REVIEW ARTICLE

Recent Advances in Diagnosis of Tuberculosis: A Review

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Received: 28 Oct 2017/Revised: 31 Nov 2017/Accepted: 29 Dec 2017

ABSTRACT- Globally tuberculosis remains a challenge from the point of diagnosis, detection of drug resistance, and treatment. Treatment can only be initiated, when infection is detected and it's based on the results of AST, recently there has been a marked increase in the development and testing of novel assays designed to detect *Mycobacterium tuberculosis.* Although most important advances that would develop tuberculosis (TB) analysis have not been realized, we are beginning to see the innovations that have been prompted by the recognition of the economic potential of the market for new diagnostic tests for TB and considerably increased public and private funding and awareness. In this present review, we focused on the newer tests that are accessible for the analysis of suppressed and active tuberculosis and rapid detection of drug resistance, nucleic acid amplification for identification of *M. tuberculosis* complex, and rapid tests for detecting drug resistance. PCR-based technologies and hybridization assays used for the recognition of the mycobacteria. Though these newer techniques are useful for a rapid result, emphasizing that culture-based diagnosis is still the 'gold standard' for the diagnosis and follows up on tuberculosis.
Key-words- Drug Sensitivity Testing (DST), *M. tuberculosis*, Molecular diagnosis, Tuberculosis infection, PCR,

INTRODUCTION

Tuberculosis (TB) is one of the leading infectious diseases in the world and is responsible for more than 2 million deaths and 8 million new cases annually [1] and in India, accounts for one-fifth of this global burden of TB [2]. The disease is caused by a bacterium called *M. tuberculosis.* The bacteria usually attack the lungs, but can infect any part of the body such as the kidney, intestine, pleura, spine, and brain. If not treated properly, this infectious disease can be fatal [1].

TB and HIV have been closely linked since the emergence of AIDS and both diseases is a major public health challenge. It is estimated that 60-70% of HIV positive persons will develop tuberculosis in their lifetime [3]. Smear microscopy has suboptimal sensitivity and detects only about 60-70% of the TB cases. The implementation of culture for the diagnosis can improve the TB detection rate of a laboratory by about 30-40%. These two laboratory methods, smear microscopy and culture are still the "gold standards" for the diagnosis of TB and culture is considered as the most sensitive method.

Access this article online	
Quick Response Code	Website: www.ijlssr.com
	DOI: 10.21276/ijlssr.2018.4.1.8

Yet, due to the slow growth of mycobacteria, results can take 3-4 weeks or longer and faster and more sensitive diagnostic tests are required to improve patient management. New laboratory techniques for the diagnosis of TB have been developed based on the use of liquid culture medium, nucleic acid amplification techniques (NAATs), DNA hybridization and mutation detection techniques, and antibody and antigen detection. This review is designed to offer some general information about new laboratory technique currently available for the diagnosis of active TB or the detection of latent TB infection [4].

Tuberculosis disease has still prevalent in many countries like Bangladesh [5]. The national TB prevalence survey is considered to be another success of Bangladesh's against TB disease, so new era of drug lines shown complaisant respond against tuberculosis and prevent epidemic condition [5]. Islam *et al.* [5] have been published one review paper, which was summarized on the novel drugs, treatment phenomenon, and overall condition of tuberculosis in Bangladesh. In future, better technology, advanced diagnosis systems, skilled full manpower, enough funds, and well equipped laboratory will help us to achieve desired control and management systems against TB disease [5].

