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The cost effectiveness of assays of genetic markers for antibiotic resistance in tuberculosis

F Drobniewski, I Abubakar, J Lord, M Lipman, M Jit, A Charlett, and P White

Content

Summary: This review will answer key questions on the clinical impact and cost effectiveness for the use and role of different assays identifying genetic markers associated with multidrug and extensively drug resistant TB in patients with tuberculosis across the UK through
a. systematic review of the published and grey literature
b. transmission dynamic model to determine the implications of secondary transmission.
c. decision analytic health economic model of various screening strategies (including different commercial/in house assays, geographically dispersed versus centralised models of service and targeting of rapid testing at various high-risk sub-groups)

1.0 Background

1.1 Background and International Policy Context

Tuberculosis is an airborne disease caused by bacteria belonging to the Mycobacterium tuberculosis complex (MTBC). Most infections in humans result in an asymptomatic, latent infection, and about one in ten latent infections eventually progresses to active disease (30 and 50% in patients co-infected with HIV).

Drug resistance is a growing international problem, which with HIV co-infection, threatens the success of national TB programmes. Multi- drug-resistant tuberculosis (MDRTB) (i.e resistance to at least isoniazid and rifampicin) is a growing threat to national tuberculosis programmes world-wide. Extensive drug resistance (XDRTB), i.e. additional resistance to fluoroquinolones (FQ) and the injectable agents (amikacin, capreomycin or kanamycin) decreases chances of cure and also survival and success further (Kim et al 2008; Shah et al 2008). So far co-infection with HIV and XDRTB has been largely fatal (Koenig et al 2008; Gandhi et al 2006)

At the end of 2010, the World Health Organisation (WHO) endorsed a new assay (GeneXpert Xpert MTB/RIF) globally for the rapid diagnosis of tuberculosis (TB) and rifampicin resistance (as a surrogate for detecting MDRTB. It had endorsed the use of molecular Line Probe Assays (LPA) (which are not automated) in 2008 for the rapid screening of TB, rifampicin, isoniazid and MDRTB. Adoption of LPAs did not eliminate the need for conventional culture and DST capability; culture remains necessary for definitive diagnosis of TB in smear negative patients, while conventional DST is required to diagnose XDR-TB. Following on from this several countries (eg Lesotho, South Africa and Ethiopia) implemented a strategy of centralized screening of all smear-positive sputa.

However the Xpert MTB/RIF assay is simpler and automated and requires much less technical skill; it was proposed that the system could be introduced closer to the patient at the clinic level.

1.2 UK TB epidemiology and drug resistance

Around 9000 cases of TB are currently reported each year in the United Kingdom. Most occur in major cities, particularly in London. The incidence of MDR-TB in the UK is low (~1%) and has remained relatively constant over recent years. However, in some areas of the country such as London and in certain population groups the incidence is much higher. Institutional outbreaks of MDRTB have occurred in the UK (eg Breathnach et al 1998), notably in London hospitals, and wider pan-institutional outbreaks such as one involving isoniazid-resistant strains have been reported

1.3 Summary of Existing Research/Reviews

Molecular Basis of Drug Resistance

Mycobacterium tuberculosis drug resistance emerges via a variety of mechanisms. Many of the mutations leading to resistance are recognised, however, further work is required to fully elucidate the mutations responsible for resistance against some drugs and to determine the predictive value of finding a particular mutation in a strain of *M. tuberculosis* (eg Drobniewski et al 2003; Baker et al 2004, 2005; Sandgren et al 2009)

Significant examples of recognised mechanisms include the acquisition of mutations in the chromosomal sequence that encode changes that 1) block the activity of a drug (e.g mutations in *rpoB* prevent binding of rifampicin to RNA polymerase and inhibition of transcription), 2) block activation of a prodrug (e.g., mutations in *katG* lead to loss of the ability of catalase to activate the prodrug isoniazid to its active form), or 3) produce an activity that binds or destroys the drug (e.g., mutations in *inhA* increase the amount of *Inh*A product which interferes with the activity of isoniazid by binding sufficient

isoniazid to reduce its effective concentration in the bacterium to below an inhibitory level) (Drobniewski F A et al 2003; Telenti et al 1993; De Beenhouwer,et al 1995)

A high proportion of rifampicin resistance is associated with concurrent resistance to isoniazid (~95%) enabling the detection of resistance to rifampicin to be used as a marker for MDR-TB with a high level of accuracy. Assays to detect mutations associated with other key resistances, especially XDR TB have been developed but the scientific understanding of all the mechanisms of resistance is less well understood; nevertheless several prototype assays have been developed and are being evaluated.

