Cost-effectiveness analysis of the Gen-Probe amplified mycobacterium tuberculosis direct test as used routinely on smear-positive respiratory specimens

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of the amplified Mycobacterium tuberculosis direct test (MTD) (Gen-Probe), a rapid diagnostic test for tuberculosis (TB) based on nucleic acid amplification techniques. The MTD is used to rapidly exclude Mycobacterium tuberculosis (M. tuberculosis) complex organisms as the cause of disease in smear-positive and smear-negative respiratory specimens.

Type of intervention
Diagnosis.

Economic study type
Cost-effectiveness analysis.

Study population
The authors evaluated the laboratory records of all smear- or culture-positive specimens submitted from patients who provided at least one smear-positive sample to the Johns Hopkins hospital between 1996 and 2001. The base-case was an inpatient subject with symptoms consistent with active pulmonary TB and positive AFB smear results on at least one respiratory specimen.

Setting
The study setting was tertiary care. The economic study was carried out in Baltimore (MD), USA.

Dates to which data relate
The effectiveness data were obtained from studies published between 1998 and 2000. The resource data were gathered between January 2000 and December 2001. The price year was 2001.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of published comparative studies, and estimates derived from hospital records.

Modelling
A decision-tree model and sensitivity analyses were performed to measure the cost-effectiveness of implementing MTD for the routine detection of M. tuberculosis in smear-positive respiratory specimens.

Outcomes assessed in the review
The outcomes assessed in the review were:
the sensitivity and specificity of the MTD test;

the proportion of smear-positive specimens containing detectable MTD inhibitors; and

the proportion of smear-positive respiratory specimens that was culture-positive for M. tuberculosis.

These parameters, along with the estimates listed below, formed the principal effectiveness parameters used by the model.

**Study designs and other criteria for inclusion in the review**

For inclusion in the review, the studies had to report sufficient data to determine the sensitivity and specificity of the MTD in smear-positive respiratory specimens. The validity of the MTD test was determined using culture as the 'gold' standard, or culture plus clinical criteria when reported.

**Sources searched to identify primary studies**

MEDLINE was searched for primary studies.

**Criteria used to ensure the validity of primary studies**

TB status was determined by culture result, combined with clinical criteria when reported. The estimation of MTD validity measures considered only smear-positive specimens. It was assumed that the MTD strategy was run on the first smear-positive respiratory specimen submitted from any patient in whom a diagnosis of mycobacterial disease had not been made in the previous 30 days. Samples found to contain MTD-inhibitory substances were considered to provide insufficient evidence for the exclusion of M. tuberculosis and were not re-tested. Two studies used a different diagnostic algorithm, whereby MTDs giving results between 30,000 and 500,000 relative light units were re-tested. The sensitivity and specificity were reported after the removal of specimens with MTD inhibitors.

**Methods used to judge relevance and validity, and for extracting data**

Not stated.

**Number of primary studies included**

Nine primary reports were included in the review.

**Methods of combining primary studies**

The mean values for sensitivity and specificity were determined from the included studies.

**Investigation of differences between primary studies**

Not reported.

**Results of the review**

Figures in parentheses indicate the lower and upper values used in the sensitivity analyses.

When considering only smear-positive specimens, the analysis of compiled studies from the literature review indicated an overall sensitivity of 99.6% (91.8, 100) and specificity of 99.7% (95, 100).

The proportion of smear-positive specimens containing detectable MTD inhibitors was 0% (without TB) or 2.3% (with TB) (0, 7.2).

The proportion of smear-positive respiratory specimens that were culture-positive for M. tuberculosis was 31.4% (25,
Methods used to derive estimates of effectiveness
The estimates were derived from records at the authors' hospital.

