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RESEARCH ARTICLE

Changing Trends in the Diagnosis of Genitourinary Tuberculosis in Post Covid-19 Pandemic Era

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ABSTRACT

Introduction: Tuberculosis continues to be a global threat to humankind. Every year, more than a million deaths occur across the globe due to this disease. The Global plan to eradicate and eliminate tuberculosis took off very well with the launch of the End-Tuberculosis campaign until the COVID-19 pandemic created a severe dent in the efforts to achieve a tuberculosis-free-world by 2030.

Impact of the COVID-19 pandemic: Health professionals and the health care support team suffered a major setback in reaching out to patients due to various restrictions imposed on them during this pandemic period. Patients found it difficult to reach out to the health care team, owing largely to the fear factor and also due to inaccessibility to health care services. The delay in tuberculosis notifications, the emergence of drug-resistant strains and restrictions in the supply chain further added to the difficulties faced.

Government efforts: India is a nation with one of the largest numbers of tuberculosis victims. The strategic measures taken by the Government of India took a sudden jolt with the onset of the COVID-19 pandemic. The Tuberculosis elimination measures reverted to tuberculosis containment measures. Various African countries recorded a massive fall out of more than 75% during the various lockdown measures imposed. However, India took collateral measures to combat this setback. Its National Tuberculosis Elimination Programme involved private players to combat the tuberculosis epidemic, recruited Patient-provider support agencies and actively engaged Private Sectors through innovative patient-provider incentives to bring down numbers of the tuberculosis victims.

Changing trends in diagnostics: The diagnostic methods that took about 4 to 6 weeks to confirm the diagnosis of tuberculosis had earlier put the diagnosis and management of tuberculosis into the back seat. However, recent innovations in molecular biology, immunology and genomic sequencing techniques have greatly aided an earlier and more accurate diagnosis of tuberculosis. One individual, one health agency or one Government cannot achieve tuberculosis elimination by 2030. A global effort is the basic pre-requisite, incorporating advanced molecular diagnosis and appropriate treatment would ensure achieving a tuberculosis-free world by 2030.

Keywords: tuberculosis, gene expert, Covid-19, pandemic, drug resistance.

Introduction

Tuberculosis (TB) continues to be a major threat to the global community. Every year, around 10 million people get affected and nearly 1.4 million TB-related mortalities happen due to this infection [1]. It is a major cause of infections related mortality in the world. Various data indicate that nearly 1000 individuals succumb to this illness in some corners of the world [2].

The End-TB campaign, a global plan to end tuberculosis by the year 2030 has shifted the United Nations (UN) Sustainable Development Goals (SDG) from TB eradication to TB elimination from our society [3]. Continuous progress is achieved in this ambitious goal over the past two decades. The current anti-TB drugs are effective and are readily available in all places. When administered at appropriate doses and regular intervals, they exhibit cure from illness in the majority of the affected victims.

One of the major hurdles in accomplishing this goal was multi-drug resistance (MDR). The World Health Organization (WHO) in the pre-pandemic period focused mainly on a systematic collection of data related to multi-drug resistance and identifying those who needed second-line therapy. Since this initiative in 2008, the WHO observed that more than 300,000 patients were found to have MDR-TB [4]. About 100 countries worldwide have reported cases of MDR-TB that are resistant to all available anti-tuberculous drugs. The pre-pandemic data from WHO reported that only less than 50% of those with MDR-TB were successfully treated and cured [5].

The other daunting task for TB control committees worldwide is the emergence of increased knowledge and awareness of the entity, Latent TB infection (LTBI). LTBI patients harbour the bacilli throughout their lives without showing up any signs or symptoms. About 5 to 15% of these LTBIs may break out in their lifetime when the immunity is compromised and become not just symptomatic but also become transmissible [6]. HIV, diabetes and malnutrition were the common reasons attributed to the flaring up of active disease until the COVID-19 pandemic swept across the world, resulting in a resurgence of the active TB illness.

Aim and Scope

This mini-review focuses on the havoc created by the recent pandemic and the efforts taken by the authorities worldwide and by the Government of India in controlling the further spread of active TB infection. This manuscript also focuses on the recent advances in diagnostic facilities that greatly aided an earlier diagnosis, ensuring appropriate treatment for tuberculosis victims.

