Systematic review, meta-analysis and economic modelling of molecular diagnostic tests for antibiotic resistance in tuberculosis

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Declared competing interests of authors: Peter J White reports grants from Medical Research Council (MRC) and from the National Institute for Health Research (NIHR) during the conduct of the study, and grants from Otsuka outside the submitted work. Francis Drobniewski reports grants from EU FP7, European Centre for Disease Control, the World Health Organization and the Technology Strategy Board, outside the submitted work. Ibrahim Abubakar reports grants from NIHR and MRC outside the submitted work. Joanne Lord reports grants from NIHR outside the submitted work.
Scientific summary

Background

Tuberculosis (TB) is a major global health problem, killing 1.3 million people annually. Around 9000 cases of TB are currently reported each year in the UK, and London has the highest rate of TB of any Western European capital. The increasing prevalence of drug resistance threatens TB control programmes worldwide. Multidrug-resistant (MDR) TB is defined as resistance to, at least, rifampicin and isoniazid – the two most powerful first-line anti-TB drugs. MDR-TB has a worse patient outcome than drug-sensitive (DS) disease.

The conventional diagnostic work-up for patients with suspected respiratory TB disease includes sputum smear microscopy to provide an early indication of infectivity, followed by culture to confirm diagnosis and for drug susceptibility testing (DST). Culture is considered the gold standard but takes up to 42 days, and sometimes longer, for a definitive result. Rapid molecular assays can return a result in as little as 1–3 days. This may be beneficial for patients, the community and the UK NHS. People incorrectly considered to have TB may benefit from an early rule out: avoiding or shortening unnecessary isolation and treatment with its associated high costs (for the patient as drug-related adverse events and for the NHS in terms of hospital admission and negative pressure isolation). For patients with disease, early accurate diagnosis will ensure that they commence effective treatment promptly and that, when necessary, they are isolated earlier.

However, rapid assays are less accurate than culture, raising the possibility of false-positive (FP) and false-negative (FN) results. Both types of error can be costly and harmful. FN results provide inappropriate reassurance and may harm the patient by delaying time to effective treatment and placing contacts at risk if infection control measures are relaxed. FP results may unnecessarily expose patients to the inconvenience of isolation and adverse effects of medication. These costs and harms are likely to be particularly acute for patients with, or at high perceived risk of, MDR-TB. Current guidance, therefore, recommends that rapid molecular tests may have a role alongside culture but that they should not replace culture. This limits, but may not eliminate, potential costs and harms of misdiagnosis, as clinicians can take corrective action when culture results arrive. The additional cost of the molecular test also cannot be offset by savings from reduced need for culture. There is, therefore, a trade-off between the costs and health impacts of adding a rapid molecular test to the current diagnostic pathway.

Objectives

1. To conduct a systematic review of evidence, in the available published and ‘grey’ literature in medical, scientific and economic databases, on the diagnostic accuracy of genetic tests for detecting TB drug resistance compared with culture-based methods.
2. To utilise this information to conduct a health-economic evaluation of various screening and diagnostic strategies, including comparison of alternative models of service provision (centralised vs. disseminated) and assessment of the value of targeting rapid testing at various high-risk subgroups.
3. To construct a transmission-dynamic mathematical model to explore the extent to which the use of more rapid diagnostic tests may interrupt the transmission of drug-resistant TB, including MDR-TB, and produce public health benefit.
Methods

Systematic review
A standardised search strategy was used to generate a comprehensive list of relevant studies from six electronic literature databases: EMBASE, PubMed, MEDLINE, Bioscience Information Service (BIOSIS), System for Information on Grey Literature in Europe Social Policy & Practice (SIGLE) and Web of Science (PROSPERO CRD42011001537). The search strategy was confined to any paper published on 1 January 2000 to 15 August 2013. Additional sources included Cumulative Index to Nursing and Allied Health Literature (CINAHL), NHS Economic Evaluation Database (NHS EED), diagnostic equipment manufacturer websites, published diagnostic accuracy reviews and experts within the field. All articles that could potentially meet defined eligibility criteria were selected for initial review. Two reviewers independently evaluated eligible full-text papers. Key data variables extracted included patient characteristics, drug resistance(s) investigated, test used and test characteristics. Publication details, sensitivity and specificity were recorded. Study quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies tool version 2 (QUADAS-2). Each group of tests, with sufficient studies available, was analysed separately. For each test comparison, the sensitivity, specificity and their exact 95% confidence intervals (CIs) were calculated using Stata version 13.1 (StataCorp LP, College Station, TX, USA). Diagnostic accuracy across studies was summarised using a summary receiver operating characteristic curve. Variability across studies was assessed and modelled using this approach.