Estimates of effectiveness and key assumptions
The annual number of MTD-candidate patients submitting smear-positive respiratory samples was 14 (1,500). The relative prevalence of TB among individuals with smear-positive respiratory specimens, as well as the average length of time between the smear and culture results, was ascertained directly using data from the hospital's clinical microbiology laboratory. This facility processed 4,607 specimens for mycobacterial culture in 2001. The records of all smear- or culture-positive specimens submitted from patients who provided at least one smear-positive sample to the hospital between 1996 and 2001 inclusive were evaluated. Eighty-two specimens met these criteria and were used for this analysis. The presence or absence of co-morbid conditions, such as human immunodeficiency virus and acquired immune deficiency syndrome, was not ascertained.

Measure of benefits used in the economic analysis
The outcome measure used in the economic analysis was the number of early TB exclusions. "Early exclusion of TB" was defined as the proper exclusion of M. tuberculosis as the etiologic agent of smear-positive respiratory disease on the basis of the MTD results.

Direct costs
The estimated costs of MTD detection reagents (kits of 50 tests), training sessions for new technicians, technician time for MTD, supplies, drug costs, patient respiratory isolation, HEPA filters (two annually) and pre-filter changes, and the costs of control samples maintained in the laboratory, were summarised for January 2000 to December 2001. The quantities and the costs were not analysed separately. The marginal costs of personal protective equipment (masks) and additional costs for proficiency testing were not included in this analysis. An annual discount rate of 5% per year was reported only for the cost amortised for the negative-pressure isolation room. The price year was 2001.

Statistical analysis of costs
No statistical analysis of the costs was reported.

Indirect Costs
No indirect costs were included in the analysis.

Currency
US dollars ($).

Sensitivity analysis
One-way sensitivity analyses were performed for all variables, except the drug costs. The ranges used were derived from literature reports covering a range of reasonable possibilities (see 'Results of the Review' and 'Estimates of Effectiveness' sections). If one-way variation of a variable throughout its entire range did not change the estimated MTD cost-effectiveness by more than 10%, the analysis was reported as insensitive to that variable.

A three-way sensitivity analysis (marginal MTD cost/patient, number of early TB exclusions/100 patients and cost/early exclusion of TB) was carried out on the relative prevalence of TB, the annual number of specimens processed and the marginal cost of respiratory isolation. The relative prevalence of TB in smear-positive patients was evaluated using a range of 25 to 98.4% for the sensitivity analysis. The cost of labour was evaluated using a range of $15 to 35/hour.
Estimated benefits used in the economic analysis
Full details of the results were tabulated in the paper (table 3). The following provide a representative sample.

The number of early TB exclusions/100 patients with the MTD was 68 in the base-case.

For the sensitivity analysis of the relative prevalence of TB in smear-positive patients, the number of early TB exclusions/100 patients with the MTD was 75 when assuming a rate of 25%. When this rate was assumed to be over 50%, the number of early TB exclusions/100 patients with the MTD was successively decreased to 2 with a prevalence rate of 98.4%.

When the number of smear-positive specimens processed annually by the MTD was varied over a range from 1 to 500, the number of early TB exclusions/100 patients with MTD test was always 68.

Cost results
In the base-case, the marginal MTD cost per patient was $338 and the cost per early exclusion of TB was $494. The cost of isolation plus presumptive therapy for a base-case was calculated to be $201.

When the relative prevalence of TB in smear-positive patients was in the range 25 to 75%, the marginal MTD cost per patient was $338, but the cost of early exclusion of TB increased from $452 to $1,355. A prevalence rate over 90% had a small effect in decreasing the marginal MTD cost for patient, but had a higher impact on increasing the cost of early exclusion of TB.

Maintaining the number of early TB exclusions/100 patients constant at 68 (as in the base-case), when one smear-positive specimen/year was processed by MTD, the marginal MTD cost per patient was $2,564 and the cost of early exclusion of TB was $3,750. With the same condition, when the annual number of smear-positive specimens processed by MTD was in the range 10 to 500, the marginal MTD cost per patient varied between $407 and $114, and the cost of early exclusion of TB varied from $595 to $168.

