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Innovative COVID-19 point-of-care diagnostics suitable for tuberculosis diagnosis: a scoping review protocol

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ABSTRACT

Introduction In 2014, the WHO published high-priority target product profiles (TPPs) for new tuberculosis (TB) diagnostics to align end-user needs with test targets and specifications; nevertheless, no TB test meets these targets to date. The COVID-19-driven momentum in the diagnostics world offers an opportunity to address the long-standing lack of innovation in the field of TB diagnostics. This scoping review aims to summarise point-of-care (POC) molecular and antigen tests for COVID-19 diagnosis that, when applied to TB, potentially meet WHO TPPs. This summary of currently available innovative diagnostic tools will guide the development of novel TB diagnostics toward the WHO-set targets.

Methods and analysis We will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension Scoping Reviews recommendations. MEDLINE (via PubMed), bioRxiv, MedRxiv and other publicly available in vitro diagnostic test databases were searched on 23 November 2022. POC antigen or molecular tests developed for SARS-CoV-2 detection that meet the eligibility criteria will be included in the review. Developer description, test description, operation characteristics, pricing information, performance and commercialisation status of diagnostic tests identified will be extracted using a predefined standardised data extraction form. Two reviewers will independently perform the screening and data extraction. A narrative synthesis of the final data will be provided.

Ethics and dissemination No ethical approval is required because individual patient data will not be included. The findings will be published in open-access scientific journals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Our search strategy is based on a solid framework and involves multiple sources of information.
⇒ Technologies from a wide range of developers are identified by searching both literature and in vitro diagnostic (IVD) medical device databases (academics, start-ups, large-scale IVD diagnostic companies).
⇒ Two reviewers will independently work on the screening process.
⇒ Our search is focused on late-stage products that can be quickly adapted to tuberculosis (Web of Science and Embase are not searched) and IVD medical device database that are publicly available.
⇒ The data will be extracted by a single reviewer but will be reviewed by a second reviewer.

INTRODUCTION

Rationale

Until COVID-19, tuberculosis (TB) was the leading single infectious cause of death in the world, responsible for approximately 10 million new cases and 1.5 million deaths each year, primarily among the most socioeconomically vulnerable.[1] Delayed and missed diagnosis is a major impediment to improving individual TB outcomes and control.[2–4] Every year, more than one-third of all TB cases go undiagnosed. This diagnostic gap has been further widened by COVID-19.[1] Sputum smear microscopy remains the predominant TB microbiological test, despite WHO recommendations for the adoption of rapid molecular testing for TB diagnosis.[5 6] The varying clinical sensitivity of smear microscopy, as well as the difficulties in obtaining sputum from patients and access to healthcare, are among the key contributors to missed TB diagnosis.[7]

In 2014, WHO defined four target product profiles (TPP) that were deemed of high priority: a point-of-care (POC) non-sputum-based biomarker test, a POC triage test, a POC smear microscopy replacement and a rapid drug-susceptibility test.[8] The TPPs were designed to guide developers towards fit-for-purpose TB diagnostics in terms of test performance and operational characteristics. The currently available TB tests hold the promise of helping close the TB diagnostic gap, but still fall short of meeting the TPPs either due to low accuracy or limited operational suitability.[8 9]

The GeneXpert Dx System (Cepheid, Sunnyvale, California, USA), an integrated, single-use cartridge-based diagnostic system, has been the molecular

diagnostic test of choice for TB since its market release in 2010.[10] The Xpert MTB/RIF (Xpert and Xpert MTB/RIF Ultra (Xpert Ultra) cartridges detect *Mycobacterium tuberculosis* (MTB) DNA along with mutations associated with rifampicin resistance, with the latter being an improved version with increased sensitivity.[9] Despite its promise as a POC TB test, the system has considerable drawbacks, such as the need for continuous power, high maintenance and low operating temperatures, low specificity in individuals with a history of TB and the use of sputum as the sample type. Truenat TB assays (Molbio Diagnostics, Bangalore, India) have lately emerged as a true POC alternative to the GeneXpert system, owing to its improved operational aspects; nonetheless, Truenat still relies on sputum.[9 11 12]

The only non-sputum TB tests on the market are Alere Determine TB LAM Ag test (Abbott, Chicago, Illinois, USA) and Fujifilm SILVAMP TB LAM assay (FujiFilm, Tokyo, Japan). Both tests are lateral flow assays (LFA) that detect lipoarabinomannan (LAM), a component of mycobacterial cell wall, in urine. They are best suited for use in resource-constrained settings due to their quick turnaround time (less than 30 min), instrument-free operation and minimal training needs.[12] However, these rapid tests show reasonable performance only in specific populations (eg, people living with HIV) and require a confirmatory test due to their suboptimal specificity.[13 14] The limit of detection (LoD) of a rapid, low-cost POC LAM detection test capable of detecting TB in all patient groups and meeting the WHO TPP is estimated to be 5 pg/mL, compared with the current tests' LoD of >25 pg/mL.[15] As a result, instrument-based, high-sensitivity antigen detection systems are more likely than conventional LFAs to hit this target.