As described above, at the end of 2010, the World Health Organisation (WHO) endorsed a new assay (GeneXpert Xpert MTB/RIF) globally.

So how revolutionary is the assay?

We have had the ability to rapidly and accurately diagnose TB and rifampicin resistance in sputum microscopy-smear positive specimens (S+) in 1-2 days since the 1990s (Telenti et al 1993; De Beenhouer et al 1995; Drobniewski F A et al 2003; Dinnes, J, et al 2007). Most systems are based on nucleic acid amplification technology (NAAT) and employ a combination of Polymerase Chain Reaction (PCR) or comparable amplification systems with an additional detection system for the mutation associated with drug resistance. For example detection can utilise methods such as DNA sequencing, pyrosequencing, electrophoretic detection methods (e.g., single strand conformation polymorphism), methods for detecting mismatches in heteroduplexes (e.g., temperature gradient HPLC analysis or branch migration inhibition) and hybridization assays (e.g., molecular beacons, microarrays, membrane hybridization, or line-probe assays).

Several commercial kits are available including line-probe assays for rifampicin resistance conferring mutations (INNO-LiPA® Rif.TB, Innogenetics and GenoType® MTBDR(*plus*), Hain LifeScience GmbH), microarray assays (CombiChip Mycobacteria DR, GENE IN) and the GenExpert (Cepheid) described above. Some also detect mutations associated with isoniazid resistance. In addition, several in house assays have been used by national reference centres to test for rifampicin resistance.

In 1998, national/population-based services for the diagnosis of TB and rifampicin resistance directly from patient S+ specimens were proposed (Drobniewski F A. 1998) and the concept presented at the WHO in 2000. Then, it did not fit with WHO policy which focused on sputum microscopy as the core practical and globally available tool especially in low/middle income countries (LMIC).

The model was adopted in the UK in 1999 (and later elsewhere) and the UK Health Protection Agency National Mycobacterium Reference Laboratory (NMRL) began the world's first nationally available 'drop-in' service (*Fastrack)* for the molecular detection of Tuberculosis (TB) and rifampicin resistance (as a surrogate for multidrug resistant TB (MDRTB) in sputum smear- positive TB cases. This had followed on from research and development/evaluation of several techniques including both in-house and commercial new 'Line Probe' Assays (LPA). The new service using LPAs, produced good results: in an analysis of 1,997 primary clinical specimens (of all types)for which conventional drug susceptibility data (DST) was available, the concordance, sensitivity, specificity, positive (PPV) and negative (NPV) predictive value for detecting rifampicin susceptibility were 99.1%, 95.0%, 99.6%, 92.7% and 99.7% respectively (Sam et al 2006). The UK *Fastrack* service sensitivity for TB detection of over 70% for smear-negative sputum samples received in 2006-9 (unpublished data). A similarly high performance using the same LPA was shown in Latvia, a high MDRTB burden country (Skenders et al 2007).

The diagnostic accuracy of these assays internationally have been assessed in previous systematic reviews and meta-analyses (Morgan et al 2005; Ling et al 2008; WHO Expert Group 2008). For example, for the INNO-LiPA Rif.TB assay, used in the UK above, the pooled sensitivity was 0.97 (95%CI 0.95–0.98) and the pooled specificity was 0.99 (95%CI 0.98–1.00) for detecting rifampicin resistance in *M. tuberculosis* isolates. Overall discriminatory ability of the assay was 99% and overall accuracy was 97%, with all studies yielding consistently high performances.

