Rapid diagnostic tests for the detection of tuberculosis infection

A systematic review of rapid diagnostic tests for the detection of tuberculosis infection

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Executive summary

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Executive summary

Background

Globally, there are 8 million new tuberculosis (TB) cases and 2 million deaths per year. Once infected, active disease develops in about 10% of cases, usually within 1–2 years after exposure. Remaining individuals enter into a state of latentcy [latent tuberculosis infection (LTBI)], which can reactivate at a later stage, particularly if the individual becomes immunocompromised.

Active TB is predominantly pulmonary in nature. Extra-pulmonary TB occurs in approximately 41% of TB cases in England and Wales and includes lymphatic, pleural, meningeal, pericardial, skeletal, gastrointestinal, genitourinary and miliary TB. LTBI has no clinical manifestations and is not contagious.

Given the infectious nature of pulmonary TB, fast and accurate diagnosis is an important element of TB treatment and control.

Objectives

1. For each form of active tuberculosis, to conduct systematic reviews to evaluate the accuracy of the following groups of tests in patients suspected of active TB:
   (a) nucleic acid amplification tests
   (b) amplification molecular probe tests
   (c) serodiagnostic and biochemical assays
   (d) phage-based tests.
2. To conduct a systematic review to evaluate how effective fully automated liquid culture systems are for isolating and identifying TB.
3. To conduct a systematic review to evaluate the use of interferon-γ assays for detection of latent TB infection.
4. To examine the likely NHS and societal consequences of false-positive and-false negative tests.

Methods

Data sources

Literature was identified from electronic databases and other sources. All databases were searched from 1975 to August 2003 for tests for active TB and to March 2004 for tests for LTBI. Reference lists of included studies and relevant review articles were scanned for additional studies.

Study selection

Tests for active TB

Any study comparing a **rapid** test for detection of active tuberculosis with any reference standard was included. 'Rapid' tests were those for which a result could be obtained in less than the time taken for standard culture. Only case series studies were included. Accuracy studies had to report sufficient information to allow the construction of a 2 × 2 contingency table.

Tests for latent TB infection

The study selection criteria were (1) testing for LTBI, (2) comparison between tuberculin skin test (TST) and interferon-γ assays based on ESAT-6 and CFP-10 antigens and (3) information on TB exposure or bacille Calmette–Guérin (BCG) vaccination or HIV status.

Data extraction

Data extraction and study quality assessment were undertaken independently by two reviewers.

Data synthesis

Tests for active TB

For each test comparison, the sensitivity, specificity and 95% confidence intervals (CIs) were calculated. The method proposed by Moses and colleagues to fit both symmetric and asymmetric summary receiver operating characteristic (SROC) curves was used. Sources of heterogeneity were investigated by adding covariates to the standard regression model.

Tests for latent TB infection

Interferon-γ assays were examined to establish whether they were more strongly associated with high versus low TB exposure than TST. Odds ratios (ORs) were calculated for the association between test results and exposures from each study along with their 95% CIs. Within each study, the OR value for one test was divided by that for another to produce a ratio of OR (ROR).

Results

Tests for active TB

A total of 212 studies were included, providing 368 data sets. A further 19 studies assessing fully automated liquid culture were included.

Overall, nucleic acid amplification test (NAAT) accuracy was far superior when applied to respiratory samples as opposed to other body fluids. The better quality in-house studies were, for pulmonary TB, much better at ruling out TB than the commercial tests (higher sensitivity), but were less good at ruling it in (lower specificity), but it is not possible to recommend any one over another owing to a lack of direct test comparisons.

The specificity of NAAT tests was high when applied to body fluids, for example for TB meningitis and pleural TB, but sensitivity was poor, indicating that these tests cannot be used reliably to rule out TB. High specificity estimates suggest that NAAT tests should be the first-line test for ruling in TB meningitis, but that they need to be combined with the result of other tests in order to rule out disease. Evidence for NAAT tests in other forms of TB and for phage-based tests is significantly less prolific than for those above and further research is needed to establish accuracy.

There is no evidence to support the use of adenosine deaminase (ADA) tests for diagnosis of pulmonary TB; however, there is considerable evidence to support their use for diagnosis of pleural TB and to a slightly lesser extent for TB meningitis.

Anti-TB antibody test performance was universally poor, regardless of type of TB. Fully automated liquid culture methods were superior to culture on solid media, in terms of their speed and their precision.

Tests for latent TB infection

In total, 13 studies were included. Assays based on RD1-specific antigens, ESAT-6 or CFP-10, correlate better with intensity of exposure, and therefore are more likely than TST/purified protein derivative (PPD)-based assays to detect LTBI accurately. An additional advantage is that they are more likely to be independent of BCG vaccination status and HIV status.

Conclusions

Implications for healthcare

The NAAT tests provide a reliable way of increasing the specificity of diagnosis (ruling in disease) but sensitivity is too poor to rule out disease, especially in smear-negative (paucibacillary) disease where clinical diagnosis is equivocal and where the clinical need is greatest.

For extra-pulmonary TB, clinical judgement has both poor sensitivity and specificity. For pleural TB and TB meningitis, adenosine deaminase tests have high sensitivity but limited specificity. NAATs have high specificity and could be used alongside ADA (or interferon-γ) to increase sensitivity for ruling out disease and NAAT for high specificity to rule it in.

All studies from low-prevalence countries strongly suggest that the RD1 antigen-based assays are more accurate than TST- and PPD-based assays for diagnosis of LTBI. If their superior diagnostic capability is found to hold up in routine clinical practice, they could confer several advantages on TB control programmes.

Recommendations for research

Active TB

Diagnostic accuracy must be established, preferably prospectively, in a wide spectrum of patients, against an appropriate reference test, and avoiding the major sources of bias such as verification bias, lack of blinding, and inclusion of all indeterminate results.

- For pulmonary TB, a study of the accuracy of NAAT in clinically equivocal smear-negative patients is needed, to identify how high a proportion of false-positive results would be generated in this population.
- The place of ADA, interferon-γ and lysozyme for diagnosis of pleural TB requires further investigation
- The place of ADA, for diagnosis of TB meningitis, needs to be established
- For both pleural and TBM, the combination of NAAT tests with other tests such as ADA should be examined
- The incremental value of combinations of tests, particularly for samples of biological fluids, needs assessment in large, prospective, well-designed studies recruiting representative samples of patients.

Interferon-γ assays for the rapid identification of latent tuberculosis infection

- Research is needed in different epidemiological and clinical settings, not only in developed countries, but also in developing countries, and countries with a high prevalence of TB, of non-tuberculous mycobacteria, in ▶

populations with high BCG coverage and in immunosuppressed populations.
- Trials to evaluate the performance of the main existing commercial assays [whole blood interferon-γ enzyme-linked immunosorbent assay (ELISA) and enzyme-linked immunospot assay (ELISPOT)] in head-to-head comparison should be done in both developed and developing countries.
- The role of adding more TB-specific antigens to try to improve diagnostic sensitivity needs to be assessed.
- Longitudinal cohort studies to confirm the positive predictive value of interferon-γ assays for subsequent development of active TB should also be performed.

Publication

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NIHR Health Technology Assessment Programme

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The research reported in this monograph was commissioned by the HTA Programme as project number 01/02/07. The contractual start date was in May 2002. The draft report began editorial review in January 2006 and was accepted for publication in February 2006. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health.

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