A comprehensive comparison of Ziehl-Neelsen and fluorescence microscopy for the diagnosis of tuberculosis in a resource-poor urban setting

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 tuberculosis (TB) were examined. The strategies were based on two tests, Ziehl-Neelsen (ZN) and fluorescence microscopy (FM). Both techniques were based on the examination of sputum for an acid-fast bacilli smear examination and were followed by chest X-ray (CXR). Three sputum samples (spot, early morning, spot) were collected in sterile sputum bottles. Therefore, a total of six diagnostic strategies were considered.

Type of intervention
Diagnosis.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised TB suspects aged 15 to 65 years presenting at primary care clinics.

Setting
The setting was primary care. The economic study was carried out in Kenya.

Dates to which data relate
The effectiveness and resource use data were gathered from March 2000 to March 2001. 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 carried out prospectively on the same sample of patients as that used in the clinical study.

Study sample
Power calculations were not reported. Patients were identified among those presenting at the study centre from March 2000 to March 2001. Every tenth TB suspect presenting at the Rhodes Chest Clinic was referred to enter the study voluntarily. Contaminated cultures were excluded from the analysis. A total of 1,398 patients were enrolled in the study. However, a third sputum culture was missing for 169 suspects and another 236 suspects had no CXR results. Thus, the final study sample comprised 993 cases (71%) with complete data. There were 596 men (median age 30 years; age range: 16 - 60) and 397 women (median age 27 years; age range: 24 - 56), giving a male-to-female ratio of 1.5. The
male participants were significantly older than the female participants.

**Study design**
This was a diagnostic study that was carried out at the Rhodes Chest Clinic in Nairobi, Kenya. All of the patients underwent routine sputum diagnostic procedures according three steps: selection of suspects, smear microscopy, and CXR for those suspects who are smear-negative. Each sputum specimen was used for ZN, FM and culture examination. HIV testing was also performed. All investigators and radiologists were blinded to the diagnostic test used. No follow-up was carried out.

**Analysis of effectiveness**
The analysis of the clinical study included all patients with complete data. The effectiveness analysis evaluated the accuracy of the diagnostic tests in comparison with culture. Thus, several outcomes measures were used. For example, culture-positive and culture-negative cases, diagnosed cases, sensitivity and specificity, and positive and negative predictive values. A suspect with at least one positive culture result was considered a proven TB case, while a suspect with three negative culture results and a CXR showing abnormalities consistent with pulmonary TB was regarded as a non-TB case. Logistic regression was performed on culture-positive TB patients to assess the impact of HIV on test performance.

**Effectiveness results**
Of the 993 individuals enrolled, 554 (56%) were culture-positive: 332 TB cases (59.9%) were detected by ZN and an additional 177 (31.9%) were detected by CXR, while 430 TB cases (77.6%) were detected by FM and CXR added another 83 (15%). The first specimen detected 53% of the total cases detected by ZN (38.8% with the second specimen and 8.1% with the third specimen). The first specimen detected 86% of the total cases detected by FM (13.3% with the second specimen and 0.7% with the third specimen). Overall, examination of the three specimens and CXR diagnosed 91.9% of all culture-positive suspects when using ZN, and 92.6% of all culture-positive suspects when using FM.

The sensitivity and negative predictive value with ZN were, respectively, 32% and 54% with the first (spot) specimen, 47% and 60% with the second (early morning) specimen, 31% and 53% with the third (spot) specimen, 60% and 66% with any specimen with one positive, and 35% and 55% with any specimen with two positives. The corresponding values with FM were 67% and 70% (first specimen), 73% and 75% (second specimen), 70% and 72% (third specimen), 78% and 78% (any specimen with one positive), and 72% and 74% (any specimen with two positives).

There was no statistically significant difference in specificity and positive predictive value between the two techniques.

The analysis revealed that irrespective of HIV status, FM was significantly more sensitive than ZN. However, the sensitivity of ZN was significantly lower among HIV-positive than HIV-negative individuals. The sensitivity in HIV-negative individuals was 57% in ZN-positive suspects and 84% in FM-positive suspects. The sensitivity in HIV-positive individuals was 36% in ZN-positive suspects and 73% in FM-positive suspects. Logistic regression showed that the probability of smear positivity was lower in HIV-positives than HIV-negatives, and that this effect was stronger using ZN compared with FM.

**Clinical conclusions**
The effectiveness analysis showed that FM was generally more accurate than ZN and was not affected by HIV status.

**Measure of benefits used in the economic analysis**
The summary benefit measure was the number of correctly diagnosed cases. This was derived from the diagnostic study.

**Direct costs**
The time horizon of the study was not stated clearly and discounting was not reported. The unit costs were not reported separately from the quantities of resources used for all items. The economic evaluation included clinic costs, laboratory service costs and CXR costs (labour, equipment and material, investment, and running services). Such costs were relevant to the health care system. Some costs borne by the patients (e.g. travel, food, and antibiotics) were also considered. Some resource use data were obtained from random samples of patients enrolled in the clinical study, while other data came from the study clinic. The source of the costs was not given. The cost-savings due to false TB patients who were correctly diagnosed were also included in the analysis. The price year was not reported.