The desire to gain a share of the COVID-19-generated diagnostic market drove developers to innovate and speed up their development pipelines over the last 2 years. As the market reaches saturation, developers are looking for new avenues to apply their innovations. TB would be a viable option for these developers, given the extremely high disease burden, supportive government initiatives, lower validation costs thanks to no-cost TB clinical platforms (eg, R2D2 TB Network, FEND-TB) and economies of scale resulting from a large available market despite the low margin. It is critical to identify promising innovations early on and connect their developers with assay developers and other key stakeholders in order to capitalise on the COVID-19-driven momentum.

Objectives

In this scoping review, we will summarise POC molecular and antigen tests for COVID-19 diagnosis with the potential of meeting the WHO TPPs for new TB diagnostics. This summary of currently available innovative diagnostic tools will aid the development of novel TB diagnostics to meet WHO TPP targets by informing developers, funders of TB diagnostic tools and also advocates for access to TB diagnostic testing.

METHODS

Overview

This is a scoping review of the scientific literature and COVID-19 test databases. This protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) guidelines,[16] and the methodological framework developed by Levac *et al*.[17] The final publication of this study will follow the PRISMA extension Scoping Reviews (PRISMA-ScR) recommendations.[18]

In this review, we aim to address which innovative diagnostic tools developed for COVID-19, if successfully applied to TB, may fulfil the WHO TPPs of TB diagnostics for use in high TB burden settings. The focus will be on POC molecular and antigen tests.

Definitions

For this work, we will follow the following definitions:

- Diagnostic test: 'a test that is used to determine, verify or confirm a patient's clinical condition as a sole determinant'.[19]
- POC in vitro diagnostic (IVD) testing: 'testing that can be performed by a lay user or a minimally trained healthcare professional at home and/or near a patient and outside of central laboratory testing facilities and can result in an immediate decision for next steps of care'.[20]
- TPPs that define high priority development targets for new tests, specifying performance and operational characteristics and the cost range of desired new tests.[8]

Eligibility criteria

We will include all POC antigen or molecular tests developed and used for SARS-CoV-2 detection that meet the inclusion criteria outlined below, which were adapted from the Cochrane review by Dinnes *et al*.[21]

- Portable or easily transportable equipment for running and/or reading the assay (mains-/battery-powered).
- Minimal sample preparation requirements (eg, single-step mixing, no requirement for additional equipment or precise sample volume transfer unless a disposable automatic fill or graduated transfer device is used).
- Minimal biosafety requirements (eg, personal protective equipment, good ventilation and a biohazard bag for waste disposal).
- No requirement for a temperature-controlled environment.
- Test results available within a single clinical encounter (less than 2 hours of sample collection).[22]

We will include studies of all designs, as well as case reports, reviews, letters and editorials, which use or report on a POC molecular or antigen test for

