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[Qualitative Protocol]

Rapid molecular tests for tuberculosis and tuberculosis drug resistance: provider and recipient views

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (qualitative). The objectives are as follows:

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 providing and receiving low-complexity NAATs to diagnose tuberculosis and tuberculosis drug resistance?

Answering this question will allow us to identify the implications for effective implementation and health equity.

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BACKGROUND

Description of the topic

Tuberculosis is a leading cause of infectious disease-related death and is one of the top 10 causes of death worldwide (WHO Global Tuberculosis Report 2020). In 2019, an estimated 10 million people developed tuberculosis and 1.4 million people died from tuberculosis, including 208,000 with HIV (WHO Global Tuberculosis Report 2020). Drug-resistant tuberculosis is also a major concern. There were around 500,000 new cases of rifampicin-resistant tuberculosis, of which 78% had multidrug-resistant tuberculosis (MDR-tuberculosis, tuberculosis that is resistant to at least rifampicin and isoniazid, two of the core tuberculosis medicines) (WHO Global Tuberculosis Report 2020). 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, the COVID-19 pandemic threatens to reverse the gains made in recent years (WHO Global Tuberculosis Report 2020). 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).

WHO-recommended rapid tuberculosis diagnostics and drug susceptibility testing (DST, testing to determine the drugs that the tuberculosis bacteria are susceptible to) should be available to all people with signs and symptoms of tuberculosis to meet the targets of the End TB Strategy. Yet, tuberculosis diagnosis is a crucial problem in many countries with around three million people going undiagnosed in 2019 (WHO Global Tuberculosis Report 2020). Recently, the diagnosis of tuberculosis and drug-resistant forms has seen important innovations. One of these has been the introduction of low-complexity 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. These low-complexity NAATs are the topic of interest of this review. Until 2018, all MDR-tuberculosis regimens employed at least five second-line drugs for up to 24 months. The arrival of the novel or repurposed drugs, such as bedaquiline, clofazimine, and linezolid, has revolutionized the efficacy of longer regimens, dispensing with the need for injectable drugs and promising to deliver shorter all-oral regimens (WHO Consolidated Guidelines (Module 4) 2020). Early recognition and characterization of resistance as quickly as possible to those who could benefit is a prerequisite for effective delivery of these new treatment strategies for drug-resistant tuberculosis. This draws attention to the need for faster, sustainable, and more easily deployable diagnostic technologies and testing programmes (Pillay 2021).

While the availability of DST using culture-based and molecular methods (tests based on detection of genetic material) is increasing, the coverage, utilization, and availability of these technologies varies widely. For example, globally in 2019, only 59% of people with bacteriologically confirmed new tuberculosis were tested for rifampicin resistance (WHO Global Tuberculosis Report 2020). 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). 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). However, given the recent introduction of shorter all-oral tuberculosis treatment regimens, it is critically important to perform DST to ensure people who start new regimens take the most effective drugs (drugs to which the patient's *Mycobacterium tuberculosis* isolate has documented, or high likelihood of, susceptibility) such that there is a high chance of successful treatment (WHO Consolidated Guidelines (Module 4) 2020).

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 or PCR procedures) are performed within the container (cartridge) 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 patients and their contacts, clinic staff, laboratory managers, programme officers, and implementers. 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 patients and contacts to a person with infectious tuberculosis who seek care, produce a sample, and return for results; professional users involve healthcare workers who order, conduct the diagnostic, 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 the functioning and utilization and therefore the impact the diagnostic can have. In particular, the work of patients involved in acquiring a diagnosis and following through diagnostic and treatment journeys is considerable and largely remains invisible in policy discussions. One study on diagnosing at point-of-care in India showed how patients 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 patients opt out (Yellapa 2017). What is more, diagnostics can also harm relationships between

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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 patients to come to the public clinics. Yet, if done inconsistently, the same test can damage these relationships (Engel 2015a). 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) 2020). 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) 2020; 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 2015a; Engel 2015b; 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 2015b).