Impact of the Covid-19 pandemic

Extensive medical literature is available on the impact of the Covid-19 pandemic on human health. In 2015, TB became the major reason for infection-related mortality worldwide. It continued to be the leading cause of mortality until the onset of the COVID-19 pandemic. The year 2020 saw a new pandemic surpassing tuberculosis-related deaths per day [7]. Multiple cases of synchronous TB and COVID-19 infections were reported [8, 9]. Elderly patients with co-morbidities were associated with higher mortality. The migrant population, though affected in higher numbers, carried lower mortality, largely due to their younger age at presentation and lesser comorbidities.

The striking similarities between the two infections make it more complex to understand the progress of the illness or the responses to treatment. Both infections are airborne, and transmitted through droplet infections. Both infections present with respiratory problems and resemble each other in their clinical presentations. As prevention of the onset of infection is better than cure, both need extensive awareness, ardent public cooperation, prompt diagnosis and early/appropriate treatment. The government and private TB control programmes took a massive hit, as many patients failed to turn up for receiving their next course of treatment. The government-imposed lockdowns prevented the health authorities from visiting the patients who failed to make the next visit to collect their next round of medications. Adding fuel to the fire, the use of immunosuppressive agents in critically ill COVID-19 patients resulted in a reactivation and/or reinfection of TB in the pandemic-affected patients.

On the contrary, the Centers for Disease Control and Prevention (CDC) factsheet revealed a reduction in the true incidence and delayed diagnoses of TB during the pandemic period. The likely reasons attributed could be a reduction in the rate of droplet infection due to the imposed social distancing or wearing masks. The various interruptions in the healthcare system during the pandemic could have also reduced the overall incidence of new cases of TB. Also, as a majority of funding was diverted towards diagnosing COVID-19 infection, those TB patients with respiratory illness were mistakenly diagnosed as suffering from the pandemic and missed an early diagnosis.

While many authors across the globe call this a 'cursed duet', the Indian authors have called this, a 'double trouble' [10]. Dheda calls it an intersecting Twin Epidemic, as TB has been a constant epidemic in India [11]. The nationwide lockdown, social distancing, self-quarantine of affected individuals and various containment policies adopted by the Government of India to prevent further dissemination of the pandemic resulted in a 78% decline in the reporting of new TB cases across the country [12]. The initial decline could foresee a significant negative impact of new TB cases on a later date, as the COVID-19 outbreak resulted in an uninhibited transmission of infection and an overall increase in the incidence of new TB cases in the subsequent periods. However, aggressive measures are taken by the Government of India by providing medicines for 2 to 3 months, forecasting the availability of medicines to avoid a short supply, using courier services to reach out to those in remote areas and easy access to newer drugs and novel technologies for monitoring, which brought down the incidence largely under control.

