Can study design features explain the failure of studies to demonstrate an impact of Xpert MTB/RIF testing on mortality?

ABSTRACT

Background

Most clinical trials evaluating the impact of Xpert MTB/RIF testing for pulmonary tuberculosis have not demonstrated a statistically significant impact on mortality. This may have occurred if specific factors related to study design or execution resulted in lower mortality than what one might observe in actual usual care. We aim to explore if study design features could explain the failure of studies to demonstrate an impact of Xpert MTB/RIF testing on mortality by means of a narrative review.

Methods

We will search electronic databases to identify all clinical trials that evaluated the impact of Xpert MTB/RIF on mortality compared to sputum microscopy in participants with presumptive active pulmonary TB. We will search PubMed, the Cochrane Library, and Scopus for English literature published from 1 January 2009. We will also search references of relevant reviews for eligible studies. Focusing on how the trial arms mirror usual care, we will critically review the study features of included trials across the following areas 1) Study setting and context; 2) Study population; 3) Participant recruitment and enrollment; 4) Study procedures; and 5) Study follow-up. We will present our review findings narratively and in tabular form.

Conclusion

Trials identified as pragmatic may still offer higher quality of care than what occurs in usual care. Better care offered particularly in the control arm (standard of care) may minimize potential differences in mortality between control and intervention arm.

BACKGROUND

Tuberculosis (TB) is a global leading infectious cause of morbidity and mortality. The 2017 World Health Organization (WHO) TB report estimates that there were 10.4 million incident TB cases, 600,000 new cases of multi-drug resistant TB and about 1.674 million TB-related deaths in the year 2016[1]. Early TB case detection and treatment initiation are critical for global TB control and elimination.

Sputum smear microscopy remains the primary method for diagnosing pulmonary TB. Microscopy requires patients to submit multiple sputum samples usually over several days, leading to loss to follow-up, and has low sensitivity, leading to missed opportunities for case detection and treatment. Nucleic acid amplification tests (NAAT) are known to increase sensitivity but until recently were not feasible in high burden countries.[2] In 2011, WHO recommended a semi-automated, cartridge-based NAAT (Xpert MTB/RIF, Cepheid, Sunnyvale, CA, USA) as a first-line TB test for pulmonary TB where resources permit.[3] Since then, market penetration has increased with over 34.4 million Xpert cartridges being purchased in the public sector to date.[4] A newer and more sensitive version of Xpert, Xpert Ultra has also been released and recommended by the WHO in 2017. [5]

To support Xpert MTB/RIF scale-up, several trials have examined its impact on mortality relative to smear microscopy or pre-existing diagnostic algorithms. Of these trials, [6-14] only two [15, 16] have showed a statistically significant impact on mortality. Published literature cites possible reasons to explain Xpert's apparent lack of impact on mortality. These include limitations in trial design, deficiencies in trial conduct and the health systems in which the trials are conducted[17],

persistent use of empirical therapy[18], limitations in interpreting trial results by focusing on statistical significance rather than clinically important differences[19] and enrolling patients whose test results are not likely to influence treatment.[20] A methodological review of all test-treatment trials published between 2004 and 2007 revealed that such trials are susceptible to under powering, lack of blinding, attrition and inadequate primary analyses. These factors could also explain the lack of impact on mortality in Xpert trials. [21]

The lack of impact could also have occurred if specific factors related to study design or execution resulted in lower mortality than what one might observe in actual usual care. All trials evaluating the impact of Xpert have been conducted in usual health care settings and are therefore considered pragmatic (trials conducted in real life settings to inform decision making on real effectiveness). Nonetheless, trials identified as pragmatic may still offer higher quality of care than what occurs in usual care. [22, 23] Better care may be of particular benefit to patients in the standard of care arm, who usually receive limited diagnostic testing, ultimately leading to lower mortality in this arm. This may lead to minimal differences in mortality between the experimental arm and the control arm. Both trial arms may also demonstrate lower mortality and reduce the power of the trial if better care is offered in the trial. In this review, we aim to explore if study design features can explain the failure of studies to demonstrate an impact of Xpert MTB/RIF testing on mortality in patients undergoing evaluation for pulmonary tuberculosis.

