Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2023.50.008002

Revolutionary Advances in Diagnostic Tests for Tuberculosis Infection and Disease

Sreenivas A Nair*

Senior Advisor, Country and Community Support for Impact, CCS4i Team, Switzerland

***Corresponding author:** Sreenivas A Nair, Senior Advisor, Country and Community Support for Impact, CCS4i Team, Switzerland

ARTICLE INFO

Received: May 24, 2023

Published: June 01, 2023

Citation: Sreenivas A Nair. Revolutionary Advances in Diagnostic Tests for Tuberculosis Infection and Disease. Biomed J Sci & Tech Res 50(5)-2023. BJSTR. MS.ID.008002.

ABSTRACT

Abbreviations: TB: Tuberculosis; WHO: World Health Organization; AI: Artificial Intelligence; CAD: Computer Aided Detection; DCXR: Digital Chest X Ray; LAM: Lipoarabinomannan; CRP: C Reactive Protein; NGS: Next Generation Sequencing; POCUS: Point-of-Care Ultrasound

Introduction

Tuberculosis (TB) remains a significant global cause of death. However, the response to TB care has been hindered by the diversion of resources and laboratory capacity for COVID-19, resulting in a decline in the number of reported people with TB from 7.1 million in 2019 to 5.8 million in 2020 [1]. Even before the COVID-19 pandemic, individuals being evaluated for TB often faced long delays and missed opportunities for diagnosis. The quality of TB symptom screening is often poor and primary care facilities lacked access to proper diagnostic tests. Closing the diagnostic gap is not just a technological challenge: it also requires ensuring that high-quality and modern tests are available, in a manner that enables people with TB to be promptly linked to care. New technologies should be implementable at point-of-care by health care workers with minimal training. Yet, despite the advent of World Health Organization (WHO)-recommended rapid molecular tests (mWRDs) such as Xpert MTB/RIF Ultra (Ultra) (Cepheid, Sunnyvale, USA) and Truenat MTB/RIF (Molbio Diagnostics, Verna, India), much of the world still relies on sputum smear microscopy as the initial and often only diagnostic test despite its poor sensitivity.

There is growing recognition of the high proportion of TB identified in prevalence surveys with no symptoms (subclinical TB), underscoring how large numbers will be missed by current symptom screening approaches [2]. Furthermore, since patients who screen positive but have early disease may not expectorate sputum, sputum confirmatory testing may not be possible. Earlier diagnosis in such people with minimal symptoms can, on an individual-level, prevent disease progression, subsequent morbidity and mortality and, on a population-level, reduce as much as 50% of transmission [3]. This reinforces the urgent need for rapid, accurate, non-invasive, and sputum-free tests for triage and confirmatory diagnosis for Tuberculosis.

Imaging

Imaging technologies, specifically Artificial Intelligence (AI)-based digital chest X-ray (dCXR) are currently the only suitable primary screening tests for pulmonary TB. AI Computer-Aided Detection (CAD) software platforms for TB triage are recommended by WHO as an alternative to human reading, given their potential to overcome the lack of qualified readers, especially in community level active TB case finding activities. An evaluation demonstrated that six out of 12 CAD platforms (Qure.ai, DeepTek, Delft Imaging, JF Healthcare, OXIPIT, Lunit) performed similarly to an expert reader, three of which (Qure.ai, Delft Imaging and Lunit) performed significantly better than an intermediate reader [4]. The availability of ultraportable, handheld X-Ray devices combined with AI based reading has made this tool cost effective and highly appealing. Point-of-Care Ultrasound (POCUS) is another imaging technologies of interest.

Audio

In the audio domain, the use of artificial intelligence opens up the possibility of non-invasively detecting cough sounds or lung sounds that can differentiate individuals with and without pulmonary TB, with potential for use as a triage test. Portable digital recording and signal processing mobile applications or digital stethoscopes [5,6] can be used to capture and analyse cough sounds. Such specimen free technologies offer a more objective measure of symptoms like cough, in contrast to subjective and challenging syndromic screening, and have the potential for scalability due to their ease of use and rapid turn over time.

Compounds in Breath

Analysing the volatile organic compounds expelled in breath using an "electronic nose" devise is another approach for detecting pulmonary diseases such as tuberculosis. Differences in signatures of volatile organic compounds expelled in breath can be This method most likely can be used as a triage test. A recent systematic review suggested that electronic nose diagnostic tests may have high accuracy (pooled sensitivity and specificity both 93%) [7].

