RIF assay as usual Diagnostic test for TB in patients with suspected MDR-TB or TB in Association with HIV infection.

The Aim of the present Study was use of CBNAAT in tuberculosis and impact on rate of detection of TB and MDR and XDR TB in Rajasthan

## Materials and Methods

A retrospective study was conducted by analyzing data from Year 2015 to 2018 in the state of Rajasthan. Data was collected for total notified cases of Tuberculosis of Rajasthan along with total MDR and total XDR notified cases confirmed by CBNAAT method. Data includes 33 districts and 59 other centers including some Primary health centers and community health centers and one private set up till year 2018.

## Result

### Total notified TB cases (Public plus Private)

Sl. NO	year	Public	Private	Total
1	2015	90296	11736	102032
2	2016	90032	16724	106756
3	2017	84774	29979	105953
4	2018	113591	46634	160225

There has been a total increase of 57 percent over the period of 4 years from the year 2015 to 2018 in the number of tb notified cases.

### Total Cases of MDR (Public plus Private)

Sl. NO	Year	Data
1	2015	1750
2	2016	2094
3	2017	2559
4	2018	2659

There has been a total increase of 51 percent over the period of 4 years from the year 2015 to 2018 in the number of MDR TB notified cases.

### Total Cases of XDR (Public plus Private)

Sl. NO	Year	Data
1	2015	114
2	2016	128
3	2017	136
4	2018	190

There has been a total increase of 66 percent over the period of 4 years from the year 2015 to 2018 in the number of XDR tb notified cases.

## Discussion

As per the WHO global report of Tuberculosis 2010-13 India accounts for 64,000 MDR TB cases out of 3, 00,000 cases estimated globally to occur among the notified pulmonary TB cases annually<sup>7</sup>. Cartridge based nucleic acid amplification test is the latest system recommended by WHO. Results from 12 single-centre evaluation studies showed the sensitivity in detecting TB from 72 -100 % in culture positive patients and around 60% in those with serum negative disease and specificity ranging from 91 to 100 percent and average rifampicin sensitivity and specificity around 98% and 99% respectively<sup>8</sup>. Studies from various parts of world have reported high sensitivity and specificity by using expert MTB/RIF test based on this essay. In a study by raizada et al , covered population of 8.8 million across 18 Sub District level tuberculosis units in India, overall 28% cases were bacteriologically confirmed of which 27.6% TB cases were detected on expert MTB/RIF against smear positivity rate of 12.9%. However of 9 Xpert MTB/RIF negative and culture positive cases, 8 were detected on smear microscopy too. Positive predictive value for rifampicin resistance detection by Xpert MTB/RIF was 97.7 percent<sup>9</sup>. In a similar study raizada et al, Reported among the 485 bacteriologically confirmed pediatrics (0-14y) PTB cases, 98.4 % had positive TB result on Xpert MTB/RIF and of these 54.9 % were Xpert MTB/RIF positive and smear negative<sup>10</sup>. Similar study on HIV positive adult referred to dots centre with pulmonary symptoms suggestive of tuberculosis and Singh and Co authors concluded that (CBNAAT is easily done, valid, more accurate and reliable alternative to sputum microscopy for detection of Pulmonary tuberculosis in HIV patients). Steingrat et al, performed updated cochrane review as a part of a WHO process to develop updated guidelines on the use of Xpert MTB/RIF assay and reported test to be sensitive and specific in adults thought to have TB with or without HIV infection , compared with smear microscopy, Xpert MTB/RIF substantially increases TB detection among culture confirm cases. For rifampicin resistance detection, Xpert MTB/RIF provide accurate results and can allow Rapid initiation of MDR TB treatment<sup>11</sup>.

Few studies have given contradictory results too as in a study conducted in Durban South Africa on patients detected with rifampicin resistance on Xpert MTB/RIF , The Xpert MTB/RIF showed 8.8% discordance when compared to culture and the overall rate of rifampicin monoresistance was 13.4%<sup>12</sup> .