A different LPA (MDRTBPlus) used directly on 536 sputum specimens in South Africa (Barnard et al 2008) gave a sensitivity, specificity, PPV and NPV predictive value of 98.9, 99.4, 97.9, and 99.7%, respectively, for detection of rifampicin resistance; 94.2, 99.7, 99.1, and 97.9%, for isoniazid resistance; and 98.8, 100, 100, and 99.7%, for detection of MDRTB. The assay also performed well with smear negative, culture-positive specimens (Barnard et al 2008). A meta-analysis of the performance of the Hain MTBDR*(plus)* assay in ten studies demonstrated excellent results; for rifampicin resistance sensitivity was 98.1% (95% CI: 95.9, 99.1) and 98.7% (95% CI: 97.3, 99.4) for specificity with no significant heterogeneity (Ling et al). For detecting isoniazid there was a pooled sensitivity of 0.85 (95%CI 0.77– 0.90) which ranged from 57%–100% and a pooled specificity of 0.99 (95%CI 0.98–1.00) (Ling et al; WHO Expert Group)

Multiple review and primary studies have been performed internationally on cultures (eg Bwanga et al; Coronel et al 2010) and on primary specimens including those produced by this team and have produced excellent results in comparison with internationally quality-assured standard phenotypic culture-based methods. (eg Hillemann et al 2007; Nikolayevskyy et al 2009).

So how does the new XpertTBRif assay perform?

It reliably detects TB and rifampicin resistance in S+ specimens. In a series of well designed and comprehensive multicenter studies co-ordinated by the Foundation for Innovative and Novel Diagnostics (FIND), a single Xpert MTB/RIF had a sensitivity of 98.2% (551/561) when used directly on sputum from patients with S+, culture positive TB and a sensitivity of 72.5% (124/171) on patients with smear-negative TB (with sensitivity increasing if additional specimens were tested) (Boehme, et al 2010). The higher sensitivity, in part, reflects the large sample volume analysed. Automated liquid culture remained the most sensitive method for detection but requires a complex infrastructure and well trained staff for success.

Where the new assay scored highly is that the high sensitivity and specificity results are produced within 2 hours and with minimal staff training. The high cost of the assay is a problem but FIND has negotiated discounts for the public sector (including NGOs, charities etc) in 116 LMIC and high TB/MDRTB burden countries.

Current UK practice

In a retrospective analysis of specimens sent from a Liverpool hospital, where NAAT testing was indicated in 87/123 smear-positive samples and was performed in 51 (59%), it was estimated that NAAT testing had had a clinical impact in 20/51 (39%) tested patients (Taegtmeyer M et al 2008). Several UK institutions now refer all smear positive sputa routinely to NMRL but many refer only specimens form ‘high risk groups’. Although efficiency servings at the NMRL over the last decade have been used to keep the cost relatively constant with only a single cost increase during this period, it is possible that the cost has deterred routine screening of all infectious pulmonary cases. A rigorous economic analysis is needed to establish the merits of a selective versus general screening approach (eg for all smear positive sputum specimens) and a centralised versus disseminated model.

2.0 OBJECTIVES

To assess the clinical impact and cost effectiveness of use of genetic markers for identifying multidrug and extensively drug resistant TB in specified patients with tuberculosis across the UK through:

a. systematic review of the published and grey literature

b. transmission dynamic model to determine the implications of secondary transmission.

c. decision analytic health economic model of various screening strategies (including different commercially/in house assays, geographically dispersed versus centralised models of service and targeting of rapid testing at various high-risk sub-groups)

3.0 PLANNED INVESTIGATION

3.1 Systematic review of the literature (diagnostic performance)

This review will include a broad and comprehensive search for and a critical assessment of studies on diagnostic accuracy (i.e sensitivity, specificity, positive and negative predictive values) of molecular tests for tuberculosis drug resistance and other data required to parameterise the mathematical and economic modelling.

Types of studies: all types of diagnostic studies that compared a molecular test with a gold standard. No restrictions on study setting would be applied. Studies from all countries would be eligible for inclusion in review of evidence for the effectiveness of the diagnostic tests on detecting MDR and XDR TB. Only cohort or case series type studies that compared a test for MDR or XDR TB with an established reference standard would be eligible for inclusion in the review.

We are employing a heterogeneous approach to the literature ranging from PRISMA assured systematic review with meta-analysis when homogenous quantitative diagnostic accuracy data are available, to rapid synthesis of qualitative information where necessary to inform the parameterisation of the mathematical and economic models. Where there are already recent published systematic reviews, we will assess whether a rapid update of the evidence is adequate. In addition some elements of the systematic review will include a narrative synthesis for assays with evidence of clinical and/or statistical heterogeneity.

Types of participants: We will include studies of adults or children with suspected MDR or XDR TB. Co-morbidity (including HIV infection) would be considered and addressed through sub group analysis as appropriate. We will only include studies were clinical samples are used and would excluded where specimens are 'spiked' with mycobacteria.

