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ABSTRACT

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

To assess the impact of Xpert MTB/RIF on important patient outcomes for people with tuberculosis.

BACKGROUND

Description of the condition

Tuberculosis is caused by Mycobacterium tuberculosis, an obligate aerobe bacilli that belongs to the Mycobacteria tuberculosis complex (MTBC) (Cook 2008). Transmission of tuberculosis most commonly occurs through the inhalation of droplets containing bacilli from a person with pulmonary tuberculosis who has coughed or sneezed. It is estimated that two to three billion people are infected by M. tuberculosis globally without having tuberculosis disease, and that about 5% to 15% will develop tuberculosis disease (WHO 2016a). The probability of developing tuberculosis is higher in immunocompromised individuals and among those infected with HIV (WHO 2016a). Tuberculosis primarily affects the lungs (pulmonary tuberculosis); however, the disease can involve virtually any extrapulmonary sites in the human body.

In 2015, there were 10.4 million new tuberculosis cases globally and people living with HIV accounted for 1.2 million new cases (WHO 2016a). In the same year, tuberculosis was associated with 1.4 million deaths and a further 0.4 million deaths from tuberculosis disease among people living with HIV (WHO 2016a). One million children were newly infected with tuberculosis globally in the same year. The proportion of tuberculosis cases living with HIV was highest in the World Health Organization (WHO) African Region, accounting for 31% of all tuberculosis cases notified and exceeding 50% in parts of southern Africa (WHO 2016a). The emergence of and under-reporting of drug resistance to antimicrobials used to treat tuberculosis remain major problems. In 2015, there was a gap of 4.3 million between the estimated number of new incident tuberculosis cases and the number of notified cases (WHO 2016a). It was estimated that 580,000 new cases of multidrug-resistant (MDR) tuberculosis occurred in the same year, but only 20% received appropriate MDR treatment (WHO 2016a).
Consequently, there is a need for early, accurate diagnosis of tuberculosis and for universal drug susceptibility testing of individuals diagnosed with tuberculosis.

Commonly used diagnostic techniques for tuberculosis have limitations. Culture, which is the gold standard for diagnosis, is normally centrally located, requires a set of biocontainment precautions, and takes time before results can be obtained (Corbett 2006). For many years, sputum smear microscopy has been the method used to diagnose bacteriologically confirmed tuberculosis, particularly in low- and middle-income countries (LMICs) (Corbett 2006; Parsons 2014), and it remains the main diagnostic technique in primary healthcare facilities in LMICs. However, the sensitivity of smear microscopy is limited, ranging from 20% to 80% (Levy 1989; Parsons 2011); sensitivity is further reduced in HIV-seropositive individuals (Corbett 2006). Other limitations of smear microscopy include that it is labour intensive, dependent on individual skills and experience, and unable to detect drug resistance (Parsons 2011). An insensitive diagnostic technique is likely to affect patient outcomes in addition to under-reporting of the disease: the proportion of tuberculosis cases being effectively treated, the time to treatment, transmission in the community, and mortality may all suffer.

Description of the intervention

New molecular diagnostic tools have been developed to improve tuberculosis detection and decentralize drug resistance testing. The Xpert MTB/RIF assay is an automated nucleic-acid amplification test. It consists of a single-use multichambered cartridge preloaded with liquid buffers and lyophilized reagent beads that are required for sample processing, DNA extraction, and hemi-nested real-time polymerase chain reaction. The assay can be used with sputum samples, and also, with varying sensitivity, with other specimens including cerebrospinal fluid, lymph node tissue or aspirates, pleural fluid, ascitic fluid, urine, dialysis fluid, and pus (Denkinger 2014; Scott 2014). The assay can be performed at peripheral laboratories or health facilities without biosafety cabinets, and minimal training for laboratory staff is required (Bohme 2010; Bohme 2011). Xpert MTB/RIF can detect MTBC and rifampicin resistance within two hours (Helb 2010).

A Cochrane Review on the accuracy of Xpert MTB/RIF for the detection of tuberculosis estimated the pooled sensitivity of the assay to be 89% and the specificity to be 99% (Steingart 2014). When compared with smear microscopy, the Xpert MTB/RIF assay showed an absolute increase of 23% in tuberculosis detection among culture-confirmed cases; the pooled sensitivity in smear-negative, culture-positive individuals was only 67% (Steingart 2014). Sensitivity was lower in people with HIV infection (79%) than in those without HIV infection (86%). Additionally, the Xpert MTB/RIF assay had a pooled sensitivity of 95% and pooled specificity of 98% for the detection of rifampicin resistance (Steingart 2014).

