Tuberculosis Diagnostics, a journey from the past Experiences to the Future Directions, Review

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Abstract

Purpose: Tuberculosis caused by Mycobacterium tuberculosis is believed to have been acquired from animals especially cattle. Not one country across the globe is spared of the disease. The infection gets established through respiratory system where they are either latent or active. Depending upon the immune status or coexisting infection or other health disorders the infection may be either contained within the lungs or spread to other parts of the body. Hence rapid and accurate diagnosis is needed to initiate appropriate treatment. Sputum studies are being followed for diagnosis of tuberculosis but has few disadvantages. Xpert MTB/RIF, an automated, molecular test has been in vogue now. Biomarkers such as complete blood count, inflammatory and oxidative stress markers are being measured. Recently epigenetic markers like microRNA are being analyzed to differentiate the various presentations of tuberculosis. This review has been undertaken to understand the various diagnostic strategies being followed from the old times to the newer novel techniques.

Methods: The narrative review was undertaken by searching the original and review articles in the past 20 years. The articles were obtained by searching through various search engines. Since this was a review article ethics committee approval was not required.

Results: The traditional methods have inherent limitations of high expertise, prolonged procedure, not cost effective and require good infrastructure. Newer methods are found to be sensitive, specific, reproducible and cost effective. But require validation to be implemented into routine use.

Conclusions: Validating the new markers such as epigenetic markers – microRNAs should pave way for diagnosis and management of pulmonary TB, extrapulmonary TB, TB in HIV infected individuals, pregnant women and children. This could serve as a finger-print sort of diagnosis once validated on large scale community-based studies.

Keywords: Tuberculosis, biomarkers, imaging techniques, Xpert MTB, microRNA.

Introduction

Tuberculosis (TB), a bacterial disease, known to be affecting humans and decreasing their quality almost for more than forty thousand years (Wirth et al., 2008). Tuberculosis is caused by *Mycobacterium tuberculosis* (Mtb). According to the data projected by World Health Organisation (WHO), worldwide one out of three individuals are affected by tuberculosis; this counts approximately 90% of TB infections (Bottai et al., 2020). In addition to mycobacterium tuberculosis, Mycobacterium bovis and Mycobacterium africanum are the other mycobacteria species infecting human beings; all the three mycobacteria aggregate to form the Mycobacterium tuberculosis complex (MTBC) (Bottai et al., 2020).

Epidemiology

TB has claimed the lives of over 1.4 million people in 2019 as per the WHO estimate. When an individual comes in contact with the exhaled droplet containing mycobacterium tuberculosis from an active tuberculosis patient, the bacteria get the opportunity to get access to the lungs of the individual without the disease. In the lungs, the mycobacteria are engulfed by the macrophages present in the alveoli, within which they replicate forming granulomas (Hunter, 2018). Till this stage the infection is localized within the lungs only. (Figure 1) Most of the individuals do not present any of the clinical features of pulmonary tuberculosis and the disease is in its latent stage as well as the patients are infective to others (Spekker et al., 2020; Tilahun et al., 2019). In 10 percent of infected individuals, the infection is not limited to lungs. It progresses further beyond lungs to various organs as a result of the rupture of the granulomas. These individuals are highly infective to other neighbouring individuals. Also, the bacterium gets lodged in organs other than lungs, which is termed extrapulmonary tuberculosis.