The specificity of Xpert MTB/RIF In detecting rifampicin resistance is very high 98% and increasing evidence has shown that the in frequent occurrence of so called false-positive results may be linked to the detection by Xpert MTB/RIF of strains that are truly resistance to rifampicin but which are not detected by the phenotypic culture based DST, the present reference standard. A study on previously treated TB patient showed false positive by Xpert MTB/RIF assays due to the presence of dead mycobacterium tuberculosis in lung and

sputum<sup>13</sup> .Vassal et al, reported the cost for the Xpert test (include all cost sectors cartridge equipment salaries) ranging from US dollars 22.6 3 in India to 27.5 5 US dollars in Uganda<sup>14</sup>. Due to IPAQT (www.ipaqt.org ) collision of private Labs in India supported by industry in nonprofit groups), the maximum price labs can charge patient for Xpert MTB/RIF is now 1700 rupees<sup>15</sup>. A few limitations exist with device like incomplete sensitivity of a negative TB and rifampicin resistance as well as inability to detect resistance to isoniazid and other drugs, nonstop power supply, ambient temperature not exceeding 30 degree centigrade, biosafety comparable to smear microscopy, waste disposal system for cartridges, trained laboratory and clinical staff, annual calibration of expert models and revision of Diagnostic algorithms, policy, form and guidance<sup>16</sup>.

There are only a few studies on CBNAAT from India. A study done in 2011 in Hyderabad Showed an incremental case detection of 10.8% when CBNAAT was used to diagnose tuberculosis over and above fluorescent microscopy<sup>17</sup>. Our data is concordant with the previous studies .our data shows that over a period of 4 years there was 57 percent increase in the number of TB notified cases, 51 percent increase in MDR TB and 66 percent in XDR TB cases.

Multicentre assessment at five trial sites in Peru, Azerbaijan, Cape Town, Durban, and India by boehme et al Demonstrated sensitivity of nearly 100 percent by CBNAAT. Under RNTCP, impact study on CBNAAT found that additional 2,493 patients were diagnosed with Pulmonary TB by CBNAAT in 2012 among more than 30,000 TB suspects as compared to sputum microscopy<sup>18</sup>.

The WHO policy guidance on the use of CBNAAT was issued in December 2010. The recommendations were that it should be used as initial Diagnostic test in individuals at the risk of having MDR TB or HIV-associated TB (strong recommendation), and that it could be used as a follow-up to microscopy in settings where MBR and/ or HIV is of less concern, especially in smear negative specimens ( this was a conditional recommendation, recognizing meta resource implications). This recommendation applied to the use of CBNAAT in sputum specimen is only, as data on its performance (sensitivity and specificity) for testing of extrapulmonary specimens at that time was Limited<sup>19</sup>.

RNTCP adopted CBNAAT in India in April 2012. In the government setup, CBNAAT was launched in April 2012 as a pilot project in Maharashtra by the state tuberculosis department. By the end of 2012, under EXPANDx-TB project, 12 CBNAAT Labs were established all over India across different states. CBNAAT is currently being made available to more centers with the aim to establish that every Hospital associated with the medical college throughout the country and also in private institutions.

### Conclusion

Use of CBNAAT significantly increased the detection of TB cases as well as MDR and XDR TB cases. For future clinical practice, it is however of Paramount importance to ascertain that these patients detected by Xpert MTB/RIF assay only are unambiguously true TB cases that were missed by sputum culture and therefore a more thorough clinical evaluation study which specifically addresses these cases would be warranted. Furthermore, it will also be necessary to explore how this new and promising assay can be made accessible to developing countries. As with any new Diagnostic test the impact of Xpert MTB/RIF will depend upon the reproducibility of the results under actual field conditions, the manner and extent of their introduction, the strength of Laboratories and the degree to which access to appropriate therapy follows access to diagnosis. Our data suggest that especially smear -negative TB patients could benefit from the new assay in those areas where no culture is available. Both aspects, that analysis of only one single spot sputum sample by Xpert MTB/RIF can already reach reasonable sensitivity and that the result would be available on the day of sputum collection could result into more patients with active TB being diagnosed avoiding loss of patients and treatment delay in those TB suspects with a negative smear result who would undergo two ineffective empirical courses of antibiotics before TB treatment could be initiated. Finally this new sensitive and Rapid Diagnostics could lead to the reduction of infections pool and improvements in TB control.

Note- The data is of notified Tb Cases and may represent some cases being from outside Rajasthan as testing is free in Rajasthan.

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