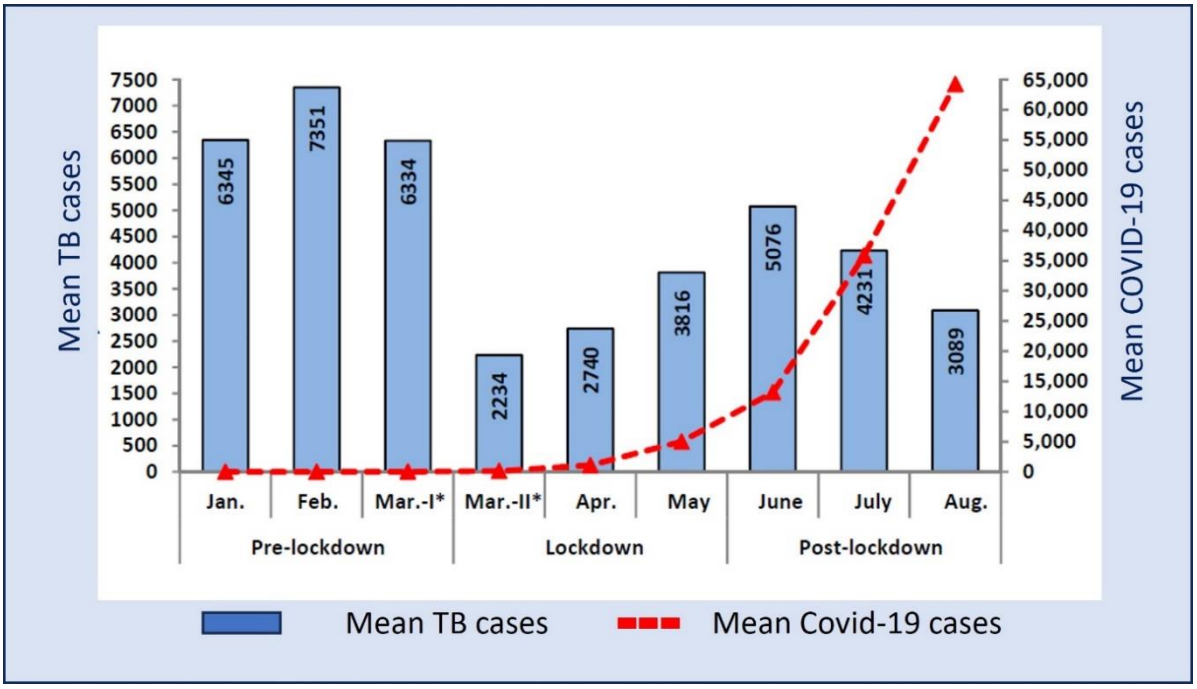

Fig 1. Changing trends in the mean number of TB and COVID-19 cases in India, 2020. *(Source: adapted with written permission from Prof Golandaj JA, Ref 10)*.

The above figure (Fig 1) illustrates the rising trend in the incidence of new TB cases after the lockdown was lifted. The month of March 2020 alone is divided into two parts: March 1st to 24th March and 25th to 31st March respectively, as the nationwide lockdown was imposed on March 24th 2020. The other factor that was even more distressing was the reduced number of TB notifications during the post-lockdown period. The below figure (Fig 2) suggests a significantly lower number of TB cases reported even after the lockdown was lifted. This gap was widening gradually month after month, which posed a significant challenge to the health authorities of India.

Problems in Screening for Tuberculosis

The nationwide lockdowns imposed in various countries during the first and second waves of the COVID-19 pandemic caused a severe dent in TB screening and notifications. As most citizens remained indoors, as the commutation was seriously hampered during these periods, and as there was a paucity of doctors and other health care professionals to attend to these patients, a smaller number of TB-affected victims were reported and/or treated. Countries with more TB victims like India reported a nearly 80% reduction in daily notifications during this period. South Africa reported a nearly 50% reduction in the number of cases notified [13]. Such reductions will have a cascading effect resulting in a delay in diagnosis, delay in initiation of treatment and also will substantially increase the impact of TB burden on the nation. Delays in screening would also augment the possibilities for increased transmission of the disease.