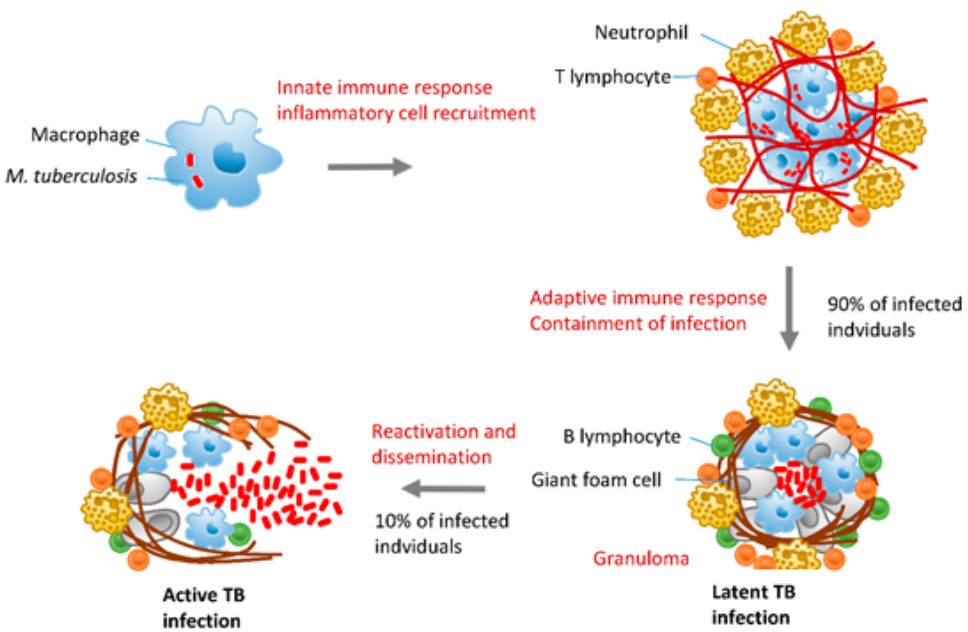

Figure 1. Pathogenesis of the disease following reactivation of mycobacterium tuberculosis infection

According to the National Institute for Health and Care Excellence (NICE), six-month course of combinations of rifampicin with isoniazid would be beneficial. But rifampicin was responsible for drug toxicity related to various organs such as hepatitis, gastrointestinal upset, joint pain, peripheral neuropathy etc (Araujo-Mariz et al., 2016; Boeree et al., 2017; Yang et al., 2017). In the further years of management of tuberculosis, there were issues related to unresponsive to routine tuberculous medication, such as multi-drug resistant tuberculosis (MDR-TB). This resulted in death of 1,82,000 patients in 2019 (Tiberi, Zumla and Migliori, 2019). This is a issue globally and few countries report extensive drug resistant tuberculosis (XDR-TB) (Dadu et al., 2020; Pang et al., 2017; Shah et al., 2017; Sharma et al., 2017; Wilson and Tsukayama, 2016). This scenario is further worsened in the presence of Human Immunodeficiency Virus (HIV) co-infection especially in South Africa, where 36% of its population being infected with HIV (Kharsany et al., 2020).

Diagnostics of mycobacterium tuberculosis:

Diagnosis of tuberculosis is highly complex with utility of multiple techniques such as molecular markers, immunological markers, culture, smear involving microscopy etc. But these are highly challenging in individuals with human immune deficiency virus infection, latent infection, pregnant women and children who cannot bring out sputum, thus limiting the efficacy of the above-mentioned diagnostic modalities (Petruccioli et al., 2020). Furthermore, a steady supply of electricity, expertise and lab modules are basic requirements for these diagnostic methods. These often pose problems in resource limited settings as in the low- and middle-income countries (Nkengasong et al., 2018). In patients with extra-pulmonary tuberculosis, Invasive biopsies for tissue diagnosis is often needed for establishing the diagnosis (Lee, 2015). Thus, there is an urgent need to develop diagnostic methods that could produce results accurately, rapidly, and as well as cost effective and further help in implementing the WHO guidelines for combatting and eradicating TB (Fairlie, 2020).

