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Rapid molecular tests for tuberculosis and tuberculosis drug resistance: a qualitative evidence synthesis of recipient and provider views (Review)

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[Qualitative Review]

Rapid molecular tests for tuberculosis and tuberculosis drug resistance: a qualitative evidence synthesis of recipient and provider views

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ABSTRACT

Background

Programmes that introduce rapid molecular tests for tuberculosis and tuberculosis drug resistance aim to bring tests closer to the community, and thereby cut delay in diagnosis, ensure early treatment, and improve health outcomes, as well as overcome problems with poor laboratory infrastructure and inadequately trained personnel. Yet, diagnostic technologies only have an impact if they are put to use in a correct and timely manner. Views of the intended beneficiaries are important in uptake of diagnostics, and their effective use also depends on those implementing testing programmes, including providers, laboratory professionals, and staff in health ministries. Otherwise, there is a risk these technologies will not fit their intended use and setting, cannot be made to work and scale up, and are not used by, or not accessible to, those in need.

Objectives

To synthesize end-user and professional user perspectives and experiences with low-complexity nucleic acid amplification tests (NAATs) for detection of tuberculosis and tuberculosis drug resistance; and to identify implications for effective implementation and health equity.

Search methods

We searched MEDLINE, Embase, CINAHL, PsycInfo and Science Citation Index Expanded databases for eligible studies from 1 January 2007 up to 20 October 2021. We limited all searches to 2007 onward because the development of Xpert MTB/RIF, the first rapid molecular test in this review, was completed in 2009.

Selection criteria

We included studies that used qualitative methods for data collection and analysis, and were focused on perspectives and experiences of users and potential users of low-complexity NAATs to diagnose tuberculosis and drug-resistant tuberculosis. NAATs included Xpert MTB/RIF, Xpert MTB/RIF Ultra, Xpert MTB/XDR, and the Truenat assays. Users were people with presumptive or confirmed tuberculosis and

drug-resistant tuberculosis (including multidrug-resistant (MDR-TB)) and their caregivers, healthcare providers, laboratory technicians and managers, and programme officers and staff; and were from any type of health facility and setting globally. MDR-TB is tuberculosis caused by resistance to at least rifampicin and isoniazid, the two most effective first-line drugs used to treat tuberculosis.

Data collection and analysis

We used a thematic analysis approach for data extraction and synthesis, and assessed confidence in the findings using GRADE CERQual approach. We developed a conceptual framework to illustrate how the findings relate.

Main results

We found 32 studies. All studies were conducted in low- and middle-income countries. Twenty-seven studies were conducted in high-tuberculosis burden countries and 21 studies in high-MDR-TB burden countries. Only one study was from an Eastern European country. While the studies covered a diverse use of low-complexity NAATs, in only a minority of studies was it used as the initial diagnostic test for all people with presumptive tuberculosis.

We identified 18 review findings and grouped them into three overarching categories.

Critical aspects users value

People with tuberculosis valued reaching diagnostic closure with an accurate diagnosis, avoiding diagnostic delays, and keeping diagnostic-associated cost low. Similarly, healthcare providers valued aspects of accuracy and the resulting confidence in low-complexity NAAT results, rapid turnaround times, and keeping cost to people seeking a diagnosis low. In addition, providers valued diversity of sample types (for example, gastric aspirate specimens and stool in children) and drug resistance information. Laboratory professionals appreciated the improved ease of use, ergonomics, and biosafety of low-complexity NAATs compared to sputum microscopy, and increased staff satisfaction.

Challenges reported to realizing those values

People with tuberculosis and healthcare workers were reluctant to test for tuberculosis (including MDR-TB) due to fears, stigma, or cost concerns. Thus, low-complexity NAAT testing is not implemented with sufficient support or discretion to overcome barriers that are common to other approaches to testing for tuberculosis. Delays were reported at many steps of the diagnostic pathway owing to poor sample quality; difficulties with transporting specimens; lack of sufficient resources; maintenance of low-complexity NAATs; increased workload; inefficient work and patient flows; over-reliance on low-complexity NAAT results in lieu of clinical judgement; and lack of data-driven and inclusive implementation processes. These challenges were reported to lead to underutilization.

Concerns for access and equity

The reported concerns included sustainable funding and maintenance and equitable use of resources to access low-complexity NAATs, as well as conflicts of interest between donors and people implementing the tests. Also, lengthy diagnostic delays, underutilization of low-complexity NAATs, lack of tuberculosis diagnostic facilities in the community, and too many eligibility restrictions hampered access to prompt and accurate testing and treatment. This was particularly the case for vulnerable groups, such as children, people with MDR-TB, or people with limited ability to pay.

We had high confidence in most of our findings.

Authors' conclusions

Low-complexity diagnostics have been presented as a solution to overcome deficiencies in laboratory infrastructure and lack of skilled professionals. This review indicates this is misleading. The lack of infrastructure and human resources undermine the added value new diagnostics of low complexity have for recipients and providers. We had high confidence in the evidence contributing to these review findings.

Implementation of new diagnostic technologies, like those considered in this review, will need to tackle the challenges identified in this review including weak infrastructure and systems, and insufficient data on ground level realities prior and during implementation, as well as problems of conflicts of interest in order to ensure equitable use of resources.

PLAIN LANGUAGE SUMMARY

Rapid molecular tests for tuberculosis and tuberculosis drug resistance: the views and experiences of people who are tested and healthcare providers

What is the aim of this review?

We aimed to understand the experiences and opinions of people using rapid automated tests that identify tuberculosis and resistance to tuberculosis drugs (molecular diagnostic tests). Users include people who might have tuberculosis and their families or caregivers, doctors, nurses, laboratory staff, and managers of services or programmes.

What was studied in this review?

Rapid molecular diagnostic tests were designed to make diagnosis easier and faster for people with signs and symptoms of tuberculosis, because they do not require a well-equipped laboratory, but can be done in clinics closer to where people live. Since these tests can also suggest whether an individual suffers from drug-resistant tuberculosis (including multidrug-resistant tuberculosis (MDR-TB)), the right treatment can be started earlier. We collected and analysed all relevant studies and found 32 studies conducted in areas where tuberculosis is common in low- and middle-income countries.

MDR-TB is tuberculosis caused by resistance to at least rifampicin and isoniazid, the two most effective first-line drugs used to treat tuberculosis.

This qualitative evidence synthesis links to another Cochrane Review that examines the diagnostic accuracy of a rapid molecular test for tuberculosis drug resistance. Yet, diagnostic tests only have an impact on health if they are put to use in a correct and timely manner. Accuracy studies do not reveal what users think of or how they experience the test in question. We need to understand the perspectives and experiences of all users. Otherwise, we risk these tests not fitting settings where they are to be used or not being accessible for those in need.

What are the main findings?

People with tuberculosis value knowing what is wrong with them. People valued having an accurate diagnosis, avoiding delays in being diagnosed, having accessible testing facilities, and keeping cost low. Similarly, healthcare providers value having accurate tests that give them confidence in the diagnosis, rapid results, and keeping cost low, being able to use different specimens (such as sputum and stool) and receiving information about drug resistance as part of the test results. Laboratory personnel appreciated that laboratory work was made easier and that staff was more satisfied thanks to rapid molecular diagnostic tests.

Our review also identified several challenges to realizing these values. Some people with tuberculosis and some healthcare providers were reluctant to use rapid molecular diagnostic tests because of fears of testing positive, concerns of stigma or discredit in the community, or expenses related to the testing. Additional support is required to overcome these barriers that are common to other approaches to testing for tuberculosis. Other challenges that led to delays and underuse of rapid molecular diagnostic tests were health system inefficiencies; poor quality of specimens; difficulty in transporting specimens; lack of sufficient resources such as staff or equipment; increased workload for providers; inefficiencies in integrating the test into routines at clinics; the complicated or lengthy steps involved in obtaining a tuberculosis diagnosis; clinicians relying too much on the test result while neglecting their own experience with diagnosing tuberculosis; and processes of implementing the test in national programmes that lacked data about real-life situations and did not include all relevant stakeholders such as local decision-makers, providers or people seeking a diagnosis.

Lastly, people expressed concerns about unsustainable funding, maintenance requirements of the tests, lengthy delays in diagnosis, underuse of rapid molecular diagnostic tests, lack of tuberculosis diagnostic facilities in local communities, conflicts of interest between donors and people who utilize the tests, and too many restrictions on who was allowed to access the test. These concerns hampered access to prompt and accurate testing and treatment. This was particularly the case for vulnerable people, such as children, people with MDR-TB, or those with limited ability to pay.

Overall, these challenges risk undoing the added value of rapid molecular diagnostic tests. They risk leading to less frequent use of these tests. Implementation of new diagnostic tests, like those considered in this review, will need to tackle the challenges identified in this review including weak infrastructure and systems, as well as insufficient data about real-life situations before and during implementation in order to ensure the tests are accessible for those in need.

How up to date is this review?

We included studies published between 1 January 2007 and 20 October 2021. We limited all searches to 2007 onward because the development of Xpert MTB/RIF, the first rapid molecular diagnostic test in this review, was completed in 2009.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of qualitative findings

Finding #	Review finding	CERQual assessment of confidence in the evidence	Explanation of CERQual assessment	Studies contributing to review finding
Critical aspects users value				
1	People with TB, the vast majority from high-TB burden countries, value: 1) getting an accurate diagnosis and reaching diagnostic closure (finally knowing what is wrong with me), 2) avoiding diagnostic delays as they exacerbate existing financial hardships and emotional and physical suffering and make patients feel guilty for infecting others (especially children), 3) having accessible facilities, and 4) reducing diagnosis-associated costs (travel, missing work) as important outcomes of the diagnostic.	Moderate confidence	We had minor concerns about methodological quality and adequacy and we had minor concerns about relevance (because of the mostly urban study locations).	De Camargo 2015; Joshi 2018; Medina-Morino 2021; Naidoo 2015; Phyo 2019; Raizada 2021; Royce 2014; Vijayageetha 2019
2	Compared to existing tests such as sputum microscopy, healthcare providers appreciate the rapidity and accuracy of low-complexity NAAT results, the diversity of sample types, ability to detect drug resistance, as well as the consequence of avoiding costlier investigations or hospital stays when using low-complexity NAATs.	High confidence	Mainly because we had no concerns about coherence and relevance and only minor concerns about methodological quality and richness of a few studies	De Camargo 2015; Joshi 2018; McDowell 2018; Mwaura 2020; Naidoo 2015; Newtonraj 2019; Rendell 2017; Vijayageetha 2019
3	Low-complexity NAATs allow healthcare providers to detect drug resistance earlier and paediatricians in particular mentioned how it heightened their perception of drug resistance in children; yet in a context with widespread severe forms of drug resistance and a habit of treating empirically first, clinicians see the inability of some NAATs to detect resistance beyond rifampicin as a hindrance.	High confidence	Mainly because quality of studies was high and we only had a minor concern about coherence due to number of studies contributing to each part of the finding	De Camargo 2015; Joshi 2018; McDowell 2016; McDowell 2018; Naidoo 2015
4	Clinicians value the confidence that low-complexity NAAT results provide. Having confidence helps in starting treatment, reassuring and motivating people with TB and their caregivers, justifying management decisions to other doctors, and increasing collaboration between private and public providers.	High confidence	We had no concerns or very minor concerns across all components.	McDowell 2018; Oliwa 2020; Raizada 2021
5	Laboratory technicians appreciate the improvement of overall laboratory work that low-complexity NAATs bring compared to sputum microscopy in terms of ease of use, ergonomics, and biosafety.	High confidence	We had no concerns or very minor concerns across all components.	Creswell 2014; De Camargo 2015; Newtonraj 2019

6	Laboratory managers appreciate that monitoring of laboratory work and training is easier than with sputum microscopy and that low-complexity NAATs ease staff retention, as these tests increase staff satisfaction and have a symbolic meaning of progress within the TB world.	Low confidence	We had serious or moderate concerns about adequacy and relevance and no concerns about methodological quality and coherence.	De Camargo 2015
Challenges to realizing these values				
7	People with presumptive TB can be reluctant to test for TB or MDR-TB because of stigma related to MDR-TB or related to having interrupted treatment in the past, because of fears of side effects, the failure to recognize symptoms, the inability to produce sputum and the cost, distance and travel concerns related to (repeat) clinic visits. Thus, low-complexity NAAT testing is not operationalized with sufficient support or discretion to overcome barriers that are common to other approaches to testing for TB.	High confidence	We had no concerns or very minor concerns across all components.	Ismail 2020; Medina-Morino 2021; Naidoo 2015; Phyo 2019; Royce 2014; Saria 2020; Shewade 2018
8	Healthcare workers can be reluctant to test for TB or MDR-TB because of TB-associated stigma and its consequences, fears of acquiring TB themselves, fear from supervisors when reclassifying people already on TB treatment who turn out to be misclassified, fear of adverse effects of drugs in children, and lack of community awareness of disease manifestations in children. Thus, low-complexity NAAT testing is not operationalized with sufficient support or discretion to overcome barriers that are common to other approaches to testing for TB.	High confidence	We had no concerns across all components.	Oliwa 2020; Royce 2014
9	Rapid turn-around time is an important potential of diagnostic algorithms involving NAATs of low complexity. Yet, diagnostic delays are accumulated because of various health system factors (i.e. non-adherence to testing algorithms, testing for (MDR-)TB late in the process, empirical treatment, false negatives due to technology failure, large sample volumes and staff shortages, poor or delayed sample transport and resulting delays in communication, delays in scheduling follow-up visits and recalls, inconsistent result recording) and, to a lesser extent, delays related to people seeking a diagnosis (i.e. missed follow-up appointments, competing family demands and seeking traditional healthcare).	High confidence	We had no or very minor concerns across the components, also because diagnostic delay was well established and the weaker studies' findings pointed to the same direction.	Cattamanchi 2020; Creswell 2014; Davids 2015; Engel 2015a; Ismail 2020; Ketema 2020; McDowell 2016; Mohammed 2020; Naidoo 2015; Nalugwa 2020; Nathavitharana 2017; Oo 2019; Rendell 2017; Royce 2014; Stime 2018
10	Challenges with sample quality, collection and transport can cause error results and underutilization of low-complexity NAATs. Specifically, providers struggle with poor sample quality, sample collection facilities that are inconveniently located for people seeking a diagnosis, non-functioning sample transport mechanisms	High confidence	Mainly because we had no concerns about coherence and relevance and only minor concerns about the methodological	Cattamanchi 2020; Creswell 2014; Davids 2015; Hoang 2015; Ketema 2020; McDowell 2016; McDowell 2018;

	that can damage samples or deter providers from ordering tests, and difficulty of obtaining paediatric samples.		quality of half the studies contributing and no concerns about the quality and richness of the remaining ones	Nathavitharana 2017; Newtonraj 2019; Oliwa 2020; Oo 2019; Phyo 2019; Raizada 2021; Rendell 2017; Royce 2014; Saria 2020; Shewade 2018; Vijayageetha 2019
11	The lack of sufficient resources to conduct low-complexity NAATs and of maintenance challenges (i.e. stock-outs; unreliable logistics; lack of funding, electricity, space, air conditioners, and sputum containers; dusty environment, and delayed or absent local repair option) lead to higher test failure rates and underutilization of low-complexity NAATs.	High confidence	Mainly because we had no concerns about coherence and relevance and only minor concerns about methodological quality and richness of about half the studies	Creswell 2014; De Camargo 2015; England 2019; Hoang 2015; Joshi 2018; Mohammed 2020; Mwaura 2020; Nalugwa 2020; Nathavitharana 2017; Oliwa 2020; Rendell 2017; Shewade 2018; Stime 2018
12	Low-complexity NAATs may be promoted as decreasing workload by freeing up time for laboratory staff, but in most settings staff may be hesitant to accept testing with low-complexity NAATs because it increases workload if added onto existing laboratory work without adjusting staffing arrangements, or if it does not replace existing diagnostic tests.	Moderate confidence	Mainly because of the minor concern with coherence where only one study contributed to the point on acceptance	De Camargo 2015; Joshi 2018; Oo 2019; Phyo 2019; Rendell 2017; Shewade 2018; Stime 2018; Vijayageetha 2019
13	Workflows, professional roles, and the flow of people seeking care matter for utilizing low-complexity NAATs, for instance, inefficient organizational processes, poor links between providers, unclear follow-up mechanisms or where people need to go for testing can deter utilization.	High confidence	No concerns about methodological quality, coherence and relevance, we only had minor concerns about the degree of richness.	De Camargo 2015; Hoang 2015; Mnyambwa 2018; Oliwa 2020; Royce 2014; Saria 2020; Stime 2018
14	Too much confidence in low-complexity NAATs' accuracy can mean blindly accepting results without using clinical impressions or, for people with presumptive TB, trusting a low-complexity NAATs result because it is computer-based.	Moderate confidence	Mainly because of the moderate concerns with methodological quality and richness of data	Joshi 2018; Mwaura 2020; Newtonraj 2019
15	Insufficient attention to responsive and inclusive implementation processes can hamper the impact of low-complexity NAATs. Specifically, implementation processes have been challenged by lack of data from pragmatic studies addressing effectiveness in operational conditions, lack of knowledge and awareness among providers beyond laboratory personnel, lack of guidelines and standardized training modules and instructions, and a lack of national policy consensus and inclusive decision-making prior to roll out.	High confidence	Mainly because we had no concerns about coherence and relevance and only minor concerns about methodological quality and richness of about half the studies and the thin studies did not challenge the re-	Colvin 2015; Creswell 2014; Davids 2015; De Camargo 2015; England 2019; Hoang 2015; Joshi 2018; Mnyambwa 2018; Naidoo 2015; Newtonraj 2019; Oo 2019; Rendell 2017; Shewade 2018

			view finding but confirmed it	
Concerns for access and equity				
16	Uncertainty around sustainability of funding and maintenance and the strategic and inequitable use of resources negatively affects creating equitable access to low-complexity NAATs.	High confidence	We had no concerns except minor concerns about coherence because part of the finding relied on only one study.	Colvin 2015; Creswell 2014; De Camargo 2015; England 2019; Jaroslawski 2012; Nathavitharana 2017
17	Access to prompt and accurate testing and treatment is hampered, particularly for the vulnerable groups, by the challenges outlined above for realizing recipient and provider values.	High confidence	We had only very minor concerns about methodological quality and richness of half the studies.	Engel 2015a; England 2019; Hoang 2015; Joshi 2018; McDowell 2016; McDowell 2018; Naidoo 2015; Nalugwa 2020; Newtonraj 2019; Oliwa 2020; Oo 2019; Phyo 2019; Royce 2014
18	Test users described how implementation challenges lead to accumulated delays that undo the improvements they value in these new tests, and so discourage test use and reduce access and equity.	High confidence	No concerns	Engel 2015a; McDowell 2018; Naidoo 2015; Shewade 2018; review finding #1-15

Abbreviations: CERQual: Confidence in the Evidence from Reviews of Qualitative Research; MDR-TB: multidrug-resistant tuberculosis; NAAT: nucleic acid amplification test; TB: tuberculosis

BACKGROUND

Description of the topic

Tuberculosis is one of the top causes of death worldwide and the second leading cause of infectious disease-related death after COVID-19 (WHO Global Tuberculosis Report 2021). In 2020, an estimated 10 million people became ill with tuberculosis and 1.5 million people died from tuberculosis, including 214,000 people with HIV (WHO Global Tuberculosis Report 2021). Drug-resistant tuberculosis is also a major concern. In 2019, there were around 500,000 new cases of rifampicin-resistant tuberculosis, of which 78% had multidrug-resistant tuberculosis (MDR-TB, tuberculosis that is resistant to at least rifampicin and isoniazid, the two most effective first-line drugs used to treat tuberculosis) (WHO Global Tuberculosis Report 2020).

Tuberculosis is an airborne infection caused by the bacterium *Mycobacterium tuberculosis* (*M tuberculosis*). Although pulmonary tuberculosis (infection in the lungs) is the most common form of the disease, tuberculosis can affect almost any other site in the body (extrapulmonary tuberculosis). Signs and symptoms of pulmonary tuberculosis include cough, fever, chills, night sweats, weight loss, haemoptysis (coughing up blood), and fatigue. Signs and symptoms of extrapulmonary tuberculosis depend on the site of disease (Nathavitharana 2021).

When tuberculosis is detected early and effectively treated, the disease is largely curable. The World Health Organization (WHO) estimates that, from 2000 to 2019, more than 60 million lives were saved by diagnosing and treating tuberculosis. However, tuberculosis care is too often low-quality care. In fact, a landmark report estimated that of the more than 900,000 tuberculosis deaths amenable to healthcare, 50% were due to poor quality of health services and 50% due to underutilization (Kruk 2018; Pai 2019). In trying to obtain tuberculosis care, people struggle with long and complex pathways, characterized by initial contacts with private providers, lack of primary care services, and poor quality of care in both public and private sectors (Daniels 2019; Hanson 2017; Yellapa 2017), as well as stigma and discrimination (Macyntire 2017). What is more, COVID-19 is reversing years of progress in responding to tuberculosis and, for the first time in over a decade, annual deaths from tuberculosis have increased (WHO Global Tuberculosis Report 2021). Ending the global tuberculosis epidemic will be achievable over the next 20 years only if there is intensive action by all countries that have endorsed the End TB Strategy and its ambitious targets (WHO End TB 2015) and if there is access to *quality* diagnosis, treatment, and care. High-quality care for tuberculosis includes access to affordable diagnostic tools (United Nations General Assembly 2018).

The WHO End TB Strategy recommends early diagnosis of tuberculosis by a WHO-recommended rapid diagnostic test and drug susceptibility testing (DST, testing to determine the drugs that the tuberculosis bacteria are susceptible to) be available to all people with signs and symptoms of tuberculosis. Yet, in many countries, tuberculosis diagnosis is a crucial problem with around four million people going undiagnosed in 2020, up from three million in 2019 (WHO Global Tuberculosis Report 2021). Reasons include long delays in diagnosing and initiating treatment (Sreeramareddy 2009; Sreeramareddy 2014) and poor diagnostic management of people presenting with symptoms (Daniels 2019). In the latter situation, providers do not implement best practices they report to know but attune care to an individual's perceived needs (e.g. use low-cost pharmaceuticals as diagnostic tools and place symptom relief above diagnostic certainty) (McDowell 2016). As a result, people with presumptive tuberculosis opt out of complex and frustrating diagnostic journeys and the presence or absence of diagnostic technologies at point-of-care does not always imply their expected use in care (Engel 2015c; Yellapa 2017). Presumptive tuberculosis refers to an individual who presents with symptoms or signs suggestive of tuberculosis (WHO Definitions and Reporting 2020). In high-burden tuberculosis settings, clinicians may initiate tuberculosis treatment based on clinical criteria or chest radiography, rather than microbiological tests, raising questions about the benefit of new diagnostics for tuberculosis (Theron 2014).