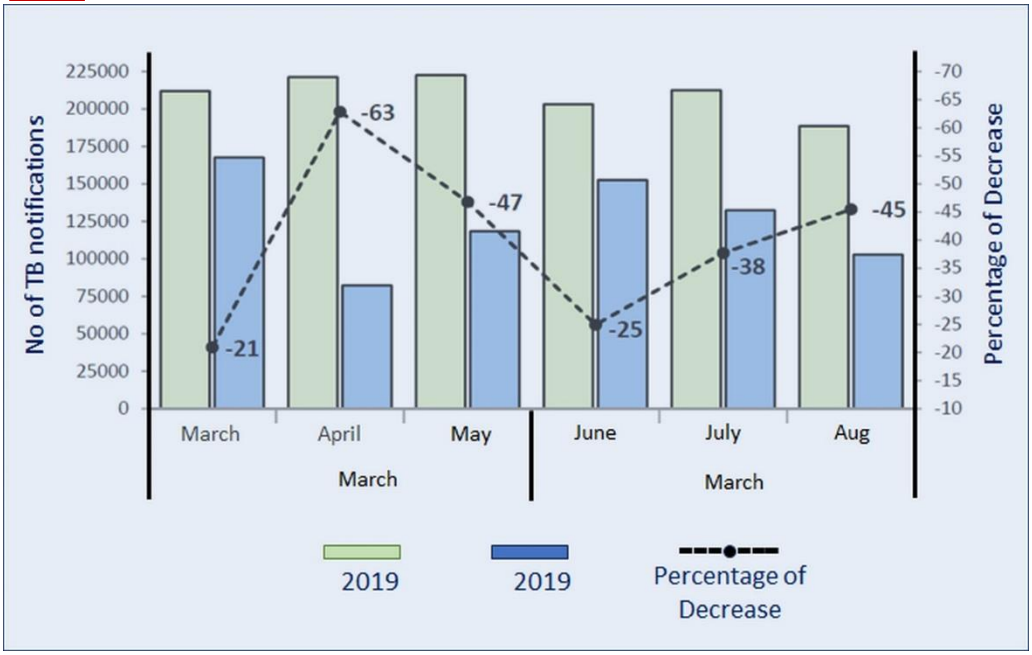

Fig 2. New TB notifications and percentages decrease during and after Lockdown in India. *(Source: adapted with written permission from Prof Golandaj JA, Ref 10)*.

Muniz Salazar and his colleagues studied the impact of the pandemic on the detection and treatment of TB. They observed a significant limitation in accessibility of TB diagnostic and treatment supply chains, ever since the pandemic was officially announced. They also observed promising reworking strategies adopted by health professionals, by increasing the use of telemedicine facilities and by a well-organized case referral process [14].

Urban Zambia undertook a rather unique initiative. It was quick to officially recognize and announce the arrival of a new pandemic. This early announcement facilitated the Zambian Ministry of Health to initiate supportive measures for health professionals as early as May 2020. Despite these aggressive measures, fear of reaching out to hospitals, supply chain disruption, transportation hindrances and redirection of TB screening platforms to pandemic screening and testing brought down the case detection rates by over 25%. It is expected that TB-related mortality could see an upsurge of over 20% by the year 2025 [15].

Problems in Directly Observed Therapy

India, the country with one of the largest numbers of TB victims, announced the nationwide lockdown on March 25th 2020 [16]. All the strategic interventional measures taken by the Government of India (GOI) were disrupted all of a sudden. Focus shifted from Directly Observed Therapy, Short Course (DOTS) therapy to containment of the COVID-19 pandemic. A 60% reduction in the case detection of TB occurred during this time, which had a cascading effect on the DOTS therapy as well. Also, the fear of contracting the Covid-19 virus prevented patients from approaching health workers to collect their medicines. Fund allocation also shifted gears, with more funds from DOTS being allocated to contain the COVID-19 virus spread. Access to drugs and supply took a massive hit, as transportation modes decreased and transportation expenses increased multi-fold. Various authors reported a 55 to 69.5% fall in receiving medication due to fear to visit the health centre. Some countries recorded massive fallout of more than 80% during the lockdown periods [17, 18].

Another cross-sectional questionnaire-based study on 55 patients receiving anti-tuberculous treatment suggested that the major cause for DOTS failure during the pandemic period was non-adherence to treatment [19]. Such non-adherence would not just result in treatment failure but also would lead to dismal outcomes and the emergence of drug resistance. DOTS is thus faced with the daunting task of not only making patients compliant with drug intake but also ensuring that friends and family members are educated enough on the growing need to complete full course of anti TB treatment schedule. Rapid restoration of treatment services and incorporation of digital technology to cope with the twin epidemic are the essential requisites deployed by DOTS to reinitiate the tuberculosis elimination programme [20, 21].

Government of India measures to tackle the pandemic related problems

The year 2021 witnessed a staggering 32% of TB-related deaths happening in India [22]. The National TB Prevalence Survey (NTPS) indicates that nearly 50% of patients with TB-related symptoms seek medical attention from the private sector, despite free evaluation and free treatment available under the government sector. Inadequate standardization of care, lack of resources to monitor an uninterrupted supply and intake of medicines, lack of adherence to treatment and added expenditure to follow-up investigations are the inherent limitations of treatment under private care. To negate this drawback in private facilities, the National TB Elimination Programme (NTEP) has involved many private organizations for effective TB care, especially in the post-pandemic period. Arinaminpathy and his colleagues suggested combination packing of all TB medicines together to ensure optimal patient compliance [23].