Mycobacterium tuberculous culture

Culture is considered to be the gold standard in the diagnosis of tuberculosis using traditional plate culture (Du et al., 2019). The culturing of Mtb has several problems, due to the slow growth rate of Mtb, taking about few weeks to months duration (Feng et al., 2020). This could be the pressure exerted as an advantage by the bacteria. An advantage of plate culture bears the advantage of concurrently performing drug sensitivity testing, enabling clinicians to guide antimicrobial therapy more effectively (Kenaope et al., 2020). Using the traditional Lowenstein–Jensen (LJ) medium, Mtb takes more than four weeks to produce colonies. Mycobacteria growth indicator tubes (MGIT) use fluorescent probe which involves the culture medium containing dissolved oxygen. On successful growth of Mtb, the oxygen in the medium gets lowered resulting in activation of the probe, which can subsequently be detected by light sensor. MGITs reduce the mean detection time of Mtb from 38.6 days to 21.4 days (Ma et al., 2020).

Mtb is an airborne pathogen which could spread to community; this is included in Risk Group 3 according to the UK's Advisory Committee on Dangerous Pathogens requiring safe handling of the containment facilities. This would also require the relevant personnel expertise and logistics for proper functioning, which is highly challenging (Maehira and Spencer, 2019). Further, with inconsistent sampling methods of Mtb, the sensitivity varies between 16–60% (Ahmad et al., 2019). Sampling methods could

range from simple sputum collection in a sterile container to more invasive methods like bronchoalveolar lavage and bronchial washing exhibiting sensitivity of 85.7% vs 50.0%, respectively impacting also the detection rates (Kim et al., 2020; Neves et al., 2020). In under-resourced settings, smear microscopy is often used in tandem with culture. Ziehl-Neelsen stain is used to dye the Mtb, but in early cases can have a low sensitivity of only 56% (Chadha et al., 2019). The efficacy of smear microscopy and culture though is fair when combined together, drops significantly in children, HIV or immunocompromised patients (Getahun et al., 2010; Kunkel et al., 2016; Park et al., 2019).

The chest X-ray and the Tuberculin skin test have been used in combination with the smear microscopy and culture, for improving the diagnostic efficacy (Ruhwald et al., 2017). However, observer bias has attributed to many at times diagnostic flaws, which is now being attempted to be overcome by the use of Artificial Intelligence in chest X-ray interpretation (Qin et al., 2019; Saktiawati et al., 2019).

Molecular and immunological detection

Recently, there is a shift towards, molecular or immunological methods for the diagnosis of tuberculosis, where the emphasis lies on the detection of Mtb associated molecules or compounds rather than the entire organism or the detection of antibodies to Mtb. The molecular methods which are of diagnostic use in tuberculosis include polymerase chain reaction (PCR) based GeneXpert MTB/RIF® assay and the immunological-based, QuantiFERON-TB gold® assay. In GeneXpert the bacteria extracted from the sputum is subjected to PCR to detect the Mtb gene involved in production of RNA polymerase B (rpoB). This test also helps us in detecting the rifampicin resistance, a first line anti-tuberculous drug. Gamma interferon release assay (QuantiFERON-TB gold®) is utilized to analyse the levels of gamma interferon which released in the blood sample by immune cells in response to TB antigens. A patient is considered positive for TB if the release is beyond the cut-off value (Pai et al., 2014). There are several additional diagnostic methods for diagnosing TB, like the loop-mediated isothermal amplification (LAMP), which utilises the isothermal amplification procedure. This method is recognised by the WHO, though it's use is hampered by the poor sensitivity among the sputum negative samples and the prohibitive costs of the reagents used (Gelaw et al., 2017; Toonkomdang et al., 2020). The line probe assay (LPA), is yet another test that uses PCR to amplify DNA from Mtb and the output is applied to immobilised oligonucleotides on a strip which emits a colorimetric signal, signifying the presence of drug sensitive and drug resistant strains to isoniazid and rifampicin by the presence of gene mutations within the sample. Their utility falls in sputum negative samples, due to their poor detection rate (Singh et al., 2017). The urine-based lipoarabinomannan assay is a WHO approved method to identify Mtb compounds in the urine samples of TB patients, though their role is limited to HIV and the severely sick patients due to poor sensitivity in other patient groups (Bjerrum et al., 2019).