The introduction of new and repurposed drugs (bedaquiline, clofazimine, linezolid, pretomanid, delamanid) has revolutionized tuberculosis treatment regimens, dispensing with the need for injectable drugs and promising to deliver shorter all-oral regimens in combination with fluoroquinolones (WHO Consolidated Guidelines (Module 4) 2020). To promote the uptake of these new regimens, including new shortened regimens for drug-susceptible tuberculosis, rapid DST is required which can also minimize delays in starting appropriate treatment (WHO Consolidated guidelines (Module 3) update 2021).

DST can be done using culture-based and molecular methods (tests based on detection of genetic material). Culture involves growing bacteria on nutrient-rich media. Culture is essential for species identification. However, culture takes several weeks for a result, requires a highly-equipped laboratory, has reduced sensitivity in paucibacillary disease (tuberculosis disease caused by a small number of bacteria), as may be seen in people with extrapulmonary tuberculosis (Kohli 2021), children (Kay 2020) and people living with HIV (Bjerrum 2019). Recently, the diagnosis of tuberculosis and drug-resistant forms has seen important innovations. One of these has been the introduction of low-complexity automated nucleic acid amplification tests (NAATs) designed to work outside well-equipped, often centralized, laboratories that are difficult to access for most people. NAATs, also referred to as molecular DST, are described in detail below. Low-complexity NAATs are tests that provide rapid DST and are the topic of interest of this review. Low-complexity NAATs are one of three new NAAT classes recommended by the WHO and included in their updated guidelines (WHO Consolidated guidelines (Module 3) update 2021).

NAATs are molecular systems that can detect small quantities of genetic material (DNA or ribonucleic acid) from micro-organisms, such as *M tuberculosis*, by amplifying the quantities to an amount large enough for studying in detail. Several molecular amplification methods are available, of which polymerase chain reaction (PCR) is the most common. This review focuses on low-complexity NAATs. Low complexity refers to a situation where no special infrastructure is required and basic laboratory skills are suitable to run the test. However, equipment may still be required. For example, Xpert MTB/XDR is a low-complexity test where almost all processes (such as DNA extraction and PCR procedures) are performed within the container linked to the diagnostic platform. The automation makes this test easier to use and reduces turnaround times. A presumed key advantage of NAATs is that they are rapid diagnostic tests, potentially providing results in a few hours. This is particularly promising for tuberculosis,

where diagnostic and treatment delays are often substantial (Sreeramareddy 2014).

Diagnostic devices only have an impact if they are put to use in a correct and timely manner. The users of diagnostics include people with tuberculosis and their contacts, clinic staff, laboratory managers, tuberculosis programme officers and staff. The user, in this understanding, is a relational term that describes the relation some people have to an object, service, or technology (Hyysalo 2015). We further differentiate people receiving and providing diagnostics, or between end-users and professional users (Shah 2009). In the case of low-complexity NAATs for tuberculosis and drug-resistant forms of tuberculosis, the end-users involve people with tuberculosis and contacts of a person with infectious tuberculosis who seek care, produce a sample (such as sputum), and return for results; professional users involve healthcare workers who order, run the diagnostic test, and act on the result, healthcare workers and technicians or suppliers who order stock and maintain the machines, but also programme officers who deploy and monitor these devices. The work of these diverse end-users and professional users matters in ensuring functioning and utilization and, therefore, the impact the diagnostic can have. In particular, the work of people involved in acquiring a diagnosis and following through diagnostic and treatment journeys is considerable and largely remains invisible in policy discussions. One study, in India, showed how people need to continuously make sense of illnesses and diagnosis, overcome cost and distance, produce and transport samples, collect and return results to providers, negotiate social relations, and deal with the social consequences of diagnosis. If diagnostics are inaccessible or poorly implemented and results, for instance, delayed or unavailable, this work can become too costly or harmful, and people seeking care opt out (Yellapa 2017). What is more, diagnostics can also harm relationships between patients and their providers when a test's rapidity and ease of use allows providers to circumvent counselling, explanations, or approval for testing. Conversely, rapid diagnostics can support these relationships and instil trust into the healthcare system, when testing at the doorstep supports community health workers in convincing people to come to the public clinics. Yet, if done inconsistently, the same test can damage these relationships (Engel 2015b). Therefore, it is essential to understand the perspectives and experiences of all these users with low-complexity NAATs to inform policy, funding, research, and development.

How this review might inform or supplement what is already known in this area

Current WHO guidance on low-complexity NAATs for tuberculosis diagnosis is based on systematic reviews of diagnostic accuracy and cost-effectiveness (WHO Consolidated guidelines (Module 3) update 2021). Qualitative evidence on user perspectives has only recently been commissioned as stand-alone primary studies for specific technologies to inform WHO guidance (WHO Consolidated guidelines (Module 3) update 2021; WHO Evidence Synthesis 2020), but has never been systematically reviewed for a group of technologies.

We know from earlier research on diagnostics in use that diagnostics that are cheaper, faster, or involve fewer user steps are not always used (as envisioned or at all) or automatically fit into user settings or cut diagnostic delay as desired (Albert 2016; Angotti 2010; Beisel 2016; Engel 2015b; Engel 2015c; Engel 2017). What is more, the very strategies that healthcare workers apply to deal with diagnostic delays can create new problems, such as artificially prolonged turnaround times, further strains on human resources, and quality of testing. These problems then compound additional diagnostic and treatment delays (Engel 2015c).

Accuracy studies do not reveal what users think of or experience with the diagnostic in question. Yet to understand why and how diagnostics are utilized and how they impact on health equity, it is essential to answer questions around perspectives and experiences, including preferences and values, feasibility, and acceptability – considerations that our review findings provide.

How the intervention might work

The promise of low-complexity NAATs for tuberculosis and drug-resistant forms of tuberculosis is that they can be administered closer to where people with tuberculosis are, in more peripheral settings of the community. The hope is that this would cut diagnostic delay and provide a more accurate diagnosis of tuberculosis and tuberculosis drug resistance, which has important implications for health outcomes (Bainomugisa 2020; Pooran 2019). Quantitative studies on the impact of low-complexity NAATs have measured health outcomes that are important to people such as more rapid tuberculosis diagnosis and treatment initiation, reduced mortality, and improved treatment outcomes (Schumacher 2016). As mentioned, low complexity refers to a situation where no special infrastructure is required and basic laboratory skills are suitable to run the test. However, equipment may still be required. While there is, for instance, no clear statistical evidence of a significant effect of Xpert MTB/RIF, an example of a low-complexity NAAT, on all-cause mortality (Di Tanna 2019; Haraka 2021), it has been shown that Xpert MTB/RIF can increase the number of people with a bacteriologically confirmed diagnosis, reduce time to treatment initiation, and decrease the number of people who are lost to follow-up (Stevens 2017). Yet, early detection of tuberculosis and rifampicin resistance may not lead to improved health outcomes if the test result is not linked to appropriate treatment and other quality healthcare services (Pai 2018).

Our review does not consider the accuracy of low-complexity NAATs or their quantifiable impact on people-important outcomes. Rather, we are concerned with the perspectives and experiences of end-users and professional users in dealing with these technologies in their health-seeking practices, daily work, and routines. For end-users (i.e. people with presumptive or confirmed tuberculosis or drug-resistant tuberculosis and their contacts or families), the intervention could be beneficial in terms of the convenience of more immediate test results, easier access to drug resistance testing, an altered diagnostic journey, or a reduced period of anxiety while waiting for results. For professional users such as healthcare providers, the intervention could be beneficial in terms of enabling better-informed treatment decisions, altered workload and procedures due to more automation, and freeing up time in central laboratories. Such a technology-in-practice perspective recognizes that the result of medical practice is always a combination of very different elements including bodies, samples, equipment, materials, clinic organizations, professionals, people receiving healthcare services, conversations, etc. (Timmermans 2003). Studying user perspectives and technology in use is essential to understand aspects of feasibility, uptake, and integration into and linkages to existing services and care and the wider implications for access and health equity.

Why is it important to do this review?

If we do not take the perspective of all users, professional and end-users, into consideration, we risk that these technologies do not fit their intended use and setting, cannot be made to work and scale up, and are not utilized or not accessible for those in need. Users' experiences and perspectives on new diagnostics relate to their preferences and values, and have implications for acceptability and feasibility, all of which are important considerations during decision-making on new diagnostics and guideline development.

Challenges with implementation and underutilization

The United Nations Sustainable Development Goals (SDGs) represent a collective plan to end poverty, decrease inequality, and protect the planet from degradation by 2030 (United Nations Sustainable Development Goals 2030). Ending the tuberculosis epidemic by 2030 is among the health-related targets described in the sustainable development goals (WHO End TB 2015). Low-complexity NAATs for drug-resistant tuberculosis have had an immense influence on tuberculosis policy and care in high-burden settings, but there are persistent concerns about underutilization and sustainability around NAATs for decentralized testing in low-resource settings (Albert 2016; Cazabon 2017; England 2019). These concerns include high cost and slow policy uptake (among 24 surveyed high-burden countries only eight had revised their national guidelines to include Xpert MTB/RIF as the initial test for people with presumptive tuberculosis, replacing smear microscopy (England 2019)), as well as weak health systems that blunt the impact (Albert 2016), poor sensitization of clinical staff, high laboratory staff turnover, cost inflation during distribution and shipping processes, insufficient service and maintenance provision, and over-reliance on donor funding (England 2019). This review contributes to reaching SDGs by ensuring that the perspectives and experiences of end-users (survivors, people with tuberculosis, and their contacts) and professional users (healthcare workers, laboratory technicians, suppliers, and programme officers), including their preferences and values, and considerations of the feasibility, acceptability, and equity of low-complexity NAATs, are being considered systematically and inform WHO decision-making on these diagnostics.

Alignment with World Health Organization priorities

This qualitative review complements a Cochrane diagnostic test accuracy review in progress, 'Xpert MTB/XDR for detection of pulmonary tuberculosis and resistance to isoniazid, fluoroquinolones, ethionamide, and amikacin' (Pillay 2021). These reviews informed the WHO Guideline Development Group Meeting on 'Nucleic acid amplification tests to detect tuberculosis and drug-resistant tuberculosis' on 7 to 18 December 2020.

A qualitative evidence synthesis adds value by providing decision-makers with additional evidence to improve understanding of intervention complexity, contextual variations, implementation, and stakeholder preferences and experiences. Specifically, it generates data for the following decision-making domains as part of the GRADE approach: patient values, feasibility, equity, acceptability, and balance of effects (Lewin 2019).

OBJECTIVES

To synthesize end-user and professional-user perspectives and experiences with low-complexity nucleic acid amplification tests (NAATs) for detection of tuberculosis and tuberculosis drug resistance.

Review question

What are the perspectives and experiences of people receiving and providing low-complexity NAATs to diagnose tuberculosis and tuberculosis drug resistance?

We explored the implications of our findings on effective implementation and health equity.

METHODS

Criteria for considering studies for this review

Types of studies

We included primary studies that used qualitative study designs such as ethnography, phenomenology, case studies, grounded theory studies, and qualitative process evaluations. We included studies that used both qualitative methods for data collection (e.g. focus group discussions, individual interviews, observation, diaries, document analysis, open-ended survey questions) and qualitative methods for data analysis (e.g. thematic analysis, framework analysis, grounded theory, narrative analysis). We excluded studies that collected data using qualitative methods but did not analyse these data using qualitative analysis methods (e.g. open-ended survey questions where the response data were analysed using descriptive statistics only) because such studies rarely offer the conceptual or contextual detail for understanding the complexities of interventions and their implementation, how these vary with context, or users' perspectives or experiences (Noyes 2021).

We included mixed methods studies where it was possible to extract the data that were collected and analysed using qualitative methods.

We included both published and unpublished studies and studies published in any language (see also section on 'Translation of languages other than English' below).

We included studies regardless of whether they were conducted alongside studies of the diagnostic accuracy of NAATs for tuberculosis and drug-resistant forms of tuberculosis (Cochrane Diagnostic Test Accuracy Review in progress, see Pillay 2021) or independently.

We did not exclude studies based on our assessment of methodological limitations. We used this information about methodological limitations to assess our confidence in the review findings.

Topic of interest

Any qualitative study related to the application of low-complexity NAATs for tuberculosis and tuberculosis drug resistance, including, for instance, pathways from diagnosis to treatment including low-complexity NAATs, intervention studies, operational research, feasibility, and acceptability assessments.

Participants

This review focuses on users and potential users of low-complexity NAATs. Users include people with presumptive or confirmed tuberculosis or drug-resistant tuberculosis, including MDR-TB, and their caregivers, laboratory technicians, healthcare providers, and tuberculosis programme officers and staff who are involved in diagnosing and treating tuberculosis and drug-resistant forms of tuberculosis as well as ordering, operating, maintaining diagnostics, and acting on diagnostic test results. Presumptive tuberculosis refers to an individual who presents with symptoms or signs suggestive of tuberculosis (WHO Definitions and Reporting 2020). Potential users include users who do not (yet) utilize the diagnostic, for instance, because they are unable to access it or make it work within their routines or setting.

Setting

We included studies on low-complexity NAATs located in any country, including low-, middle-, and high-income countries and located in any setting, including centralized, often well-equipped laboratories and more peripheral locations at district or subdistrict level in a health system and any type of health facility (hospital, peripheral laboratory, clinic, community health centre, or mobile testing vehicle).

Intervention

Diagnostic testing that involves low-complexity NAATs, for example, but not limited to the Xpert assays (Xpert MTB/RIF, Xpert MTB/RIF Ultra, Xpert MTB/XDR, Cepheid, Sunnyvale, USA), and the Truenat assays (Truenat MTB and MTB Plus, and Truenat MTB-RIF Dx assay, Molbio Diagnostics, Goa, India). Using as an example Xpert MTB/XDR, the test would be administered as follows. An individual would be asked to provide a sputum specimen into a container, which would be transported to the laboratory. In the laboratory, the technician would perform an initial manual treatment step, by adding the test's sample reagent to the specimen in the container. This initial step, which takes about 15 minutes, helps to homogenize (blend) the specimen and prepare (sterilize) it for testing in the automated cartridge. Then, the prepared sample would be added to the cartridge and the cartridge inserted into the test platform, which is usually located in the laboratory space. All other steps are performed automatically within the cartridge. Results are reported electronically by the instrument within two hours.

Search methods for identification of studies

We developed the search strategy in collaboration with the Cochrane Infectious Diseases Group (CIDG) Information Specialist. We also consulted the Cochrane Effective Practice and Organisation of Care (EPOC) Information Specialist before developing the strategy. We attempted to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and in progress). We included relevant conference abstracts in the search strategy. We used abstracts to identify published studies and included the full publications when they met our inclusion criteria.

Electronic searches

We searched the following databases from 1 January 2007 to 20 October 2021, using the search terms and strategy described in Appendix 1:

- MEDLINE (Ovid);
- Embase (Ovid);
- CINAHL (EBSCOHost; Cumulative Index to Nursing and Allied Health Literature);
- PsycInfo (EBSCOHost);
- Web of Science Core Collection .

We limited all searches to 2007 onward because the development of Xpert MTB/RIF, the first rapid molecular test in this review, was completed in 2009 and the first paper describing its clinical use was published electronically in 2009 (Helb 2010).

Searching other resources

We contacted researchers within our personal networks for any additional eligible studies. We checked the references of relevant reviews and studies to identify additional studies.

Grey literature

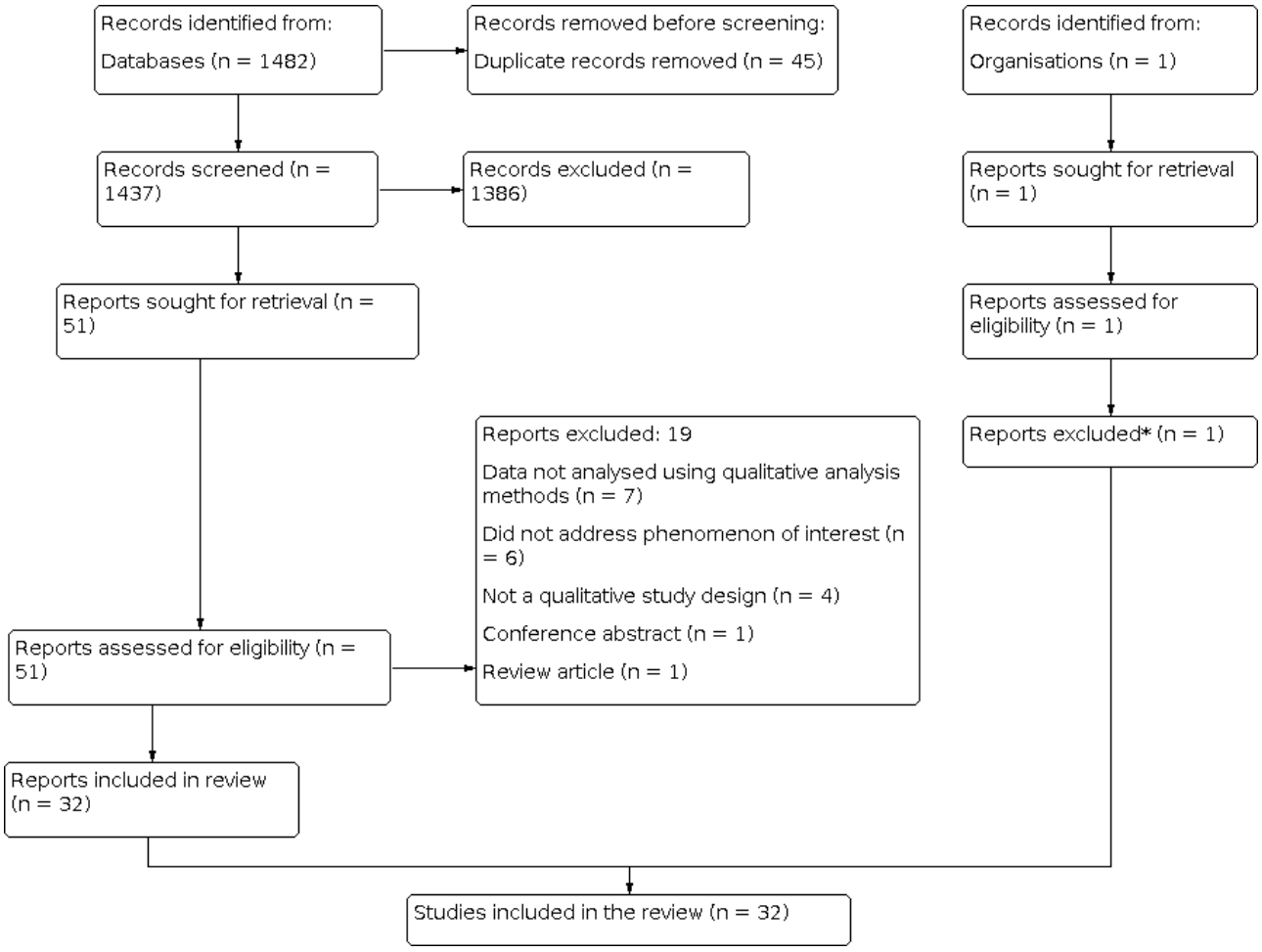
Owing to time and resource constraints, we did not conduct an extensive grey literature search. We asked investigators within our personal networks for unpublished reports of implementing partners and technical agencies.

We used available reports by advocates or implementing partners to inform the background section and discussion.

Selection of studies

We used Covidence to manage the selection of studies (Covidence). Two review authors independently and in parallel scrutinized all titles and abstracts identified from literature searching to identify potentially eligible studies. We retrieved the full text of any citation considered by one of the review authors as potentially eligible. Then, two review authors independently and in parallel assessed full-text articles for inclusion using predefined inclusion and exclusion criteria. For the full-text screening steps, we resolved disagreements by discussion or, if necessary, with a third review author. We recorded all studies excluded after full-text assessment and their reasons for exclusion in Characteristics of excluded studies. We illustrated the study selection process in a PRISMA diagram, Figure 1 (Page 2021).

Figure 1. PRISMA flow diagram * Not a qualitative study design



Language translation

We included primary studies irrespective of their language of publication. For titles and abstracts that were published in a language that none of the review team were fluent in (i.e. languages other than English, French, German, Russian, Dutch, and Spanish), we planned to conduct an initial translation through open source software (Google Translate). If this translation indicated inclusion, or if the translation was inadequate to make a decision, we would retrieve the full text of the paper. Any studies included in full text written in a language not spoken by a review team member would be listed in an appendix but not analysed due to the difficulty of translating qualitative data. We did not identify any included studies in a language other than English.

Sampling of studies

This qualitative evidence synthesis aims to describe the experiences of people using low-complexity NAATs for tuberculosis in a coherent way. Once we identified all studies that were eligible for inclusion, we assessed whether the number of studies or data richness were likely to represent a problem for the analysis. Because we found a rather large number of studies that met our inclusion criteria (32), we purposefully selected a sample of eligible studies with rich data. To do so, we first categorized the eligible studies into rich and thin studies depending on the depth of the analysis undertaken. A rich study is one in which the author: 1) analyses their findings beyond a descriptive list of barriers/facilitators, 2) demonstrates insights into participants perspectives and experiences, 3) portrays richness and complexity of the data (i.e. explains variation and illustrates meanings), and 4) develops or contributes to theory (this approach has been used in Rohwer 2021). Accordingly, a thin study is one which does not demonstrate any of these points and a study of medium richness is one which meets one or two but not all of these criteria. This generated six studies with very rich data, and eight studies with very thin data. The remaining 18 studies had data of medium richness. The six studies sampled for high degree of richness were located in South Africa, India, Brazil and Kenya, focused on urban clinics and hospitals and covered a diverse range of public and private health care providers, policymakers, as well as adults and children with presumptive tuberculosis or MDR-TB. The 15 studies in the medium richness group addressed additional study settings and experiences with the intervention that were not covered by the initial six. After data extraction and analysis of the rich and medium rich studies, one review author scrutinized the studies with thin data for additional or contradictory insights and added them to the analysis.

Data extraction

Five review authors (EO, NE, BS, PWK, RJ) extracted the following data from eligible studies.

- Descriptive study-related information: study author, year of publication, language, study location (country, rural/urban, public/private, type of facilities), background prevalence of MDR-tuberculosis.
- Study objectives and rationale, method of data collection, method of data analysis, conceptual framework if used, how the study was conceived (independence of those designing, implementing, or evaluating the intervention).
- Intervention-related information: type of (potential) user involved (e.g. people thought to have tuberculosis or drug-resistant tuberculosis, clinicians, nurses, laboratory staff, tuberculosis programme officers and staff); diagnostic tools used; programmatic features of the intervention (e.g. testing model/algorithm/programme in which the diagnostic was used, including the target population, setting, and eligibility criteria; envisioned role of the cartridge-based diagnostic (e.g. replacement, add-on); sample transport; and result communication).
- Key study findings were extracted in narrative form in Microsoft Word, for instance, qualitative themes/categories/findings/supporting quotations and conclusions, the type and rate of use emerging from the study findings (e.g. batching, number of tests run on average, underutilization). Among the key study findings, we also extracted data (if available) on the following factors that, based on our prior research experience, we expected to be important to user experiences: added value to the particular user, workflow, resources involved in implementing it, confidence in test results, implementation process, and access/equity.