Patient-Provider Support Agencies (PPSA): The GOI recruited certain third-party agencies to facilitate government doctors in providing end-to-end services for TB-affected victims. These services include diagnosing a patient with TB, notifying them in the centralized Nikshay e-portal, promoting patient adherence and support, and facilitating the availability of adequate treatment linkages. These agencies were initially recruited in a few cities in India. Through these measures, the number of TB notifications increased by 3 to 5 times [24]. On seeing the phenomenal success of these recruitments, the project JEET (Joint Effort for Elimination of Tuberculosis) scaled up these agencies' country-wide, making the PPSA services available in 385 districts all over the country.

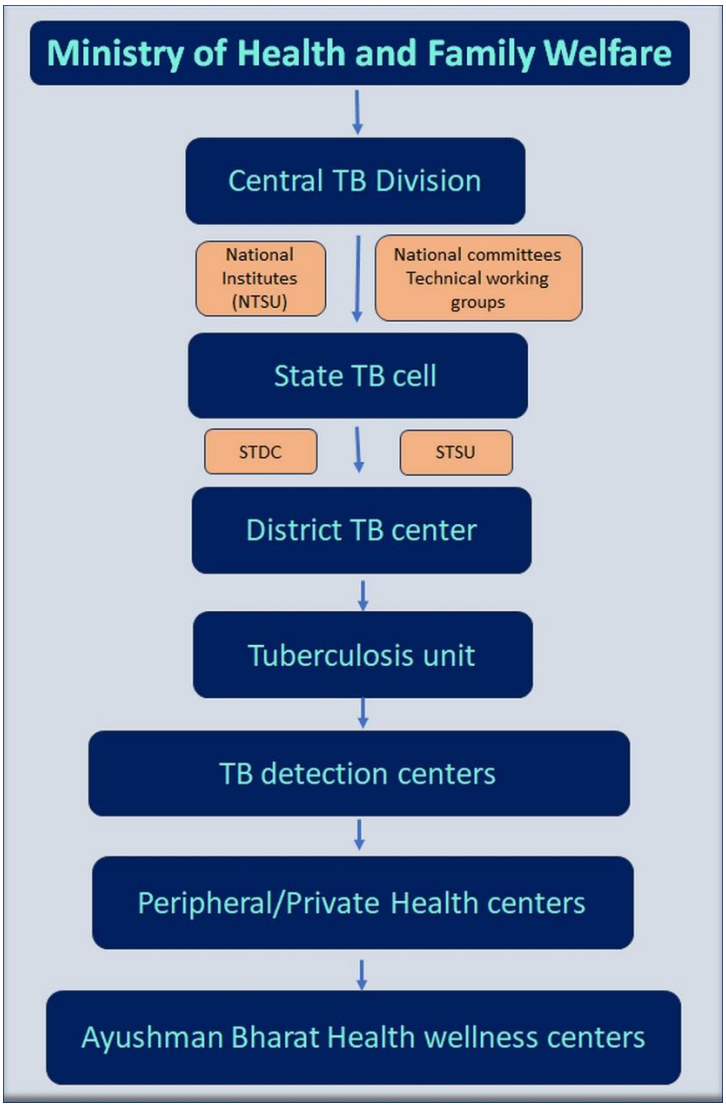

Fig 3. Organization Hierarchy of National Tuberculosis Elimination Program (NTEP). (Source: India TB report 2023).

System for TB Elimination in Private Sector (STEPS): STEPS is a low-cost regionally configured private sector model that adopts a patient-centric strategy to promote TB notifications. This model was piloted in 14 districts of one particular state of India, where 318 private hospitals were attached to this program. The three major components of this program included (i) the formation of a conglomeration of private hospitals; (ii) the union of all professional medical associations and (iii) the formation of a STEPS centre in each of those private hospitals. This program acts as a single window for notification to the Nikshay e-portal, facilitating diagnosis, enabling a direct benefit transfer and encouraging patients to adhere to treatment support programs. STEPS augmented the TB notifications from the private sector to the NTEP by 26% compared to the previous years. STEPS continues to provide a major liaison between the patients reaching the private sector and the NTEP.