Though the molecular or immunological tests produce results in considerably shorter time compared to the conventional cultures, they are prone to false positives. Thus, a combined use of both these methods enables better accuracy in diagnosis. Their use is limited in the setting of HIV, immunocompromised, paediatric or latent patients, their cost of deployment, infrastructure and expertise required (Ayubi et al., 2016; Benachinmardi et al., 2019; Subbaraman et al., 2016). The major limitations of the currently available TB tests are time-consuming, requiring specialist infrastructure and laboratory

equipment and strong expertise, exhibiting low specificity, which further fails in HIV and immunocompromised patients and children, as shown in the Table 1. Newer methods have been incorporated which could reduce the above-mentioned limitations as well as introducing cost-effective infrastructure requirements.

Table 1. Currently available diagnostic tests of mycobacterium tuberculosis (Fairlie, 2020)

S No	Test Method	Sensitivity	Specificity	Advantages	Disadvantages
1.	Bacterial Culture	100%	100%	Gold standard, drug sensitivity testing done in tandem, cheap	Time consuming, requires stringent containment biosafety measures
2.	Smear microscopy	60-69	97-98	Rapid, immediate results, cheap, few reagents required	Personnel training required
3.	MGIT	86-93	99.99	Faster than culture	Expensive, specialist training, labour intensive, containment labs
4.	Chest Xray	73-79	60-63	Easily available, non-invasive	Low sensitivity and specificity, incurs initial high cost
5.	Tuberculin skin test	48-78	57-81	Cheap, easily deployed, used for Latent TB, Requires no handling of Mtb	Results in 2-5 days, repeated visits to healthcare professional, variable sensitivity and specificity
6.	GeneXpert MTB/ RIF	88%–82	98%–96	Test Mtb as well as rifampicin resistance, fast turnaround time, Cartridges stored at room temperature	High start-up cost, Variable sensitivity in Immunocompromised patients, Low sensitivity in smear-negative patients
7.	QuantiFERON-TB Gold	86%–61	81%–57	Used for Latent TB, Blood sample easier to acquire than a sputum sample, Rapid detection	Sensitivity falls in Immunocompromised individuals and children Requires handling of blood samples and specialist training, Relatively expensive
8.	TB LAMP	85.6– 92.6	91.0– 96.1	Sensitivity and specificity are comparable to PCR, Cheaper than PCR, Rapid detection	Infrastructure prohibitively expensive, cannot be used for Latent TB Infection
9.	Line probe assays	95.6– 97.5	98.7– 99.5	Rapid detection, detect resistance to isoniazid and/or rifampicin	Less sensitive and specific in smear-negative samples, requires electricity, reagents require refrigeration, not used for LTBI
10.	Determine TB LAM Ag test	93–13	99%–87	Non-invasive, Rapid detection, Useful in immunocompromised and seriously ill patients	Variability in sensitivity, Not recommended in immunocompetent individuals

Recent developments in diagnostics

Digital Droplet PCR: ddPCR is a more recent innovation which splits up the amplification reaction seen in PCR, thereby providing an absolute rather than relative quantification of gene expression. This has higher sensitivity than qPCR, and can detect Mtb DNA

present in small quantities in sputum and blood and also for better understanding of drug-resistance (Luo etal., 2019; Nyaruaba et al., 2019). Hence it is useful in the detection of pulmonary, extrapulmonary, LTBI and active TB infection. The main drawback is the prohibitively high costs (Kuypers and Jerome, 2017). Clustered Regularly Inter SPaced Repeats (CRISPR): CRISPR and its combined use with CRISPR ASsociated nuclease 9, Cas9 is a gene-editing technique, which cut DNA at specific sequences supported by whole array of enzymes, thus possessing the ability to target single-stranded DNA have been identified, like the Cas12a (Li et al., 2018). This technique has used the potential to be lyophilized with lateral flow of very high sensitivity, which enables its deployment even in areas without electricity (Gootenberg et al., 2018). One of the major advantages of CRISPR based diagnostic tests is its rapid development and quick identification of novel drug resistance mechanisms (Mukama et al., 2020). It is also used along with PCR to improve detection in high resource settings (Wang et al., 2021).