When the cost of labour was evaluated over a range of $15 to $35/hour, with the number of early TB exclusions/100 patients being held constant at the base-case level, the marginal MTD cost per patient ranged from $306 to $366. The cost of early exclusion of TB ranged from $448 to $535. Similarly, when the marginal cost of reagents was evaluated over the range $0 to $100/test, the marginal MTD cost per patient varied between $144 and $952. The cost of early exclusion of TB varied between $210 and $1,392.

Synthesis of costs and benefits
The estimated benefits and costs were combined as the cost per early exclusion of TB and an incremental analysis was not performed. The MTD was not cost-effective in the base-case. A routine MTD testing programme is expected to cost $494 per early exclusion of TB. By contrast, the expected cost of isolation plus presumptive therapy was $201.

The cost-effectiveness of MTD testing was highly sensitive to changes in the relative prevalence of TB in smear-positive specimens, the number of specimens processed per year, and the marginal daily cost of respiratory isolation. Further, the estimates of savings depended heavily on the marginal daily cost of respiratory isolation, and the speed with which MTD and culture results would become available. The model was not sensitive to changes in MTD sensitivity, specificity, or probability of inhibition (less than 10% change in cost-effectiveness across the range of the variable).

Authors' conclusions
Routine testing of smear-positive specimens with the amplified Mycobacterium tuberculosis direct test (MTD) is not expected to be cost-saving for most individual hospitals. However, centralised reference laboratories may be able to implement the MTD in a cost-effective option, as a component of the standard diagnostic evaluation for TB if at least two factors were favourable for MTD testing. For example, the relative prevalence of TB among the candidate population to be tested, the number of smear-positive respiratory specimens processed per year, the marginal cost of placing a patient in respiratory isolation, and the marginal cost of test reagents. Moreover, the greatest promise of rapid
molecular diagnostics is for use in tuberculosis (TB) suspects whose specimens are smear negative.

**CRD COMMENTARY - Selection of comparators**
The choice of the comparator was justified. It represented a valid and routine diagnostic strategy for TB patients. You should decide whether it represents a valid comparator in your own setting.

**Validity of estimate of measure of effectiveness**
The analysis of the effectiveness used a review of primary studies that appear to have been reliable sources. In addition, the criteria for the MTD strategy were reported clearly. Variability in the estimates was assessed extensively in the sensitivity analyses. This enhances the internal and external validity of the results.

**Validity of estimate of measure of benefit**
The estimation of benefit (early exclusion of TB) appears to have been appropriate for the analysis. The model used to derive the measure of health benefit was described clearly.

**Validity of estimate of costs**
All the categories of relevant costs associated with the MTD testing programme at the hospital's clinical microbiology laboratory appear to have been included in the analysis. The source of the cost and resource consumption data was reported in detail. The price year was reported. Sensitivity analyses were carried out for labour costs and the marginal cost of the reagents.

**Other issues**
The authors commented on some limitations of their analysis. For example, the under and overestimation of the cost-effectiveness of MTD testing in relation to the potential costs and outcomes due to false-negative MTD results, and the fact that the analysis was restricted to the inpatient setting.

The results of the study were presented in full. The authors compared the main study results with those from other studies. The generalisability of the study was discussed in that the authors stated that the cost-effectiveness of MTD testing is likely to be cost-effective in laboratories processing large number of specimens, with a TB prevalence of 70% among smear-positive samples and a marginal cost of $100 for respiratory isolation.

**Implications of the study**
The authors concluded that the routine MTD testing of smear-positive specimens is not expected to be cost-saving for most individual hospitals. However, centralised reference laboratories may be able to implement MTD in a cost-effective manner, in certain circumstances, for routine testing of smear-positive respiratory samples. The authors agreed with other authors that routine MTD testing could play a vital role in disease-prevention efforts by identifying smear-negative TB patients days or weeks before culture results become available. Nevertheless, cost-effectiveness remains a critical obstacle to the routine use of MTD for smear-negative patients.

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**Bibliographic details**
Other publications of related interest


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