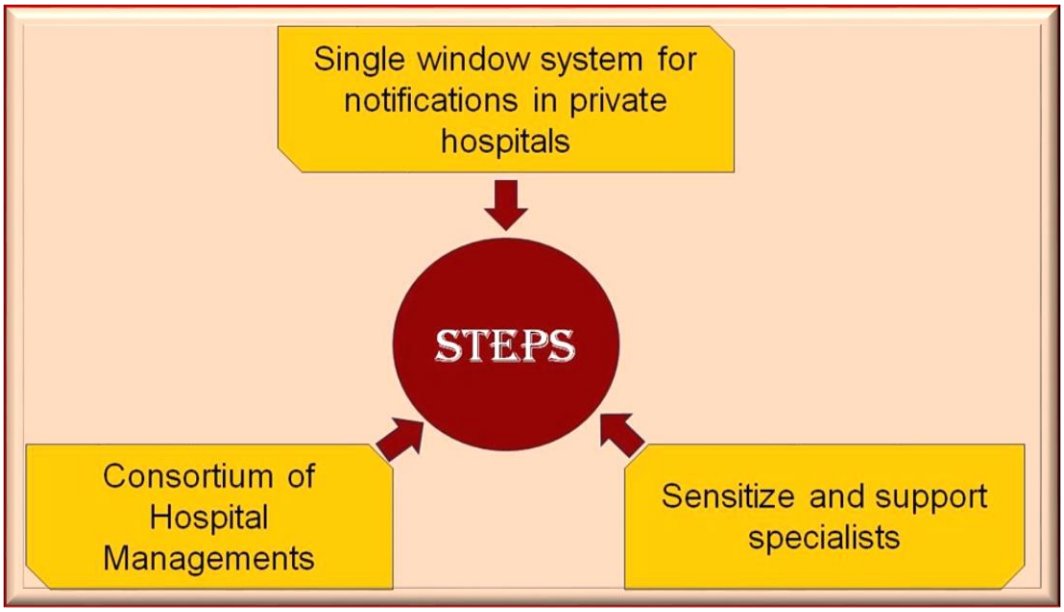

Fig 4. STEPS Model for Private Sector Engagement

Patient-Provider Incentive Scheme (PPIS): The success of any government rests on the contribution played by the private players of that nation. Private health service providers play an indispensable role in the tuberculosis support and treatment facilities of a nation. The private player may either be a general practitioner, a private nursing home or a hospital, a private laboratory or chemists and druggists, who can identify the potentially TB-affected individuals and either treat them or notify about them to the nearest government health authorities. Private Health service providers are entitled to payments for TB notifications in the TB care mission. The GOI has assured a financial incentive of 500 Indian rupees for any information/notification issued about a TB victim. This had a direct impact on the private sector, urging them to notify more cases to the GOI, through the Nikshay e-portal.

Such innovative measures taken by the GOI, enable individual states of the country to augment and motivate the involvement of private health service agencies and general practitioners to notify TB victims. The availability of the Nikshay e-portal has greatly aided in increasing the notification numbers multifold [25]. The Indian Medical Association (IMA), a national voluntary organization, comprising physicians and general practitioners of India has gone one step further to recruit the chemist associations in this program. This ensured an uninterrupted supply of anti-tubercular drugs to the affected patients. The National Tuberculosis Elimination Program (NTEP) engaged private diagnostic laboratories by signing formal MoUs with them. Through this, free diagnostics were made available to the victims, ensuring a regular follow-up of these patients. Incentives and financial assistance were given to the patients as well under the Nikshay Poshan Yojana, motivating them to complete the full course of treatment.

Newer diagnostic methods and treatment strategies

The diagnosis and diagnostics of tuberculosis have undergone a paradigm change in the last 2 decades. Gone are the days when the diagnosis of tuberculosis with mycobacterial culture took about 4 to 6 weeks. The newer immunological and molecular

biology diagnostics have revolutionized the diagnosis of TB and have also significantly reduced the time to diagnosis.