Next-generation sequencing (NGS): NGS helps in diagnosis, screening for specific gene polymorphisms which could confer drug resistance, thus having public health implications. Targeted or whole-genome sequencing (WGS) approaches can be applied for Drug sensitivity testing (DST) which could scan the entire genome (Nguyen et al., 2019). Whilst molecular methods such as ddPCR, CRISPR and the NGS methods are useful in analysing sputum samples and thus help in rapid diagnosis of infection as well as resistance, its utility in patients with HIV/ immunocompromised state and in children are questionable.

MicroRNA detection

There is a growing interest in identifying relevant miRNAs in patients' blood using a PCR based assay, these are highly useful in pediatric and immunocompromised patients (Correia et al., 2017; Cui et al., 2017; Ndzi et al., 2019). These microRNAs have the potential to diagnose latent as well as active TB; and also cases of extrapulmonary tuberculosis. The methodology for identification of microRNA is highly complex and not cost-effective, which pose a drawback for its exploitation (Figures 2,3). The need for the correct miRNA sequences was highlighted by Togun et al.; they have also shown that only few microRNAs were isolated from childhood TB (Togun et al., 2018)

Several studies were carried out in active TB with the aim of identifying deregulated miRNAs. Very few original studies addressed the diagnostic performance of microRNAs in TB (Fu et al., 2011; Maertzdorf et al., 2017; Zhang et al., 2013). There is not inconsistency of the types and the degrees of the expression of the various microRNAs (Maertzdorf et al., 2017). This could be due to the inter-individual variation in the miRNA expression. When considered in combination, the miRNAs demonstrated reasonable sensitivities and specificities (Zhang et al., 2013). The studies using serum samples identified 6 miRNAs (miR-378, miR-483-5p, miR-22, miR-29c, miR-101 and miR-320b) and 15 miRNAs (let-7e, miR-146a, miR-148a, miR-16, miR-192, miR-193a-5p, miR-25, miR-365, miR-451, miR-532-5p, miR-590-5p, miR-660, miR-885-5p, miR-223* and miR-30e) respectively. The role microRNAs in the pathogenesis or management of tuberculosis remains unclear. Ma et al. found that upregulated miR-29 has role in suppression of the immune response by targeting IFN- mRNA (Ma et al., 2011). The upregulated miR-21 is involved in the suppression of host T-helper (Th) 1 responses (Wu et al., 2012). miR-194 and miR-29 targets Wnt signalling pathway thus having a role in TB pathogenesis (Krutzfeldt et al., 2012). miR-150 is under-expressed in active TB, which is a negative

regulator of NK cell maturation (Benzman et al., 2011). Thus, deregulated miRNAs can create an immunologically favourable environment for M. tuberculosis in the host's body.