Health economics
For each diagnostic strategy and population subgroup, a care pathway was defined. This specified which medical treatments and health services individuals would receive, from presentation to the point where they either did or did not complete TB treatment successfully. The pathways were defined by perceived risk of MDR-TB, smear status, the result of the molecular test, and the culture and DST results. These factors gave 12 unique pathways for which only culture testing was used, and a further 32 for which rapid molecular assays were added, alongside confirmatory culture testing. A total cost was estimated for each care pathway, including the cost of consultations and investigations prior to referral to TB services, TB diagnosis, medication, inpatient care and isolation, outpatient care, and contact tracing and associated treatment of any latent TB cases. Costs were taken from the Personal Social Services Research Unit, NHS reference costs or published literature and uprated if necessary to 2011–12 prices. All costs were estimated from a NHS perspective. For each care pathway the health impact was estimated in terms of the mean discounted quality-adjusted life-years (QALYs) lost as a result of TB disease and treatment. Costs and QALY outcomes were discounted at an annual rate of 3.5%.

Transmission modelling
An integrated transmission-dynamic and economic model was used to evaluate the cost-effectiveness of introducing rapid molecular testing into the diagnostic pathway, alongside culture and DST. The model used is a compartmental (state transition) model. This approach divides the population up according to infection status, each contained in a separate compartment. There are flows between compartments as individuals become infected, progress to disease, are diagnosed and placed on treatment, etc. The compartmental model is used to describe the infection and treatment dynamics for both non-MDR-TB and MDR-TB strains. Economic parameters were derived as described above and epidemiological parameter estimates were obtained from the Office for National Statistics, Enhanced Tuberculosis Surveillance data and the literature. Probabilistic sensitivity analysis (PSA) was performed to evaluate the impact on cost-effectiveness of diagnostic and treatment time delays, diagnosis costs and treatment costs, and associated QALYs. Parameters relating to diagnostic test performance were subject to deterministic sensitivity analysis, in which each parameter was varied individually across its range.
Results

Systematic review
A total of 8922 titles and abstracts were identified through database searches and hand-searching. After the first phase of screening, 557 papers were identified as potentially eligible for the review. A total of 56 studies contained sufficient information on the performance of the rapid diagnostic tests to be included in the review. The findings of the systematic review suggest that all three commercial tests, INNO-LiPA Rif.TB® (Fujirebio Europe, Ghent, Belgium), Xpert® MTB/RIF (Cepheid Inc., Sunnyvale, CA, USA) and GenoType® MTBDRplus (Hain Lifescience, Nehren, Germany) demonstrate promising levels of diagnostic discrimination when detecting rifampicin and/or isoniazid susceptibility in clinical samples. The pooled sensitivity and specificity estimates for detecting isoniazid resistance by MTBDR plus were 83.4% (95% CI 66.3% to 100.0%) and 99.6% (95% CI 99.0% to 100.0%), respectively. The pooled specificity for detecting rifampicin resistance was 98.2% (95% CI 97.2% to 99.3%) and pooled sensitivity was 94.6% (95% CI 91.6% to 97.6%). The pooled estimates of sensitivity for INNO-LiPA (95.4%, 95% CI 92.2% to 98.3%) and specificity (99.7%, 95% CI 99.5% to 100.0%) suggested good levels of diagnostic accuracy when used to detect rifampicin resistance in clinical samples. For the detection of rifampicin resistance by GeneXpert, the pooled sensitivity was 96.8% (95% CI 94.2% to 99.4%) and pooled specificity was 98.4% (95% CI 97.8% to 99.0%). Although there was evidence of heterogeneity between included studies, the findings of these analyses are consistent with previous estimates.

Health economics
Costs and QALYs were estimated for 44 unique care pathways. With a culture-only strategy, the total estimated cost ranged from £2252 per patient (smear-negative patient correctly identified as free from TB) to £130,214 (smear-positive patients with MDR-TB not identified as high risk and, therefore, not treated presumptively). The range was similarly wide with molecular testing: from a minimum of £2334 (correctly diagnosed smear-negative patients without TB) to a maximum of £131,771 (smear-positive patients with MDR-TB thought to be at high risk and with an inaccurate molecular test result indicating DS disease). It should be noted that the incidence of the very-high-cost pathways is likely to be low (as both MDR-TB and misdiagnoses are rare). The expected cost for a patient with smear-positive DS disease (deemed low risk of MDR-TB, correctly diagnosed by molecular test and treated appropriately) is £9392. The cost for a similar patient, correctly diagnosed and treated under the culture strategy is slightly lower, at £8670.

Estimated mean QALY losses ranged from 0 (for patients without TB who are correctly diagnosed and treated) to about 1.205 QALYs lost (for patients with smear-positive MDR-TB with a FN molecular test result for MDR-TB, who are not treated presumptively but are subsequently correctly diagnosed by confirmatory culture and DST). A large proportion of the estimated QALY losses were attributable to adverse events related to MDR-TB treatment.