**Statistical analysis of costs**

The costs were not considered in the economic evaluation.

**Indirect Costs**

Income losses were also considered in the analysis, although the method used to estimate them was not described. Resource use was derived from interviews with a sub-group of patients. The price year and other information on the analysis of indirect costs were not given.

**Currency**

US dollars ($).

**Sensitivity analysis**

Univariate sensitivity analyses were carried out to examine the robustness of the cost-effectiveness ratios to variations in some cost and clinical data. For example, changes in the use of CXR, TB prevalence, daily workload, labour costs, patient costs and equipment prices. The authors reported the alternative values used in the sensitivity analysis, which were presumably based on their opinions.

**Estimated benefits used in the economic analysis**

In a cohort of 1,000 TB suspects, the number of correctly diagnosed cases with ZN was 512 on first sample, 515 on first and second sample, and 513 on first, second and third sample. The corresponding numbers with FM were 512 (first sample), 515 (first and second sample) and 516 (first, second and third sample), respectively.

**Cost results**

In a cohort of 1,000 TB suspects, the total costs with ZN were $9,653 for first sample, $18,787 for first and second sample, and $20,951 for first, second, and third sample. The corresponding costs with FM were $15,443 (first sample), $19,097 (first and second sample) and $21,754 (first, second and third sample), respectively.

**Synthesis of costs and benefits**

Average cost-effectiveness ratios (i.e. the cost per correctly diagnosed case) were calculated to combine the costs and benefits of the alternative diagnostic strategies.

When cost-savings were not considered, the average cost-effectiveness ratio with ZN was $30.7 for first sample, $36.5 for first and second sample, and $40.8 for first, second and third sample. The corresponding values with FM were $30.2 (first sample), $37 (first and second sample) and $42.1 (first, second and third sample), respectively.

When cost-savings were included, the average cost-effectiveness ratio with ZN was $44.2 for first sample, $35.1 for first and second sample, and $40.8 for first, second and third sample. The corresponding values with FM were $26.3 (first sample), $33.9 (first and second sample) and $39.2 (first, second and third sample), respectively.

The sensitivity analysis showed that the ratio between the two strategies was almost unaffected by changes in clinical
and economic data.

**Authors' conclusions**
In a resource-poor setting, fluorescence microscopy (FM) used on one or two specimens for the detection of tuberculosis (TB) was more cost-effective than a Ziehl-Neelsen (ZN) approach, and it shortened the diagnostic process.

**CRD COMMENTARY - Selection of comparators**
The authors justified the choice of the comparators, that is, FM and ZN followed by CXR. Culture was considered the 'gold' standard. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness evidence came from a diagnostic study, which used a single cohort of patients. The outcome assessment was blinded and a large sample of patients was considered. Moreover, the method used to select the sample was described. These aspects of the study increase the internal validity of the analysis. However, no follow-up was carried out and only patients with complete data were considered in the effectiveness analysis.

**Validity of estimate of measure of benefit**
The summary benefit measure was specific to the disease considered in the study and appears hardly comparable with the benefits of other health care interventions.

**Validity of estimate of costs**
The perspective adopted in the study reflected the costs borne by both the health system and the patients. The information on the approach used to assess the costs and quantities of resources used was limited. The unit costs were not reported separately from the quantities of resources used, which limits the possibility of replicating the study in other settings. Similarly, the price year was not reported, which makes reflation exercises difficult. The costs were treated deterministically and were broken down in macro-categories. Some categories of costs were varied in the sensitivity analysis.

**Other issues**
The authors compared their findings with those from published studies. However, most comparisons were limited to the effectiveness side of the analysis. The issue of the generalisability of the study results to other settings was addressed in the sensitivity analysis, which enhances the external validity of the study. The authors noted some advantages of FM over ZN, including independence from HIV status, a more use-friendly approach, and the need for one spot (which improved adherence with the diagnostic process).

**Implications of the study**
The study results supported the use of FM in resource-poor settings to detect TB cases. In particular, with high numbers of suspects and high prevalence of HIV, the authors recommended the use of FM on two specimens.

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**Bibliographic details**
Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Adolescent; Adult; Aged; Bacteriological Techniques /economics /methods; Confidence Intervals; Cost-Benefit Analysis; Cross-Sectional Studies; Developing Countries; Female; Health Resources; Humans; Kenya; Logistic Models; Male; Microscopy, Fluorescence; Middle Aged; Mycobacterium tuberculosis /isolation & purification; Poverty; Probability; Reagent Kits, Diagnostic /economics; Sensitivity and Specificity; Tuberculosis, Pulmonary /diagnosis /economics; Urban Population