Performance of purified antigens for serodiagnosis of pulmonary tuberculosis: a meta-analysis


CRD summary
This review identified a number of potential purified antigen tests for the serodiagnosis of pulmonary tuberculosis. Combinations of antigens produced higher specificities than single antigens, but none was sufficiently sensitive as to replace sputum smear microscopy. However, the findings of this review may not be reliable given the limitations of the included studies and the potential for missing unpublished data.

Authors' objectives
To compare the performance of purified antigens for the serodiagnosis of pulmonary tuberculosis (TB).

Searching
PubMed, EMBASE, BIOSIS Previews and the Web of Science were searched from 1990 to November 2007 for studies published in English. Search terms were reported. Additional studies were identified through screening the reference lists of primary studies and reviews, and through contacting topic experts.

Study selection
Cross-sectional and case control studies that included at least 25 participants with sputum smear-positive or smear-negative pulmonary tuberculosis (TB), evaluating the diagnostic performance of purified antigens, were eligible for inclusion in the review. Eligible studies had to report sufficient data to construct 2x2 tables. Eligible index tests comprised serological antibody detection tests using in-house purified antigens. Studies of purified protein derivatives, culture filtrates or sonicated antigens were excluded. Eligible reference standards were: the isolation of Mycobacterium tuberculosis using sputum culture or the detection of acid-fast bacilli using a sputum smear (for countries where TB is endemic and where routine sputum cultures are not performed). Studies of latent M. tuberculosis infection or non-tuberculosis mycobacteria were excluded. Scientific studies concerning the cloning of antigens or their immunological assessment were also excluded.

Included studies compared a number of single and combination antigens (details reported in the review). The more commonly assessed antigen was 38kDa. The most commonly evaluated index tests were enzyme-linked immunosorbent assays (ELISAs). In the majority of studies, index tests were compared to mycobacterial culture as the reference standard (78%) and included sputum smear-positive patients (84%). Human immunodeficiency virus (HIV) positive patients were included in 12% of the studies.

Studies were independently assessed by two reviewers and any discrepancies were resolved through consensus.

Assessment of study quality
Validity was assessed using the QUADAS (Quality Assessment of Diagnostic Accuracy Studies) scale, including the following criteria: study design, participant recruitment methods, description of selection criteria, verification by reference standard, description of test, and blinding of index test. The overall percentage of studies fulfilling each criterion was reported.

The authors did not state how the validity assessment was performed.

Data extraction
Study data were extracted by two reviewers using a standardised form; discrepancies were resolved through consensus. The authors of included studies were contacted for additional information if required. For each individual study, 2x2 data were extracted and estimates of sensitivity and specificity, with 95% confidence intervals (CIs), were calculated.
Methods of synthesis
In order to reduce clinical heterogeneity, studies were split into subgroups with similar antigen and patient status. Subgroups with at least four studies were combined. Data were combined in a meta-analysis using hierarchical summary receiver operator curve models (HSROC) estimated using Bayesian methods with non-informative prior distributions. Mean values for sensitivity, specificity and likelihood ratios were calculated together with 95% credible intervals (CrI).

Results of the review
Two hundred and fifty-four studies (39 cross-sectional studies, 208 case-control and 7 nested case-control studies) were included in the review. Fifty-one distinct single agents and 30 multiple-antigen combinations were evaluated. The quality of the included studies was variable but many were of poor or questionable quality: only 20 studies used consecutive or random recruitment of participants; 141 adequately described the selection criteria used; 107 were completely verified through the use of a reference standard; and only 65 used a blinded interpretation of the index test. All but one study adequately described the execution of the index test.

Antigens associated sensitivities of 50% or more in sputum smear-positive patients included recombinant malate synthase (Rv1837c 73% sensitivity, 95% CrI 58 to 85) and TbF6 plus DPEP multiple antigen (75% sensitivity, 95% CrI 50 to 91). Overall, protein antigens were associated with high specificities (95% to 97%).

Amongst the lipid antigens, cord factor had the best performance (sensitivity 69%, 95% CrI 28 to 94; specificity 91%, 95% CI 78 to 97).

Multiple antigens generally achieved better sensitivities than single antigens; median sensitivity 76% (range 16 to 96%) versus 53% (range 2 to 100%). The median specificity for multiple antigens was 96% (range 79 to 100%).

Several single and multiple antigens were detected in HIV-infected (31 studies) sputum smear-positive individuals. There were too few studies of paediatric (four studies) and sputum smear-negative patients (41 studies) to reach any conclusions regarding the performance of any of the antigens.

Authors' conclusions
This review identified a number of potential tests using purified antigens, for the serodiagnosis of pulmonary TB in HIV infected and uninfected patients. Combination of antigens produced higher specificities than single antigens. However, none was sufficiently sensitive to replace sputum smear microscopy.

CRD commentary
This review answered a well-defined review question including a broad range of interventions and patients. Literature searches were performed but may have missed unpublished data and studies not written in English. Consequently, the review may, as acknowledged by the authors, be at risk from both publication and language bias. However, the review methods were designed to try and reduce the risk of reviewer error and bias when selecting studies and extracting the study data. It was unclear whether similar precautions were taken when determining the quality of the studies, despite the use of an appropriate and validated assessment scale, specifically designed for diagnostic studies.

Overall, there were a number of concerns about the quality of the included studies. Few details of the individual studies were reported but, given the large number of included studies, this was not surprising and additional information was available in online appendices. The large number of studies also increased the potential for heterogeneity. Clinical heterogeneity was addressed by grouping the studies with similar characteristics, but statistical heterogeneity was not reported. In general the presentation of the methods and results was confusing. The methods used in the meta-analysis were appropriate, but without the data for individual studies it was difficult to assess the reliability of the findings.

In conclusion, the findings of the review may not be reliable given the limitations of the included studies and the potential for missing data.

Implications of the review for practice and research

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Practice: The authors stated that none of the assessed tests achieved sufficient sensitivity to replace current sputum smear microscopy.

Research: The authors stated that future research is required to evaluate the diagnostic potential of combinations of existing antigens and to develop new antigens and tests which improve upon microscopy. In particular, studies should investigate the potential of tests, as well as the potential and feasibility of combinations of microscopy and antibody detection methods, using multiple antigens in high-prevalence countries. Any future studies should adhere to current reporting guidelines (Diagnostics Evaluation Expert Panel and the Standards for Reporting of Diagnostic Accuracy) and use rigorous methods. Outcomes should also extend beyond the conventional assessment of diagnostic accuracy (sensitivity and specificity), using outcomes such as the accuracy of by assessing diagnostic algorithms (as compared to single tests), the added value of new tests, and their impact on clinical decision making and therapeutic choices. Further studies are also required to investigate the cost-effectiveness of different purified antigen tests.

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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.