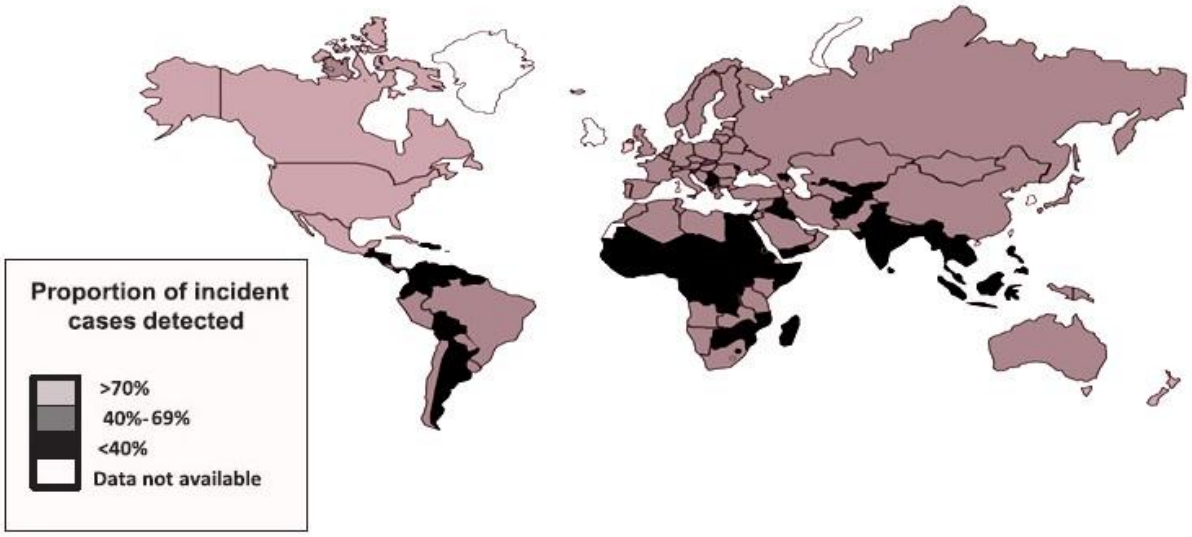

Fig. 1: Estimated global tuberculosis case detection rates [6]

Many organizations have acknowledged the urgent need for improved TB diagnostics, and have advocated for additional research. [7-10] Recommendations stemming from these groups have been incorporated into TDR's (Special Programme for Research and Training in Tropical Diseases) strategic plan for TB diagnostics research, and a targeted diagnostics research agenda aims at stopping TB, with a Partnership second Global Plan to stop TB implemented during 2006-2015 [11].

Tuberculosis (TB) and HIV have been closely linked [14] since the emergence of AIDS and both diseases is a major public health challenge. It is estimated that 60-70% of HIV positive persons will develop tuberculosis in their lifetime. Approximately, 50% of adult Indian population is infected with *M. tuberculosis* and the spread of HIV infection could lead to a potentially explosive increase in the number of cases of tuberculosis. [3] About 1.8 million new cases of tuberculosis are occurring annually in India, whereas the pool of HIV infected individual is quite large (2.5 million). Therefore, there is always a propensity for deadly synergic interactions between HIV and tuberculosis [12].

Tuberculosis is one of the most common infectious diseases and it is highly endemic in India. It kills 5 lakh patients every year. Oxidative stress plays an important role in inflammatory and progressive diseases including pulmonary tuberculosis [13]. HIV/AIDS pandemic is responsible for the reappearance of Tuberculosis which results increase in morbidity and mortality rate [14]. Co-infection with HIV leads to difficulty in both the diagnosis and treatment of Tuberculosis, increased risk of death, treatment failure and relapse [14]. Patients with complaints of pyrexia, weight loss, anorexia, frequency, urgency in urine and complicated renal cyst may be tubercular etiology [15]. Multiplex PCR method will detect in less number of infectious mycobacteria present in clinical specimens and hence the treatment will be started after the diagnosis and detection of mycobacterium [16]. The significance of the proposed study includes quick method, reduction in cost of test; use of DNA sequences for the detection of Multidrug Resistance in *M. tuberculosis* depends on the right choice of the target sequences [16].

The pattern of clinical presentation of TB depends on the host immune status which is reflected in the microbiological, radiological and histological characteristics of TB. The CD4 T-cell count is one of the best indicators of the immediate state of immunologic competence of the patient with HIV infection. The appearance of many opportunistic infections correlates with the CD4 count. TB generally develops at CD4 counts of 200-500 cells/mm^3. Thus determinations of CD4 cell counts provide a powerful tool for determining prognosis, diagnosis and monitoring response to HAART. [17]

Epidemiology- Tuberculosis (TB) is generally affected the humans from the beginning of their history and remains it's one of the leading causes of death worldwide contempt the spotting of fruitful and affordable chemotherapy more than 50 to 60 year ago [18,19]. In India, the overall prevalence of HIV infection is less than 1 per cent and India continues to be in the category of low prevalence countries [20]. However, this blurs the actual picture of the epidemic in a vast, populous country like India. As per estimates, about 5.1 million people were infected with HIV in the year 2003, in India [20]. TB accounts for about 13 per cent of all HIV-related deaths worldwide [21,22].

