Induced sputum and bronchoscopy in the diagnosis of pulmonary tuberculosis

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
Strategies for the diagnosis of pulmonary tuberculosis (TB) were examined. These were based on the combination of the two main diagnostic techniques (induced sputum test and bronchoscopy). The strategies were:

- bronchoscopy alone (strategy 1);
- induced sputum test alone (strategy 2);
- bronchoscopy, then induced sputum test if bronchial wash smear negative (strategy 3);
- induced sputum test, then bronchoscopy if induced sputum smear negative (strategy 4);
- bronchoscopy alone for those with any features of active TB on chest radiograph (strategy 5);
- induced sputum test alone for those with any features of active TB on chest radiograph (strategy 6);
- induced sputum test and, if those specimens smear negative, bronchoscopy for those with any feature of active TB on chest radiograph (strategy 7).

For the induced sputum test, the three procedures were usually performed on consecutive days.

Type of intervention
Diagnosis.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients suspected of having TB whose spontaneous sputum was smear negative, or who could not produce spontaneous sputum. The inclusion criteria were clinical suspicion of active TB and clinical suspicion of inactive previous TB (where important) for immigration, or for clinical purposes, to exclude active disease. The exclusion criteria were severe asthma or severe chronic obstructive pulmonary disease, oral steroid treatment for either of these conditions in the last month, or inability to give informed consent.

Setting
The setting was secondary care. The economic study was conducted in New Zealand.

Dates to which data relate
The effectiveness and resource use data were gathered from January 1996 to December 1998. The price year was not reported.
Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was conducted prospectively on the same sample of patients as that used in the effectiveness analysis.

Study sample
The use of power calculations was not reported. A sample of 160 individuals was referred for investigation of pulmonary TB to the study centre and was enrolled. However, 31 patients (19.4%) did not complete the three induced sputum tests and/or bronchoscopy. The reasons (mainly smear positive on induced sputum testing) for this were reported. Therefore, the final study sample comprised 129 people with a median age of 38 years (age range: 15 - 85). The ethnicity distribution was 9.3% European, 8.5% Maori, 11.6% Polynesian, 31% Asian, 20% African and 19.4% other.

Study design
This was a prospective diagnostic study in which the study participants underwent both induced sputum testing and bronchoscopy. The study was conducted at a single centre, the Department of Respiratory Services at the Green Lane Hospital in Auckland. The length of follow-up was unclear, but the patients were likely to have been followed until a diagnosis was made. No patient was lost to the follow-up assessment. The outcome assessment was not blind. Chest radiographs were carried out on each patient to determine the extent, grade and activity of disease. Two respiratory physicians evaluated the results of the radiographic tests without access to other information. In cases of divergent assessments, the final agreement was reached by consensus.

Analysis of effectiveness
The analysis of effectiveness considered all patients who completed the diagnostic procedures. The outcome measures used were:

the proportion of patients who tolerated the induced sputum test without difficulty;

the diagnostic results of the two techniques; and

the results of chest radiography.

Observer variation in the evaluation of radiographs was assessed using the kappa coefficient of agreement. Stepwise logistic regression was used to identify the independent determinates of test results.

Effectiveness results
The proportion of patients who tolerated the induced sputum test without difficulty was 96%.

Of the 129 patients who completed all tests, 27 had active TB, one had active non-tuberculous mycobacteria (NMT), 3 had NMT (probable contaminant), and 98 had no mycobacterial disease.

Of the 27 patients testing positive for TB, 13 were identified by induced sputum test alone, one by bronchoscopy, and 13 by both tests. Therefore, of the 27 positive cases, induced sputum testing identified 26 (96.3%) while bronchoscopy identified 14 (51.9%). Consequently, the induced sputum test was more sensitive than bronchoscopy in diagnosing TB. The difference was statistically significant.

Of the 26 patients who were culture positive on induced sputum testing, 6 were positive on one test, 7 were positive on two tests, and 13 were positive on all three samples.
Fifty-four of 129 cases had a recent history of respiratory symptoms or systemic symptoms.

The prevalence of culture positivity on induced sputum was marginally higher in symptomatic patients than in those without symptoms, but the difference was not statistically significant.

Similarly, culture positivity on induced sputum was more frequent in those with respiratory symptoms, (p=0.02), but only marginally more frequent in those with systemic symptoms, (p=0.07).

For chest radiography, inter-observer agreement was good-to-excellent for the assessment of extent of disease, the grading of abnormalities (inactive or potentially active), and the categorisation of disease (unilateral or bilateral).

Of the 129 patients considered in the analysis, 22 had a normal result on chest radiography and were excluded. Thus, 107 patients were left in the sample.

The yield from induced sputum was unrelated to disease extent. However, those in whom radiographic abnormalities suggested possibly active TB had a higher yield from induced sputum (32%) than in patients with inactive appearances (2%). This difference was statistically significant, (p<0.0005).

The logistic regression showed that culture positivity of induced sputum was the only variable associated with radiographic appearances of possibly active disease (odds ratio 23.4; 95% confidence interval: 2.9 - 189.3; p=0.003). This was independent of the radiographic extent of disease and the presence of respiratory or systemic symptoms.