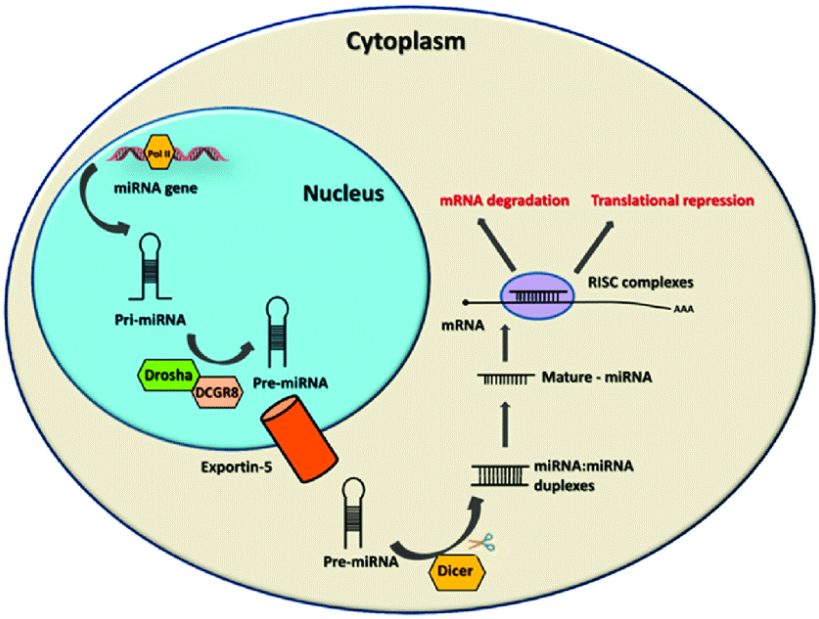

Figure 2. miRNAs formation in the cell

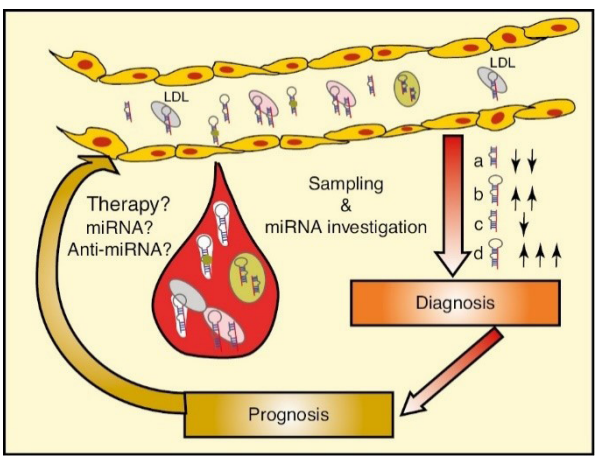

Figure 3. Diagnostic and therapeutic role of miRNA

eNose: These are portable, handheld devices which can analyze volatile organic compounds (VOC), present in the exhaled breath of TB patients. The Aeonose (eNose BV, Zutphen, Netherlands) is a point of care testing device and it has been tested in the field, but the results are not very good (Saktiawati et al., 2019; Saktiawati et al., 2019). But the portability nature of the device and the rapid turnaround time of results (<5 min) makes the prospect of this technology highly promising in rural areas. Mycobacterium tuberculosis produces VOCs inside human body which come out in exhaled breath, whose detection in the breath as apparent biomarkers of tuberculosis infection has created great interest. Volatile organic compounds (VOCs) in breath may contain biomarkers of active pulmonary tuberculosis derived from the infectious organism (metabolites of Mycobacterium tuberculosis) and from the infected host (products of oxidative stress).

Detection of volatile disease biomarkers is technically difficult because most breath VOCs are excreted in picomolar concentrations (parts per trillion), and most analytical instruments in current use cannot detect VOCs in such low concentrations.

VOCs are molecules such as 2,2-diethyl-1,1-biphenyl or 2-methyl-1(1,1-dimethylethyl)-2-methyl-1,3-propanediyl propanoic acid ester apart from methanol, ethanol, acetone, acetaldehyde and isoprene. About 130 different biomarkers were detected consistently; with naphthalene, 1-methyl-, 3-heptanone, methylcyclododecane, heptane, 2,2,4,6,6-pentamethyl-, benzene, 1-methyl-4-(1-methylethyl)-, and cyclohexane being the most abundant. Monomethylated alkanes, like dimethylcyclohexane, methylheptane, methylcyclododecane, and tetramethylbenzene, have been identified in pulmonary tuberculosis, antigen 85, urease activity, and even detection by trained rats of disease-specific odour in sputum have been tried. Exhaled nitric oxide from tuberculosis patients, though selective in many other diseases, produced equivocal results in case finding (Beccaria et al., 2018; Chen, Bryden and Wood, 2020; Phillips et al., 2007).