Of the 5.1 million HIV-infected people in India, about half of them are co-infected with *M. tuberculosis*; approximately 200,000 of these co infected persons will develop active TB each year in association with HIV infection. [23] In Asia, the rate of HIV infection among TB patients has been lower. Studies from India have reported HIV sero positivity rates ranging from 0.4 to 20.1% [24-34]. In India, 0.5 million patients died due to the pulmonary TB disease in every year. The scientists try to find out the associated causes such oxidative stress, degenerative disease, and antioxidant status [13].

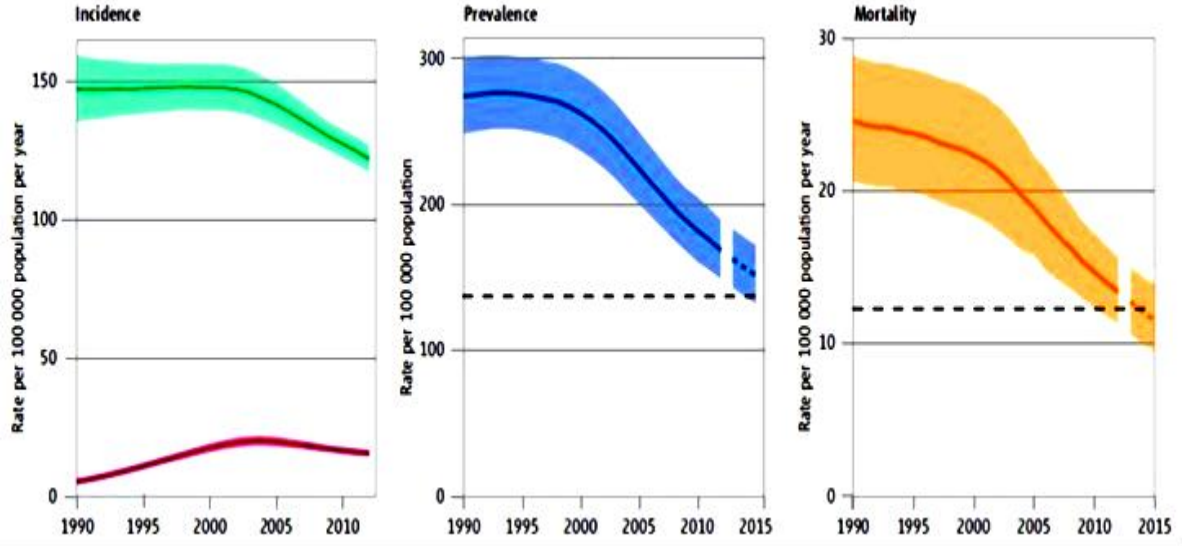

Fig. 2: Global trends in estimated rates of TB incidence, prevalence and mortality 1990–2012 and forecast TB prevalence and mortality rates 2013–2015 [World Health Organization (WHO), Global Tuberculosis Report 2013]
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During 2000-2015, India's estimated mortality rate dropped down from 55 to 36 per 0.1 million populations per year with estimated 480 thousand people died of TB in 2015. [35] Extra pulmonary TB accounts for 15–20% of all TB cases; skeletal TB comprises about 10% of these cases. TB spondylitis accounts for 50% of the skeletal TB cases. Hence, in all, osteoarticular TB represents 1-2% and TB spondylitis represents 0.5–1% of all TB cases [36]. Immunosuppressed persons have a higher likelihood of skeletal TB. Moon noted up to 60% of skeletal involvement in those with TB who are HIV co-infected [37].

The 2015 World Health Organization (WHO) global TB report estimates that there were 480,000 pulmonary MDR-TB cases worldwide and 15,000 cases of MDR-TB in the Eastern Mediterranean Region in 2014, but there is no mention of the incidence of extra pulmonary TB [38].

Diagnostics method- Past 5 years, several new tests have become available for detecting active tuberculosis disease, screening for latent *M. tuberculosis* infection, and identifying drug-resistant strains of *M. tuberculosis*. [39-41] Contribution made toward improving the case detection and cure rates as well as global control of drug-susceptible and drug-resistant tuberculosis will vary depending on the accuracy, cost, and complexity of the test and funder investment available to ensure delivery [42].

AFB smear microscopy and culture- For pulmonary TB, sputum is the most critical sample for laboratory testing. Direct sputum smear microscopy is the most widely used method for diagnosing pulmonary TB and is available in most primary health-care laboratories at the health-center level [43,44]. Smear microscopy may, however, be costly and inconvenient for patients, who must make multiple visits to health facilities and submit multiple sputum specimens over several days.