Table 1 Search strategy

PubMed/MEDLINE (searched on 23 November 2022)		Items found
Condition of Interest	"2019 nCoV"[Title/Abstract] OR "2019nCoV"[Title/Abstract] OR "2019 novel coronavirus"[Title/Abstract] OR "COVID-19"[Title/Abstract] OR "covid-19"[Title/Abstract] OR "COVID19"[Title/Abstract] OR "covid 19"[Title/Abstract] OR "new coronavirus"[Title/Abstract] OR "novel coronavirus"[Title/Abstract] OR "novel corona virus"[Title/Abstract] OR "sars cov 2"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "severe acute respiratory syndrome coronavirus 2"[Title/Abstract]	298 019
Type of Technology	"molecular"[Title/Abstract] OR "isothermal"[Title/Abstract] OR "PCR"[Title/Abstract] OR "polymerase chain reaction"[Title/Abstract] OR "LAMP"[Title/Abstract] OR "CRISPR" [Title/Abstract] OR "immunoassay"[Title/Abstract] OR "antigen"[Title/Abstract]	2 781 618
Intended Setting	"point of care"[All Fields] OR "POC"[All Fields] OR "near patient"[All Fields] OR "rapid test*"[All Fields] OR "bedside test*"[All Fields] OR "laboratory-independent"[All Fields] OR "point-of-care"[All Fields] OR "POCT"[All Fields] OR "portable"[All Fields]	83 363
Intended Use Case	"diagnos*"[Title/Abstract] OR "detect*"[Title/Abstract]	5 169 560
Search Term	("2019 nCoV"[Title/Abstract] OR "2019nCoV"[Title/Abstract] OR "2019 novel coronavirus"[Title/Abstract] OR "COVID-19"[Title/Abstract] OR "covid-19"[Title/Abstract] OR "COVID19"[Title/Abstract] OR "covid 19"[Title/Abstract] OR "new coronavirus"[Title/Abstract] OR "novel coronavirus"[Title/Abstract] OR "novel corona virus"[Title/Abstract] OR "sars cov 2"[Title/Abstract] OR " SARS-CoV-2 "[Title/Abstract] OR "severe acute respiratory syndrome coronavirus 2"[Title/Abstract]) AND ("molecular"[Title/Abstract] OR "isothermal"[Title/Abstract] OR "PCR"[Title/Abstract] OR "polymerase chain reaction"[Title/Abstract] OR "LAMP"[Title/Abstract] OR "immunoassay"[Title/Abstract] OR "antigen"[Title/Abstract]) AND ("point of care"[All Fields] OR "POC"[All Fields] OR "near patient"[All Fields] OR "rapid test*"[All Fields] OR "bedside test*"[All Fields] OR "laboratory-independent"[All Fields] OR "point-of-care"[All Fields] OR "POCT"[All Fields] OR "portable"[All Fields]) AND ("diagnos*"[Title/Abstract] OR "detect*"[Title/Abstract])	1646
medRxiv (searched on 23 Nov 2022)		Items Found
Condition of Interest	"2019 nCoV", "2019nCoV", "2019 novel coronavirus", "COVID-19", "covid-19","COVID19","covid 19", "new coronavirus", "novel coronavirus", "novel corona virus", "sars cov 2", "SARS-CoV-2", "severe acute respiratory syndrome coronavirus 2"	18 990
Type of Technology	"molecular", "isothermal", "PCR", "polymerase chain reaction", "LAMP", "immunoassay", "antigen", "CRISPR"	5547
Intended Setting	"point of care", "POC", "near patient", "rapid test*", "bedside test*", "laboratory-independent", "point-of-care", "POCT", "portable"	657
Intended Use Case	"diagnos","detect"	10 915
Search Term	"2019 nCoV" OR "2019nCoV" OR "2019 novel coronavirus" OR "COVID-19" OR "covid-19" OR "COVID19" OR "covid 19" OR "new coronavirus" OR "novel coronavirus" OR "novel corona virus" OR "sars cov 2" OR "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus 2") AND ("molecular" OR "isothermal" OR "PCR" OR "polymerase chain reaction" OR "LAMP" OR "immunoassay" OR "antigen" OR "CRISPR") AND ("point of care" OR "POC" OR "near patient" OR "rapid test*" OR "bedside test" OR "laboratory-independent" OR "point-of-care" OR "POCT" OR "portable") AND ("diagnos" OR "detect")	275
bioRxiv (searched on 23 Nov 2022)		Items Found
Condition of Interest	"2019 nCoV", "2019nCoV", "2019 novel coronavirus", "COVID-19", "covid-19","COVID19","covid 19", "new coronavirus", "novel coronavirus", "novel corona virus", "sars cov 2", "SARS-CoV-2", "severe acute respiratory syndrome coronavirus 2"	6498
Type of Technology	"molecular", "isothermal", "PCR", "polymerase chain reaction", "LAMP", "immunoassay", "antigen"	34 925
Intended Setting	"point of care", "POC", "near patient", "rapid test*", "bedside test*", "laboratory-independent", "point-of-care", "POCT", "portable"	652
Intended Use Case	"diagnos","detect"	25 150
Search Term	"2019 nCoV" OR "2019nCoV" OR "2019 novel coronavirus" OR "COVID-19" OR "covid-19" OR "COVID19" OR "covid 19" OR "new coronavirus" OR "novel coronavirus" OR "novel corona virus" OR "sars cov 2" OR "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus 2") AND ("molecular" OR "isothermal" OR "PCR" OR "polymerase chain reaction" OR "LAMP" OR "immunoassay" OR "antigen") AND ("point of care" OR "POC" OR "near patient" OR "rapid test*" OR "bedside test" OR "laboratory-independent" OR "point-of-care" OR "POCT" OR "portable") AND ("diagnos" OR "detect")	33

SARS-CoV-2 detection. No restrictions on language or date will be applied. Translations will be carried out using Google Translate or DeepL as necessary. We will exclude diagnostic tests that meet the following exclusion criteria:

- Conventional lateral flow assay without any innovative features for improved performance.
- Open system molecular assays.
- Tests that are currently in use for TB.

Information sources

We will search for peer-reviewed published scientific literature in PubMed/Medline and preprints in bioRxiv and MedRxiv. In addition, the following sources will be searched:

- US Food and Drug Administration Tables of In Vitro Diagnostics Emergency Use Authorisations https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas.