Numerous confounders hinder the exhaled breath analysis. Therefore, formulating a standardized procedure that ranges from how the breath is collected, multifaceted factors of gaseous exchange, products coming out from the gastrointestinal system, influence of diurnal variation, socio-demographic correlates influencing the physico-chemical properties of breath should be considered. Human exhaled breath analysis gives us useful information about health and disease like the biometry with hidden data for recognition of diseases. The breath analysis could serve as an inexpensive, rapid point-of-care diagnostic method for the direct early diagnosis of tuberculosis.

Raman spectroscopy (RS): RS is another portable analytical diagnostic tool, that can be easily deployed in rural areas, already in vogue for diagnosing malignancies and bacterial infections (Lorenz et al., 2017). The technique utilizes the principle of Raman scattering, creates specific molecular fingerprints when excited with light of certain wavelength on various bacteria. The turnaround time by RS is very short (Kaewseekhao et al., 2020; Muhlig et al., 2016; Stockel et al., 2017).

AI processing: AI processing is being increasingly used for the analysis of chest X-rays in the detection of TB and, it is also for processing the smear microscopy micrographs (Shah et al., 2017). Human error in interpretation of results and inter-observer variation can be significantly diminished by utilising AI (Qin et al., 2019). It has not been tested with large number of samples as well as there is found to be a wide variation based on the population being studied e.g., HIV co-infected patients, children, etc. (Harris et al., 2019). This technique has been under consideration by WHO. The major advantage is that the images could be sent to the consultants via mobile phones from any remote place to the server site for analysis with AI (Wahl et al., 2019).

Graphene-based biosensors: Yet another PCR-free alternative for TB diagnostics, biosensors containing arginine film, or a graphene-based sensor which, when combined with Mtb based probes have the ability to perform electrochemical measurements following hybridisation at room temperature; hence can be easily adopted in rural areas with a portable power supply. 103 copies of DNA are defined as the detection limit of this method, which limits its role in identifying latent, immunocompromised, HIV and paediatric patients (Eloi et al., 2020; Jaroenram et al., 2020).

Currently, there are several promising diagnostics methods which could address the limitations of the diagnostic methods used routinely. Whilst they may not resolve all of

the previously identified challenges, a combined use of these tests will considerably decrease the global burden of tuberculosis, by aiding early diagnosis and suggested cost-effective management. The newer diagnostic techniques which could have a promising role are summarised in Table 2.

Table 2. Prospective newer diagnostic methods for detection of mycobacterium tuberculosis (Fairlie, 2020)

S No	Test Method	Sensitivity	Specificity	Advantages	Disadvantages
1.	ddPCR	Not available	Not available	Reported sensitivity: 1 copy of DNA/ sample, Absolute quantification of sample, Analysing sputum and blood	Expensive, Requires uninterruptible power supply
2.	CRISPR/ Cas12a	90%	98%	Fast turnaround time (<1.5 hours), High sensitivity and specificity Reaction readily visualised and readily adapted to cover other serovars of Mtb and drug-resistant strains, Culture-free, used in multiple sample sites	Non-specific targeting is feasible, Efficacy not established for paediatric or Immunocompromised patients
3.	Whole Genome Sequencing (WGS)	>95%	>95%	Detects drug resistance, global surveillance of strains	Longer turnaround (72 hr), expensive, Requires uninterruptible power supply and sputum sample, may miss novel sequences conferring resistance
4.	MinION Nanopore sequencing	94.8%	98%	Portable, detect drug resistance, Cheaper than WGS, Quick turnaround (6 hr)	Requires uninterruptible power supply, High start-up costs, Full characterisation to take place, Requires sputum
5.	miRNA	–24.7 39.9%	>90%	Culture-free, Quick turnaround (< 24 hr), Blood sample	Variability in results, Effective miRNA yet to be uncovered, must be utilised regularly
6.	eNose	92%–75	65%–44	Non-invasive, portable, Rapid turnaround time (10 min), Battery operated	Requires internet access, cannot determine drug sensitivity, Efficacy in LTBI and immunocompromised yet to be established
7.	Raman spectroscopy	Active TB: 84.62% LTBI: 86.84%	Active TB: 89.47% LTBI: 65%	Portable, Battery powered, Low cost, Fast turnaround time (<2 hr), Blood sample	No efficacy established for Immunocompromised & paediatric patients, No analysis of drug-resistance
8.	AI Processing	96%–68	85%–72	Analysed on remote servers, Non-invasive, Diminishes human error	Requires mobile phone data access, Preliminary results vary between populations
9.	Graphene based biosensors	Not available	Not available	Quick turnaround time (<2 hrs), Culture-free, PCR free, Reported sensitivity: 4.4 nM of DNA	Requires sputum sample and uninterruptible electricity supply