Fortunately, good-quality microscopy of two consecutive sputum specimens has been shown to identify the vast majority (95%–98%) of smear-positive TB patients [45,46].

A systematic review published in 2006 concluded that fluorescence microscopy with auramine staining was 10% more sensitive than and as specific as conventional microscopy [47]. Fluorescence microscopy is also less time consuming as compared with light microscopy (2 minutes vs 5 minutes for each slide) [48].

Conventional light microscopy of Ziehl-Neelsen stained smears prepared directly from sputum specimens is the most widely available test for diagnosing TB in resource limited settings. Ziehl-Neelsen microscopy is highly specific, but its sensitivity is variable (20%–80%). Conventional fluorescence microscopy is more sensitive (10%) than the Ziehl-Neelsen and takes less time, but it is limited by the high cost of mercury vapor light sources, the need for regular maintenance, and the dark room requirement [47].

Mycobacterial culture is more sensitive, but growth of TB bacilli on traditional solid medium requires 4-8 weeks, which delays appropriate treatment in the absence of a confirmed diagnosis. Therefore, liquid media remains the mycobacteriology gold standard for initial isolation, because it is significantly faster (between 10 and 14 days) and is better for isolation, compared to solid media.

Several manufacturers have recently marketed tools that can automatically detect *M. tuberculosis* growth in the laboratory, such as the Bactec "Mycobacterial Growth Indicator Tube 960" (MGIT 960; Becton-Dickinson, Sparks, MD, USA) and the MB/Bact Alert 10 3D (Biomerieux, Durham, NC, USA). Unfortunately, these automatized incubators are expensive, they do not give rapid mycobacterial species identification, and they do not identify contaminated or mixed cultures [49,50].

Molecular methods- Nucleic acid amplification is a rapid and relatively easy method for detecting MTb. Of the various techniques available, polymerase chain reaction (PCR), fully automated platform of real-time PCR, and loop-mediated isothermal amplification platform (LAMP) are noteworthy. The most significant advance toward a POC test for tuberculosis has come in the field of nucleic acid amplification with the launch of the GeneXpert MTB/RIF assay (Cepheid, Sunnyvale, CA) [51,52]. Nucleic acid amplification (NAA) tests are a reliable way to increase the specificity of diagnosis, but the sensitivity is too poor to rule out disease, especially in smear-negative (paucibacillary) disease where clinical diagnosis is equivocal and where the clinical need is greatest. [53,54] NAA tests can detect the presence of M. tuberculosis bacteria in a specimen weeks before culture for 80%–90% of patients suspected to have pulmonary TB whose TB is ultimately confirmed by culture. [53-55]