MTB in Aerosol

Tests to diagnose subclinical (asymptomatic) TB are lacking. This state (bacteriologically-positive TB in those reporting no symptoms and typically not seeking healthcare) is more prevalent than previously estimated, with highly variable duration (six months to beyond five years) and may be responsible for more than half of TB transmission [8]. The detection of MTb bacilli or DNA in aerosols has been facilitated by the development of face masks, with capture filters or absorbent materials, or blow tubes with a capture filter [9]. Although capture methods are still under development, early results have been promising, suggesting high diagnostic yield. Furthermore, these methods can be applied to people before they cough. Detection of MTb in expelled aerosols may thus play a role in identifying early disease; however, this technology remains early stage.

Tongue Swabs

MTb in tongue papillae biofilms may be detected using existing molecular technologies such as Ultra with high sensitivity. Tongue swab-based diagnoses are also possible using TB-LAMP. Next-generation ultra-sensitive tests may further increase the feasibility of tongue swab-based methods [10].

Stool

Tests on stool currently have the most utility in diagnosing childhood TB, given the challenges in obtaining sputum; although their suboptimal sensitivity remains a barrier [11]. In adults, stool-based tests may play a role in the diagnosis of extrapulmonary TB, particularly in groups such as PLHIV who are more likely to have disseminated disease. Rectal swabs may facilitate specimen collection and processing, making the approach more amenable to POC during a single encounter, although accuracy data are limited.

Urine

Urine is appealing given ease-of-collection, limited infection control requirements, and potential for extrapulmonary and pulmonary TB. MTb cellular components (nucleic acids, molecules, cells) can filter through the kidney barrier into urine. Urine lipoarabinomannan (LAM) is the only WHO-recommended biomarker for TB diagnosis (specifically the AlereLAM test) [12]. Other next-generation LAM assays from FujiFilm, SD Biosensor, Biopromic, Salus, and others are at different developmental stages. Studies comparing SILVAMP TB LAM (FujiFilm) to AlereLAM demonstrate a higher sensitivity Several ultra-sensitive 3rd generation LAM assays to be used irrespective of HIV status will enter trials in 2023. Emerging data also points to a potential role for urine cell-free DNA for TB diagnosis.

Blood

While there are no validated blood tests for active TB, there is increasing optimism regarding the detection of antigens, immune cell profiling, host transcriptomics, or cell-free MTb DNA. Tests that measure T-cell activation such as TAM-TB have demonstrated potential for active TB in children (83% sensitivity vs. culture) [13]. Detection of TB antigens [14] and other molecular biomarkers also holds great potential for scale-up in POC tests. For example, despite being a non-specific biomarker of inflammation, C-reactive Protein (CRP) is recommended by the WHO as a screening test in PLHIV given its superior accuracy for TB compared to symptom screening [15]. Biomarkers like host RNA and CRP have potential for point of care TB diagnosis. Although rapid POC biosignature tests may contribute substantially to reducing those patients lost to follow up

between diagnosis and treatment, one limitation (especially for host biomarker tests) is that they are unlikely to provide drug susceptibility information to guide appropriate treatment, in contrast to tests that directly detect MTb.

Next Generation Sequencing

Next Generation Sequencing (NGS) technologies have opened up new avenues for TB diagnostics. NGS allows for comprehensive analysis of the entire TB genome, enabling the identification of drug resistance mutations and the characterization of bacterial strains. This approach not only aids in accurate diagnosis but also provides valuable insights into the transmission dynamics and epidemiology of TB. NGS based tests are expected to play a crucial role in personalized treatment strategies and targeted interventions.

TB Infection Tests

Currently IGRA and Tuberculin skin tests are recommended by WHO. However newer skin tests such as CyTB developed by SII as an India innovation has recently approved by regulatory authority and soon will be available in the programme. The test is as sensitive as IGRA and coupled with AI based reading, could be a real game changer in Latent TB infection management. Most upcoming technologies for sputum-free TB tests are at an early developmental phase. Nonetheless, given growing recognition of the high proportion of people with subclinical TB and the nuances of use case scenarios for screening versus triage, these tests are urgently needed. Key needs to accelerate test development include publicly available standardised datasets and large-scale validation cohorts that facilitate test design and evaluation from the outset in populations and settings that reflect their final intended field of use [16]. In the near future, we will see a number of points of care tests for TB, meanwhile we need to scale up the use of the existing tools, AI supported digital X-Ray and rapid molecular tests to replace the century old sputum smear microscopy for diagnosis of TB.