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diagnostic and pretreatment loss to follow-up as well as time to treatment. A larger proportion of true tuberculosis cases may receive effective therapy and fewer individuals may be falsely diagnosed with the disease and incorrectly treated. These factors could improve important patient outcomes, such as treatment outcome, morbidity, mortality, and quality of life, and potentially have an impact on onward transmission.

Why it is important to do this review

Recent evidence from pragmatic trials in programme settings has indicated inconsistent results for the impact of Xpert MTB/RIF on different patient outcomes. A growing body of evidence has shown limited benefits of Xpert MTB/RIF on loss to follow-up and mortality (Churchyard 2015; Trajman 2015), whereas other studies have found Xpert MTB/RIF to reduce time to treatment, particularly among HIV-positive individuals (Cox 2014; Theron 2014). A recent narrative review by Auld 2016 reported little impact on morbidity and mortality; however, the review included studies that demonstrated an impact of Xpert MTB/RIF on increasing the diagnostic yield of bacteriologically confirmed tuberculosis and reducing the time to the start of treatment.

A systematic review enables us to include a very large number of study participants in the analysis. A very large number are needed to conclusively demonstrate the presence or absence of an effect of meaningful size on mortality (Schumacher 2016); to date no single published trial has been sufficiently powered to obtain a conclusive result. A systematic review also enables us to investigate factors that affect patient outcomes across study settings. Hence, this review will help elucidate the impact, and inform the further scale-up, of this diagnostic test (and other similar tests in future), and the allocation of resources in LMICs compared with other interventions.

OBJECTIVES

To assess the impact of Xpert MTB/RIF on important patient outcomes for people with tuberculosis.

METHODS

Criteria for considering studies for this review

Types of studies

Cluster randomized trials, individual randomized controlled trials (RCTs), and quasi-experimental trials (pre-/post-implementation). We will perform separate meta-analyses for randomized and non-randomized studies.

Types of participants

Individuals with suspected tuberculosis presenting with one or more symptoms of the disease and able to provide a sputum sample.

Types of interventions

Intervention

Diagnostic strategies that use Xpert MTB/RIF.

Control

Diagnostic strategies that use smear microscopy.

Types of outcome measures

Primary outcomes

- All-cause mortality during trial follow-up by time from first contact with health care
- Number of tuberculosis cases reported, and number of drug-sensitive and drug-resistant tuberculosis cases
- Proportion of patients treated
- Proportion of patients microbiologically confirmed and treated
- Proportion of patients not microbiologically confirmed, but treated

Secondary outcomes

- Time from first contact to initiation of treatment
- Proportion of pre-treatment loss to follow-up
- Proportion of study participants who were diagnosed with or treated for MDR/TB
- Number of visits prior to diagnosis
- Patient reported satisfaction

Search methods for identification of studies

We will attempt to identify all potential trials regardless of language or publication status (published, unpublished, in press, and in progress).
Electronic searches

We will search the following databases using the search terms detailed in Appendix 1: Cochrane Infectious Disease Group (CIDG) Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library; MEDLINE OVID; Embase OVID; CINAHL EBSCO; LILACS (Latin American and Caribbean Health Science Information database; BIREME); Science Citation Index Expanded (Web of Science), Social Sciences citation index (Web of Science), and Conference Proceedings Citation Index - Social Science & Humanities (Web of Science). We will also search the WHO International Clinical Trials Registry Platform (www.who.int/ictrp/search/en/), ClinicalTrials.gov (clinicaltrials.gov/), and the Pan African Clinical Trials Registry (www.pactr.org/) to identify ongoing trials using (tuberculosis OR TB) AND (Xpert or GeneXpert or "sputum microbiology" or "sputum microscopy") as search terms.

Searching other resources

Conference proceedings

We will search the past two years’ proceedings of the International Union Against Tuberculosis and Lung disease (UNION) conference, the Conference on Retroviruses and Opportunistic Infections (CROI), and the International AIDS Conference (IAS). We will search for additional trials by reviewing the reference lists of all included trials and relevant systematic reviews. We will also contact leading researchers at the Foundation for Innovative New Diagnostics (FIND), the WHO, Centers for Disease Control and Prevention (CDC), and TB-REACH to identify unpublished data.