Two review authors extracted data independently. They resolved any conflicts in a consensus meeting. To ensure coherence in data extraction, one review author (NE) extracted every study except where she was involved as study author. Authors of primary studies did not extract data from their own study or studies. Instead, another review author extracted these data.

Assessing the methodological limitations of included studies

Two review authors (any pair from NE, BS, PWK, EO) independently assessed methodological limitations for each study using the EPPI-Centre tool (Evidence for Policy and Practice Information and Co-ordinating Centre; Rees 2014). This started with two studies, after which review authors discussed their data extraction, considered any differences in interpretation and, if necessary, added prompts to the tool to clarify how data should be extracted from subsequent studies. We resolved disagreements by discussion or, when required, by involving a third review author (SO, KRS). Team members who were also authors of included studies did not assess the methodological limitations of their own studies. We assessed methodological limitations according to the following domains.

Rigour in sampling:

- the sampling strategy was appropriate to the questions posed in the study (e.g. was the strategy well reasoned and justified?);
- attempts were made to obtain a diverse sample of the population in question (considering who might have been excluded, who may have had a different perspective to offer);
- characteristics of the sample critical to the understanding of the study context and findings were presented (i.e. do we know who the participants were in terms of, for example, basic sociodemographics, characteristics relevant to the context of the study, etc.).

Rigour in data collection:

- data collection tools were piloted or validated or both (if quantitative);
- (if qualitative) data collection was comprehensive, flexible, sensitive enough (or a combination of these) to provide a complete or vivid and rich description (or both) of people's perspectives and experiences (e.g. did the researchers spend sufficient time at the site or with participants, or both? Did they keep 'following up'? Was more than one method of data collection used?);
- steps were taken to ensure that all participants were able and willing to contribute (e.g. processes for consent, language barriers, power relations between adults and children/young people).

Rigour in data analysis:

- data analysis methods were systematic (e.g. was a method described/could a method be discerned?);
- diversity in perspective was explored;
- (if qualitative) the analysis was balanced in the extent to which it was guided by preconceptions or by the data;
- the analysis sought to rule out alternative explanations for findings (in qualitative research, this could be done by, for example, searching for negative cases/exceptions, feeding back preliminary results to participants, asking a colleague to review the data, or reflexivity; in quantitative research, this may be done by, for example, significance testing).

Extent to which findings are grounded in/supported by the data:

- enough data were presented to show how the authors arrived at their findings;
- the data presented fitted the interpretation/support claims about patterns in data;
- the data presented illuminated/illustrated the findings;
- (for qualitative studies) quotes were numbered or otherwise identified and the reader could see that they did not just come from one or two people.

Breadth and depth of findings: consider whether (note: it may be helpful to consider 'breadth' as the extent of description and 'depth' as the extent to which data have been transformed/analysed):

- a range of issues were covered;
- the perspectives of participants were fully explored in terms of breadth (contrast of two or more perspectives) and depth (insight into a single perspective);
- richness and complexity have been portrayed (e.g. variation explained, meanings illuminated);

- there has been theoretical/conceptual development.

We reported our assessments in a 'Methodological limitations' table, Table 1. We also assessed if ethical clearance was sought. We based our work on the principle of justice having a value of doing good, in particular, listening to those commonly unheard, alongside the other value of avoiding harm (Takala 2019), which is cited more often by ethics reviewers. In cases where ethical clearance was not sought, excluding the data from a systematic review compounds the injury to participants who have given their time to the research. We paid additional attention to ensuring that participants could not be recognized by readers.

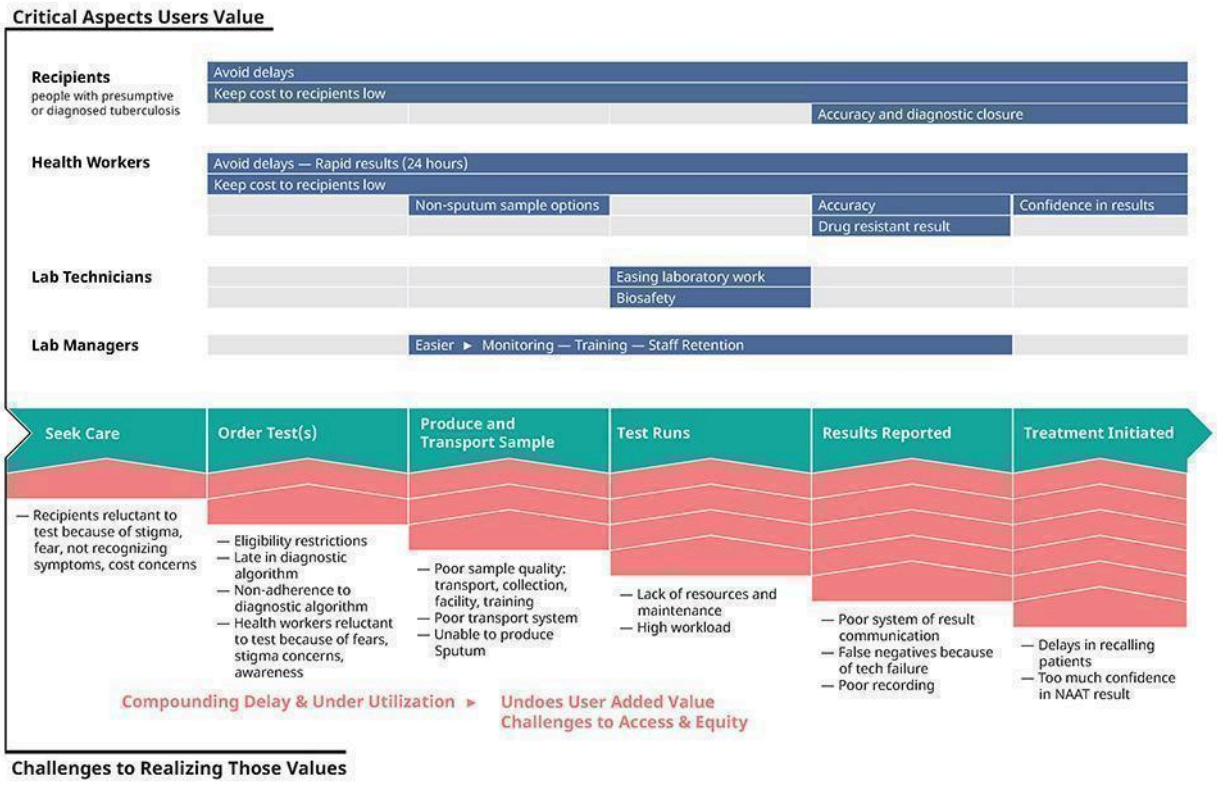
Data management, analysis, and synthesis

We used a thematic approach to guide data analysis (Braun 2006; Thomas 2008). We synthesized qualitative research to better understand views and experiences with the intervention in the context of use. Our data extraction was informed by two theoretical frameworks. First, a theoretical framework for involving users in the development of new medical device technologies encouraged us to distinguish between professional and end-users (Shah 2009). We also adopted a technology-in-practice perspective (Timmermans 2003) which guided us to look not only for opinions and preferences of users but actual experiences and day-to-day practices of making diagnostics work. This approach helped us transform the conceptualization of the intervention from a technical innovation designed for rapid testing to a testing programme implemented within a complex health system linking laboratories to (peripheral) communities.

Based on the key findings extracted by four review authors (EO, NE, PWK, BS) from the initial set of six rich studies, one review author (NE), in close discussion with the other review authors, developed a coding scheme. Using the coding scheme and developing it further in an iterative manner, NE coded the extracted key study findings of the six studies with rich data using NVIVO (version 12) and wrote memos on selected codes, which were discussed with the other review authors. We wrote memos on codes that were deemed important during coding to answer the review question. Some memos combined several codes that turned out to have a lot of overlap. Memo-writing allowed moving from codes to themes through summarizing, looking for examples, reordering, sorting, and going back and forth between the coded material and the initial analysis (Rubin 2005). In a second round of analysis, data from the 18 studies of medium richness was extracted by NE, EO, PWK, and BS; and NE coded these summaries in the same way as the six rich studies. NE then added the emerging additional insights and data to the existing memos. In a next step, NE translated the themes from the memos into the 18 summary finding statements, which were revised and finalized after discussion with the other review authors. In a third round of analysis, the eight studies with thin data were scrutinized by NE for additional or contradictory insights and added to the review findings.

At this stage, we applied the stages of the diagnostic pathway to frame the emerging findings to understand testing programmes as a whole. When these findings were plotted visually against the diagnostic pathway, distinguishing findings related to professionals and end users, we recognized how key positive views and experiences could be clustered as ‘critical aspects that users value’, and key negative experiences could be clustered as ‘challenges to realizing those values’. Both positive and negative experiences were related to feasibility, acceptability, accessibility and equity considerations of low-complexity NAATs for tuberculosis and drug-resistant tuberculosis. This allowed the findings to be aligned with the GRADE framework to maximize the utility of the review for policymakers and people implementing these technologies (Figure 2).

Figure 2. Critical aspects users value and challenges to realizing those values



Assessing our confidence in the review findings

Two review authors (NE, EO in consultation with BS) used the GRADE-CERQual (Confidence in the Evidence from Reviews of Qualitative research) approach to assess our confidence in each finding (Lewin 2018a). CERQual assesses confidence in the evidence, based on the following four key components.

- Methodological limitations of included studies: the extent to which there are concerns about the design or conduct of the primary studies that contributed evidence to an individual review finding.
- Coherence of the review finding: an assessment of how clear and cogent the fit is between the data from the primary studies and a review finding that synthesizes those data. By cogent, we mean well supported or compelling.
- Adequacy of the data contributing to a review finding: an overall determination of the degree of richness and quantity of data supporting a review finding.
- Relevance of the included studies to the review question: the extent to which the body of evidence from the primary studies supporting a review finding is applicable to the context (perspective or population, phenomenon of interest, setting) specified in the review question.

After assessing each of the four components, we made a judgement about the overall confidence in the evidence supporting the review finding. We judged confidence as high, moderate, low, or very low. The final assessment was based on consensus among the review authors. All findings started as high confidence and were downgraded if there were important concerns regarding any of the CERQual components.

The criteria 'Breadth and depth of findings' of the EPPI-Centre tool for judging primary studies' methodological limitations and the component 'adequacy' of CERQual both rely on judgements about richness of studies. To avoid applying judgements about richness of studies contributing to findings twice, in the 'methodological limitations' and the 'adequacy' criteria of CERQual, we did not use the information on breadth and depth of findings of individual studies in our assessment of their 'methodological limitations' but only for assessing 'adequacy' of data supporting review findings.

Summary of qualitative findings table(s) and evidence profile(s)

We present summaries of the findings and our assessments of confidence in these findings in the summary of qualitative findings table(s), which include summaries of the review findings, the overall CERQual assessments, an explanation of each CERQual assessment, and references to the studies contributing to each review finding. We present detailed descriptions of our confidence assessments in an evidence profile table(s) which is more detailed and includes summaries of the review findings, information on the judgements for each CERQual component underlying the overall CERQual assessment, and the overall assessment with its

explanation. Together, these tables provide a structured summary of the review findings and the information contributing to the assessment of each finding and, importantly, ensure transparency of the judgements made by the review authors (Lewin 2018b).

Integrating the review findings with the Cochrane intervention review(s)

We used our review findings to complement a Cochrane diagnostic test accuracy review in progress, 'Xpert MTB/XDR for detection of pulmonary tuberculosis and resistance to isoniazid, fluoroquinolones, ethionamide, and amikacin'. Accuracy studies do not reveal what users think of or experience with the diagnostic in question. Yet to understand why diagnostics are utilized, how effective they are, and their impact on health equity, it is essential to answer questions around feasibility, added value, and experiences – which our review findings aim to provide – alongside questions of technical accuracy.

This review will be integrated with other systematic reviews on active tuberculosis disease and drug resistance as part of the Cochrane Special Collection – Diagnosing Tuberculosis. Curated by Cochrane contributors, the Special Collection describes key WHO guidelines on tuberculosis diagnostics, and their underpinning systematic reviews from Cochrane Infectious Diseases and other international teams (Cochrane Special Collection 2020).

Review author reflexivity

The author team represents a diversity in disciplinary backgrounds, research foci, and experiences with both qualitative and quantitative study designs for both primary empirical research and evidence synthesis. Together, they have experience with diverse fields of study (public health (RJ, SO, EO, KRS, BS); science and technology studies (NE, RJ); medical sociology and anthropology (NE, BS, RJ); epidemiology (EO, KRS); health systems (SO); qualitative synthesis methodology (SO); pharmacoepidemiology and pharmacovigilance (PWK)); experience with different geographical settings (NE, EO, PWK, BS, RJ, KRS, SO); and experience with researching diagnostic processes and technologies (ranging from technical accuracy studies (EO, KRS) to studies of healthcare seeking, implementation challenges, point-of-care testing processes, and evaluation of specific diagnostic devices (NE, EO, RJ, SO)). Such a multidisciplinary team facilitated analysis and identification of multiple factors influencing user perspectives and feasibility considerations.

At the outset of the review, some authors would anticipate that low-complexity NAATs have the potential to improve tuberculosis care, but that critical barriers exist to their implementation. Others might be more hesitant about the presumed automatic benefit of introducing advanced technologies but then not investing in strengthening weak health systems or wonder how inclusive the diagnostic design process was. All authors have been in contact with different types of users throughout their research career. Future reviews should consider involving users in the review process in the form of an advisory group or similar. We minimized the risk that our perspectives as authors influenced the analysis and interpretation by using refutational analysis techniques, such as taking seriously contradictory findings between studies and further exploring and analysing them. We used the different perspectives represented in the author team productively in regular meetings with the aim of identifying our underlying assumptions in the data synthesis, clarifying procedures, and documenting challenges faced. This supported and enhanced the reflexivity of the review team.

NE has conducted a range of primary studies in India's and South Africa's health systems examining challenges to diagnosing and diagnostic processes at point-of-care. She has also undertaken studies on the attempts of innovating and implementing point-of-care diagnostics for tuberculosis and HIV, among them cartridge-based tests. She uses a constructivist viewpoint/epistemology that is sensitive to how technology design and use mutually constitute each other, meaning that users are influenced by and also shape technologies, not only once technologies are developed and in use, but also when assumptions about users are inscribed into material characteristics of technologies such as cartridge-based diagnostics. These prior experiences might make her particularly sensitive to challenges in implementation and the perspectives of a wide variety of users.

EO is a public health physician and methodologist. She has 10 years' experience in evidence synthesis specializing in methodology, systematic reviews, and meta-analysis of diagnostic tests. She has conducted systematic reviews on tuberculosis tests, some of which have informed WHO guidelines on tuberculosis tests. She is also an academic editor with the Cochrane Infectious Disease Group.

PWK has no prior experience with tuberculosis diagnostics research. Her views on tuberculosis diagnostics are primarily influenced by being a healthcare worker involved in a multidisciplinary review of management of people with MDR-tuberculosis.

BS is a public health researcher with experience in conducting qualitative and quantitative Cochrane and non-Cochrane systematic reviews. She has conducted some primary research on tuberculosis-related topics previously. Her systematic review expertise was valuable in guiding the review team with specific processes, specifically in terms of data extraction and analysis, and assessing the confidence in review findings.

RJ has minimal experience in the field of tuberculosis diagnostics. She has conducted qualitative research regarding the implementation of digital strategies for HIV self-testing and HIV testing at point-of-care in South Africa. She also has a background in biological sciences and some practical and theoretical knowledge regarding basic laboratory methodology. These experiences make her sensitive to the importance of valuing new diagnostics for their accuracy and reliability within the laboratory, but also the necessity of implementing new diagnostics such that the information they provide can be applied in clinical practice to enable good care.

KRS is a public health physician and methodologist. She has performed over 20 systematic reviews on tuberculosis diagnostics and contributed to several recent WHO policies on tuberculosis diagnostics. Karen is an Editor with the Cochrane Infectious Disease Group and Cochrane Diagnostic Test Accuracy Editorial Team.

SO has no personal experience regarding tuberculosis diagnostics and began this work agnostic about cartridge-based tests. She views interventions primarily from the standpoint of healthcare service users, families, and the wider public. She has been

systematically reviewing research about programme effectiveness and implementation, and experiences of the providers and potential recipients, for 25 years. She is an editor with the Cochrane Consumers and Communication Review Group and the CIDG.

RESULTS

Results of the search

We found 32 studies that met our inclusion criteria, Figure 1. All of the sampled studies were published between 2012 and 2021. For an overview of the studies that were excluded and reasons for their exclusion, see Characteristics of excluded studies.

Description of the studies

A summary of the key characteristics of studies included in this review is presented in Table 2. Also, see Characteristics of included studies.

Of the included studies, all were conducted in low- and middle-income countries. Twenty-seven studies (84%) were conducted in high-tuberculosis burden countries with six in South Africa, one in Vietnam, nine in India, one in Bangladesh, two in Uganda, one in Brazil, one in Kenya, one in Tanzania, two in Ethiopia, two in Myanmar, and one in Mongolia. Of the remaining five, three covered both high and lower-burden countries (Creswell 2014; England 2019; Mwaura 2020). Of the included studies, 21 studies were conducted in high-MDR-TB burden countries (Colvin 2015; Davids 2015; Engel 2015a; Hoang 2015; Ismail 2020; Jaroslawski 2012; McDowell 2016; McDowell 2018; Medina-Morino 2021; Mnyambwa 2018; Naidoo 2015; Nathavitharana 2017; Newtonraj 2019; Oo 2019; Phyo 2019; Raizada 2021; Rendell 2017; Saria 2020; Shewade 2018; Stime 2018; Vijayageetha 2019). In addition, one study covered projects in nine countries (Democratic Republic of Congo, Kenya, Pakistan, Bangladesh, Mozambique, Cambodia, Malawi, Nepal, Moldova) and another discussed outcomes of a survey conducted in 16 countries. Of the included studies, 16 studies focused on urban areas alone, eight studies were located in both rural and urban areas (Cattamanchi 2020; Engel 2015a; Joshi 2018; Mohammed 2020; Nalugwa 2020; Shewade 2018; Ismail 2020), and seven studies did not report if the setting was urban or rural (England 2019; Hoang 2015; Mnyambwa 2018; Mwaura 2020; Newtonraj 2019; Oliwa 2020; Royce 2014).

The included studies researched a variety of users including people with tuberculosis or MDR-TB, household contacts, private and public physicians, paediatricians, nurses, community health workers, laboratory technicians, policymakers, and tuberculosis programme officers and staff. While it was difficult to quantify the number of participants as not all studies reported this information in detail, for those studies that did report, there were 1102 participants in total. For those studies that reported the number of participants by type of user, there were in total 201 people with presumptive or confirmed tuberculosis or drug-resistant tuberculosis or their guardian, 47 household contacts of people with tuberculosis or MDR-TB, 759 healthcare workers and tuberculosis programme managers (of which 39+ laboratory personnel), and eight manufacturers.

All studies considered Xpert MTB/RIF, except one study that focused on Xpert MTB/RIF Ultra (Mwaura 2020) and one study that focused on portable Gene Xpert single module (GX-I) instrument (Medina-Morino 2021). Several studies did not report in detail how the diagnostic was used. Among those studies that provided details, a few reported that low-complexity NAATs were used as the initial test for all people with presumptive tuberculosis (Colvin 2015; Mohammed 2020; Naidoo 2015; Nathavitharana 2017; Saria 2020). In many studies, low-complexity NAATs were used as the initial diagnostic test only for selected groups (McDowell 2018; Mnyambwa 2018; Nalugwa 2020; Newtonraj 2019; Oliwa 2020; Oo 2019; Rendell 2017; Vijayageetha 2019; Raizada 2021; Ketema 2020), household contacts of people with tuberculosis (Medina-Morino 2021) or MDR-TB (Phyo 2019), for people previously treated for tuberculosis (McDowell 2016; Royce 2014) or as a follow-up test for people who were smear negative (Cattamanchi 2020; Creswell 2014; Newtonraj 2019; Rendell 2017; Shewade 2018).

The included studies covered a range of facilities including clinics, (district) hospitals, microscopy centres, NAAT testing sites, national reference laboratories and provincial laboratories and community outreach settings. Some studies combined clinics, hospitals and NAAT testing facilities; others focused on one type of facilities alone. Most studies reported results from public facilities (16), nine studies reported results from both public and private facilities (Creswell 2014; Davids 2015; Engel 2015a; Jaroslawski 2012; McDowell 2018; Mohammed 2020; Newtonraj 2019; Ismail 2020; Raizada 2021), one study reported results from a non-governmental organization (NGO)-led project (Phyo 2019) and two from just private facilities (McDowell 2016; Saria 2020). Finally, three studies did not report whether the facility was public or private (Medina-Morino 2021; Naidoo 2015; Royce 2014).

Of the included studies, 13 used a mixed-method design (Cattamanchi 2020; Davids 2015; Ismail 2020; Joshi 2018; Ketema 2020; Nalugwa 2020; Oo 2019; Phyo 2019; Raizada 2021; Royce 2014; Stime 2018; Vijayageetha 2019) while the remaining 19 were purely qualitative in nature. Most studies were descriptive in nature with only six studies applying a theoretical framework. The study objectives focused mainly on understanding the perspectives of healthcare providers, managers, or people engaged in tuberculosis diagnosis or screening and low-complexity NAATs use and challenges to their implementation (Cattamanchi 2020; Creswell 2014; Davids 2015; De Camargo 2015; Ismail 2020; Jaroslawski 2012; Joshi 2018; Ketema 2020; McDowell 2018; Medina-Morino 2021; Mnyambwa 2018; Mwaura 2020; Naidoo 2015; Newtonraj 2019; Oo 2019; Phyo 2019; Raizada 2021; Rendell 2017; Royce 2014; Shewade 2018). A second set of studies had a more procedural approach where understanding the process of using or implementing diagnostics was the main aim which generated data on the perspectives as well as practices of users (Colvin 2015; Engel 2015a; Hoang 2015; McDowell 2016; Oliwa 2020; Stime 2018).

Methodological limitations of the studies

The sampled studies were overall of good quality, with about half of them having undertaken a thorough attempt or several steps towards methodological quality across the assessed components and the other half having mostly undertaken at least a few steps towards methodological quality. Details of the assessments of methodological limitations for individual studies can be found in Table 1.

Confidence in the review findings

Out of 18 findings, we graded 14 as high confidence, three as moderate confidence, and one as low confidence using the

CERQual approach. For summary and explanations of our CERQual assessment, see Summary of findings 1 and Table 3.

Review findings

From our synthesis, we developed 18 individual findings, which we organized into three overarching categories related to: 1) critical aspects users value; 2) challenges reported to realizing those values; and 3) concerns for access and equity. In the sections below, we present each finding followed by the detailed results. We developed a figure to illustrate how these findings interacted (see conceptual model and Figure 2).