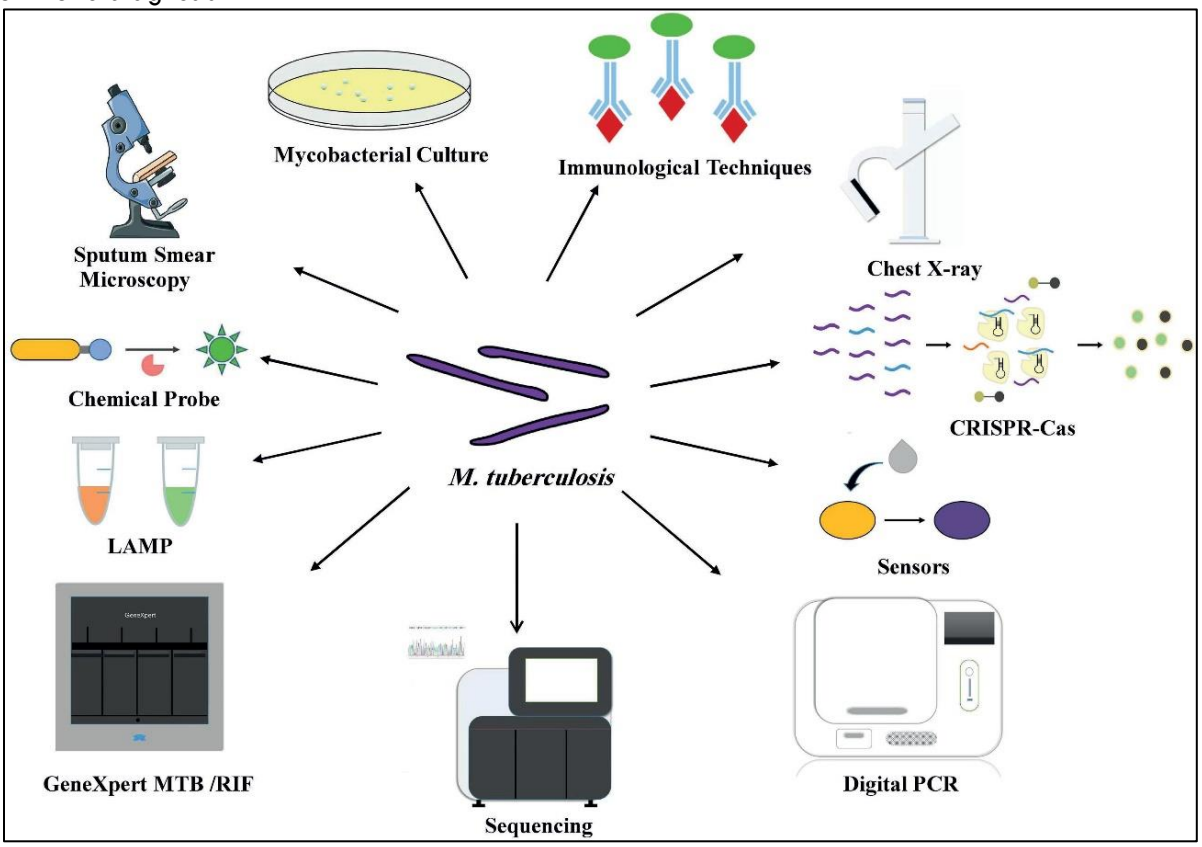

Fig 5. Various diagnostic tests for tuberculosis *(adopted with written permission from Dong B, Ref 26)*

Conventional methods: Many developing countries still have sputum testing as the primary modality of diagnosis of TB. The staining techniques commonly used include Ziehl Neelsen Acid-fast stain and Auromine-rhodamine fluorescent staining methods. Culture methods including the Lowenstein-Jensen (L-J) medium continue to be the gold standard for making a diagnosis of tuberculosis, though the time taken to culture the mycobacteria was about 4 to 6 weeks [26]. The Bactec MGIT 960 is an automated test that monitors the growth and activity of mycobacteria in the tube. The Bactec method helps in making the diagnosis much earlier than the culture by L-J medium [27]. The VersaTREK detects the growth of mycobacteria by assessing the pressure changes above the broth medium [28]. Most of these techniques demonstrate the growth of the bacilli in 1 week [29].

Molecular methods: Molecular diagnostics have completely revolutionized the detection methods for TB. GeneXpert MTB is the most widely adopted method for diagnosis. This technology aids in detecting the mycobacterial DNA, giving results in 2 hours [30]. GeneXpert also aids in detecting drug resistance to Rifampicin. Digital PCR is a nucleic acid quantification method for the diagnosis of TB. It is highly sensitive and accurate in diagnosis. Even a single copy of DNA could be detected by this technique [31]. Single Step Loop-Mediated Isothermal Amplification Techniques (SS-LAMP) employ DNA polymerase and a set of primers that detect pathogenic DNA with a high degree of precision. WHO recommends this technique as a replacement for microscopic techniques in the diagnosis of TB. However, this technique had higher sensitivity but lower specificity for sputum-positive cases [32]. Though it looks promising, the LAMP assay needs to be improved further to make it competitive against the well-established PCR techniques that are already in use. These immunologic techniques help in making an accurate diagnosis within a few hours.