Table 2 Data extraction strategy

Developer description	Developer name, business type, website, country
Test description	Product name, technology type, technology description, primary use case, target population, technology readiness/maturity level, target end user, target setting
Operation characteristics	Sample type, number of manual sample processing steps, biomarker target, multiuse platform, throughput capacity, time-to-result, hands-on-time, ease of use, infrastructure requirements, operating temperature, operating humidity level, shelf life, connectivity, biosafety
Pricing	Estimated price range per test, estimated price range per instrument
Performance	Limit of detection, diagnostic sensitivity, diagnostic specificity
Commercialisation status	Current regulatory status

- EUDAMED—European Database on Medical Devices https://ec.europa.eu/tools/eudamed/#/screen/search-device.
- NMPA—China Medical Products Administration Database https://udi.nmpa.gov.cn/.
- MFDS—Republic of Korea's Ministry of Food and Drug Safety (MFDS) https://www.mfds.go.kr/eng/brd/m_41/list.do.
- MDALL—Health Canada Medical Devices Active Licence Listing https://health-products.canada.ca/mdall-limh/index-eng.jsp.
- CDSCO—Government of India, Central Drugs Standard Control Organisation https://cdsco.gov.in/opencms/opencms/en/Medical-Device-Diagnostics/InVitro-Diagnostics/.
- FIND, the Global Alliance for Diagnostics COVID-19 Test Directory https://www.finddx.org/COVID-19/test-directory/.
- Johns Hopkins Centre for Health Security Antigen and Molecular-based Tests Tracker https://www.centerforhealthsecurity.org/covid-19TestingToolkit/molecular-based-tests/current-molecular-and-antigen-tests.html.
- National Institutes of Health (NIH) Rapid Acceleration of Diagnostics (RADx) https://www.nih.gov/research-training/medical-research-initiatives/radx.

Search strategy

The search term used is shown in table 1. The search term will be adapted as necessary for the other databases. The medrxivr package in R (V.4.0.5; R Foundation for Statistical Computing) is used to search the bioRxiv and MedRxiv databases to overcome the limitations of the search functionality of these websites and allow for reproducibility.

Study records

All retrieved articles will be collated using the Covidence software and duplicates will be removed. The same software will be used for screening. Two reviewers will independently screen the titles and abstracts of the initial search results against the eligibility criteria. Following that, full-text screening will be performed by the same reviewers using standardised forms on Covidence. Any discrepancies that arise during the screening will be resolved through consensus or by a third reviewer.

Data collection process

Covidence will also be used for data extraction. Developer description, test description, operation characteristics, pricing information, performance and commercialisation status will be extracted based on the predefined variables (table 2). One reviewer will extract data from the selected reports, which will then be reviewed by a second reviewer. Any discrepancies will be resolved through consensus or by a third party. At this step, additional information sources, such as the developer's website or the developer contact person, will be reviewed for each test included in the review to acquire any missing or additional data on the test of interest.

Risk of bias in individual studies

Risk of bias in individual studies will not be assessed because this is a scoping review aiming to summarise diagnostic innovations developed for COVID-19 diagnosis that could potentially meet the WHO TPPs and be deployed in low- and middle-income countries (LMICs) for TB diagnosis.

Data synthesis

Given the scope of the study, only a narrative synthesis will be provided. Information will be presented in the text and tables to summarise and explain key characteristics of the tests included, in accordance with current recommendations for scoping reviews and evidence mapping.

Study status

The literature searches were run on 23 November 2022, as outlined above. The two reviewers are currently performing screening in line with the protocol. We plan to finalise the study by July 2023 for publication.

Strengths

Our study has several strengths. Our search strategy is based on a solid framework and will involve multiple sources of information. We hope to find technologies from a wide range of developers, from academics to start-ups to large-scale IVD diagnostic companies, by searching both literature and IVD medical device databases. Two reviewers will work independently on the screening process.

Limitations

There are several limitations to our study. First, we will not attempt to search literature databases like Web of Science or Embase, preferring to focus on late-stage products that can be quickly adapted to TB. Second, we limited our search in IVD medical device databases to those that were publicly available and thus limited to high-income countries. This raises the possibility of a narrow focus on technologies developed in LMICs. We will try to address this by looking through databases from FIND and John Hopkins, which any developer from anywhere in the world can submit to. Finally, the data will be extracted by a single reviewer, but the extracted data will be reviewed by a second reviewer.

ETHICS AND DISSEMINATION

This scoping review will not require ethical approval because it does not involve individual patient data and uses sources that are in the public domain. We intend to publish our findings in open access scientific journals.

Contributors SY developed the scoping review protocol. LM-LH, TB, CI, PN, AC and CD provided critical editing and review.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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