Critical aspects users value

Summary of Qualitative Findings table: finding 1-6 (see Summary of findings 1)

Finding 1: People with tuberculosis, mostly from high-tuberculosis burden countries, value: 1) getting an accurate diagnosis and reaching diagnostic closure (finally "knowing what is wrong with me"); 2) avoiding diagnostic delays as they exacerbate existing financial hardships and emotional and physical suffering and make patients feel guilty for infecting others (especially children); 3) having accessible facilities; and 4) reducing diagnosis-associated costs (travel, missing work) as important outcomes of the diagnostic (moderate confidence; (De Camargo 2015; Ismail 2020; Joshi 2018; Medina-Morino 2021; Naidoo 2015; Phyo 2019; Raizada 2021; Royce 2014; Vijayageetha 2019)).

Even though a diagnosis of MDR-TB is devastating for people, they value reaching diagnostic closure through an accurate diagnosis and finally knowing what is wrong with them (Naidoo 2015). Families of children suffering from tuberculosis experience considerable distress upon receiving a diagnosis which is increased by lengthy diagnostic delays (Raizada 2021). People with MDR-TB highlighted how diagnostic delays exacerbate existing financial and other hardships or create new ones (avoidable delays that lead to emotional and physical suffering and onwards transmission of MDR-TB to children). Diagnostic delays make people feel guilty of infecting others and they experience distress when they are on first-line tuberculosis treatment that does not help (Naidoo 2015).

An individual with MDR-TB in South Africa highlights this: *"it hurts me a lot, I don't even want to go there, I am feeling very bad, very, very bad, because if this was detected earlier I was not going to go through some difficulties that I went through. You know… when I think that I even infected my child it makes me feel very bad. Because if this was detected early and [I was] started on the right treatment, maybe some of the problems would have been eliminated"* (Naidoo 2015).

Reducing time to diagnosis and saving cost (including travel cost) is important for people undergoing testing (Ismail 2020; Joshi 2018; Medina-Morino 2021; Phyo 2019; Royce 2014; Vijayageetha 2019). In South Africa, for instance, people with tuberculosis would recommend that family and friends avoid private sector services and instead immediately go to the public primary care facilities despite perceptions of long waiting times, lack of privacy and poor staff attitudes associated with public facilities (Naidoo 2015). In a study from Brazil, people with presumptive tuberculosis did not struggle with delays or cost, because they either lived close by testing facilities and those who did have to take a long bus trip were on medical leave (i.e. had time) and got the bus ticket subsidized (no extra cost) (De Camargo 2015).

Finding 2: Compared to existing tests such as sputum microscopy, healthcare providers appreciate the rapidity and accuracy of low-complexity NAAT results, the diversity of sample types, ability to detect drug resistance, as well as the consequence of avoiding costlier investigations or hospital stays when using low-complexity NAATs (high confidence; (De Camargo 2015; Joshi 2018; McDowell 2018; Mwaura 2020; Naidoo 2015; Newtonraj 2019; Rendell 2017; Vijayageetha 2019)).

Several studies mentioned how healthcare providers value the time-saving potential of low-complexity NAATs when receiving results more quickly (Joshi 2018; Mwaura 2020; Newtonraj 2019; Rendell 2017). Especially if same-day results allow same-day treatment initiation, this is considered a vast improvement (McDowell 2018). Healthcare professionals valued the ability to diagnose in paucibacillary (tuberculosis disease caused by a small number of bacteria) samples (Joshi 2018; Newtonraj 2019) and in a diversity of sample types (such as sputum, gastric aspirate specimens, and stool), especially important for diagnosis of children (McDowell 2018). Finally, the accuracy and reliability of results is considered an important benefit (De Camargo 2015; Vijayageetha 2019) and, with it, particularly for Xpert MTB/RIF Ultra, the improved tuberculosis case detection among people who are hard to diagnose (Mwaura 2020), less ordering of other expensive investigations (CT scan, bronchoscopies), and avoidance of longer hospital stays for children (McDowell 2018).

According to one study, it is the experience of using low-complexity NAATs and of its added value (especially speed, affordability and generation of additional insights or increased confidence in results) that drives behaviour change among clinicians, more than education and information about the product (McDowell 2018).

Finding 3: Low-complexity NAATs allow healthcare providers to detect drug resistance earlier and paediatricians in particular mentioned how it heightened their risk perception of drug resistance in children; yet in a context with widespread severe forms of drug resistance and a habit of treating empirically first, clinicians see the inability of some NAATs to detect resistance beyond rifampicin as a hindrance (high confidence; (De Camargo 2015; Joshi 2018; McDowell 2016; McDowell 2018; Naidoo 2015)).

The ability to detect drug-resistant tuberculosis early is appreciated among healthcare providers (De Camargo 2015; Joshi 2018). Particularly in children, where physicians do not typically expect drug resistance, low-complexity NAATs' use altered physicians' risk perception of MDR-TB in children and reduced empirical treatment among children (McDowell 2018). Yet, in a context of severe forms of drug-resistant tuberculosis and where treating empirically is common, such as in the private sector in Mumbai, India, the added value of low-complexity NAATs that only detect rifampicin resistance is questioned.

"*An MBBS doctor [with a a Bachelor of Medicine and Bachelor of Surgery degree] in Mumbai commented: But why should I use Xpert? It only tells if the patient is rifampicin susceptible or not, but it does not tell me anything else. It is better to give first-line drugs and see if the patient responds. After some time we will know if the first-line drugs are working and if they do not we know we need to move on. Xpert tells us about rifampicin quickly but what we really need is a*

*culture and that takes time. In Mumbai, Xpert is not enough to decide on a proper second-line regimen." (*McDowell 2016*).*

This provider would rather treat empirically first and wait for culture results that test resistance to more drugs than just rifampicin. This is partly explained by the context of widespread severe forms of drug resistance and by the provider's clients' limited financial capability and the risk of losing clients in a competitive private health care marketplace.

Finding 4: Clinicians value the confidence that low-complexity NAAT results provide. Having confidence helps in starting treatment, reassuring and motivating people with tuberculosis and their caregivers, justifying management decisions to other doctors, and increasing collaboration between private and public providers (high confidence; (McDowell 2018; Oliwa 2020; Raizada 2021)).

Having confidence in diagnostic test results is valued as important for initiating treatment, reassuring and motivating people with tuberculosis to begin and adhere to treatment, and justifying management decisions to other clinicians. Experience with successful treatment following a positive NAAT result increases that confidence among paediatricians and other clinicians (McDowell 2018; Oliwa 2020). Among private paediatricians in India, availability of low-complexity NAATs and fast turnaround times increased confidence in the quality of public sector laboratories; private paediatricians were willing to collaborate and refer people seeking care (McDowell 2018). While low-complexity NAATs provided diagnostic certainty to paediatricians and families in India, the test was still treated as a last resort and not used as an initial diagnostic test, prompting the study authors to call for increased awareness of tuberculosis diagnosis in children (Raizada 2021).

Finding 5: Laboratory technicians value the improvement of overall laboratory work that low-complexity NAATs bring compared to sputum microscopy in terms of ease of use, ergonomics, and biosafety (high confidence; (Creswell 2014; De Camargo 2015; Newtonraj 2019)).

The improved laboratory conditions, compared to sputum smear microscopy, work as an incentive for workers (Creswell 2014; De Camargo 2015). Laboratory technicians reported appreciating not having to deal with fire or foul odours when staining the slides or having to bend over a microscope for hours to identify bacilli, risking reader fatigue, as they would have to do using sputum smear microscopy. Low-complexity NAATs improve biosafety because samples do not need to be handled once they are added to the cartridge and inserted in the platform. While the machine processes the samples, laboratory technicians are free for other activities (De Camargo 2015). This and the fewer steps involved add to the reported ease of use (Creswell 2014; Newtonraj 2019).

Finding 6: Laboratory managers are appreciative that monitoring of laboratory work and training is easier than with sputum microscopy and that low-complexity NAATs ease staff retention, as these tests increase staff satisfaction and have a symbolic meaning of progress within the tuberculosis world (low confidence; (De Camargo 2015)).

Monitoring of laboratory work is easier because low-complexity NAATs produce digital results and error reports. Consequently, the training was reported to be easier, also in terms of logistics, because it involves operating automated equipment rather than working with a microscope and laboratory bench (De Camargo 2015). According to laboratory managers in Brazil, low-complexity NAATs ease staff retention as they have a symbolic meaning in the tuberculosis diagnostic field that has spent decades without innovation: "*The emotional and psychological factors of the workers who will be most pleased to do its work, will get sick less often, take fewer licenses, will be less prone to giving up working in that area. We saw a great satisfaction*." (Manager 1, Manaus) (De Camargo 2015).

Challenges to realizing those values

Summary of Qualitative Findings table: finding 7-15 (see Summary of findings 1)

Finding 7: People with presumptive tuberculosis can be reluctant to test for tuberculosis and MDR-TB because of stigma related to MDR-TB or related to having interrupted treatment in the past, because of fears of side effects, the failure to recognize symptoms, the inability to produce sputum and the cost, distance and travel concerns related to (repeat) clinic visits. Thus, low-complexity NAAT testing is not operationalized with sufficient support or discretion to overcome barriers that are common to other approaches to testing for tuberculosis (high confidence; (Ismail 2020; Medina-Morino 2021; Naidoo 2015; Phyo 2019; Royce 2014; Saria 2020; Shewade 2018)).

Associated stigma, discriminatory attitudes at clinics, mistrust in providers and fear prevent people with presumptive tuberculosis from returning for providing second sputum for DST according to studies in India (Saria 2020; Shewade 2018). The fear of treatment-associated side effects can prevent people from testing (Phyo 2019). Stigma can lead to misclassifications and thereby further diagnostic delays as became clear in a study on healthcare workers' perspectives on potential barriers to the detection of MDR-TB in people previously treated for tuberculosis in Cambodia. The healthcare workers mentioned how people were ashamed to reveal previous interrupted treatment to health workers leading to misclassification (Royce 2014). *"Some participants noted that .. . many patients hide their previous treatments. .. they are ashamed [of revealing that they interrupted treatment previously]" ((*Royce 2014*) p. 1303).* Healthcare workers observed how people with MDR-TB are afraid to reveal a MDR-TB diagnosis to others at home (Royce 2014).

Failure to recognize symptoms (not as tuberculosis-related, or associating them with HIV instead) and denying or minimizing symptoms can lead to delays and explains why many patients are very ill at first contact (Naidoo 2015).

The inability to produce sputum and not having symptoms can prevent contacts of people with MDR-TB to agree to being tested (Phyo 2019). Inability to produce sputum after a certain period of tuberculosis treatment could be a reason why patients did not return with two specimens for DST (especially because of the delays between initial tuberculosis diagnosis and DST) (Shewade 2018).

Long distances, financial constraints and inconvenient clinic hours can prevent patients from testing (Phyo 2019; Royce 2014; Saria 2020). In a study that examined the use of low-complexity NAATs as

a home testing device, operated by health workers visiting homes, study participants appreciated the convenience and the possibility of avoiding the stigma of testing household members at home (Medina-Morino 2021).

Finding 8: Healthcare workers can be reluctant to test for tuberculosis or MDR-TB because of tuberculosis-associated stigma and its consequences, fears of acquiring tuberculosis, fear from supervisors when reclassifying people already on tuberculosis treatment who turn out to be misclassified, fear of side effects of drugs in children, and lack of community awareness of disease manifestations in children. Thus, low-complexity NAAT testing is not operationalized with sufficient support or discretion to overcome barriers that are common to other approaches to testing for tuberculosis (high confidence; (Oliwa 2020; Royce 2014)).

In the context of child tuberculosis in Kenya, health workers can be reluctant to test for tuberculosis because of the association of tuberculosis with being HIV-positive. This makes healthcare workers worry about the emotional burden a diagnosis would inflict upon people, which the following quote of a paediatrician illustrates:

" … And then there is that thing people thinking TB is equal to HIV, so when now someone has been told that they have TB now everyone thinks that they are HIV positive, so there is that even being shunned by the family. I have a mother right now who was actually chased away by her extended family because of the TB diagnosis…" Paediatrician_SSI_03 ((Oliwa 2020 , p. 8)).

Additionally, the fear of acquiring tuberculosis as a healthcare provider, the fear of adverse effects of drugs in children, and the belief that children do not get tuberculosis contribute to underutilization of tuberculosis diagnostics (Oliwa 2020). In another study, healthcare providers did not want to do DST in people who originally had been categorized as new patients (if it emerged that people had been previously treated) because of fear of what their supervisor would think when controlling the register and discovering a change in classification. If people who were previously treated are not registered accordingly, it delays DST (Royce 2014).

Finding 9: Rapid turn-around time is an important potential of diagnostic algorithms involving NAATs of low complexity. Yet, diagnostic delays are accumulated because of various health system factors (i.e. non-adherence to testing algorithms, testing for (MDR-)TB late in the process, empirical treatment, false negatives due to technology failure, large sample volumes and staff shortages, poor/delayed sample transport and resulting delays in communication, delays in scheduling follow-up visits and recalls, inconsistent result recording) and, to a lesser extent, delays related to people seeking a diagnosis (i.e. missed follow-up appointments, competing family demands and seeking traditional healthcare) (high confidence; Cattamanchi 2020; Creswell 2014; Davids 2015; Engel 2015a; Ismail 2020; Ketema 2020; McDowell 2016; Mohammed 2020; Naidoo 2015; Nalugwa 2020; Nathavitharana 2017; Oo 2019; Rendell 2017; Royce 2014; Stime 2018)).

Rapid turn-around time is an important potential of diagnostic algorithms involving low-complexity NAATs and an important outcome for healthcare providers and people seeking a diagnosis. For some providers, cutting diagnostic delay is the main reason for using these diagnostics. Users value receiving results more quickly to speed up clinical work and to free time in the laboratory while a cycle is running (De Camargo 2015). The potential of an algorithm involving low-complexity NAATs to reduce diagnostic delays is emphasized across studies (Naidoo 2015; Newtonraj 2019; Rendell 2017) and illustrated with two examples in Naidoo 2015 where rapid initiation of MDR-TB treatment happened within six and eight days of the first health contact, respectively. "*Early access to treatment was enabled by the correct tests being requested which yielded a positive result, results being available when patients returned and decentralised treatment being available*." (Naidoo 2015).

But in many places, the overall turnaround time of low-complexity NAATs is increased due to accumulation of delays and how diagnostic and treatment algorithms are organized. Many authors differentiate between health system factors and factors related to people seeking a diagnosis causing these delays.

Health system factors include: failure to adhere to testing algorithms (providers not testing for tuberculosis or MDR-TB at initial visits; correct tests not initially done (Naidoo 2015) or providers preferring empirical treatment over testing (McDowell 2016); failure in the testing technology [false negatives mostly]; problems with receiving the results, scheduling follow-up visits and recalling patients with positive results (Cattamanchi 2020; Naidoo 2015; Nalugwa 2020); increased turn-around times due to large number of samples being tested and machines not running over night (Davids 2015; Engel 2015a; Stime 2018); staff shortages leading to delays in conducting tests (Davids 2015; Nathavitharana 2017; Oo 2019; Stime 2018); high turnover of trained staff delaying implementation and challenging sustainability of testing in peripheral settings (England 2019; Ketema 2020); delays in transporting samples to NAAT testing sites and in reporting and receiving results(limited communication possibilities via phone, SMS, overextended courier system, or reliance on paper-based system), inconsistent recording of tuberculosis results at facilities (Creswell 2014; Mohammed 2020; Nalugwa 2020; Oo 2019; Royce 2014); and lack of a follow-up system when patients are being referred to testing sites (Engel 2015a). In Moldova, participants reported a delay (1-2 weeks) in initiating MDR-TB treatment because of the procedural requirement to determine the MDR-TB treatment plan at a weekly consensus meeting (Rendell 2017).

In South Africa, "*delays overall were longer for patients in whom initial tests were negative with 1st-line TB treatment started on clinical or chest x-ray findings*."(p. 9) (Naidoo 2015). Strategies by providers to deal with associated delays create new problems such as artificially prolonging turnaround times when asking people to come back later, anticipating delays. The provider gave a (too) long follow-up date to ensure even delayed results are available when people return to the clinic (Engel 2015a). Passage of time and multiple failed empirical broad-spectrum antibiotic trials are necessary before private practitioners in India consider tuberculosis, resulting in long delays in diagnosing tuberculosis (McDowell 2016).

Factors related to people seeking a diagnosis were reported less frequently in the included studies. In South Africa, a study reported that delays related to people seeking a diagnosis contributed to a lesser extent, but can happen due to not recognizing symptoms,

missed follow-up appointments, competing family demands, and seeking traditional healthcare." (Naidoo 2015).

Finding 10: Challenges with sample quality, collection and transport can cause error results and underutilization of low-complexity NAATs. Specifically, providers struggle with poor sample quality, sample collection facilities that are inconveniently located for people seeking a diagnosis, non-functioning sample transport mechanisms that can damage samples or deter providers from ordering tests, and difficulty of obtaining paediatric samples (high confidence; (Cattamanchi 2020; Creswell 2014; Davids 2015; Hoang 2015; Ketema 2020; McDowell 2016; McDowell 2018; Nathavitharana 2017; Newtonraj 2019; Oliwa 2020; Oo 2019; Phyo 2019; Raizada 2021; Rendell 2017; Royce 2014; Saria 2020; Shewade 2018; Vijayageetha 2019)).

Providers struggle with poor sample quality causing errors in the results (Newtonraj 2019; Oo 2019; Rendell 2017; Royce 2014). Reasons for poor sample quality can be delays and inadequate sample transportation, insufficient instructions for patients (Creswell 2014; Saria 2020) and collecting sputum many days after retreatment initiation (by which time the cough may be resolved and it is harder to provide a specimen) (McDowell 2016; Royce 2014), and specimens may have a very low bacteria count (McDowell 2016). For children with presumptive tuberculosis, families reported concerns about invasive sample collection procedures for non-sputum samples (e.g. gastric lavage) (Raizada 2021) and providers reported difficulties with obtaining paediatric samples and few staff trained to do so (Ketema 2020; McDowell 2018).

Convenient sample collection facilities and functioning sample transport are essential to ensure utilization of Xpert and avoid delays (Cattamanchi 2020; Creswell 2014; Hoang 2015; Nathavitharana 2017; Newtonraj 2019; Oo 2019; Phyo 2019; Shewade 2018; Vijayageetha 2019). Among the involved studies, turnaround times of low-complexity NAATs ranged from the same day to one to two weeks. In India, healthcare providers reported difficulties in convincing people with presumptive tuberculosis to produce two sputum samples for low-complexity NAAT if sputum was negative or they had to travel long distances to come for a chest x-ray and then might not be able to return again for second sample. Sample collection facilities would be more convenient if patients could provide sputum specimens at the nearest primary healthcare clinic (Newtonraj 2019). At a public MDR-TB treatment programme in Vietnam, the lack of a functioning sputum transport system (no appropriate financial compensation mechanisms for consumable procurement and transportation fees; no agreements with postal services, using health staff and public transport instead) led to underutilization of NAAT machines (Hoang 2015). In India, the lack of assured specimen transport after patient identification required the co-ordinating health worker (to transport sample) and returning patients (to provide samples) to be present on the same day which was challenging (Shewade 2018).

Finding 11: The lack of sufficient resources to conduct low-complexity NAATs and maintenance challenges (i.e. stock-outs; unreliable logistics; lack of funding, electricity, space, air conditioners, and sputum containers; dusty environment, and delayed or absent local repair option) lead to higher test failure rates and underutilization of low-complexity NAATs (high confidence; (Creswell 2014; De Camargo 2015; England 2019; Hoang 2015; Joshi 2018; Mohammed 2020; Mwaura 2020; Nalugwa 2020; Nathavitharana 2017; Oliwa 2020; Rendell 2017; Shewade 2018; Stime 2018)).

For instance, several studies reported stock-outs and unreliable logistics around cartridges among common resource challenges at sites running Xpert (Hoang 2015; Joshi 2018; Mohammed 2020; Mwaura 2020; Nalugwa 2020; Nathavitharana 2017; Oliwa 2020; Rendell 2017). In one study, the researcher summed up the implications stock-outs have for underutilization: "*Stock-outs (..) led to delays in making a diagnosis and reinforced a reluctance in ordering the tests in future. This shows how age-old system issues like stock-outs potentially affect adoption of new diagnostics*." (Oliwa 2020).

Poor laboratory infrastructure, including frequent power cuts, lack of air conditioners and/or dusty environment and lack of adequate rooms or proper furniture, can challenge proper testing (Creswell 2014; Joshi 2018; Nalugwa 2020) and explain high test failure rates and indeterminate results (Joshi 2018). Yet, differences between types of failed tests are unclear and available data not always used. 'No result' test results were often caused by a power failure (Creswell 2014).

There was need for more basic office equipment including functioning internet connections to cater for the introduction of new equipment (De Camargo 2015; Rendell 2017; Shewade 2018). Sputum collection facilities in a hub and spoke model struggled with lack of sputum transport containers and lack of electricity to enable refrigeration. This meant people with presumptive tuberculosis needed to come back to provide a sputum sample on transport day, which many people would not do (Nalugwa 2020).

Delays in calibration and replacement of damaged modules (Creswell 2014; England 2019; Joshi 2018; Nathavitharana 2017) and absence of local repair options challenge sustainability of low-complexity NAATs. A study from Mongolia, for instance, reported difficulties in arranging repairs when required because of limited availability of trained mechanics and how having internal capacity for repair helps to prevent interruption of workflows (Rendell 2017).

Finding 12: Low-complexity NAATs may be promoted as decreasing workload by freeing up time for laboratory staff but, in most settings, staff may be hesitant to accept testing with low-complexity NAATs because it increases workload if added onto existing laboratory work without adjusting staffing arrangements, or if it does not replace existing diagnostic tests (moderate confidence; (De Camargo 2015; Joshi 2018; Oo 2019; Phyo 2019; Rendell 2017; Shewade 2018; Stime 2018; Vijayageetha 2019)).

In settings where testing with a low-complexity NAAT is introduced without replacing existing diagnostics or adequate staffing arrangements, it generates more work for laboratory technicians (De Camargo 2015; Joshi 2018; Oo 2019; Rendell 2017): "*Because you're working with two methods instead of one.*" (De Camargo 2015). The high workload for laboratory technicians can then mean that, for instance, investigations are not offered to contacts of an individual with MDR-TB in Myanmar (Phyo 2019), that there is a lack of accountability in tracking people after identification and referral as reported in a study from India (Shewade 2018), and that staff are hesitant to accept point-of-care testing with Xpert as reported in a study from South Africa (Stime

2018). Lack of dedicated staff and high workload of existing staff is hindering implementation of screening for tuberculosis among pregnant women in a setting in South India (Vijayageetha 2019).

Finding 13: Workflows, professional roles and the flow of people seeking care matter for utilizing low-complexity NAATs, for instance, inefficient organizational processes, poor links between providers, unclear follow up mechanisms or where people need to go for testing can deter utilization (high confidence; (De Camargo 2015; Hoang 2015; Mnyambwa 2018; Oliwa 2020; Royce 2014; Saria 2020; Stime 2018)).