Transmission modelling
An integrated transmission-dynamic and economic model was used to evaluate the cost-effectiveness of introducing rapid molecular testing for TB infection and DST in England and Wales, including accounting for effects of more rapid diagnosis and treatment in averting transmission of infection. The evaluation considered three ethnic groups: Black African, South Asian and Eastern European. The first two groups represent a large proportion (61%) of the TB cases in England and Wales, and the available data allow us to estimate numbers of transmission events expected to be averted by faster diagnosis and treatment of TB and MDR-TB. The Eastern European group is of interest because of its high proportion of TB cases that are MDR (≈27%). Three different molecular test combinations were considered (GeneXpert only, and GeneXpert combined with INNO-LiPA or MTBDRplus), in two locations (either local to the hospital or in a regional laboratory).
The introduction of molecular testing had a small impact on transmission, as current practice is effective in limiting transmission from patients with TB while they are undergoing clinical examination. There is benefit for smear-negative patients, most of whom test positive by molecular methods and therefore can be diagnosed promptly and start treatment earlier than if they were to wait for culture confirmation. The major benefit of molecular testing is faster diagnosis of MDR-TB, which produces cost savings as patients with smear-positive disease and suspected MDR-TB are isolated until their MDR status is known and then appropriate treatment commenced. The cost saving resulted from the high daily cost of isolation. The imperfect specificity of molecular tests increases annual numbers of TB diagnoses attributable to FP results and the consequent inappropriate treatment of some patients incurs a QALY loss as well as a financial cost.

The results of the transmission modelling suggest that all assays are cost saving and achieved a reduction in the QALY loss from TB compared with that expected under current practice. Across the Black African and Eastern European populations the GeneXpert scenario was the most cost-effective rapid test, at both 10- and 20-year time horizons, and £20,000 or £30,000 willingness-to-pay threshold per QALY. For the South Asian population, using a 10-year time horizon, the MDRTBplus scenario was the most cost-effective rapid test, with the highest estimated incremental net benefit compared with current practice, although the difference with GeneXpert was very small. At a 20-year time horizon, the MTBDRplus scenario was also the most cost-effective test.

Differences in the cost-effectiveness of local compared with regional testing were small and subject to considerable uncertainty.

**Discussion and conclusions**

Rapid molecular tests such as the manual line probe assays (LPAs) and automated GeneXpert are able to identify rifampicin resistance (and isoniazid resistance for some LPAs) with promising levels of specificity and are almost as sensitive as microbiological culture, but produce results more quickly (within 1 day of the sample being obtained). Their sensitivity approaches that of microbiological culture but provides results much faster.

The positive predictive value (PPV) for resistance is dependent on the prevalence of drug resistance in the background population. This is low in the UK, and hence a proportion of rifampicin resistance results will be FPs if used in a general screen, although the corresponding negative predictive value (NPV) will be high. PPV will be > 90% only when the underlying prevalence is > 15%. This is seen within populations in countries such as the Baltic States, Russia and Ukraine and from where active migration to the UK occurs. This low PPV associated with low prevalence is linked to the earlier World Health Organization advice to perform a confirmatory test (either a second molecular or culture-based test). Further caution is also urged because of the heterogeneity observed between studies. Realising the benefit of molecular testing will rely on the effectiveness of the means by which suspected MDR-TB is established.

Overall, the results suggested that adding any of the rapid assays assessed here to the current diagnostic pathway was likely to be cost-effective in the UK context, in which patient samples are routinely cultured. The GeneXpert and MTBDRplus scenarios appear to be more cost-effective than INNO-LiPA in most scenarios. These results are subject to uncertainty, as some key assumptions and parameters were based on expert judgement or literature published some time ago. However, results were informed by detailed estimates of diagnostic assay costs based on a time-and-motion study and bed-stay durations from audit data. They also incorporated estimated impacts of transmission based on dynamic modelling.

The performance of these tests is less clear-cut for non-pulmonary material and other low-bacillary specimens, such as from children or human immunodeficiency virus (HIV)-positive patients.
**Recommendations for research**

There is a need to assess the performance of these tests in specific patient populations, such as children and those infected with HIV. Pilots need to be developed, which can provide detailed information regarding real test performance and associated cost-effectiveness when rapid tests are delivered as a near ‘point of care’ (POC) test within and outside a traditional hospital environment (e.g. in a clinic within a hospital, a mobile unit, a prison, a homeless shelter, migrant accommodation). These can be used to determine the cost-effectiveness for future POC tests compared with laboratory-based assays, particularly in the context of capital-intensive laboratory-based microbiological reference analyses and next-generation sequencing-based approaches.

**Study registration**

This study is registered as PROSPERO CRD42011001537.

**Funding**

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.
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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 10/96/01. The contractual start date was in November 2011. The draft report began editorial review in May 2014 and was accepted for publication in February 2015. 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 reviewers 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.

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