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 will 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 and thereby cut diagnostic delay, provide a more accurate diagnosis of tuberculosis and a diagnosis of drug resistance, which has important implications for patient-important outcomes (Bainomugisa 2020; Pooran 2019). Quantitative studies on the impact of low-complexity NAATs have measured patient-important outcomes 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 2019), 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 patient outcomes if the test result is not linked to appropriate treatment and other healthcare services (Pai 2018).

Our review will not consider the accuracy of low-complexity NAATs or their quantifiable impact on patient-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. patients 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, patients, 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 setting, cannot be made to work and scaled up, and are not utilized or not accessible for those in need. User 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). The proposed review will contribute to reaching SDG3 by ensuring perspectives and experiences

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of end-users (survivors, patients, and patient contacts) and professional users (healthcare workers, 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 on "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 can add value by providing decision makers with additional evidence to improve understanding of intervention complexity, contextual variations, implementation, and stakeholder preferences and experiences. Specifically, it can generate data for the following decision-making domains as part of the GRADE process: 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 providing and receiving low-complexity NAATs to diagnose tuberculosis and tuberculosis drug resistance?

Answering this question will allow us to identify the implications for effective implementation and health equity.

METHODS

Criteria for considering studies for this review

Types of studies

We will include primary studies that use qualitative study designs such as ethnography, phenomenology, case studies, grounded theory studies, and qualitative process evaluations. We will include studies that use 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 will exclude studies that collect data using qualitative methods but do not analyze these data using qualitative analysis methods (e.g. open-ended survey questions where the response data are analyzed 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 2020).

We will include mixed methods studies where it is possible to extract the data that were collected and analyzed using qualitative methods.

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

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

We will not exclude studies based on our assessment of methodological limitations. We will use 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 will focus on users and potential users of low-complexity NAATs. Users will include patients and their caregivers, laboratory technicians, healthcare providers, implementers, and programme officers 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. 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 will include 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, Xpert MTB/RIF, Xpert Ultra, Xpert MTB/XDR, and Truenat. 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.

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Search methods for identification of studies

We will develop the search strategy in collaboration with the Cochrane Infectious Diseases Group (CIDG) Information Specialist. We will also consult the Cochrane Effective Practice and Organisation of Care (EPOC) Information Specialist before developing the strategy. We will attempt to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and in progress). We will include relevant conference abstracts in the search strategy. We will use abstracts to identify published studies and include the full publications when they meet our inclusion criteria.

Electronic searches

We will search the following databases from 1 January 2007 onwards, 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);
- Science Citation Index Expanded (Web of Science).

Searching other resources

We will contact researchers and experts in the field to identify any additional eligible studies. We will check the references of relevant reviews and studies to identify additional studies.

Grey literature

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

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

Selection of studies

We will use Covidence to manage the selection of studies (Covidence). Two review authors will independently and in parallel scrutinize all titles and abstracts identified from literature searching to identify potentially eligible studies. We will retrieve the full text of any citation considered by one of the review authors as potentially eligible. Then, two review authors will independently and in parallel assess full-text articles for inclusion using predefined inclusion and exclusion criteria. For the full-text screening steps, we will resolve disagreements by discussion or, if necessary, with a third review author. We will record all studies excluded after full-text assessment and their reasons for exclusion in the 'Characteristics of excluded studies' table. We will illustrate the study selection process in a PRISMA diagram (Page 2021).

Language translation

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

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 identify all studies that are eligible for inclusion, we will assess whether their number or data richness or thickness are likely to represent a problem for the analysis. If we find numerous studies that meet our inclusion criteria, we will purposefully select the first sample of eligible studies with rich or thick data and the second sample of other studies that address various users, uses of and experiences with the intervention not addressed by the richer/thicker studies. To do so, we will first categorize the eligible studies into rich or thick and poor or thin studies depending on the depth of the analysis undertaken. A thick study is one in which the author 1. analyzes 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 Eshun-Wilson 2019). After data extraction and analysis of the sampled studies, one review author will scrutinize the unsampled studies for additional or contradictory insights.