The introduction of low-complexity NAATs often has implications for workflows and professional roles. These matter for acceptance by the users. In India, private providers took offence at the suggestion that a new technology could replace their professional expertise in diagnosing tuberculosis (Saria 2020). In Brazil, the introduction of low-complexity NAATs brought a change in workflow where the laboratory technician, after examining the quality of the sputum sample, decides if the sample can be tested on low-complexity NAAT or sputum microscopy (samples with low volume and samples with food or blood residues cannot be tested with low-complexity NAATs). This change in workflow did not translate into a change in professional roles; the laboratory technician remained responsible for the entire process including authorizing the delivery of results. The authors argued that this meant the laboratory technicians more easily accepted the technology (De Camargo 2015). Existing inefficient workflows can cause delay in making NAATs of low complexity work, for instance, when reporting results through paper-based (Rendell 2017; Royce 2014), or non-standardized systems without clear guidance or accountability (Creswell 2014; Shewade 2018), or incorrect filing of medical records (Stime 2018). In addition, unclear follow-up mechanisms (Oliwa 2020; Stime 2018), and poor links between (public and private) providers (Hoang 2015; Mnyambwa 2018) can deter utilization.
The use of low-complexity NAATs has implications for flows of people who only have to submit one sputum sample (Phyo 2019), but might find it difficult to find their way through different sites and departments (Stime 2018; Vijayageetha 2019) or know where they need to go (Oliwa 2020; Stime 2018).

Finding 14: Too much confidence in low-complexity NAAT's accuracy can mean blindly accepting results without using clinical impressions, or for people with presumptive tuberculosis trusting a low-complexity NAAT result because it is computer-based (moderate confidence; (Joshi 2018; Mwaura 2020; Newtonraj 2019)).

Owing to the confidence in low-complexity NAAT's accuracy, clinicians accept negative results without using clinical impressions to question these and are missing the diagnosis in some people infected with tuberculosis (Mwaura 2020; Newtonraj 2019). Xpert is taken as a gold standard and tuberculosis is ruled out, without being aware that results may vary in extrapulmonary tuberculosis or poor quality samples and that there might be false negatives (Newtonraj 2019). Clinicians in Kenya and Eswatini anticipated that with Xpert MTB/RIF Ultra this tendency would increase, empirical diagnosis would further decrease while the number of bacteriological confirmed cases would increase among people who are hard to diagnose because of the trace calls (Mwaura 2020). One study from Nepal where people would routinely be tested with smear microscopy reported that a computer-based test generates confidence

"Patients also prefer Xpert test thinking it will give an accurate result because it is computer-based. They will go for test (i.e. Gene Xpert). Patients demand to test by machine/computer. They have trust towards Gene X-pert. Even though we only test by X-pert if referred by physician.' (X-pert staff) (Joshi 2018)

Finding 15: Insufficient attention to responsive and inclusive implementation processes can hamper the impact of low-complexity NAATs. Specifically, implementation processes have been challenged by lack of data from pragmatic studies addressing effectiveness in operational conditions, lack of knowledge and awareness among providers beyond laboratory personnel, lack of guidelines and standardized training modules and instructions, and a lack of national policy consensus and inclusive decision-making prior to roll out (high confidence; (Colvin 2015; Creswell 2014; Davids 2015; De Camargo 2015; England 2019; Hoang 2015; Joshi 2018; Mnyambwa 2018; Naidoo 2015; Newtonraj 2019; Oo 2019; Rendell 2017; Shewade 2018)).

Generating data on how new diagnostics should best and most effectively be integrated into a local operational context of use, including practical feasibility planning, is crucial prior to implementation as well as during early implementation to inform roll out and impact on tuberculosis control (Colvin 2015; Joshi 2018). The early Xpert MTB/RIF (and line probe assays (LPA)) demonstration studies in South Africa were assessing accuracy but not pragmatic effectiveness in operational conditions which is a missed opportunity (Colvin 2015).

When introducing new diagnostics, several studies cited challenges with ensuring knowledge and awareness about the diagnostic and guidelines (Colvin 2015; England 2019; Joshi 2018; Newtonraj 2019; Rendell 2017; Shewade 2018) not only among laboratory technicians or managers, but also among the public, clinicians and healthcare workers (Colvin 2015; Mnyambwa 2018; Oo 2019). Lack of clear and updated guidelines and poor dissemination at peripheral levels and among private providers challenges implementation (Creswell 2014; Davids 2015; Hoang 2015; Newtonraj 2019; Rendell 2017). Clinicians should be included in training (De Camargo 2015). If not done, this led to poor referral to low-complexity NAATs (Joshi 2018; Newtonraj 2019; Shewade 2018) or inconsistency in what samples were used (Rendell 2017). In the TB REACH projects, for instance, staff rotation and new practices around request forms, specimen transport and clinical decisions for rifampicin-resistant results posed crucial training challenges (Creswell 2014). In Vietnam, a lack of standardized training modules and instructions led to failures in identifying presumptive patients, especially among risk groups (Hoang 2015). Insufficient attention to change management processes at facility level can hamper the impact of diagnostics (Colvin 2015; Naidoo 2015). In South Africa, changes to tuberculosis testing algorithms, laboratory request forms, and national tuberculosis registers happened only later after implementation (Colvin 2015).

When introducing new diagnostics, it is equally important to include relevant stakeholders in decision-making processes and in planning regarding implementation, and allow a national policy consensus process. This could involve national and provincial programme managers and health officers, clinicians,

and laboratory staff. In South Africa, Xpert had high visibility but its introduction was not inclusive, and was focused around Foundation for Innovative New Diagnostics (FIND), WHO, National Health Laboratory Services (NHLS), and the Ministry of Health, sidelining key national and provincial actors in the tuberculosis programme. The lack of inclusion and communication was perpetuated by the fast pace of implementation and high international pressure to act (rescue (the need — and desire — to save lives through medical rescue) versus management (the equally important need to produce strong evidence, carefully manage change in the system, and evaluate the process and impact of new interventions)) (Colvin 2015). The study authors highlighted:

"TB managers and local health services staff alike experienced the decision making about and implementation of Xpert as fast-paced, with little horizontal co-ordination or communication, although Xpert involved more on-the-ground changes than LPA. (…) The rapid pace of implementation meant there was little time to assess its operation and integration into local contexts, and in the words of one manager, many staff felt that Xpert seemed to have just 'fallen out of the sky' at a time when their focus was still on the completion of the LPA rollout." ((Colvin 2015) p. 1333)

Concerns for access and equity

Summary of Qualitative Findings table: finding 16-18 (see Summary of findings 1)

Finding 16: Uncertainty around sustainability of funding and maintenance and the strategic and inequitable use of resources negatively affects creating equitable access to low-complexity NAATs (high confidence; (Colvin 2015; Creswell 2014; De Camargo 2015; England 2019; Jaroslawski 2012; Nathavitharana 2017)).

Staff and managers expressed concerns about the high cost and sustainability of low-complexity NAATs (Colvin 2015; Creswell 2014; De Camargo 2015; England 2019; Nathavitharana 2017) and the challenges of funding maintenance of the devices (De Camargo 2015). Donor funding might have led to insufficient attention being paid to ongoing resource requirements (i.e. masking startup and recurrent cost, appearing more feasible) (Colvin 2015). Affordability is crucial for utilization of diagnostics in the private sector in India, where prices are often inflated, because people have limited financial capabilities and providers respect this to avoid losing clients. This meant that inadequate alternatives such as serology were preferred by people with presumptive tuberculosis, laboratory technicians, and providers over molecular tests (Jaroslawski 2012).

Participants in a study in South Africa voiced concerns about strategic and equitable use of resources, because low-complexity NAATs were placed in hospitals (which already have LPA) and selected, often well-functioning, subdistricts and not in primary health clinics or areas with no access to improved tuberculosis diagnostics. The decision of where to deploy NAATs of low complexity, was not made by provincial and district managers (Colvin 2015). Complex conflict of interest between donors and people implementing these tests created dependence on a single provider of low-complexity NAAT cartridges and platforms. Colvin and colleagues recommend carefully managing these conflicts prior and during development and implementation of diagnostics:

"Among our recommendations is the need to identify and manage conflicts of interest that may arise when innovative partnerships are established to address public health issues. We suggest that the role of committed leadership in fast-tracking processes needs to be matched with a national policy consensus process and careful, transparent planning."((Colvin 2015) p. 1337)

Finding 17: Access to prompt and accurate testing and treatment is hampered, particularly for the vulnerable groups, by the challenges outlined above for realizing recipient and provider values, (high confidence; (Engel 2015a; England 2019; Hoang 2015; Joshi 2018; McDowell 2016; McDowell 2018; Naidoo 2015; Nalugwa 2020; Newtonraj 2019; Oliwa 2020; Oo 2019; Phyo 2019; Royce 2014)).

Several studies showed how lengthy diagnostic delays, underutilization of low-complexity NAATs, and lack of tuberculosis diagnostic facilities at lower levels where many people with presumptive tuberculosis present, hamper access to prompt and accurate treatment for those that are eligible for testing (Nalugwa 2020; Oo 2019) with vulnerable groups and patients with difficult disease patterns (including children (Joshi 2018; McDowell 2018; Oliwa 2020), people with MDR-TB (Hoang 2015; Naidoo 2015)), or patients with limited ability to pay (for fees or transport cost to overcome distance and produce second samples) (Engel 2015a; Joshi 2018; McDowell 2016; Newtonraj 2019; Phyo 2019; Royce 2014) affected the worst. Limited ability to pay means private providers treat rather than order tests (McDowell 2016). Deployment and eligibility decisions by policymakers and the ability of recipients and providers to overcome challenges to diagnostic delay and underutilization are crucial in enabling access. McDowell and colleagues concluded:

"Only when each pediatric presumptive TB patient is offered (initial) Xpert testing, a more synchronized pediatric TB case management, same day TB diagnosis, and access to prompt and accurate TB treatment can be guaranteed. Locating Xpert at the end in the diagnostic process or placing too many restrictions on the criteria of patients who can access the test will limit its impact significantly". ((McDowell 2018), p. 13).

Finding 18: Test users described how implementation challenges lead to accumulated delays that undo the improvements they value in these new tests, and so discourage test use and reduce access and equity (high confidence; review finding #1-15, (Engel 2015a; McDowell 2018; Naidoo 2015; Shewade 2018)).

The implementation challenges identified in findings 7-15 risk undoing the added value as identified by different users in findings 1-6. For instance, diagnostic delays can further compound underutilization of low-complexity NAATs and risk loss of people from diagnostic and treatment pathways. An overall turnaround time within 24 hours (including transportation mechanisms and quick reporting of results electronically) was essential for use of low-complexity NAATs among paediatricians. The impact of low-complexity NAAT with a longer turnaround time is less certain (McDowell 2018). The delays between initial tuberculosis diagnosis and DST mean that some people with tuberculosis are unable to produce sputum after a certain period of first-line tuberculosis treatment and therefore will not return with the second specimen for DST (Shewade 2018). Individual and health system delays interact. Professionals responding to anticipated

health system delay, create further delays to avoid additional delays of individuals seeking diagnosis, who in turn have to wait or return again later if results are not yet available (Engel 2015a).

Conceptual model

Based on these review findings, we have summarized how these findings interact in a conceptual model illustrated in Figure 2. The upper half of the figure illustrates the critical aspects that people with tuberculosis, healthcare workers, laboratory technicians and managers value (review findings 1-6). These aspects are mapped along a simplified diagnostic process to illustrate typical steps of using low-complexity NAATs, consisting of the following: seek care, order test(s), product and transport sample, test runs, results reported and treatment initiated. The length of the blue bars indicates at what step in the process these user values matter (it does *not* indicate a weighted importance). The lower half of the figure illustrates the challenges to realizing those values that we identified (review findings 7-15). These challenges are listed per step in the diagnostic process at which they happen, meaning some review findings cover several steps (i.e. review finding 9 on diagnostic delays). At every step, and indicated with the red shapes piling up, these challenges compound diagnostic delay and underutilization of low-complexity NAATs with important implications for access and equity (review findings 17, 18). And at every step, these challenges risk undoing the added values that users perceive low-complexity NAATs offer (review finding 18). We can assume that if these values are not met, users are less likely to find low-complexity NAATs acceptable.

DISCUSSION

This review synthesized qualitative research on end-user and professional-user perspectives and experiences with NAATs of low complexity for detection of tuberculosis and tuberculosis drug resistance. We organized the 18 individual review findings into the following three overarching categories:

1. Critical aspects users value. People with tuberculosis valued reaching diagnostic closure with an accurate diagnosis, avoiding diagnostic delays and keeping diagnostic-associated cost low. Similarly, healthcare providers valued aspects of accuracy and the resulting confidence in low-complexity NAAT results, rapid turnaround times, and keeping cost to patients low. In addition, providers valued a diversity of sample types (e.g. gastric aspirate specimens and stool in children) and drug resistance information. Laboratory professionals appreciated the improved ease of use, ergonomics, and biosafety of low-complexity NAATs compared to sputum microscopy, and increased staff satisfaction.

2. Challenges reported to realizing those values. People with tuberculosis and healthcare workers were reluctant to test for tuberculosis (including MDR-TB) due to fears, stigma, or cost concerns. These concerns have been reported in the literature on diagnostic delay prior to introduction of low-complexity NAATs as well (Cattamanchi 2015; Storla 2008). Poor quality of sputum samples, lack of sufficient resources and high workload are key barriers found to challenge implementation of tuberculosis diagnosis using sputum smear examination (Cattamanchi 2015). The introduction of low-complexity NAATs has not solved these. Instead, our review specified these and identified additional implementation challenges: delays were reported at many steps of the diagnostic pathway due to poor sample quality; difficulties with transporting specimens; lack of sufficient resources; maintenance of low-complexity NAATs; increased workload; inefficient work and patient flows; over-reliance on low-complexity NAAT results in lieu of clinical judgement; and lack of data-driven and inclusive implementation processes. These challenges were reported to lead to underutilization.

3. Concerns for access and equity.The reported concerns included sustainable funding and maintenance of low-complexity NAATs and equitable use of resources to access low-complexity NAATs. Also, lengthy diagnostic delays, underutilization of low-complexity NAATs, lack of tuberculosis diagnostic facilities in the community, and too many eligibility restrictions hampered access to prompt and accurate testing and treatment. This was particularly the case for vulnerable groups, such as children, people with MDR-TB, or limited ability to pay.

Furthermore, the review found that use of low-complexity NAATs is diverse but rarely used as an initial diagnostic test for all people with presumptive tuberculosis. WHO's policy of Xpert for all patients is insufficiently implemented (England 2019). Low-complexity NAATs were used in many countries for people previously treated for tuberculosis or people who were smear-negative and only as the initial diagnostic for selected groups, including for people living with HIV, pregnant women, children, or household contacts of people with MDR-TB. Future research should investigate if there are differences in using low-complexity NAATs for active versus passive case-finding. The studies included in this review used low-complexity NAATs mostly for passive case-finding, except one study which reported on several countries using them for either active or a mix of both active and passive case-finding (Creswell 2014). Future research should also examine the implications of repurposing diagnostic infrastructure and equipment for COVID-19 and the issue of competition for diagnostic resources more generally.

We identified only one study that mentioned Xpert MTB/RIF Ultra. In the future, we might see more experiences and perspectives on the question of overtreatment versus under-diagnosis and how different actors handle such trade-offs that come with diagnostic devices. We expect to see more comments about how to interpret Xpert MTB/RIF Ultra trace-positive results.

We note that no users mentioned Truenat assays. The WHO recommends their use in adults and children with signs and symptoms of pulmonary tuberculosis (WHO Consolidated guidelines (Module 3) update 2021). Future research should address user perspectives on this particular low-complexity NAAT as well.

The main conclusion is that focusing predominantly on the technological aspects of an innovation introduces serious limitations by ignoring: (a) the social context (particularly the stigma that discourages people to seek a diagnosis for themselves or family members and discourages health professionals to offer tests); (b) the logistics and implementation processes of delivering a technological innovation to peripheral, resource-constrained settings and responding effectively to the test results; and (c) clinical acumen to complement and question test results.

Overall, this review confirms that testing in more peripheral settings still requires strong health systems, laboratory infrastructure and human resources, albeit in slightly different forms (Beisel

2016; Engel 2016). This means infrastructure strengthening and innovation of affordable and available diagnostic technologies needs to happen jointly (Kelly-Cirino 2019). Testing in more peripheral settings will equally require tackling the related challenges of stigma and social inequity that continue to hamper the success of tuberculosis diagnostics. Medical sociologists, anthropologists, and historians have long identified the inextricably and mutually reinforcing relationship between tuberculosis and social inequity (Farmer 1996; Gandy 2002). The people most affected by tuberculosis are often facing other social disadvantages related to their race, ethnicity, and country of origin. Tuberculosis then mounts additional vulnerabilities and instabilities such as lost productivity, cost, stigma, and discrimination (Atre 2011; Craig 2017; Daftary 2021; Murray 2013; Tanimura 2014; Wingfield 2016). These need to be addressed and factored into implementation of low-complexity NAATs.

This review underlines earlier calls for the importance of improving implementation processes of new diagnostics (Albert 2016), including early and inclusive engagement of diverse in-country stakeholders, broader systems strengthening, improved data on ground level realities prior and during implementation, as well as pro-active management of conflicts of interests, in order to ensure equitable use of resources. Implementation processes that do not pay attention to these aspects can hamper feasibility, as well as further uptake and impact of diagnostics. In order to address these questions, innovative research designs, ideally longitudinal and alongside technology development, are required that combine approaches from implementation sciences (structured evaluations of interventions at multiple sites), complexity science (adaptive approaches to dynamic change in self-organizing systems) and social sciences (examinations of why people act the way they do) (Greenhalgh 2019).

All sampled studies included in this review were conducted in low- and middle-income countries and many in high-tuberculosis and/or MDR-TB burden countries. Only one study took place solely in a country in Eastern Europe. More research from that region could have added additional insights given the high MDR-TB burden in the region.

Most studies used interview or focus group methods while only four also used observations. It may be useful to make more use of longer-term ethnographic methods, such as observations, to better understand processes and practices of using low-complexity NAATs.

The multidisciplinary author team brought a substantive, contextual, and methodological expertise to this review. Our findings were strengthened by a detailed, rigorous, and iterative process of data extraction and analysis involving the entire author team and a considerable body of evidence presented in this synthesis. We included studies from across different high-tuberculosis burden countries and did not identify any major themes that only occurred in one specific setting, making these findings generalizable to countries with a considerable tuberculosis burden and low-complexity NAAT testing. Our review findings are likely not directly transferable to high-income countries where health systems are better resourced, the number of people with presumptive tuberculosis is lower, and diagnostic testing for tuberculosis is concentrated in intermediate and central-level laboratories.

AUTHORS' CONCLUSIONS

The perspectives and experiences of people receiving and providing low-complexity NAATs to diagnose tuberculosis and tuberculosis drug resistance reveal key desirable outcomes of accessible, affordable, accurate, timely diagnosis for framing an evaluation of testing along the intervention pathway. Yet, the findings reveal how multiple challenges risk undoing the added values new diagnostics of low complexity can bring for people with tuberculosis and healthcare professionals. These challenges compound underutilization of low-complexity NAATs. Overall, the review findings suggest that the promise of low-complexity diagnostics to overcome deficiencies in laboratory infrastructure and skilled professionals is misleading. We had high confidence in the evidence contributing to these review findings.

The findings reveal a fundamental paradox between supporting technological innovations but not in parallel investing in health system infrastructure strengthening, and in responses to the social context of an intervention, when these aspects are in fact inseparable from the technological innovation. Without jointly addressing these sociotechnical aspects, equitable and quality care is impossible. This paradox needs to be addressed at global and country level because ignoring it harms the implementation and impact of the technology and renders it in many settings underutilized. Implementation of new diagnostic technologies, like those considered in this review, will need to tackle the challenges identified in this review including weak infrastructure and systems, and insufficient data on ground level realities prior and during implementation, as well as problems of conflicts of interest in order to ensure equitable use of resources.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cattamanchi 2020

Study characteristics	
Country (income classification)	Uganda (low income)
Programmatic features of the intervention (Where and how)	Sputum samples collected at testing sites (i.e. hubs), present in most districts, and transported to peripheral microscopy units (i.e. spokes). Intervention: daily sputum transport to Xpert testing hubs to facilitate same-day (or next-day) Xpert testing for all people who were smear-negative.
Research questions/ objectives	To identify key reasons at multiple levels for attrition along the TB diagnostic evaluation cascade of care (within a larger mixed-method implementation research)
Notes	

Colvin 2015

Study characteristics	
Country (income classification)	South Africa (upper middle income)
Programmatic features of the intervention (Where and how)	Initial TB testing with Xpert, ultimately located primarily in laboratories and not primary care clinics
Research questions/ objectives	To examine policy transfer for GenoType LPA and Xpert to understand how new technologies were taken up, adapted and delivered within local health systems
Notes	

Creswell 2014

Study characteristics	
Country (income classification)	9 countries (Democratic Republic of Congo - low income, Kenya - lower middle income, Pakistan - lower middle income, Bangladesh - lower middle income, Mozambique - low income, Cambodia - lower middle income, Malawi - low income, Nepal - lower middle income, Moldova - lower middle income)
Programmatic features of the intervention (Where and how)	Countries used different approaches (active, passive, mixed, screening); placements included public and private hospitals and primary care facilities, private diagnostic laboratories, HIV centres, prisons, reference laboratories and mobile units. The projects were able to run the machines at district hospitals and at lower levels of care although in only a few situations were peripheral microscopy centres included, mostly because of throughput concerns.
Research questions/ objectives	To present results from nine TB REACH interventions, review the main challenges experienced and formulate recommendations for other early implementers; mixed methods
Notes	

Davids 2015

Study characteristics	
Country (income classification)	South Africa (upper middle income)
Programmatic features of the intervention (Where and how)	Point-of-care testing of people with presumptive TB
Research questions/ objectives	To examine how primary healthcare providers diagnose TB in their specific setting and what their perspectives are on an ideal POC TB test
Notes	

De Camargo 2015

Study characteristics	
Country (income classification)	Brazil (upper middle income)
Programmatic features of the intervention (Where and how)	Not reported
Research questions/ objectives	To qualitatively evaluate the repercussions of the adoption of the Xpert MTB/RIF from the perspective of people with (presumed) TB, health professionals and managers, considering aspects such as understanding, perception and meaning
Notes	

Engel 2015a

Study characteristics	
Country (income classification)	South Africa (upper middle income)
Programmatic features of the intervention (Where and how)	People present at different levels of care (in clinics, health posts, laboratories or hospitals) with multiple or unspecific symptoms (e.g. acute febrile illness) and possibly needing several diagnostic tests. Testing mostly centralised, but in some district hospitals Xpert was available.
Research questions/ objectives	To examine POC testing across major diseases in South Africa contributing to burden of disease (mainly HIV, TB, diabetes mellitus, diarrhoeal diseases and hypertension); to assess what tests are performed and how and whether they can ensure successful POC testing
Notes	

