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

J Dinnes,¹* J Deeks,² H Kunst,³ A Gibson,⁴ E Cummins,⁵ N Waugh,⁶ F Drobniewski⁴ and A Lalvani⁷

¹ Wessex Institute for Health Research and Development, University of Southampton, UK
² Centre for Statistics in Medicine, University of Oxford, UK
³ Department of Respiratory Medicine, Royal Brompton Hospital, London, UK
⁴ HPA National Mycobacterium Reference Unit, London, UK
⁵ McMaster Development Consultants, Glasgow, UK
⁶ Department of Public Health, University of Aberdeen, UK
⁷ Nuffield Department of Clinical Medicine, University of Oxford, UK

* Corresponding author

Executive summary

Health Technology Assessment 2007; Vol. 11: No. 3
How to obtain copies of this and other HTA Programme reports.

An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (http://www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public and private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

- fax (with credit card or official purchase order)
- post (with credit card or official purchase order or cheque)
- phone during office hours (credit card only).

Additionally the HTA website allows you either to pay securely by credit card or to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK
Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can only be purchased for the current or forthcoming volume.

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in pounds sterling, made payable to Direct Mail Works Ltd and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of HTA on CD?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. HTA on CD is currently free of charge worldwide.

The website also provides information about the HTA Programme and lists the membership of the various committees.
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 latency [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-\(\gamma\) 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-\(\gamma\) 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-\(\gamma\) 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 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 pulmonary 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**

The Health Technology Assessment (HTA) programme, now part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the costs, effectiveness and broader impact of health technologies for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care. The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the ‘National Knowledge Service’.

The HTA Programme is needs-led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, the public and consumer groups and professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA Programme then commissions the research by competitive tender.

Secondly, the HTA Programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Thirdly, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer-reviewed by a number of independent expert referees before publication in the widely read monograph series *Health Technology Assessment*.

Criteria for inclusion in the HTA monograph series

Reports are published in the HTA monograph series if (1) they have resulted from work for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed ‘systematic’ when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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.

Editor-in-Chief: Professor Tom Walley
Series Editors: Dr Aileen Clarke, Dr Peter Davidson, Dr Chris Hyde, Dr John Powell, Dr Rob Riemsma and Dr Ken Stein
Managing Editors: Sally Bailey and Sarah Llewellyn Lloyd

© Queen’s Printer and Controller of HMSO 2007

This monograph may be freely reproduced for the purposes of private research and study and may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising.

Applications for commercial reproduction should be addressed to: NCCHTA, Mailpoint 728, Boldrewood, University of Southampton, Southampton, SO16 7PX, UK.

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.