CRD summary
The review assessed performance of in-house PCR (polymerase chain reaction) in diagnosing pulmonary tuberculosis in smear-positive patients and found that in-house PCR can exclude TB, but specificity was not adequate to confirm diagnosis. These conclusions are based on pooled estimates derived from a heterogeneous data set from which relevant studies may have been omitted and should be viewed with caution.

Authors' objectives
To evaluate the diagnostic accuracy of in-house PCR for pulmonary tuberculosis (TB) in acid-fast bacillus smear microscopy (AFB)-positive patients.

Searching
MEDLINE (to June 2008) and EMBASE (to March 2005) were searched. The search strategy was reported as supplemental material. The bibliographies of retrieved articles were screened to identify additional studies. Only English-language publications were included.

Study selection
Studies that assessed the diagnostic accuracy of in-house PCR in AFB-positive respiratory samples (studies with <5% non-respiratory samples were also included) and used *Mycobacterium tuberculosis* culture as the reference standard were eligible for inclusion. Included studies were required to report sufficient data for the calculation of the sensitivity and specificity of in-house PCR. Studies of in-house PCR for the determination of drug resistance and studies that reporting revised sensitivity and specificity values based upon re-analysis of discrepant samples were excluded.

The in-house PCR techniques used varied widely across the included studies: the repetitive sequence IS6110 was the most frequently used amplification target and conventional gel electrophoresis was the most frequently used detection technique.

Two reviewers independently assessed studies for inclusion. Disagreements were resolved by consensus.

Assessment of study quality
The methodological quality of the included studies was assessed on the basis of the appropriateness of the patient spectrum, the technical quality of the reference standard and the blinding of those interpreting test and reference standard results.

The authors did not state how many reviewers assessed methodological quality.

Data extraction
Data were extracted on the techniques and procedures used for in-house PCR, culture and AFB staining. Numbers of true and false positives and negatives were extracted. Sensitivity and specificity values and diagnostic odds ratios, with 95% confidence intervals (CIs), were calculated for each included study. Where studies included data for a number of different in-house PCR techniques, only the technique with the highest accuracy was included.

Two reviewers extracted data independently. Disagreements were resolved by consensus.

Methods of synthesis
Pooled estimates of sensitivity, specificity, and diagnostic odds ratios were calculated using the DerSimonian and Laird
random-effects model. Between-study heterogeneity was assessed using the $X^2$ test. A summary receiver operating characteristic (SROC) curve was fitted using the Moses and Littenberg model and the area under the curve (AUC) estimated as a measure of overall accuracy. Regression analysis was used to investigate the impact of variables relating to in-house PCR technique and study quality upon the pooled estimate of diagnostic odds ratios. A full list of the variables investigated was reported in the paper. Studies were weighted in the model by the inverse variance of the diagnostic odds ratio.

Publication bias was assessed by visual examination of a funnel plot for asymmetry, Begg’s adjusted rank correlation test, and Egger’s regression asymmetry test.

**Results of the review**

Thirty-five studies with a total of 2,152 AFB-positive samples were included in the review. The median number of samples per study was 35 (interquartile range 20 to 67). Median pulmonary-TB prevalence was 0.77 (interquartile range 0.63 to 0.88). Studies were generally poorly reported: 17% of studies did not describe the reference standard and 37% applied only one culture medium. More than 50% of studies reported enrolling patients with suspected pulmonary TB, but studies often included samples from patients on treatment. Patient spectrum was rarely described and only nine studies applied any sort of blinding to sample interpretation.

The pooled estimate of sensitivity was 0.96 (95% CI 0.95 to 0.97), specificity 0.81 (95% CI 0.78 and 0.84) and diagnostic odds ratio 60 (95% CI 29 to 123); significant between-study heterogeneity was present for all parameters. SROC analysis indicated the presence of a threshold effect; variation in the diagnostic threshold across studies affected diagnostic accuracy. Regression modelling showed an association between the use of real-time PCR and diagnostic odds ratios; the diagnostic odds ratios of studies that used real-time PCR was approximately 16 times higher than that of studies that used conventional PCR (relative diagnostic odds ratio 16.44 (95% CI 1.82 to 148.41, $p=0.013$). There was no evidence of publication bias.

**Authors' conclusions**

Data on the diagnostic performance of in-house PCR in AFB-positive patients were poor. The clinical application of this test should be limited to the exclusion of the diagnosis of pulmonary TB. If used alone to confirm diagnosis, the observed low specificity of the test could result in unnecessary exposure of patients to potentially toxic and expensive treatments. Real-time in-house PCR appeared to perform better than conventional techniques.

**CRD commentary**

The review stated a clear research question defined by appropriate inclusion criteria. The search strategy was limited to two bibliographic databases with discrepant search dates and only studies published in English were included, so it was possible that relevant studies were missed. Measures to minimise errors and bias in the review process were reported, but it was unclear whether these were applied to the assessment of methodological quality. An assessment of the methodological quality of included studies was made and the impact of aspects of study quality on test performance was investigated in the analysis. There was considerable heterogeneity between studies and a threshold effect was noted. Therefore, as the authors acknowledged, the pooled estimates of sensitivity, specificity and diagnostic odds ratios presented were of limited value. The fitting of an SROC curve and accompanying regression analyses represented a more valid approach to pooling, although the model used has now been largely superseded by other methods (hierarchical or bivariate SROC).

The authors conclusions were based on pooled estimates derived from a heterogeneous data set from which relevant studies may have been omitted. They should, therefore, be viewed with caution.

**Implications of the review for practice and research**

**Practice:** In-house PCR can be used to exclude TB in smear-positive patients, but its specificity was not adequate to confirm diagnosis.
Research: The performance of in-house PCR should be evaluated in well-designed studies; particular attention should be paid to the recruitment of an appropriate study population. Mycobacterial-culture results for each sample/patient analysed, either in the TB or in the non-TB group, should be recorded.

Funding
Not reported.

Bibliographic details

PubMedID
19144797

DOI
10.1128/JCM.02051-08

Original Paper URL
http://jcm.asm.org/cgi/content/short/47/3/569

Indexing Status
Subject indexing assigned by NLM

MeSH
Humans; Polymerase Chain Reaction /methods; Predictive Value of Tests; Sensitivity and Specificity; Tuberculosis, Pulmonary /diagnosis

AccessionNumber
12009104316

Date bibliographic record published
05/08/2009

Date abstract record published
25/11/2009

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.