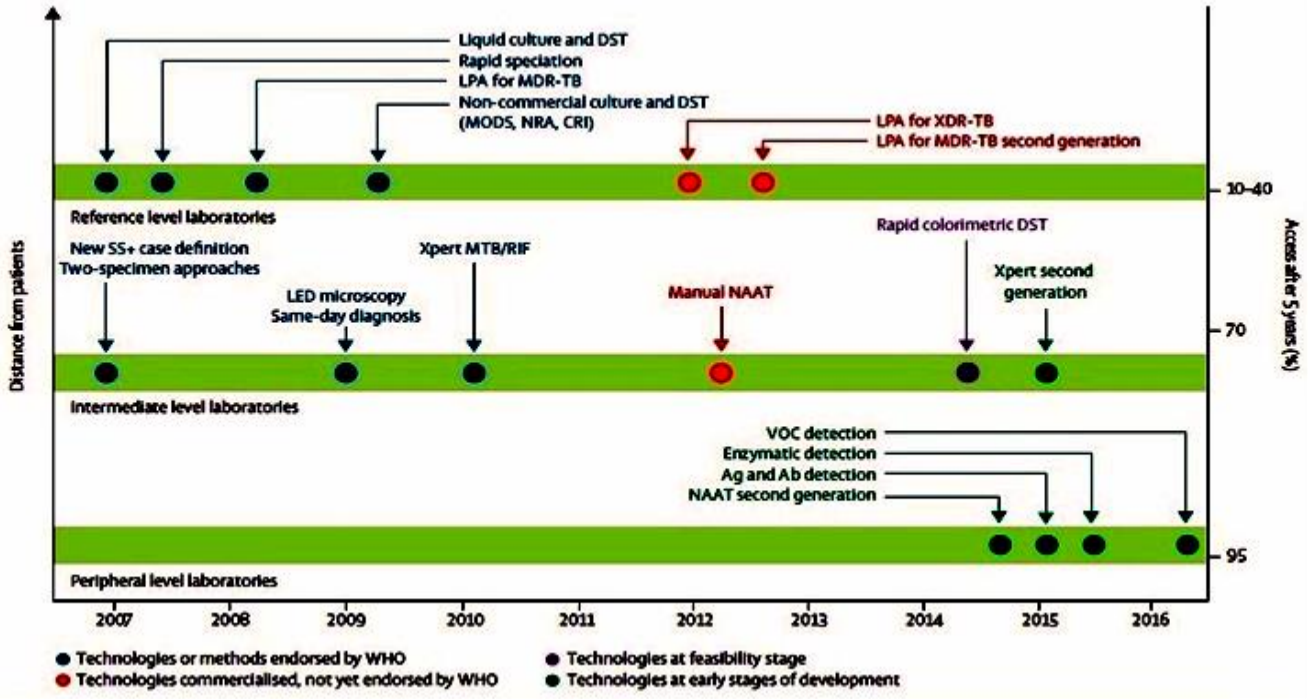

Fig. 3: Development pipeline for new Tuberculosis Diagnostics [56]

The Xpert MTB/RIF assay was shown not to be associated with generation of infectious bioaerosols and resulted in a lower biohazard risk compared with that of conventional smear microscopy. This suggests that the assay might reasonably be done without the need for special biosafety equipment, which was lacking in most resource-limited settings [57].

Conventional methods for mycobacteriological culture, identification of an *M. tuberculosis* complex and DST are slow and cumbersome, therefore, rapid DST of isoniazid and rifampicin or of rifampicin alone using molecular technologies is recommended over conventional testing in sputum smear-positive or culture proven cases at risk of multi-drug resistant (MDR)-TB, such as previously treated patients [50,58]. Line probe assay (LPA) has generally been available for this purpose in rapid DST and is a type of molecular assay that can allow specific gene markers associated with rifampicin resistance alone or in combination with isoniazid to be detected [59,60].

According to systematic reviews and meta-analyses to evaluate assay performance, results that compared conventional DST methods showed that LPA are highly sensitive (≥97%) and specific (≥99%) for detecting rifampicin resistance, alone or in combination with isoniazid (sensitivity ≥90%; specificity ≥99%), in *M. tuberculosis* isolates and in smear-positive sputum specimens [52].

Table 1: Sensitivity and specificity of MODS test in the diagnosis of Pulmonary Tuberculosis [61]

S. No	Regions	Sputum Sample (n)	Sensitivity (%)	Specificity (%)
1	Vietnam	709	77	99
2	India	302	94	89
3	India	105	92	98
4	China	275	90	96
5	South Africa	534	85	97
6	Peru	120	91	95
7	India	171	98	99
8	Vietnam	738	87	93

Polymerase chain reaction is the most commonly used technique of nucleic acid amplification. The most commonly used target for the detection of MTb is the insertion sequence IS6110. The sensitivity ranges from 4% to 80% and the specificity 80-100%. These results are not very promising [62,63].

CONCLUSIONS

Most accurate and rapid diagnosis and susceptibility testing of *M. tuberculosis* infection is now possible due to

the availability of various new diagnostic assays including LED microscopy, BACTEC culture techniques, molecular assays like PCR, Line Probe Assays. PCR is now incorporated as a routine diagnostic test at various tertiary care centers. It is essential to understand that the development of any new, cheap, easier, fast and more sensitive diagnostic tests that have been proven in scientific studies and are applicable at points of care and could enable progress toward tuberculosis control will require political assurance and resources for introduction and implementation into high quality, sustainable, ecological national tuberculosis programs. Rapid developments in nucleic acid amplification technology are powering the emergence of further fully automated systems that might be more eagerly executable at the point of care. Today, we have technologies to rapidly identify suspected TB patients with smear-positive MDR or XDR tuberculosis but we don't have the drugs to treat these patients effectively. TB remains a major killer of adults globally however, are being developed that may improve patient care and decline the incidence of TB.

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How to cite this article:
Parveen S, Arya D. Recent Advances in Diagnosis of Tuberculosis: A Review. *Int. J. Life Sci. Scienti. Res.*, 2018; 4(1): 1557-1562. DOI:10.21276/ijlssr.2018.4.1.8
Source of Financial Support: Nil, **Conflict of interest:** Nil