England 2019

Study characteristics	
Country (income classification)	16 TB burden countries
Programmatic features of the intervention (Where and how)	Examines slow uptake of Xpert for all
Research questions/ objectives	To summarise key challenges associated with the scale-up of Xpert and compare these with current ground realities as assessed through a survey exploring the barriers to the scale-up of testing; following results of this survey, to explore reasons for slow uptake of Xpert for all
Notes	

Hoang 2015

Study characteristics	
Country (income classification)	Vietnam (lower middle income)
Programmatic features of the intervention (Where and how)	Unclear
Research questions/ objectives	To understand challenges of efficient implementation of five steps from diagnosis to MDR-TB treatment (mixed method study)
Notes	

Ismail 2020

Study characteristics	
Country (income classification)	India (lower middle income)
Programmatic features of the intervention (Where and how)	Standard procedures of national TB programme for diagnosing and treating routine TB
Research questions/ objectives	Mixed methods study, to explore the reasons for not undergoing diagnostic testing and people with TB not being initiated on treatment
Notes	

Jaroslawski 2012

Study characteristics	
Country (income classification)	India (lower middle income)
Programmatic features of the intervention (Where and how)	Unclear, private providers used serology, Xpert was mentioned as one of the costly alternatives
Research questions/ objectives	To explore why serological tests are so popular in the private sector and what factors have paved the way for their widespread use
Notes	

Joshi 2018

Study characteristics	
Country (income classification)	Nepal (lower middle income)
Programmatic features of the intervention (Where and how)	Not reported
Research questions/ objectives	To explore the barriers to effective implementation of the Xpert MTB/RIF assay (mixed methods sequential explanatory design, a qualitative evaluation)
Notes	

Ketema 2020

Study characteristics

Ketema 2020 *(Continued)*

Country (income classification)	Ethiopia (low income)
Programmatic features of the intervention (Where and how)	Initial diagnostic test
Research questions/ objectives	Mixed methods study, to evaluate the integration of TB screening and contact investigation into integrated maternal, neonatal and child Illnesses and TB clinics
Notes	

McDowell 2016

Study characteristics	
Country (income classification)	India (lower middle income)
Programmatic features of the intervention (Where and how)	Highly variable, mostly empirical treatment first, then a range of tests, always including Xray. If Xpert MTB/RIF, then late in the process
Research questions/ objectives	To understand the factors contributing to the variability in care and the presence of practices diverging from the standard of TB care in India
Notes	

McDowell 2018

Study characteristics	
Country (income classification)	India (lower middle income)
Programmatic features of the intervention (Where and how)	Study focused on a project to improve the implementation of initial Xpert testing for paediatrics by free testing with quick turn around times (within 24 hours) and efforts in co-ordination with local authorities to improve provider literacy to diagnosing TB in children
Research questions/ objectives	To understand the perspective of providers engaged under the ongoing project with respect to Xpert testing in children and implementation bottlenecks; i) how do paediatricians use Xpert when accessible and free of cost, ii) how do they prioritize and evaluate Xpert in relation to other diagnostic technologies, and iii) what are the effects of Xpert on their clinical practice
Notes	

Medina-Morino 2021

Study characteristics	

Medina-Morino 2021 *(Continued)*

Country (income classification)	South Africa (upper middle income)
Programmatic features of the intervention (Where and how)	Targeted, community-wide household screening intervention; Xpert was used in the home in front of household contacts of people with TB
Research questions/ objectives	To explore the acceptability and perceived benefits of home-based TB testing using a portable GeneXpert-I instrument (GX-I) in an urban township
Notes	

Mnyambwa 2018

Study characteristics	
Country (income classification)	Tanzania (lower middle income)
Programmatic features of the intervention (Where and how)	Unclear
Research questions/ objectives	Mixed method study, to assess the effectiveness of GeneXpert GxAlert health platform for MDR-TB diagnosis and its facilitation of the linkage to healthcare services
Notes	

Mohammed 2020

Study characteristics	
Country (income classification)	Ethiopia (low income)
Programmatic features of the intervention (Where and how)	General TB screening (passive) algorithm in Ethopia
Research questions/ objectives	To assess the challenges related to TB screening and diagnosis and related to functionality, use, maintenance and supply of Xpert MTB/RIF
Notes	

Mwaura 2020

Study characteristics	
Country (income classification)	Kenya (lower middle income) and Eswatini (lower middle income)

Mwaura 2020 *(Continued)*

Programmatic features of the intervention (Where and how)	Unclear
Research questions/ objectives	To examine the views of multiple TB stakeholders on the trade-off between overtreatment versus under-diagnosis of TB, and to understand the role qualitative research can play in engaging in-country stakeholders during roll-out of new TB diagnostics
Notes	

Naidoo 2015

Study characteristics	
Country (income classification)	South Africa (upper middle income)
Programmatic features of the intervention (Where and how)	The testing algorithm changed during the study: In 2010, a smear, culture and an LPA-based diagnostic algorithm was used with LPA done on culture isolates or clinical specimens of people with high risk of MDR-TB (those with previous TB, an MDR-TB contact, or from a congregate setting). From 2011–2013, Xpert was phased in, replacing smear microscopy for all people with presumptive TB.
Research questions/ objectives	To explore and compare people's experience of their pathway to MDR-TB diagnosis and treatment initiation in LPA and Xpert-based diagnostic algorithms
Notes	

Nalugwa 2020

Study characteristics	
Country (income classification)	Uganda (low income)
Programmatic features of the intervention (Where and how)	Uganda adopted policy recommendations in line with WHO guidelines; use of smear microscopy and Xpert MTB/RIF at participating health centres
Research questions/ objectives	Mixed method, qualitative part: to assess the process of specimen collection, specimen transport, specimen testing, result reporting and linkage to treatment initiation if diagnosed with TB
Notes	

Nathavitharana 2017

Study characteristics	
Country (income classification)	Bangladesh (lower middle income)

Nathavitharana 2017 *(Continued)*

Programmatic features of the intervention (Where and how)	People admitted and those with cough or a history of lung disease underwent Xpert testing for pulmonary TB.
Research questions/ objectives	To test a new active screening strategy (FAST) since most transmission happens from unsuspecting TB cases and to better understand potential implementation challenges identified
Notes	

Newtonraj 2019

Study characteristics	
Country (income classification)	India (lower middle income)
Programmatic features of the intervention (Where and how)	Xpert MTB/RIF was located at the intermediate reference laboratory, along with culture and LPA; district microscopy centres (mostly within district hospitals and medical colleges) would send samples of people eligible for testing.
Research questions/ objectives	To explore enablers and barriers in using Xpert among the targeted groups from the providers' perspective
Notes	

Oliwa 2020

Study characteristics	
Country (income classification)	Kenya (lower middle income)
Programmatic features of the intervention (Where and how)	Initial Xpert for the diagnosis of paediatric TB in Kenyan county referral hospitals
Research questions/ objectives	To understand how context influences and shapes TB case detection and use of TB diagnostic tests including Xpert in children within hospitals
Notes	

Oo 2019

Study characteristics	
Country (income classification)	Myanmar (lower middle income)

Oo 2019 *(Continued)*

Programmatic features of the intervention (Where and how)	Mainly for the purpose of rifampicin-resistant TB diagnosis, located at district TB centres in selected townships
Research questions/ objectives	Mixed methods study; qualitative part: to understand health provider perspectives on the reasons for failure to identify and test eligible TB patients with Xpert
Notes	

Phyo 2019

Study characteristics	
Country (income classification)	Myanmar (lower middle income)
Programmatic features of the intervention (Where and how)	Household contacts of people with MDR-TB with TB symptoms should be investigated using Xpert MTB/RIF; but policy was followed poorly
Research questions/ objectives	Mixed methods study; qualitative part: to explore the barriers in implementing contact investigation from the perspective of household contacts and health care providers
Notes	

Raizada 2021

Study characteristics	
Country (income classification)	India (lower middle income)
Programmatic features of the intervention (Where and how)	Free-of-cost upfront Xpert MTB/RIF testing for TB diagnosis in paediatric populations in a project by Foundation for Innovative New Diagnostics (FIND) and national TB programme
Research questions/ objectives	Mixed methods study, to explore the experiences of children with TB and their families along the pathway to bacteriological confirmation of TB and appropriate treatment
Notes	

Rendell 2017

Study characteristics	
Country (income classification)	Mongolia (lower middle income)

Rendell 2017 *(Continued)*

Programmatic features of the intervention (Where and how)	Unclear; only eligibility criteria were reported and a weekly consensus meeting for treatment initiation was mentioned
Research questions/ objectives	To identify and understand system and context specific factors within Mongolia's National Tuberculosis Programme that are barriers or enablers to implementing the Xpert MTB/RIF test from the perspective of programme staff
Notes	

Royce 2014

Study characteristics	
Country (income classification)	Cambodia (lower middle income)
Programmatic features of the intervention (Where and how)	Cambodia's guidelines recommend that previously treated patients have sputum specimens tested using Xpert MTB/RIF (available in four provincial laboratories), followed by culture and species identification using liquid and solid media (available in three regional laboratories) and conventional DST at the national reference laboratory.
Research questions/ objectives	To quantify the gaps in the detection of MDR-TB in people previously treated for TB and to describe health workers' perspectives on barriers, facilitators and potential interventions; sequential explanatory mixed-methods design
Notes	

Saria 2020

Study characteristics	
Country (income classification)	India (lower middle income)
Programmatic features of the intervention (Where and how)	Private Provider Interface Agency (PPIA) intervention incentivized informal providers to direct patients with the classic symptoms of TB to formal providers and incentivized uptake of Xpert among formal providers.
Research questions/ objectives	To understand how the PPIA intervention was received and recognized by the various actors that comprised the medical infrastructure and market
Notes	

Shewade 2018

Study characteristics	
Country (income classification)	India (lower middle income)

Shewade 2018 *(Continued)*

Programmatic features of the intervention (Where and how)	In January-March 2014, if sample was smear positive, then LPA was used initially. Among smear-negative samples, culture was done followed by LPA. From April 2014 onwards, LPA was used for smear-positive and CB-NAAT was used for smear negative samples.
Research questions/ objectives	To explore from the healthcare provider perspective, the barriers and suggested solutions for improving DST in programmatic settings
Notes	

Stime 2018

Study characteristics	
Country (income classification)	South Africa (upper middle income)
Programmatic features of the intervention (Where and how)	On site 16 module Xpert machine, batching samples in 2-3 runs per day (approximately 48 samples/day) and in parallel HIV rapid and viral load testing (some testing for sexually transmitted diseases ongoing as well)
Research questions/ objectives	To describe clinic flow with special emphasis on the impact of POC testing at a large urban public healthcare clinic in Durban, South Africa. (mixed method, time in motion study)
Notes	

Vijayageetha 2019

Study characteristics	
Country (income classification)	India (lower middle income)
Programmatic features of the intervention (Where and how)	Symptom screening and, if positive, then sputum and culture and per discretion of chest physician in case of high index of suspicion also Xpert MTB/RIF
Research questions/ objectives	Mixed method study, to examine implementation challenges of TB screening among pregnant women from the healthcare providers perspective
Notes	

Abbreviations: CB-NAAT: cartridge-based nucleic acid amplification test; DST: drug susceptibility testing; EPTB: extrapulmonary tuberculosis; FAST: LPA: line probe assay; MDR-TB: multidrug-resistant tuberculosis; MSF: Médecins Sans Frontières; NGO: non-governmental organization; NRL: National Reference Laboratory; PLHIV: people living with HIV; POC: point of care; PPIA: Private Provider Interface Agency; STI: sexually transmitted infection; TB: tuberculosis; WHO: World Health Organization; XDR-TB: extensively drug-resistant tuberculosis.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adepoyibi 2018	Not a qualitative study design
Albert 2016	Review article
Ardizzoni 2015	Data not analysed using qualitative analysis methods
Charoensook 2018	Data not analysed using qualitative analysis methods
Chawla 2016	Not a qualitative study design
Cowan 2013	Did not address phenomenon of interest
Da Silva 2014	Not a qualitative study design
Denkinger 2015	Data not analysed using qualitative analysis methods
Lemaire 2010	Data not analysed using qualitative analysis methods
Lorent 2016	Did not address phenomenon of interest
Maraba 2018	Did not address phenomenon of interest
Mpagama 2019	Data not analysed using qualitative analysis methods
Noe 2017	Data not analysed using qualitative analysis methods
Ntinginya 2021	Data not analysed using qualitative analysis methods
Ochodo 2019	Did not address phenomenon of interest
Palupi 2019	Not a qualitative study design
Paudel 2021	Abstract
Rugera 2014	Did not address phenomenon of interest
Shewade 2015	Did not address phenomenon of interest

ADDITIONAL TABLES

Table 1. Assessment of methodological limitations

Study ID	Were steps taken to increase rigour in the sampling?	Were steps taken to increase rigour in the data collected?	Were steps taken to increase rigour in the analysis of the data?	Were the findings of the study grounded in/supported by the data?	Please rate the findings of the study in terms of their breadth and depth
Cattamanchi 2020	No, not at all/Not stated/Can't tell	No, not at all/Not stated/Can't tell	No, not at all/Not stated/Can't tell	No, not at all/Not stated/Can't tell	No, not at all/Not stated/Can't tell
Colvin 2015	Yes, several steps were taken	Yes, several steps were taken	Yes, several steps were taken	Yes, a few steps were taken	Yes, several steps were taken

Table 1. Assessment of methodological limitations *(Continued)*

Creswell 2014	Yes, a few steps were taken	Yes, a few steps were taken	Yes, a few steps were taken	No, not at all/Not stated/Can't tell	Yes, several steps were taken
Davids 2015	Yes, a fairly thorough attempt was made	Yes, a few steps were taken	Yes, a few steps were taken	No, not at all/Not stated/Can't tell	Yes, a few steps were taken
De Camargo 2015	Yes, several steps were taken	Yes, several steps were taken	Yes, several steps were taken	Yes, a fairly thorough attempt was made	Yes, several steps were taken
Engel 2015a	Yes, a fairly thorough attempt was made	Yes, a fairly thorough attempt was made	Yes, a fairly thorough attempt was made	Yes, a fairly thorough attempt was made	Yes, a fairly thorough attempt was made
England 2019	No, not at all/Not stated/Can't tell	No, not at all/Not stated/Can't tell	No, not at all/Not stated/Can't tell	No, not at all/Not stated/Can't tell	No, not at all/Not stated/Can't tell
Hoang 2015	Yes, a few steps were taken	Yes, several steps were taken	No, not at all/Not stated/Can't tell	Yes, a few steps were taken	Yes, a few steps were taken
Ismail 2020	Yes, a few steps were taken	Yes, several steps were taken	Yes, a few steps were taken	Yes, a few steps were taken	Yes, a few steps were taken
Jaroslawski 2012	Yes, several steps were taken	No, not at all/Not stated/Can't tell	Yes, a few steps were taken	No, not at all/Not stated/Can't tell	No, not at all/Not stated/Can't tell
Joshi 2018	Yes, a few steps were taken	Yes, a few steps were taken	Yes, a few steps were taken	Yes, a few steps were taken	Yes, a few steps were taken
Ketema 2020	No, not at all/Not stated/Can't tell	Yes, a few steps were taken	No, not at all/Not stated/Can't tell	Yes, a few steps were taken	Yes, a few steps were taken
McDowell 2016	Yes, a fairly thorough attempt was made	Yes, a fairly thorough attempt was made	Yes, several steps were taken	Yes, a fairly thorough attempt was made	Yes, several steps were taken
McDowell 2018	Yes, a fairly thorough attempt was made	Yes, a few steps were taken	Yes, a fairly thorough attempt was made	Yes, a fairly thorough attempt was made	Yes, several steps were taken
Medina-Morino 2021	Yes, several steps were taken	Yes, a few steps were taken	Yes, several steps were taken	Yes, a fairly thorough attempt was made	Yes, several steps were taken
Mnyambwa 2018	Yes, a few steps were taken	Yes, a few steps were taken	No, not at all/Not stated/Can't tell	No, not at all/Not stated/Can't tell	No, not at all/Not stated/Can't tell
Mohammed 2020	Yes, a few steps were taken	Yes, a few steps were taken	No, not at all/Not stated/Can't tell	No, not at all/Not stated/Can't tell	No, not at all/Not stated/Can't tell
Mwaura 2020	Yes, several steps were taken	Yes, a few steps were taken	Yes, a few steps were taken	Yes, several steps were taken	Yes, several steps were taken
Naidoo 2015	Yes, a fairly thorough attempt was made	Yes, a fairly thorough attempt was made	Yes, several steps were taken	Yes, a fairly thorough attempt was made	Yes, several steps were taken

Table 1. Assessment of methodological limitations *(Continued)*

Nalugwa 2020	Yes, a few steps were taken	No, not at all/Not stated/Can't tell	Yes, a few steps were taken	No, not at all/Not stated/Can't tell	No, not at all/Not stated/Can't tell
Nathavitharana 2017	No, not at all/Not stated/Can't tell	No, not at all/Not stated/Can't tell	No, not at all/Not stated/Can't tell	No, not at all/Not stated/Can't tell	Yes, a few steps were taken
Newtonraj 2019	Yes, a few steps were taken	Yes, a few steps were taken	Yes, several steps were taken	Yes, a few steps were taken	No, not at all/Not stated/Can't tell
Oliwa 2020	Yes, several steps were taken	Yes, several steps were taken	Yes, a fairly thorough attempt was made	Yes, a fairly thorough attempt was made	Yes, a fairly thorough attempt was made
Oo 2019	Yes, a few steps were taken	Yes, a few steps were taken	Yes, a few steps were taken	Yes, a few steps were taken	Yes, a few steps were taken
Phyo 2019	Yes, a few steps were taken	Yes, a few steps were taken	Yes, several steps were taken	Yes, a few steps were taken	Yes, a few steps were taken
Raizada 2021	Yes, a few steps were taken	Yes, several steps were taken	Yes, several steps were taken	Yes, several steps were taken	Yes, several steps were taken
Rendell 2017	Yes, a few steps were taken	Yes, several steps were taken	Yes, several steps were taken	Yes, a few steps were taken	Yes, a few steps were taken
Royce 2014	Yes, several steps were taken	Yes, several steps were taken	Yes, a few steps were taken	Yes, a few steps were taken	Yes, a few steps were taken
Saria 2020	Yes, a few steps were taken	No, not at all/Not stated/Can't tell	No, not at all/Not stated/Can't tell	Yes, a few steps were taken	No, not at all/Not stated/Can't tell
Shewade 2018	Yes, several steps were taken	Yes, several steps were taken	Yes, a fairly thorough attempt was made	Yes, several steps were taken	Yes, a few steps were taken
Stime 2018	Yes, a few steps were taken	No, not at all/Not stated/Can't tell	Yes, a few steps were taken	Yes, a few steps were taken	No, not at all/Not stated/Can't tell
Vijayageetha 2019	Yes, a few steps were taken	Yes, a few steps were taken	Yes, a few steps were taken	Yes, a few steps were taken	Yes, a few steps were taken

Table 2. Key characteristics of the included studies

Study ID (categorization richness*)	Country (income classification)	Geographical setting	Type of health facility (public or private)	Diagnostic technology	Programmatic features of the intervention (where and how)	Target population	Total number of participants and types of users	Research questions/objectives	Data collection methods
Cattamanchi 2020 (medium)	Uganda (low income)	Both rural and urban	Health centres (public)	Xpert MTB/RIF	Sputum samples collected at testing sites (i.e. hubs), present in most districts, and transported to peripheral microscopy units (i.e. spokes). Intervention: daily sputum transport to Xpert testing hubs to facilitate same-day (or next-day) Xpert testing for all people who were smear-negative	People with presumptive TB	Not clear	To identify key reasons at multiple levels for attrition along the TB diagnostic evaluation cascade of care (within a larger mixed-method implementation research project)	Consultation with stakeholders and literature review
Colvin 2015 (high)	South Africa (upper middle income)	Urban	Hospital and clinic (public)	Xpert MTB/RIF and GenoType LPA	Initial TB testing with Xpert; ultimately located primarily in laboratories and not primary care clinics	People with presumptive TB	40 (global diagnostic developer, donor, evaluator n = 3; national, provincial, and district level TB programme and hospital managers, nurses, laboratory technicians n = 21; health facility managers, TB/DR-TB doctors, nurses, clerks/assistants n = 16)	To examine policy transfer for Xpert and GenoType LPA; to understand how new technologies were taken up, adapted, and delivered within local health systems	Longitudinal, qualitative evaluation to track policy transfer. Two phases of key informant interviews complemented with document review
Creswell 2014 (medium)	Nine countries (Democratic Republic of Con-	Both rural and urban	District hospitals, laboratories, AIDS centres	Xpert MTB/RIF	Countries used different approaches (active, passive, mixed, screening); placements in-	MTB/RIF testing of people with presumptive	Unclear (project staff, implementers, manufacturer)	To present results from nine TB REACH interventions, review the main challenges experienced, and formulate recommen-	Document review and interviews with staff

Table 2. Key characteristics of the included studies *(Continued)*

	go - low income, Kenya - lower middle income, Pakistan - lower middle income, Bangladesh - lower middle income, Mozambique - low income, Cambodia - lower middle income, Malawi - low income, Nepal - lower middle income, Moldova - lower middle income)		(both public and private)		cluded public and private hospitals and peripheral primary care facilities, private diagnostics laboratories, HIV centres, prisons, reference- laboratories and mobile units. The projects were able to run the machines at district hospitals and peripheral levels of care although in only a few situations were peripheral microscopy centres included, mostly because of throughput concerns	TB; variable implementation, mostly for people who were sputum negative		dations for other early implementers; mixed methods	from each project and manufacturers
Davids 2015 (low)	South Africa (upper middle income)	Urban	Primary health care clinics (both public and private)	TB POC tests, rapid diagnostic tests, Xpert MTB/RIF	POC testing of people with presumptive TB	People with presumptive pulmonary TB, drug-resistant TB, and extrapulmonary TB	400 (doctors n = 255 and nurses n= 145)	To examine how primary healthcare providers diagnose TB in their setting and what their perspectives are on an ideal POC test for TB	Survey with recorded qualitative comments to survey questions and anecdotal notes