Data collection and analysis

Selection of studies

Two review authors (FH and RN) will independently screen studies for eligibility after the literature search, and will code studies as either 'potentially include' or 'exclude'. Based on the screening results, we will assess the full-text articles of studies in the 'potentially include' category for eligibility using an eligibility assessment form. We will resolve differences in opinion through discussion. We will contact study authors when clarification is needed. Multiple publications of the same study will be included only once; we will include the publication including the largest sample size for the outcomes assessed and the most detailed information. We will list studies excluded after full-text assessment and their reasons for exclusion in a ‘Characteristics of excluded studies’ table.

Data extraction and management

Two review authors (FH and RN) will independently extract data using a piloted data extraction tool similar to a previous used tool by our group (Schumacher 2016). We will resolve disagreements through discussion or by consulting a third review author (AR). We will extract the following data: study details (first author, year of publication), participant details, intervention, control, outcome measured and how it was measured, covariates, length of follow-up, and results.

In addition, for RCTs, we will record the number of participants or clusters randomized to each diagnostic arm, and the number of participants monitored for each outcome of interest. For binary data, we will extract the number of events in each diagnostic arm. For continuous data, we will extract the arithmetic mean, standard deviation, median and interquartile range (IQR), range, and number of participant clusters in each group, if available. For time-to-event outcomes, we will extract the log hazard ratio and its standard deviation or 95% CI. We will also extract the number of events, the number of participants, whether the hazards are proportional, and the length of follow-up.

For cluster RCTs that are adjusted for clustering, we will extract the measure of effect for each outcome (relative risk or mean difference with 95% CI or standard deviation) and method of adjustment. In studies that are not adjusted for clustering, we will extract the number of clusters randomized or the mean cluster size and the intraclass correlation coefficient (ICC), if available. We will also extract data relevant for the assessment of the risk of bias.

Assessment of risk of bias in included studies

Two review authors (FH and RN) will independently assess the risk of bias using the Cochrane ‘Risk of bias’ assessment tool for assessing risk of bias in randomized studies (Higgins 2011), and other tools for assessing risk of bias in non-randomized studies (Schumacher 2016; Sterne 2016). We will contact the corresponding study author for clarification or more information if data are missing or the procedure is unclear. We will resolve all discrepancies through discussion or by consulting a third review author (AR). We will assess the risk of bias as low, high, or unclear.

We will assess the included studies for the method of allocation sequence generation and allocation concealment (adequate, inadequate, not done, or unclear (as defined by Juni 2001), blinding (describing who was blinded, noting that the outcome assessors, clinicians, and participants cannot be blinded); completeness of information about follow-up (proportion of those presenting for care who were treated, who completed treatment, and who were lost to follow-up), outcome reporting, and selective reporting bias. We will use the Cochrane ‘Risk of bias’ assessment tool (Higgins 2011). For cluster randomized trials, we will consider additional criteria, such as recruitment bias, baseline imbalance, loss of clusters, incorrect analysis, and comparability with individually randomized trials.
Measures of treatment effect
For the outcomes that assess proportions, we will present the impact of Xpert MTB/RIF using relative risks or odds ratios with respective 95% CIs. We will present the impact of Xpert MTB/RIF on time to treatment as hazard ratios with 95% CIs, if available.

Unit of analysis issues
We will carry out the intention-to-treat (ITT) analysis based on the intervention groups. We will combine studies with multiple intervention groups to obtain the appropriate groups. We will be careful to ensure that data are included only once in the meta-analysis. For clustered studies that did not consider cluster design in the analysis, we will adjust the estimated variance for clustering using the ICC before including estimates in the meta-analysis. If the ICC is not available, we will use an ICC from another, similar study. If this is not possible, we will include the study, but note that adjustment was not possible.

Dealing with missing data
We will determine the reasons for missing data before extracting data from the studies by attempting to contact the respective corresponding study author. We will investigate whether the missingness of data is associated with attrition bias. We will carry out the analysis if we consider the missing data to be missing at random. If we suspect that missing data are due to bias, we will impute the data using specific assumptions, such as assuming all missing participants experienced or did not experience the event, in order to conduct a sensitivity analysis.