Conclusion

The traditional methods have inherent limitations of high expertise, prolonged procedure, not cost effective and require good infrastructure. Newer methods are found to be sensitive, specific, reproducible and cost effective. But require validation to be implemented into routine use. Validating the new markers such as epigenetic markers – microRNAs should pave way for diagnosis and management of pulmonary TB, extrapulmonary TB, TB in HIV infected individuals, pregnant women and children. This could serve as a finger-print sort of diagnosis once validated on large scale community-based studies.

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تشخيص السل، رحلة من التجارب الماضية إلى الاتجاهات المستقبلية، مراجعة

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المُستَخلَص

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الهدف: ويعتقد ان السل الذي يسببه داء الميكبكتريا الميكروب (Mycobacteria Tuberculosis) قد جرى الحصول عليه من الحيوانات وخصوصا الماشية. ولا يوجد بلد واحد في العالم بمنأى عن هذا المرض. وتتميز العدوى عن طريق الجهاز التنفسي حيث تكون إما كامنة أو نشطة. وبحسب حالة المناعة أو العدوى المصاحبة أو اضطرابات صحية أخرى، قد تكون العدوى إما داخل الرئتين أو تنتشر إلى أجزاء أخرى من الجسم. لذلك يلزم تشخيص سريع ودقيق للبدء بالمعالجة الملائمة. وتجري متابعة دراسات البق لتشخيص السل، ولكن مساوئه قليلة. Xpert MTB/RIF، تم إجراء إختبار جزيئي مؤتمت بنجاح الآن. ويتم قياس المؤشرات الحيوية مثل التعداد الكامل للدماء والتهابات وعلامات الإجهاد التأكيدية. في الآونة الأخيرة، يتم تحليل علامات اللاجينية مثل الميكرو رنا للتمييز بين العروض المختلفة للسل. وقد أجري هذا الاستعراض لفهم مختلف الاستراتيجيات التشخيصية التي اتبعت منذ العصور القديمة إلى تقنيات جديدة.

الطريقة: وقد أجري الاستعراض السردي عن طريق البحث في المقالات الأصلية ومراجعتها في السنوات العشرين الماضية. وقد جرى الحصول على هذه المقالات بالبحث عبر مختلف محركات البحث. وبما أن ذلك كان إستعراضا لم تكن هناك حاجة إلى موافقة لجنة الأخلاقيات.

النتائج: فالأساليب التقليدية تنطوي على قيود متأصلة في الخبرة العالية، وإجراءات مطولة، وليست فعالة من حيث التكلفة وتتطلب بنية أساسية جيدة. وتبين أن الأساليب الأحدث حساسة ومحددة وقابلة للتعديل وفعالة من حيث التكلفة. ولكن يجب تطبيق التحقق في الاستخدام الروتيني.

الاستنتاج: يجب أن تمهد الجزيئات الدقيقة الطريق لتشخيص وإدارة السل الرئوي ، والسل خارج الرئة ، والسل في الأفراد المصابين بفيروس نقص المناعة البشرية ، والنساء الحوامل والأطفال. يمكن أن يكون هذا بمثابة تشخيص بصمات الأصابع بمجرد التحقق من صحته في دراسات مجتمعية واسعة النطاق.

مفاتيح الكلمات: microRNA، Xpert MTB، السل، المؤشرات الحيوية، تقنيات التصوير.