METHODS

We will conduct a literature search to identify all trials assessing mortality following introduction of Xpert testing. We will search PubMed,the Cochrane Library and Scopus for English literature published from 1 January 2009 with the terms 'Xpert MTB/RIF' or 'Xpert' or 'GeneXpert' and 'impact' or 'effect*' or 'implementation' or 'trial*'.

((("Xpert MTB/RIF" OR Xpert OR GeneXpert))) AND ((((impact OR effect OR implementation OR trial*))))*

We will include clinical trials that directly compared Xpert MTB/RIF to a standard of care as stated by the authors (sputum microscopy), with an aim of measuring the impact of these tests on mortality in participants presumed to have active pulmonary TB. Hypothetical trials or modelling studies will be excluded.

The Pragmatic Explanatory Continuum Indicator Summary (PRECIS) is a tool that helps trialists consider how explanatory (ideal context) or pragmatic (usual care context) the study features of their trials can be in the pragmatic/explanatory continuum [24]. It guides the appraisal of trials features according to nine domains, which include eligibility, recruitment, setting, organization, flexibility (delivery), flexibility (adherence), follow-up, primary outcome and primary analysis. The results of the PRECIS assessment are summarized for each domain from a scale of 1 to 5 with 1 being very explanatory and 5, very pragmatic.

However rather than following any formal process for the PRECIS-2 tool we will critically review the how study features of included trials mirror usual care across the following areas 1) Study setting and context; 2) Study population; 3) Participant recruitment and enrollment; 4) Study

procedures; and 5) Study follow-up. These areas cover the key domains of PRECIS and would allow the evidence to be included in a PRECIS assessment should a researcher wish to do so.

Details of items to be extracted include:

1. ***Characteristics of included studies***

    - Study ID: First author name, Publication year
    - Clinical trial registration number
    - Geographical location: Country and number of settings
    - Prevalence of TB and/orTB/HIV or drug resistance

2. ***Study design characteristics***

- Sample size (including sample size calculation)
- Description of study arms: Intervention vs control arm (description of tests and testing processes, attending health workers).
    - Intervention arm: Description of Xpert test used, its administration (how and where it was conducted), turn-around times, treatment initiation, treatment adherence, rates of empirical therapy, follow-up (duration, frequency, intensity and method of follow-up, unscheduled visits, incentives), rates of lost to follow-up, co-interventions.
    - Control arm: Description of microscopy, its administration, turn-around times, treatment initiation, rates of empirical therapy, treatment adherence, (duration,

frequency, intensity and method of follow-up, unscheduled visits, incentives), rates of lost to follow-up

- Follow up duration
- Empirical treatment
- Primary outcome:
- Mortality outcome: Description, how measured, effect size and precision

3. Study design features

- Description of study setting and context
    - Setting—How different are the settings of the trial from the usual care setting?
    - Organisation—How different are the resources, provider expertise, and the organisation of care delivery in the intervention arm of the trial from those available in usual care?

  Setting: facility type, research/healthcare setting, description of health system (staffing, procurement/distribution processes, leadership, resources, access, whether process evaluation done alongside trial)

- Description of study population (demographics, inclusion/exclusion criteria)
    - To what extent are the participants in the trial similar to those who would receive this intervention if it was part of usual care?
- Description of participant recruitment and eligibility

    - How much extra effort is made to recruit participants over and above what would be used in the usual care setting to engage with patients?
- Study procedures (Implementers, quality of materials, program improvement processes, incentives, training/supervision/guidelines, partnership process, fidelity/adherence, contamination, participant and provider engagement)
    - Flexibility (delivery)—How different is the flexibility in how the intervention is delivered and the flexibility anticipated in usual care?
    - Flexibility (adherence)—How different is the flexibility in how participants are monitored and encouraged to adhere to the intervention from the flexibility anticipated in usual care?
- Study follow-up (duration and intensity of follow-up and lost to follow-up)
    - How different is the intensity of measurement and follow-up of participants in the trial from the typical follow-up in usual care?

ANALYSIS &RESULTS

We will present the results of this review narratively and in tabular form.

Characteristics of included studies

Table 1: Summary characteristics of included studies

Study design features that could explain lack of impact on mortality

Table 2: Reasons for lack of impact on mortality

- Study setting and context

- Study population
- Participant recruitment/enrolment
- Study procedures
- Study follow-up
- Other features
    - Sample size

DISCUSSION & CONCLUSION

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