Immunologic methods: Tuberculin-purified protein derivative skin tests have been in vogue since time immemorial. The major limitation is that they cannot distinguish between BCG vaccination and TB infection-induced reactions. Immuno-PCR (I-PCR) is a newer diagnostic test that detects TB antigens and circulating antibodies in body fluids. I-PCR is primarily based on gold nanoparticles or magnetic beads that produce a shortened background signal. The detection time is also significantly shortened [33].

Lateral flow urine Lipoarabinomannan assay (LF-LAM) is a test that is primarily used in the diagnosis of TB in HIV-affected individuals. LAM is a polysaccharide and a pathogenic agent seen in the cell wall of mycobacteria. The sensitivity and specificity of this test need further validation [34].

Newer Diagnostic Techniques: The chemical probes using optical imaging and real-time quantification of mycobacteria is a promising technique. Techniques using the principles of fluorescence, chemiluminescence, radioactivity and light scatter are employed, of which the fluorescence technique is the popular approach [35]. Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) is another newer diagnostic method, where there is a cleavage of the DNA or RNA of the bacteria, thereby facilitating an enhanced identification and validation of the organism. CRISPR uses endonucleases that recognize the double-stranded DNA of the mycobacteria, cleaves it into single strands and uses amplification technology to make a diagnosis. The main limitation of this test is its inability to distinguish between the live and dead bacilli and the false positive results are very high [36]. Mass spectrometry technique requires only a routine clinical laboratory but the infrastructure is very expensive and needs specially trained staff to perform these tests. However, the test results are obtained in a few minutes [37].

Genomic sequencing techniques: Whole genome sequencing is a recent technique, where the single nucleotide polymorphisms of the mycobacteria can be detected using deletion or insertion techniques. This technique gives rapid results and is highly specific and sensitive, especially useful in endemic areas where a large population needs to be tested and rapid results are to be obtained. Its higher resolution and reduced cost make this test a useful adjunct in the epidemiological investigation of mycobacteria [38].

Metagenomic sequencing, also known as Next gene sequencing is another promising technique. It allows the sequencing of millions of DNA fragments in each run. Also, it provides various profiles of drug resistance within a single analysis. The genes responsible for drug resistance are amplified and mutations associated with resistance to rifampicin, isoniazid, streptomycin and second-line drugs like ofloxacin, levofloxacin and moxifloxacin can be detected with a high degree of accuracy.

Nanoparticles: Nanoparticles are tiny particles that are less than 100 nanometers. Nano-technology-based diagnostic approaches provide a rapid and effective diagnosis that greatly aids in TB detection and elimination. The unique and salient features of nanoparticles facilitate early and prompt diagnosis. Magnetic nanoparticles are extensively used to detect TB bacilli even in unprocessed samples. The potential low cost of nanofabricated devices shows promising results and displays an encouraging trend in various biochemical and analytical methods [39].

Conclusions

The diagnosis of tuberculosis is ever-evolving. From the basic microbiological techniques of identifying, the acid-fast bacillus in the smears and cultures, we have come a long way today. The diagnosis of tuberculosis has become more immunological and molecular these days, with the recent progress in gene sequencing and nanoparticles enabling us to assess the degree of drug resistance with a higher degree of accuracy. Implementation of these rapid diagnostics has enabled us to combat TB early, appropriately and effectively. The End-TB program, aiming at the elimination of tuberculosis by the year 2030, though faced a setback due to the recent pandemic, appears a distinct possibility shortly. Each patient's treatment should be configured based on his/her own TB protein biosignatures, taking into consideration their genomic expressions of mutations. A global effort to incorporate these newer methods of molecular diagnosis and sharing the expertise on a larger international scale, ensuring an appropriate treatment would greatly aid in achieving TB elimination by 2030.

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