Clinical conclusions
The main result of the effectiveness study was that induced sputum testing detected significantly more cases of active TB than bronchoscopy.

Measure of benefits used in the economic analysis
The summary benefit measure used was the number of cases diagnosed with each diagnostic protocol. The benefit was derived from the effectiveness study after knowing the results of bronchoscopy and induced sputum testing.

Direct costs
Discounting was not relevant since the costs were incurred during a short time. The unit costs and the quantities of resources used were not presented separately. The cost analysis included hospital charges, professional fees for physicians and nurses, laboratory charges for bronchoscopy, nursing time, disposable equipment and other consumables, and laboratory charges for three induced sputum tests. The cost/resource boundary was unclear, but it could have been that of the hospital. Resource use was estimated using actual, patient level data, which were derived from the sample of patients involved in the effectiveness study. The costs came from the average of some US hospitals. The price year was not reported.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not included in the cost analysis.

Currency
US dollars ($).

Sensitivity analysis
Sensitivity analyses were not conducted.

**Estimated benefits used in the economic analysis**
The number of cases diagnosed was:

14 (13 cases missed) with protocol 1;
26 (1 case missed) with protocol 2;
27 (no case missed) with protocols 3, 4, and 7;
11 (16 cases missed) with protocol 5; and
20 (7 cases missed) with protocol 6.

**Cost results**
The total costs for the sample of 129 patients were:

$23,310 with protocol 6;
$47,730 with protocol 2;
$75,361 with protocol 5;
$123,078 with protocol 7;
$154,284 with protocol 1; and
$202,014 with protocols 3 and 4.

**Synthesis of costs and benefits**
The average cost-effectiveness ratios were calculated to combine the costs and benefits of the competing diagnostic strategies. The average cost per case diagnosed was:

$11,020 with protocol 1;
$1,836 with protocol 2;
$7,482 with protocols 3 and 4;
$6,851 with protocol 5;
$1,165 with protocol 6; and
$4,558 with protocol 7.

**Authors' conclusions**
A diagnostic strategy based on three induced sputum tests for the detection of active tuberculosis (TB) was a cost-effective strategy in comparison with bronchoscopy alone, or other combined options.
represented the two commonly used approaches for the diagnosis of active TB in patients whose spontaneous sputum was smear negative, or who could not produce spontaneous sputum. The other diagnostic approaches, based on the combination of these options, were considered so as to cover all possible strategies for the detection of active TB. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness was based on a diagnostic study. This was appropriately selected since the same group of patients underwent the two main diagnostic procedures. The sequence of the two interventions was not reported, but this should have had no impact on the results of the tests. Two physicians, who were unaware of other results, subsequently performed the radiography examinations. This enhanced the robustness of the outcome assessment. Statistical tests were conducted to determine the impact of some variables on the study results. The method used to select the sample was reported, but it was unclear whether the study sample was adequate for the study question. This was because power calculations were not reported and there was no evidence that the study sample was appropriate.

Validity of estimate of measure of benefit
The summary benefit measure was derived directly from the effectiveness analysis. The measure was specific to the interventions considered in the study, thus any comparisons with the benefits of other health care interventions would be difficult. The benefits of protocols 3 to 7 were based on the knowledge of the diagnostic results of the two simple techniques (i.e. induced sputum testing and bronchoscopy). A hypothetical calculation was therefore performed.

Validity of estimate of costs
The authors did not explicitly state the perspective adopted and the costs were estimated from US hospitals. The average estimates from different hospitals, based on reimbursement rates, were used. However, further details on the cost estimates were not provided. The unit costs were not presented separately from the quantities of resources used and the price year was not reported. This limits the possibility of replicating the study and carrying out reflaction exercises in other settings. The costs were treated deterministically and no sensitivity analyses were conducted to address the issue of variability in the data. Therefore, caution is required when extrapolating the results of the study to other settings. Some categories of costs, mainly related to the sputum test being performed on three days, were not considered. The adoption of a broader perspective, and the subsequent inclusion of indirect costs, would have been interesting. The calculation of costs for protocols 3 to 7 was based on the results of bronchoscopy and induced sputum testing alone.

Other issues
The authors compared their findings with those from other studies. Since some discrepancies between the current study and the published literature were observed, possible reasons for these differences were discussed. A possible explanation was the difference in the samples of patients enrolled in the studies. The authors also noted the advantages and disadvantages of induced sputum testing, and concluded that the favourable aspects outweighed the negative ones. The issue of the generalisability of the study results to other settings was not explicitly addressed and sensitivity analyses were not conducted. This reduced the external validity of the analysis. Finally, the use of incremental rather than average cost-effectiveness ratios would have been helpful.

Implications of the study
The study results suggested that three induced sputum tests should replace bronchoscopy in the detection of possibly acute, sputum smear negative, pulmonary TB. The authors recommended that further research investigate the economic and clinical impact of performing the three induced sputum tests over 1 to 2 days.

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