Table 2. Key characteristics of the included studies *(Continued)*

De Camargo 2015 (high)	Brazil (upper middle income)	Urban	Clinic (public)	Xpert MTB/RIF	Not reported	People with presumptive TB	Unclear (interviews with 11 people diagnosed with smears and 19 diagnosed with Xpert MTB/RIF, interviews with key informants at research sites and local health departments (number not specified), preparation of the flowcharts with physicians, nurses, laboratory technicians, administrative and managerial health, facility staff members)	To qualitatively evaluate the repercussions of the adoption of Xpert MTB/RIF from the perspective of people with (presumed) TB, health professionals and managers, considering aspects such as understanding, perception, and meaning	Interviews, group meets to produce diagnostic flowcharts
Engel 2015a (medium)	South Africa (upper middle income)	Both rural and urban	Clinics and hospitals (both public and private)	Xpert MTB/RIF at POC in district hospitals	People presenting at different levels of care (in clinics, health posts, laboratories, or hospitals) with multiple or unspecific symptoms (e.g. acute febrile illness) and may need several diagnostic tests. Testing mostly centralized but in some district hospitals Xpert is available	People with presumptive TB	141 interviews (n = 101 with doctors, nurses, community health workers, patients, laboratory technicians, policymakers, hospital managers, and diagnostic manufacturers; and focus group discussions n = 40 with people with TB, nurses and community health workers), interviews not focused on TB diagnostics exclusively	To examine POC testing across major diseases in South Africa contributing to burden of disease (mainly HIV, TB, diabetes mellitus, diarrhoeal diseases, and hypertension); to assess what tests are performed and how and whether they can ensure successful POC testing	Interviews, focus group discussions
England 2019 (low)	16 TB burden countries	Unclear/not reported	Unclear/not reported (public)	Xpert MTB/RIF	Examined slow uptake of Xpert for all	People with presumptive TB	Comments from several country stakeholders were reported	To summarize key challenges associated with the scale-up of Xpert and compare these with on	Conversations with country represen-

Table 2. Key characteristics of the included studies *(Continued)*

								the ground realities as assessed through a survey on barriers to the scale-up of testing; following results of this survey, to explore reasons for slow uptake of Xpert for all	tatives to explain results of a quantitative survey that had been conducted
Hoang 2015 (medium)	Vietnam (lower middle income)	Unclear/not reported	District health centre/hospital (public)	Xpert MTB/RIF	Unclear	People at high risk for MDR-TB	110 (TB provincial staff members n = 30, health staff n = 80 (8 central, 56 provincial, 16 district and community level))	To understand challenges of efficient implementation of 5 steps from diagnosis to MDR-TB treatment (mixed method study)	Focus group discussions, interviews, document review
Ismail 2020 (medium)	India (lower middle income)	Both rural and urban	Peripheral health institutions, tuberculosis units (both public and private)	CB-NAAT and other routine TB tests (sputum smear microscopy, culture, DST, chest X-ray)	Standard procedures of national TB programme for diagnosing and treating routine TB	People with presumptive TB	15 (different health care providers engaged along the diagnostic and treatment pathway)	Mixed methods study, to explore the reasons for not undergoing diagnostic testing and people with TB not being initiated on treatment	Qualitative part: Interviews
Jaroslawski 2012 (medium)	India (lower middle income)	Urban	Peripheral laboratory, clinic (both public and private)	Serology tests, molecular tests such as Xpert MTB/RIF	Unclear, private providers used serology, Xpert was mentioned as one of the costly alternatives	People with presumptive TB approaching private providers	41 (private doctors and private hospital laboratory staff n = 11, private stand-alone laboratories n = 7, distributors of diagnostic tests n = 7, manufacturers of diagnostic tests n = 7, government hospital doctors n = 4, and NGOs working in TB n = 5)	To explore why serological tests are so popular in the private sector and what factors have paved the way for their widespread use	Interviews

Table 2. Key characteristics of the included studies *(Continued)*

Joshi 2018 (medium)	Nepal (lower middle income)	Both rural and urban	CB-NAAT centres in district hospitals, primary health centres, district public health office laboratory (public)	Xpert MTB/RIF	Not reported	Children (< 15 years); people living with HIV (PLHIV); severe forms of TB; and people presumed to have MDR-TB	Unclear (interviews with people with presumptive TB (n = 22) and with national level TB programme officers (n = 4), 4 focus group discussions (district TB officer and/or lab personnel) of which 2 focus group discussions were replaced by in-depth interviews)	To explore the barriers to effective implementation of the Xpert MTB/RIF assay (mixed methods sequential explanatory design a qualitative evaluation)	Focus group discussions, in-depth interviews, semi-structured interviews (patients)
Ketema 2020 (low)	Ethiopia (low income)	Urban	Primary healthcare centre (public)	Xpert MTB/RIF	Initial diagnostic test	Children with presumptive TB	41 (health care workers n = 30 and heads of study health facilities n = 11)	Mixed methods study, to evaluate the integration of TB screening and contact investigation into integrated maternal, neonatal and child illnesses and TB clinics	Interviews and observation notes
McDowell 2016 (high)	India (lower middle income)	Urban	Clinic (private)	Xpert MTB/RIF, sputum smear, X-ray	Highly variable, mostly empirical treatment first, then a range of tests, always including X-ray. If Xpert MTB/RIF then late in the process	People with presumptive pulmonary TB diagnosed with HIV/AIDS	185 (private providers - different specialization n = 110, people seeking care n = 75)	To understand the factors contributing to the variability in care and the practices diverging from the standard of TB care in India	Interviews, observations of clinical practice, and continuing medical education events
McDowell 2018 (high)	India (lower middle income)	Urban	Newly established high throughput CB-NAAT labs, one per city, which linked to public/pri-	Xpert MTB/RIF	Study focuses on a project to improve the implementation of initial Xpert testing for paediatrics by free testing with quick turnaround times (within 24 hours) and efforts in co-ordination with	Children with presumptive TB with fever more than 2 weeks, unremitting cough for more than	55 physicians who had referred samples for Xpert testing (public physicians n = 20, private physicians n = 22, charitable hospitals n = 5, TB programme officers n = 8)	To understand the perspective of providers engaged under the ongoing project with respect to Xpert testing in children and implementation bottlenecks: i) how do paediatricians use Xpert when accessible and free of cost, ii) how do they pri-	Semi-structured interviews

Table 2. Key characteristics of the included studies *(Continued)*

			vate clinics and hospitals (both public and private)		local authorities to improve provider literacy to diagnosing TB in children	2 weeks, and/or weight loss or no weight gain in past 3 months		oritize and evaluate Xpert in relation to other diagnostic technologies, and iii) what are the effects of Xpert on their clinical practice	
Medina-Morino 2021 (medium)	South Africa (upper middle income)	Urban	Community, outreach (unclear, not reported)	Portable GeneXpert single module instrument (GeneXpert Model GX-I) for home-based testing	Targeted, community-wide household screening intervention; Xpert was used in the home in front of household contacts of people with TB	Household contacts	39 (interviews n = 30 and two focus group discussions n = 9)	To explore the acceptability and perceived benefits of home-based TB testing using a portable GeneXpert-I instrument in an urban township	Interviews and focus group discussions
Mnyambwa 2018 (low)	Tanzania (lower middle income)	Unclear/not reported	Unclear type, located at regional and district levels (public)	Gene Xpert, GxAlert	Unclear	People with presumptive MDR-TB	27 (interviews with Regional TB Leprosy Co-ordinators n = 10 and District TB and Leprosy Co-ordinators n = 17 from all parts of the country where patients were not enrolled in treatment)	Mixed method: To assess the effectiveness of GeneXpert GxAlert health platform for MDR-TB diagnosis and its facilitation of the linkage to healthcare services	Retrospective review of routine clinical data of a cohort of people with MDR-TB diagnostically confirmed by the GeneXpert and complemented with interviews
Mohammed 2020 (low)	Ethiopia (low income)	Both rural and urban	Outpatient department, HIV clinic, clinics	Xpert MTB/RIF	General TB screening (passive) algorithm in Ethopia	People with presumptive TB	35 (head of health facility n = 7; a focal healthcare provider at each facility's DOT clinic,	To assess the challenges related to TB screening and diagnosis and related to functionality, use,	Semi-structured interviews and quan-

Table 2. Key characteristics of the included studies *(Continued)*

			for maternal child health and diabetes (both public and private)				ART clinic, outpatient department or diabetic clinic, and maternal child health clinic n = 28)	maintenance and supply of Xpert MTB/RIF	titative document review
Mwaura 2020 (medium)	Kenya (lower middle income) and Eswatini (lower middle income)	Unclear/not reported	Unclear/unreported (unclear/not reported)	Xpert MTB/RIF Ultra	Unclear	People with presumptive TB	47	To examine the views of multiple TB stakeholders on the trade-off between overtreatment versus under-diagnosis of TB, and to understand the role qualitative research can play in engaging in-country stakeholders during roll-out of new TB diagnostics	Focus group discussions
Naidoo 2015 (high)	South Africa (upper middle income)	Urban	Primary healthcare facilities, central laboratory (unclear/not reported)	Xpert MTB/RIF, LPA	The testing algorithm changed during the study: In 2010, a smear, culture and LPA-based diagnostic algorithm was used with LPA done on culture isolates or clinical specimens of people with high risk of MDR-TB (those with previous TB, MDR-TB contact, or from a congregate setting). From 2011–2013, Xpert was phased in, replacing smear microscopy for all people with presumptive TB	People with presumptive TB	26 people with MDR-TB	To explore and compare people's experiences of their pathway to MDR-TB diagnosis and treatment initiation in LPA and Xpert-based diagnostic algorithms	Interviews
Nalugwa 2020 (medium)	Uganda (low income)	Both rural and urban	Community health centres	Xpert MTB/RIF	Uganda adopted policy recommendations in line with	People with presumptive	23 participating community health centres (clinic staff)	Mixed method, qualitative part: to assess the process of specimen col-	Qualitative data was

Table 2. Key characteristics of the included studies *(Continued)*

			(clinics) and Xpert testing sites (public)		WHO guidelines; use of smear microscopy and Xpert MTB/RIF at participating health centres	TB presenting to community health facilities linked with TB diagnostic units had access to rapid, referral-based Xpert testing. As per Uganda national guidelines, Xpert testing in people living with HIV, healthcare workers, contacts of people with DR-TB, pregnant women or breastfeeding mothers, people in prisons, patients from refugee camps, and people with diabetes		lection, specimen transport, specimen testing, result reporting and linkage to treatment initiation if diagnosed with TB	collected from field notes taken by study staff during site visits for training, surveys, and data abstraction.
Nathavitharana 2017 (low)	Bangladesh (lower	Urban	Hospital (public)	FAST (Find cases, Actively,	People admitted and those with cough or a history of lung	People with pre-	Stakeholders and staff but not further	To test a new active screening strategy (FAST) since most transmission	Discussed potential imple-

Table 2. Key characteristics of the included studies *(Continued)*

	middle income)			Separate safely, and Treat effectively) using Xpert MTB/RIF	disease underwent Xpert testing for pulmonary TB	sumptive TB	specified for qualitative part	happens from unsuspecting TB cases and to better understand potential implementation challenges identified	mentation challenges identified through a series of qualitative assessments, including staff interviews, focus groups, brainstorming and listing techniques
Newtonraj 2019 (medium)	India (lower middle income)	Unclear/not reported	Clinics, designated microscopy centres and hospitals (both public and private)	Xpert MTB/RIF	Xpert MTB/RIF was located at the intermediate reference laboratory, along with culture and LPA; district microscopy centres (mostly within district hospitals and medical colleges) would send samples of people eligible for testing	Initial diagnostic test for HIV-associated TB, EPTB, and paediatric TB and as an add-on test for people with negative sputum microscopy if chest radiography suggestive of TB	10 (healthcare workers involved in implementation; medical officers/doctors n = 5, microbiologists n = 3, lab techs n = 2)	To explore enablers and barriers in using Xpert among the targeted groups from the providers' perspective	Interviews
Oliwa 2020 (high)	Kenya (lower middle income)	Unclear/not reported	County hospitals (public)	Xpert MTB/RIF assay	Initial Xpert for the diagnosis of paediatric TB in Kenyan county referral hospitals	Children with presumptive TB	40 (interviews with front-line health workers and mid-level managers n = 29. Three small	To understand how context influences and shapes TB case detection and use of TB diagnostic tests in-	Interviews, small group discussions,

Table 2. Key characteristics of the included studies *(Continued)*

							group discussions (n = 6) and key informant interviews (n = 5) with policy makers and senior health service administrative staff (medical officers; clinical officers; nursing officers; medical officer interns; clinical officer interns; nursing officer interns and laboratory technologists)	cluding Xpert in children within hospitals	and observations of child TB training, of sensitization meetings, policy meetings, and hospital practices as well as document review
Oo 2019 (low)	Myanmar (lower middle income)	Predominantly rural	Township TB centre (public)	Xpert MTB/RIF	Mainly used for the purpose of rifampicin-resistant TB diagnosis, located at district TB centres in selected townships	People thought to have rifampicin-resistant/MDR-TB	32 (township TB coordinators n = 28 and laboratory technicians from Xpert sites n = 4)	Mixed methods study; qualitative part: to understand health provider perspectives on the reasons for failure to identify and test people eligible for TB testing with Xpert	Key informant interviews
Phyo 2019 (medium)	Myanmar (lower middle income)	Urban	Community outreach in townships (other: NGO-led)	Xpert MTB/RIF	Household contacts of people with MDR-TB with TB symptoms should be investigated using Xpert MTB/RIF; but policy is followed poorly	Household contacts of people with MDR-TB	21 (household contacts of people with MDR-TB n = 8, healthcare providers n = 13 (community volunteers, project nurses), project supervisor)	Mixed methods study; qualitative part: To explore the barriers in implementing contact investigation from the perspective of household contacts and healthcare providers	Interviews
Raizada 2021 (medium)	India (lower middle income)	Urban	Community (both public and private)	Xpert MTB/RIF	Free of cost upfront Xpert MTB/RIF testing for TB diagnosis in paediatric populations in a project by Foundation for Innovative New Diagnostics (FIND) and national TB programme	Children with presumptive TB	100 (Xpert MTB/RIF positive children and their guardians)	Mixed methods study, to explore the experiences of children with TB and their families along the pathway to bacteriological confirmation of TB and appropriate treatment	Interviews and document review

Table 2. Key characteristics of the included studies *(Continued)*

Rendell 2017 (medium)	Mongolia (lower middle income)	Urban	National TB reference laboratory, provincial TB clinics, district TB clinics, hospital (public)	Xpert MTB/RIF	Unclear; only eligibility criteria were reported and a weekly consensus meeting for treatment initiation was mentioned	All people with smear-negative pulmonary TB; people with presumptive pulmonary TB diagnosed with HIV/AIDS; people thought to have MDR-TB or XDR-TB; (All smear-positive new patients aged 15-34 years old (this guideline is yet to be implemented))	24 (laboratory staff n = 8, TB physicians n = 16)	To identify and understand system and context-specific factors within Mongolia's National Tuberculosis Programme that are barriers or enablers to implementing the Xpert MTB/RIF test from the perspective of programme staff	Semi-structured interviews
Royce 2014 (medium)	Cambodia (lower middle income)	Unclear/not reported	Regional laboratories, district and referral hospital and health centres (unclear/not reported)	Xpert MTB/RIF	Cambodia's guidelines recommend that previously treated patients have sputum specimens tested using Xpert MTB/RIF (available in four provincial laboratories), followed by culture and species identification using liquid and solid media (available in	People previously treated for TB	Unclear; 26 interviews (doctors or clinical officers n = 9, nurses n = 8, laboratory staff n = 6, and TB officers n = 3). Focused group discussions (number of participants unclear)	To quantify the gaps in the detection of MDR-TB in people previously treated for TB, and- describe health workers' perspectives on barriers, facilitators and potential interventions, sequential explanatory mixed-methods design	Focus group discussions and interviews

Table 2. Key characteristics of the included studies *(Continued)*

					three regional laboratories) and conventional DST at the national reference laboratory				
Saria 2020 (low)	India (lower middle income)	Urban	Unclear, private clinics and informal providers (private)	Xpert MTB/RIF	Private Provider Interface Agency (PPIA) intervention incentivized informal providers to direct patients with the classic symptoms of TB to formal providers and incentivized uptake of Xpert among formal providers	People with presumptive TB with classic symptoms	20 months of ethnographic fieldwork; formal and informal providers including compounders (doctors' assistants in clinics), lab owners and technicians, pharmacy shop owners and their assistants, patients, and intervention related field staff	To understand how the PPIA intervention was received and recognized by the various actors that comprised the medical infrastructure and market	Interviews and observation/shadowing formal healthcare providers trained in biomedicine, lab technicians, patients, compounders, and pharmacist
Shewade 2018 (medium)	India (lower middle income)	Both rural and urban	CB-NAAT testing at tertiary district level facility; sputum smear at microscopy centre where samples need to be sent from (public)	CB-NAAT and LPA	In January-March 2014, if sample was smear-positive, then LPA was used initially. Among smear-negative samples, culture was done followed by LPA. From April 2014 onwards, LPA was used for smear-positive and- CB-NAAT was used for smear-negative samples	People with presumptive MDR-TB or high risk patients	23 (lab technicians n = 6, treatment supporters/supervisors n = 12, microbiologist n = 2, district TB officer n = 1, senior TB lab supervisor n = 1, senior DR-TB supervisor n = 1)	To explore from the healthcare provider perspective, the barriers and suggested solutions for improving DST in programmatic setting	Interviews (10), focus group discussions (2) plus one later focus group discussion to discuss results
Stime 2018 (medium)	South Africa (upper middle income)	Urban	Busy clinic (public)	Xpert MTB/RIF (16 module)	On-site 16 module Xpert machine, batching samples in 2-3 runs per day	Not reported	20 (clinic staff: nurses n = 6, physicians n = 2, laboratory technicians n =	To describe clinic flow with special emphasis on the impact of POC testing at a large urban pub-	Semi-structured interviews

Table 2. Key characteristics of the included studies *(Continued)*

					(approximately 48 samples/day) and in parallel HIV rapid and viral load testing (some testing for sexually transmitted infections with Xpert ongoing as well)		5 administrators n = 5, security guards n = 2)	lic healthcare clinic in Durban, South Africa (mixed method, time-in-motion study)	
Vijayageetha 2019 (medium)	India (lower middle income)	Urban	Tertiary care hospital (public)	Xpert MTB/RIF	Symptom screening and if positive then sputum and culture and per discretion of chest physician in case of high index of suspicion also Xpert MTB/RIF	Pregnant women with TB symptoms, Xpert was mainly used for diagnosis of paediatric TB, HIV-associated TB, extrapulmonary TB, and MDR-TB	7 (administrator n = 1, obstetricians n = 2, chest physicians n = 1, physician n = 1, nursing officers n = 2)	Mixed method study, to examine implementation challenges of TB screening among pregnant women from the healthcare providers perspective	Interviews and observations

* Categorization of included studies for sampling purposes into high, medium and low richness prior to data extraction and methodological limitations assessment
Abbreviations: ART: antiretroviral therapy; CB-NAAT: cartridge-based nucleic acid amplification test; DOT: directly observed treatment; DR-TB: drug-resistant tuberculosis; DST: drug susceptibility testing; EPTB: extrapulmonary tuberculosis; FAST: Find cases, Actively, Separate safely, and Treat effectively; GX-I: (GeneXpert Model GX-I); LPA: line probe assay; MDR-TB: multidrug-resistant tuberculosis; MSF: Médecins Sans Frontières; NGO: non-governmental organization; NRL: National Reference Laboratory; PLHIV: people living with HIV; POC: point of care; PPIA: Private Provider Interface Agency; STI: sexually transmitted infection; TB: tuberculosis; WHO: World Health Organization; XDR-TB: extensively drug-resistant tuberculosis

Table 3. Evidence profiles

Finding #	Review finding	Methodological limitations	Coherence	Relevance	Adequacy	CERQual assessment of confidence in the evidence	Eplanation of CERQual assessment	Studies contributing to review finding

Table 3. Evidence profiles *(Continued)*

Critical aspects users value

1	People with TB, the vast majority from high-TB burden countries, value: 1) getting an accurate diagnosis and reaching diagnostic closure (finally knowing what is wrong with me), 2) avoiding diagnostic delays as they exacerbate existing financial hardships and emotional and physical suffering and make patients feel guilty for infecting others (especially children), 3) having accessible facilities, and 4) reducing diagnosis-associated costs (travel, missing work) as important outcomes of the diagnostic.	Minor concerns - across the four components of the methodological limitations tool, three of the studies contributing took a few steps to ensure methodological quality and the remaining five took several steps to ensure methodological quality.	No concerns - synthesis was directly related to primary studies; missing explanations were explored and added to the finding.	Minor concerns about study locations: studies mostly located in urban areas in high-burden settings, good variety of facility types	Minor concerns - two rich studies included, two studies undertook several steps and the remaining studies have undertaken few steps towards richness; the number of participants included was adequate for qualitative designs.	Moderate confidence	We have minor concerns about methodological quality and adequacy and we have minor concerns about relevance (because of the mostly urban study locations)	De Camargo 2015; Joshi 2018; Naidoo 2015; Phyo 2019; Royce 2014; Vijayageetha 2019; Medina-Morino 2021Raizada 2021
2	Compared to existing tests such as sputum microscopy, healthcare providers appreciate the rapidity and accuracy of low-complexity NAAT results, the diversity of sample types, ability to detect drug resistance, as well as the consequence of avoiding costlier investigations or hospital stays when using low-complexity NAATs.	Minor concerns - across the four components, the methodological quality was fairly high for three studies and the remaining studies took mostly a few steps to increase quality.	No concerns - synthesis was directly related to primary studies.	No concerns - good variety of facilities, public/private and type of healthcare workers, and fairly diverse set of countries, studies mostly located in urban areas in high-burden settings but we did not think this would affect relevance for this finding.	Minor - three rich studies included, only one thin study and the rest have undertaken several steps towards richness; number of participants included was adequate.	High confidence	Mainly because we have no concerns about coherence and relevance and only minor concerns about methodological quality and richness of a few studies	De Camargo 2015; Joshi 2018; McDowell 2018; Mwaura 2020; Naidoo 2015; Newtonraj 2019; Rendell 2017; Vijayageetha 2019
3	Low-complexity NAATs allow healthcare providers to detect drug resistance earlier and paediatricians, in particular, mentioned how it heightened their perception of drug resis-	No concerns - the majority of the studies were of good quality.	Minor concerns - good fit of finding with primary studies,	No/very minor concerns, countries with large burden of DR-TB included, ex-	No concerns - three rich studies of four; adequate num-	High confidence	Mainly because quality of studies is high and we on-	De Camargo 2015; Joshi 2018; McDowell 2016;