References

1. (2021) Tuberculosis deaths rise for the first time in more than a decade due to the COVID-19 pandemic. World Health Organization.
2. Frascella B, Richards A S, Sossen B, Jon C Emery, Anna Odone, et al. (2020) Subclinical tuberculosis disease - a review and analysis of prevalence surveys to inform definitions, burden, associations and screening methodology. Clin Infect Dis 73(3): e830-e841.
3. Emery J C, et al. (2021) Estimating the contribution of sub-clinical TB disease to transmission. Union Conference on Lung Health.
4. Qin Z Z, Ahmed S, Sarker M S, Kishor Paul, Ahammad Shafiq Sikder Adel, et al. (2021) Tuberculosis detection from chest x-rays for triaging in a high tuberculosis-burden setting: an evaluation of five artificial intelligence algorithms. The Lancet Digital Health 3(9): e543-e554.
5. Botha G, Theron G, Warren R, M Klopper, K Dheda, et al. (2018) Detection of tuberculosis by automatic cough sound analysis. Physiological measurement 39(4): 045005.
6. Becker K, Scheffer C, Blanckenberg M, Diacon A (2013) Analysis of adventitious lung sounds originating from pulmonary tuberculosis. Annu Int Conf IEEE Eng Med Biol Soc 2013: 4334-4337.
7. Saktiawati A M, Putera D D, Setyawan A, Mahendradhata Y, Van der Werf T S (2019) Diagnosis of tuberculosis through breath test: a systematic review. EBioMedicine. 46: 202-214.
8. Ku C C, MacPherson P, Khundi M, Rebecca H Nzawa Soko, Helena R A Feasey, et al. (2021) Durations of asymptomatic, symptomatic, and care-seeking phases of tuberculosis disease with a Bayesian analysis of prevalence survey and notification data. BMC medicine 19(1): 1-13.
9. Williams C M, Abdulwhhab M, Birring S S, Elasbe De Kock, Natalie J Garton, et al. (2020) Exhaled Mycobacterium tuberculosis output and detection of subclinical disease by face-mask sampling: prospective observational studies. The Lancet Infectious Diseases 20(5): 607-617.
10. Wood R C, Andama A, Hermansky G, Stephen Burkot, Lucy Asege, et al. (2021) Characterization of oral swab samples for diagnosis of pulmonary tuberculosis. PloS one 16(5): e0251422.
11. MacLean E, Sulis G, Denkinger C M, Johnston J C, Pai M, et al. (2019) Diagnostic accuracy of stool Xpert MTB/RIF for detection of pulmonary tuberculosis in children: a systematic review and meta-analysis. Journal of clinical microbiology 57(6): e02057-e02118.
12. (2015) The use of lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis and screening of active tuberculosis in people living with HIV TB. World Health Organization.
13. Portevin D, Moukambi F, Clowes P, Asli Bauer, Mkunde Chachage, et al. (2014) Assessment of the novel T-cell activation marker_tuberculosis assay for diagnosis of active tuberculosis in children: a prospective proof-of-concept study. The Lancet infectious diseases 14(10): 931-938.
14. Borain N, Petersen L, Du Plessis J, Theron G, Holm Hansen C (2017) A rapid serological triage test for detecting active tuberculosis. BMJ Global Health 2(Suppl 2).
15. (2021) WHO consolidated guidelines on tuberculosis. Module 2: Screening systematic screening for tuberculosis disease. Geneva: World Health Organization.
16. Ruvandhi R Nathavitharana, Alberto L Garcia Basteiro, Morten Ruhwald, Frank Cobelens, Grant Theron (2022) Reimagining the status quo: How close are we to rapid sputum-free tuberculosis diagnostics for all? EBioMedicine 78: 103939.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2023.50.008002

Sreenivas A Nair. Biomed J Sci & Tech Res

Submission Link: https://biomedres.us/submit-manuscript.php