Data extraction

Five review authors (EO, NE, BS, PW, RJ) will extract 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. patients, clinicians, nurses, laboratory staff, implementers); diagnostic tools used; programmatic features of the intervention (e.g. testing model/algorithm/program in which the diagnostic is 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 will be 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 will also extract data (if available) on the following factors that, based on our prior research experience, we expect 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.

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

Assessing the methodological limitations of included studies

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

Rigor 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.).

Rigor in data collection:

- data collection tools were piloted/(and if quantitative) validated;
- (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/with participants? 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).

Rigor in data analysis:

- data analysis methods were systematic (e.g. was a method described/can 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 fit the interpretation/support claims about patterns in data;
- the data presented illuminate/illustrate 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 are covered;
- the perspectives of participants are 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 will report our assessments in a 'Methodological limitations' table. We will also assess if ethical clearance was sought. We will base 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 is not sought, excluding the data from a systematic review compounds the injury to participants who have given their time to the research. We will pay additional attention to ensuring that participants cannot be recognized by readers.

Data management, analysis, and synthesis

We will use a thematic approach to guide data analysis (Braun 2006; Thomas 2008). We will synthesize qualitative research to better understand views and experiences with the intervention in the context of use. From this understanding, we will deduce values, feasibility, and acceptability considerations of low-complexity NAATs for tuberculosis and drug-resistant tuberculosis.

Based on the key findings extracted by four review authors (EO, NE, PW, BS) from an initial set of rich studies, one review author (NE), in close discussion with the other review authors, will develop a coding scheme. Using the coding scheme and developing it further in an iterative manner, NE will code the extracted key study findings of all sampled studies using NVIVO (version 12) and write memos on selected themes, which will be discussed with the other review authors. In the next step, NE will generate findings based on these memos, which will be revised and finalized after discussion with the other review authors. Finally, we aim to develop a coherent theory about low-complexity NAATs' feasibility, acceptability, and alignment with users' values. We aim to visualize these findings in a succinct figure and present findings

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for values and preferences for different users, as well as feasibility, acceptability, and equity considerations to maximize utility for policymakers and implementers.

Assessing our confidence in the review findings

Two review authors (NE, EO in consultation with BS) will use 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 will make a judgement about the overall confidence in the evidence supporting the review finding. We will judge confidence as high, moderate, low, or very low. The final assessment will be based on consensus among the review authors. All findings will start as high confidence and will be downgraded if there are important concerns regarding any of the CERQual components.

The criteria 'Breadth and depth of findings' of the EPPI-Centre tool for judging primary studies and the component 'adequacy' of CERQual both rely on judgements about richness of findings. To avoid applying judgements about richness of findings twice, we will 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 will present summaries of the findings and our assessments of confidence in these findings in the summary of qualitative findings table(s), which will 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 will 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 intend to 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 will use our review findings to complement a Cochrane diagnostic test accuracy review in progress on "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 will provide – alongside questions of technical accuracy.

When published, 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); health systems (SO); qualitative synthesis methodology (SO); pharmacoepidemiology and pharmacovigilance (PW)); experience with different geographical settings and experience with researching diagnostic processes and technologies (ranging from technical accuracy studies to studies of healthcare seeking, implementation challenges, point-of-care testing processes, and evaluation of specific diagnostic devices). We anticipate that such a multidisciplinary team will facilitate 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. We will minimize the risk that our perspectives as authors influence the analysis and interpretation by using refutational analysis techniques, such as taking seriously contradictory findings between studies and further exploring and analyzing them. We will use 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 will support and enhance the reflexivity of the review team.

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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. In case studies of her own are included, she will not be involved in extracting data from studies she co-authored.

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.

PW 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 will be 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 patient 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 patients, 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.

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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.

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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"

CONTRIBUTIONS OF AUTHORS

NE is the guarantor of the review.

NE and KRS conceived of the qualitative synthesis.

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

NE wrote the first draft of the protocol.

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

DECLARATIONS OF INTEREST

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

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

PW: none.

BS: none.

RJ: none.

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