Table 3. Evidence profiles *(Continued)*

	tance in children; yet, in a context with widespread severe forms of drug resistance and a habit of treating empirically first, clinicians see the inability of some NAATs to detect resistance beyond rifampicin as a hindrance.		but change in risk perception and need for entire resistance profile mentioned in only one study each, but these were studies well grounded in the data.	cept examples from Eastern Europe missing, public/private, urban/rural, good variety of primary care and low-complexity NAAT testing centre facilities	bers of participants		ly have a minor concern about coherence due to number of studies contributing to each part of the finding	McDowell 2018; Naidoo 2015
4	Clinicians value the confidence that low-complexity NAAT results provide. Having confidence helps in starting treatment, reassuring and motivating people with TB and their caretakers, justifying management decisions towards other doctors, and increasing collaboration between private and public providers.	No concerns - the studies were of good quality.	No concerns - good fit of finding with primary studies; other explanations of how confidence matters are captured in finding #13.	Minor concerns because it is only two countries, but good variety of participants, facilities and public/private providers	No/very minor concerns - two very rich studies and one study which undertook several steps towards richness; all three studies with adequate numbers of participants	High confidence	We have no concerns or very minor concerns across all components	McDowell 2018; Oliwa 2020; Raizada 2021
5	Laboratory technicians appreciate the improvement of overall laboratory work that low-complexity NAATs bring compared to sputum microscopy in terms of ease of use, ergonomics, and biosafety.	Minor concerns - one study of good quality; the remaining two took a few steps to ensure methodological quality.	No concerns - good fit of finding with primary study	No concerns - variety of locations, countries, facilities and users included	Minor concerns - two relatively rich studies; the third one was more thin; the number and type of participants included was adequate	High confidence	We have no concerns or very minor concerns across all components	Creswell 2014; De Camargo 2015; Newtonraj 2019
6	Laboratory managers appreciate that monitoring of laboratory work and training is easier than with spu-	No/very minor concerns	No concerns - good fit of finding	Serious concerns - just one setting (urban,	Moderate concerns - because it	Low confidence	We have serious or moderate	De Camargo 2015

Table 3. Evidence profiles *(Continued)*

	tum microscopy and that low-complexity NAATs ease staff retention, as these tests increase staff satisfaction and have a symbolic meaning of progress within the TB world.		with primary study	public clinic); study early in implementation of low-complexity NAAT	was only one study, but it was rich, with an adequate number of participants; unclear how many of these were managers		concerns about adequacy and relevance and no concerns about methodological quality and coherence	
Challenges to realizing these values								
7	People with presumptive TB can be reluctant to test for TB or MDR-TB because of stigma related to MDR-TB or related to having interrupted treatment in the past, because of fears of side effects, the failure to recognize symptoms, the inability to produce sputum and the cost, distance and travel concerns related to (repeat) clinic visits. Thus, low-complexity NAAT testing is not operationalized with sufficient support or discretion to overcome barriers that are common to other approaches to testing for TB.	Very minor concerns - four out of seven included studies had fairly good methodological quality across all four components.	No concerns - good fit of finding with primary study	No/very minor concerns; varied participants, facilities, urban/rural, even though just four countries; but we did not expect adding more countries would have altered finding substantially.	Minor concerns - one rich study and most took a few steps towards richness; the number of participants was adequate	High confidence	We have no concerns or very minor concerns across all components	Naidoo 2015; Phyo 2019; Royce 2014; Saria 2020; Shewade 2018; Ismail 2020; Medina-Morino 2021
8	Healthcare workers can be reluctant to test for TB or MDR-TB because of TB associated stigma and its consequences, fears of acquiring TB, fear from supervisors when reclassifying patients already on TB treatment who turn out to be misclassified, fear of adverse effects of drugs in children, and lack of community awareness of disease manifestations in children. Thus, low-complexity NAAT testing is not operationalized with sufficient support or discretion to overcome barriers that are common to other approaches to testing for TB.	No/very minor concerns - one study of very high quality; the other took several steps towards high quality.	No concerns - good fit of finding with primary study	No concerns - variety of facilities, participants; not the usual dominantly represented countries and at two different time points	No/very minor concerns; one rich study and one study which seemed rich but quotes were not attributable, might have been just a reporting issue; very adequate numbers of participants	High confidence	We have no concerns across all components	Oliwa 2020; Royce 2014

Table 3. Evidence profiles *(Continued)*

					for both studies			
9	Rapid turn-around time is an important potential of diagnostic algorithms involving NAATs of low complexity. Yet, diagnostic delays are accumulated because of various health system factors (i.e. non-adherence to testing algorithms, testing for (MDR-)TB late in the process, empirical treatment, false negatives due to technology failure, large sample volumes and staff shortages, poor or delayed sample transport and resulting delays in communication, delays in scheduling follow-up visits and recalls, inconsistent result recording) and, to a lesser extent, delays related to people seeking a diagnosis (i.e. missed follow-up appointments, competing family demands and seeking traditional healthcare).	Minor concerns - varied methodological quality of included studies; three of high quality; studies of lower quality did not contribute new or additional insights, rather confirmed other studies	No concerns - descriptive and specific statement based on the data from primary study	No concerns - good variety of users, facilities, public/private, urban/rural, time points and countries	Minor concerns, four relatively rich studies, adequate numbers of participants, well known descriptive finding	High confidence	We have no or very minor concerns across the components, also diagnostic delay is well established and the weaker studies' findings point into the same direction	Cattamanchi 2020; Creswell 2014; Davids 2015; Engel 2015a; McDowell 2016; Mohammed 2020; Naidoo 2015; Nalugwa 2020; Nathavitharana 2017; Oo 2019; Rendell 2017; Royce 2014; Stime 2018; Ismail 2020; Ketema 2020
10	Challenges with sample quality, collection and transport can cause error results and underutilization of low-complexity NAATs. Specifically, providers struggle with poor sample quality, sample collection facilities that are inconveniently located for people seeking a diagnosis, non-functioning sample transport mechanisms that can damage samples or deter providers from ordering tests, and difficulty in obtaining paediatric samples .	Minor concerns - the majority of studies contributing to the finding were either of good quality or took a few steps towards methodological quality; studies of lower quality did not contribute new or additional insights, rather confirmed other studies	No concerns - descriptive and specific statement based on the data from primary study	No concerns - good variety of users, facilities, public/private, urban/rural settings, time points and countries	Minor concerns, three rich studies and most studies took a few steps towards richness; adequate number of participants	High confidence	Mainly because we have no concerns about coherence and relevance and only minor concerns about the methodological quality of half the studies contributing and no con-	Cattamanchi 2020; Creswell 2014; Davids 2015; Hoang 2015; McDowell 2016; McDowell 2018; Nathavitharana 2017; Newtonraj 2019; Oliwa 2020; Oo 2019; Phyo

Table 3. Evidence profiles *(Continued)*

							cerns about the quality and richness of the remaining ones	2019; Rendell 2017; Royce 2014; Saria 2020; Shewade 2018; Vijayageetha 2019 ; Ketema 2020: Raizada 2021
11	The lack of sufficient resources to conduct low-complexity NAATs and maintenance challenges (i.e. stock-outs; unreliable logistics; lack of funding, electricity, space, air conditioners, and sputum containers; dusty environment, and delayed or absent local repair option) lead to higher test failure rates and under-utilization of low-complexity NAATs.	Minor concerns - of 13 studies contributing to the finding, about five were of fairly good or very good quality while five took a few steps towards methodological quality; the three studies of lower quality did not contribute new or additional insights, rather confirmed other studies	No concerns - captured the data from primary studies	No/very minor concerns; good variety of users, facilities, countries, urban/rural, time points; the majority of studies in public sector settings	Minor concerns - four rich studies and four thin studies; the others took a few steps towards richness; adequate number of participants; descriptive review finding with limited scope posed fewer demands on data richness	High confidence	Mainly because we have no concerns about coherence and relevance and only minor concerns about methodological quality and richness of about half the studies	Creswell 2014; De Camargo 2015; England 2019; Hoang 2015; Joshi 2018; Mohammed 2020; Mwaura 2020; Nalugwa 2020; Nathavitharana 2017; Oliwa 2020; Rendell 2017; Shewade 2018; Stime 2018
12	Low-complexity NAATs may be promoted as decreasing workload by freeing up time for laboratory staff, but in most settings staff may be hesitant to accept testing with low-complexity NAATs because it increases workload if added onto existing laboratory work without adjusting staffing arrangements, or if it does not replace existing diagnostic tests.	Minor concerns - of the eight studies contributing, most studies took a few steps towards methodological quality with three taking several steps.	Minor concerns - finding captured the primary studies well; the only minor concern was that the explicit mentioning of not accepting low-	No/very minor concerns; good variety of users, facilities, and countries, though predominantly urban and public facilities (but that was expected for this finding because of where	Minor concerns - the studies took a few steps towards richness and had an adequate number of participants.	Moderate confidence	Mainly because of the minor concern with coherence where only one study contributed to the point on acceptance	De Camargo 2015; Joshi 2018; Oo 2019; Phyo 2019; Rendell 2017; Shewade 2018; Stime 2018; Vijayageetha 2019

Table 3. Evidence profiles *(Continued)*

			complexity NAATs because of workload concerns was only mentioned in one study.	low-complexity NAATs were mainly located)				
13	Workflows, professional roles and the flow of people seeking care matter for utilizing low-complexity NAATs; for instance, inefficient organizational processes, poor links between providers, unclear follow-up mechanisms or where people need to go for testing can deter utilization.	No/very minor concerns - mainly because methodological limitations were minor and related to not being reported and two studies were well done	No concerns - captured the data from primary studies	No/very minor concerns - good variety of users, facilities, countries,and time points, but only one study focused on the private sector; the coordination between public/private sector was covered in two studies	Minor concerns - the studies took a few steps; three did not report on richness, two were rich, and there was an adequate number of participants.	High confidence	No concerns about methodological quality, coherence and relevance, we only have minor concerns about the degree of richness	De Camargo 2015; Hoang 2015; Mnyambwa 2018; Oliwa 2020; Royce 2014; Saria 2020; Stime 2018
14	Too much confidence in low-complexity NAATs' accuracy can mean blindly accepting results without using clinical impressions, or for people with presumptive TB trusting a low-complexity NAAT result because it is computer-based.	Moderate concerns - no study of very high quality; three studies took a few steps towards methodological quality.	No concerns - captured the data from primary studies	No concerns - good variety of users, facilities, countries and time points, public/private, rural/urban	Moderate concerns - because there was only one study that took several steps towards richness; the two remaining were thin or not reported; the number of participants was adequate	Moderate confidence	Mainly because of the moderate concerns with methodological quality and richness of data	Joshi 2018; Mwaura 2020; Newtonraj 2019
15	Insufficient attention to responsive and inclusive implementation processes can hamper the impact	Minor concerns - Four of 13 studies were	No/very minor concerns - cap-	No concerns - good variety of users, facilities,	Minor concerns - adequate num-	High confidence	Mainly because we have no	Colvin 2015; Creswell 2014; Davids

Table 3. Evidence profiles *(Continued)*

	of low-complexity NAATs. Specifically, implementation processes have been challenged by lack of data from pragmatic studies on effectiveness in operational conditions, lack of knowledge and awareness among providers beyond laboratory personnel, lack of guidelines, standardized training modules and instructions, and a lack of national policy consensus and inclusive decision-making prior to roll-out.	of very good quality; seven studies took few or several steps towards increasing quality and the two studies of lower quality did not contribute new or additional insights, rather confirmed other studies.	tured data from primary studies; the point on data and inclusive decision-making only made by one study but this was just a minor concern as the study was well grounded in data.	countries and time points, public/private, rural/urban	ber of participants; four of 13 studies took several steps towards richness, the others a few and two were thin.		concerns about coherence and relevance and only minor concerns about methodological quality and richness of about half the studies and the thin studies do not challenge the review finding but confirm it	2015; De Camargo 2015; England 2019; Hoang 2015; Joshi 2018; Mnyambwa 2018; Naidoo 2015; Newtonraj 2019; Oo 2019; Rendell 2017; Shewade 2018
Concerns for access/equity								
16	Uncertainty around sustainability of funding and maintenance and the strategic and inequitable use of resources negatively affects creating equitable access to low-complexity NAATs.	No concerns - three out of six studies of good quality; the two studies of lower methodological quality did not contribute new or additional insights, rather confirmed other studies.	No/very minor concerns - captured data from primary studies; the point on conflict of interest and strategic use of resources was only made by one study, but this was just a minor concern as the study was well grounded in data.	No concerns - good variety of users, facilities, countries, public/private, rural/urban, and time points of low-complexity NAAT implementation	Minor concerns - most were fairly rich studies; two were thin; the number of implementers/managers and participants for two studies was not clear.	High confidence	We have no concerns except minor concerns about coherence because part of the finding relies on only one study	Colvin 2015; Creswell 2014; De Camargo 2015; England 2019; Jaroslawski 2012; Nathavitharana 2017

Table 3. Evidence profiles *(Continued)*

17	Access to prompt and accurate testing and treatment is hampered, particularly for the vulnerable groups, by the challenges outlined above for realizing recipient and provider values.	Minor concerns - five out of 13 studies were of very good methodological quality; the remaining ones took a few steps to increase quality across the assessed domains; the one study of lower quality did not contribute new or additional insights, rather confirmed other studies.	No concerns - captured the data from primary studies and referred to summary findings #7 and #9	No concerns - good variety of users, facilities, countries and time points, public/private, rural/urban	Minor concerns - five rich studies, five took a few steps towards richness, and one thin study; adequate numbers of participants	High confidence	We have only very minor concerns about methodological quality and richness of half the studies	Engel 2015a; England 2019; Hoang 2015; Joshi 2018; McDowell 2016; McDowell 2018; Naidoo 2015; Nalugwa 2020; Newtonraj 2019; Oliwa 2020; Oo 2019; Phyo 2019; Royce 2014
18	Test users described how implementation challenges lead to accumulated delays that undo the improvements they value in these new tests, and so discourage test use and reduce access and equity.	No concerns - high quality of included studies	No concerns - captured the data from the four primary studies and from the summary findings #1-15 which all were judged to be coherent except with two where we had minor concerns	No concerns because it related to summary finding #7-15 which had no/very minor concerns about relevance; the four directly contributing studies had good variety of users, facilities, urban/rural, public/private even if only focused on two countries.	No concerns - rich studies and the large number of statements #7-15 contributing to this finding	High confidence	No concerns	Engel 2015a; McDowell 2018; Naidoo 2015; Shewade 2018; review finding #1-15

Abbreviations: DR-TB: drug-resistant tuberculosis; MDR-TB: multidrug-resistant tuberculosis; NAAT: nucleic acid amplification test; TB: tuberculosis

APPENDICES

Appendix 1. Search strategy

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to present>

Search strategy:

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1 Extensively Drug-Resistant Tuberculosis/ or Tuberculosis/ or tuberculosis.mp. or Tuberculosis, Multidrug-Resistant/ or Tuberculosis, Pulmonary/ or Mycobacterium tuberculosis/

2 (Tuberculosis or MDR-TB or XDR-TB or tuberculous).ti. or (Tuberculosis or MDR-TB or XDR-TB or tuberculous).ab.

3 1 or 2

4 (Truenat or Cepheid or Xpert*).mp.

5 Genexpert*.mp.

6 drug susceptibility test*.mp.

7 (cartridge adj3 test*).mp.

8 cartridge*.ab. or cartridge*.ti.

9 exp Point-of-Care Systems/

10 Reagent Kits, Diagnostic/

11 Max MDR-TB assay.mp.

12 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11

13 3 and 12

14 "Patient Acceptance of Health Care"/ or acceptability.mp. or acceptance.mp

15 Health Equity/ or equity.mp. or Health Services Accessibility/

16 Patient Preference/ or preference*.mp.

17 Patient Satisfaction/ or Attitude to Health/

18 barrier*.mp.

19 challenge*.mp.

20 patient experience*.mp.

21 "Attitude of Health Personnel"/ or providers experience*.mp.

22 Critical Pathways/

23 facilitator*.ab. or facilitator*.ti.

24 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23

25 13 and 24

26 Interviews as Topic/ or interview*.mp. or Interview/

27 survey*.mp. or Health Surveys/ or Health Care Surveys/ or "Surveys and Questionnaires"/

28 Qualitative Research/

29 Focus group discussion*.mp. or Focus Groups/

30 "mixed methods".ti. or "mixed methods".ab. or "mixed-methods".ti. or "mixed-methods".ab.

31 26 or 27 or 28 or 29 or 30

32 13 and 31

33 25 or 32

34 limit 33 to yr="2007 -Current"

Database: Embase <1996 to present >

Search Strategy:

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1 tuberculosis/ or tuberculosis.mp.

2 drug resistant tuberculosis.mp. or drug resistant tuberculosis/

3 multidrug resistant tuberculosis.mp. or multidrug resistant tuberculosis/

4 MDR-TB.mp.

5 XDR-TB.mp.

6 extensively drug resistant tuberculosis/

7 mycobacterium tuberculosis.mp. or Mycobacterium tuberculosis/

8 1 or 2 or 3 or 4 or 5 or 6 or 7

9 (Truenat or Cepheid or Xpert*).mp.

10 Genexpert*.mp.

11 drug susceptibility test*.mp.

12 (cartridge adj3 test*).mp.

13 cartridge*.ab. or cartridge*.ti.

14 "point of care testing"/

15 *diagnostic test/

16 diagnostic test accuracy study/

17 Max MDR-TB assay.mp.

18 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

19 8 and 18

20 patient acceptance of care.mp. or patient attitude/

21 acceptability.mp.

22 patient preference/ or patient preference*.mp.

23 health equity.mp. or health equity/

24 Health Services Accessibility.mp. or health care access/

25 patient satisfaction.mp. or patient satisfaction/

26 barriers.mp.

27 challenges.mp.

28 patient experience*.mp.

29 Attitude of Health Personnel.mp. or health personnel attitude/

30 Critical Pathways.mp. or clinical pathway/

31 facilitator*.ab. or facilitator*.ti.

32 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31

33 19 and 32

34 Diagnostic Interview Schedule/ or exp interview/ or interview*.mp.

35 health care survey/ or survey*.mp. or health survey/

36 (Surveys and Questionnaires).mp.

37 qualitative research.mp. or qualitative research/

38 focus group.mp.

39 (mixed adj2 method*).mp.

40 34 or 35 or 36 or 37 or 38 or 39

41 19 and 40

42 limit 41 to yr="2007 -Current"

Interface - EBSCOhost Research Databases

Database - CINAHL

Database - APA PsycInfo

Limiters - Published Date: 20070101-20201231

#	Query
S19	S14 OR S18
S18	S8 AND S17
S17	S15 OR S16
S16	TX focus group*
S15	TX interview* OR TX (survey* or questionnaire*) OR TX (qualitative research or qualitative study or qualitative methods or mixed methods)
S14	S8 AND S12
S13	S8 AND S12
S12	S9 OR S10 OR S11
S11	TX (barriers or challenges) OR TX critical pathway OR TX facilitator*

(Continued)

S10	TX patient preference* OR TX (patient satisfaction or patients experiences or patients perceptions or patients attitudes)
S9	TX acceptance of care OR TX health equity OR MW Health Services Accessibility
S8	S3 AND S7
S7	S4 OR S5 OR S6
S6	TX Max MDR-TB OR TI cartridge OR AB cartridge
S5	TX drug susceptibility test* OR TX cartridge N2 test* OR TX point of care testing
S4	TX Truenat or Cepheid or Xpert* or Genexpert*
S3	S1 OR S2
S2	TX extensively drug resistant tuberculosis OR MH tuberculosis, multidrug-resistant
S1	TX (tuberculosis or TB or MDR-TB or XDR-TB) OR MW mycobacterium tuberculosis OR MW multidrug resistant tuberculosis

Web of Science Core Collection

#6 (TS=(((patient* AND (preference* or attitude* or experience* or satisfaction) OR equity or acceptability or feasibility or facilitat*)))) AND #4

#5 TS=(((patient* AND (preference* or attitude* or experience* or satisfaction) OR equity or acceptability or feasibility or facilitat*)))

#4 (#2) AND #1 and 2007 or 2008 or 2009 or 2010 or 2011 or 2012 or 2013 or 2014 or 2015 or 2016 or 2017 0r 2018 or 2019 or 2021 or 2020 (Publication Years)

#3 (#2) AND #1

#2 (cartridge test*) or (Molbio or Truenat or Cepheid or Xpert* or Bioneer or Hain) or Genexpert* or Point-of-Care System* (Topic) or MeltPro or Zeesan (Topic)

#1 (tuberculosis AND (drug resistan* or multidrug resistan*)) (Topic) or MDR-TB or XDR-TB (Topic)

HISTORY

Protocol first published: Issue 9, 2021

CONTRIBUTIONS OF AUTHORS

NE is the guarantor of the review.

NE and KRS conceived the qualitative synthesis.

NE, EAO, KRS, and SO designed the synthesis approach and methods.

NE wrote the first draft of the review.

All review authors contributed to drafting the review and approved the final version.

DECLARATIONS OF INTEREST

NE received funding from the World Health Organization (WHO) Global Tuberculosis Programme, Switzerland. She was first author on one study included in this review (Engel 2015a, funded by the Bill and Melinda Gates Foundation) and senior author on a second included study (Mwaura 2020, funded by Foundation for Innovative New Diagnostics (FIND)) For both studies the funders had no role in study design or interpretation of results. Assessment of study eligibility and data extraction were checked independently by other review authors. NE did not assess the methodological limitations of these studies.

EAO received funding from the World Health Organization (WHO) Global Tuberculosis Programme, Switzerland.

PWK has no known conflicts of interest.

BS has no known conflicts of interest.

RJ has no known conflicts of interest.

KRS received funding from the World Health Organization (WHO) Global Tuberculosis Programme, Switzerland and Maastricht University, Maastricht. She has received additional financial support from Cochrane Infectious Diseases, UK; McGill University, Canada; University of Washington, Seattle; Baylor College of Medicine, Houston; and the World Health Organization Global Tuberculosis Programme, Switzerland, for the preparation of related systematic reviews and educational materials; consultancy fees from Foundation for Innovative New Diagnostics (FIND), Switzerland (for the preparation of systematic reviews and GRADE tables); consultancy fees from Stellenbosch University, Stellenbosch (for guidance on evidence syntheses); and honoraria and travel support to attend WHO guideline meetings.

SO has no known conflicts of interest.

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- Foreign, Commonwealth and Development Office (FCDO), UK

  Project number 300342-104
- World Health Organization Global Tuberculosis Programme, Switzerland

  Agreement for Performance of Work (APW) registration number 202582434

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol, we wrote, "For the diagnosis of active tuberculosis disease, culture is regarded as the best available reference standard (Lewinsohn 2017), with liquid culture being more sensitive than solid culture (American Thoracic Society 2000). However, culture is not a perfect reference standard, in particular for extrapulmonary tuberculosis (Kohli 2021) and tuberculosis in children (Kay 2020)". We have removed this text from the Background because our focus is not diagnostic test accuracy per se. However, we include this text here for completeness.

In response to editorial comments, we have revised the Background section to include more technical information on the disease as well as issues around care.

We amended the title from 'Rapid molecular tests for tuberculosis and tuberculosis drug resistance: provider and recipient views' (Engel 2021) to 'Rapid molecular tests for tuberculosis and tuberculosis drug resistance: a qualitative evidence synthesis of recipient and provider views'.

INDEX TERMS

Medical Subject Headings (MeSH)

Drug Resistance; Nucleic Acid Amplification Techniques; Rifampin [therapeutic use]; *Tuberculosis [diagnosis] [drug therapy]; *Tuberculosis, Multidrug-Resistant [diagnosis] [drug therapy]

MeSH check words

Child; Humans