Assessment of heterogeneity
We will examine heterogeneity in the intervention effect between studies using a forest plot. We will estimate heterogeneity using the $I^2$ statistic (the proportion of variance in the meta-analysis that is attributable to study heterogeneity).

Assessment of reporting biases
We will assess reporting biases using funnel plots if we include more than 10 studies in the meta-analysis. We will check the funnel plots for symmetry or asymmetry. In case of asymmetry, we will use the recommended test for funnel plot asymmetry (Harbord 2006). We will take care during our interpretation to investigate whether the asymmetry is related to publication or other biases.

Data synthesis
We will conduct analyses using Review Manager 5 (RevMan 5) (RevMan 2014). We will use a random-effects model as the intervention effect will logically vary between studies due to the participant mix, settings, and health system factors.

Subgroup analysis and investigation of heterogeneity
We will perform subgroup analyses in participants with HIV-infected versus uninfected tuberculosis, and in participants with pulmonary tuberculosis versus those with extrapulmonary tuberculosis, if the data extracted allow. Furthermore, we will perform subgroup analyses in children versus adults, as well as in participants with drug-resistant versus non-drug resistant tuberculosis.

Sensitivity analysis
We will perform sensitivity analyses on the few unexpected circumstances that are likely to influence outcomes; for example:
- missing data that are likely to influence the outcome;
- excluding studies with outliers that are suspected to influence the outcome;
- excluding studies with high risk of bias that are likely to affect the outcome.

Certainty of the evidence
We will assess the certainty of evidence using the GRADE approach (Guyatt 2011; GRADE 2014), and GRADEpro GDT software (GRADEpro GDT 2015). We will rate each important outcome as described by Balshem 2011.
- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect.
- Low: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

RCTs start as high quality evidence but can be downgraded if there are valid reasons within the following five categories: risk of bias, imprecision, inconsistency, indirectness, and publication bias. Studies can also be upgraded if there is a large effect, a dose response effect, and if all plausible residual confounding would reduce a demonstrated effect or would suggest a spurious effect if no effect was observed (Balshem 2011). We will summarize our findings in a ‘Summary of findings’ table.

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Additional references

Albert 2016

Auld 2016

Balshem 2011

Boehme 2010

Boehme 2011

Chakravorty 2017

Churchyard 2015

Cook 2008

Corbett 2006

Cox 2014

Creswell 2014

Denkinger 2014

GRADE 2014

GRADEpro GDT 2015 [Computer program]

Guyatt 2011

Harbord 2006

Helb 2010

Higgins 2011
Juni 2001

Levy 1989

Parsons 2011

RevMan 2014 [Computer program]

Schumacher 2016

Scott 2014

Steingart 2014

Sterne 2016

Theron 2014

Trajman 2015

WHO 2013

WHO 2014

WHO 2016a

WHO 2016b

WHO 2017

* Indicates the major publication for the study
APPENDICES

Appendix 1. Search strategy

MEDLINE OVID
1 Xpert*.mp.
2 geneXpert*.mp.
3 Cepheid.mp.
4 near* patient.mp.
5 1 or 2 or 3 or 4
6. (smear adj3 microscop*).mp
7. (sputum adj3 microscopy).mp
8. Sputum/ch, cy, mi [Chemistry, Cytology, Microbiology]
9. 6 or 7 or 8
10 exp Tuberculosis/
11 tubercul*.ab. or tubercul*.ti.
12 TB.ab. or TB.ti.
13 Mycobacterium tuberculosis/
14 10 or 11 or 12 or 13
15 5 or 9
16 14 and 15
17 limit 16 to yr="2007 -Current"

This is the preliminary search strategy for MEDLINE OVID, which we will adapt for other electronic databases. We will report all search strategies in full in the final version of the review.

CONTRIBUTIONS OF AUTHORS
FH, RRN, MK, and AR wrote the first draft of the protocol. KR, AR, SGS, CMD, SG, and MK reviewed the protocol. FH, KR, and AR wrote the final protocol.

DECLARATIONS OF INTEREST
FH has no known conflict of interest.
RRN has no known conflict of interest.
SGS has no known conflict of interest.
MK has no known conflict of interest.
CMD has no known conflict of interest.
SG has no known conflict of interest.
KR has no known conflict of interest.
AR has no known conflict of interest.
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