Types of diagnostic tests: All studies comparing a rapid test for the detection MDR or XDR TB with the reference standard of microbiological drug susceptibility testing (DST) i.e nucleic acid amplification based tests (NAAT) with the ability to detect mutations associated with rifampicin and/or isoniazid resistance; novel rapid culture-based assays eg phage-based assays, MODS.

Emphasis will be given to commercial assays but we will also review data on in house tests where there is sufficient information to assess their diagnostic accuracy in detecting MDR or XDR TB. We would not plan to examine the performance of culture-based methods for drug susceptibility but this would be the comparative reference methodology for the novel tests measuring genetic markers.

Search Strategy and article retrieval

a. Search Strategy: We intend to combine a standardised search strategy which creates a large set of high validity articles on diagnosis with the MESH term(s). Due to the high volume of studies in TB infection recognised from previous reviews, we will work with the study information specialist to combine tuberculosis related terms first with terms relating to the tests under evaluation and then in combination with a sensitive methodological filter developed to identify diagnostic accuracy studies.

We will apply the above strategy to search the following databases: 1. MEDLINE (1975 – DATE) 2. EMBASE (1975– DATE) and 3. BIOSIS (1975 to date). We will also search CINAHL (Cumulative Index to Nursing and Allied Health Literature), NHS EED (NHS Economic Evaluation Database), Web of knowledge, Dissertation Abstracts Online database, Database of Abstracts and Reviews and Conference proceedings. Diagnostic equipment manufacturers and individuals working in fields

relevant to TB drug resistance diagnosis will be contacted to identify grey literature. International and national experts will be contacted to check the completeness of any search conducted. The reference list of published articles including previous reviews will also be checked and authors contacted if unpublished papers are identified. Other databases that index "grey literature such as SIGLE (System for Information on Grey Literature) and British National Bibliography for Report Literature will be searched.
We will include articles in all languages and studies carried out in humans or animals.

b. Study eligibility and application of inclusion and exclusion criteria: The titles and abstracts of papers identified will be screened by two independent reviewers. All articles that are considered to potentially meet the eligibility criteria outlined above by any of the reviewers will be selected. We will, however, be willing to adjust this strategy in the event that we find more studies than anticipated. One approach, used in previous HTA funded systematic reviews, will be to have one person extracting and the second person checking the output. In addition, a random sub selection will be double extracted to check quality. The assessment of study eligibility of this initial selection will not be blinded to publication details such as journal or author names.

c. Data extraction: Two reviewers will independently use standard forms to extract information from all identified papers. Key data items will include patient characteristics, drug resistance(s) investigated, test used, characteristics of the tests (for instance nature of assay used, method of drug resistance detection/target gene analysed, quantitative or qualitative,), location, outcome measures, and the source of funding. Other characteristics to be recorded include study quality, publication details, time for analysis, sensitivity and specificity.

We will be resolving differences through consensus arbitrated by a panel consisting of the clinical reviewers. This approach has worked effectively in a previous review we have undertaken. The reviewers will have ready access to the expertise of the combined group in interpreting studies through the literature review steering group to facilitate resolution of differences.

d. Assessment of methodological quality: We will assess the quality of studies using the QUADAS tool (Whitting P et al).

e. Statistical analysis – effectiveness
Each group of tests with sufficient studies available will be analysed separately. For each test comparison, the sensitivity, specificity and their exact 95% confidence intervals (CIs) would be calculated. Statistical heterogeneity of sensitivities and specificities will be investigated (see details below). If meta analysis is not found to be appropriate due to clinical heterogeneity, qualitative narrative synthesis of the diagnostic research available will be undertaken.

Statistical analysis will follow that suggested by Lijmer et al (7). Accuracy is usually presented in individual studies in terms of sensitivity and specificity i.e. dichotomous data rather than differences in distributions. Standard meta-analytic techniques, that is a simple pooled estimated of sensitivity and another of specificity, may be inappropriate as these two statistics are likely to be correlated. Therefore, we will also summarise accuracy across studies using a Summary Receiver Operating Characteristic Curve (SROC). This will be accomplished through a meta-analytic regression model used to explain variability in study diagnostic odds ratios (DOR). In particular, variability across studies due to the use of different thresholds to define positivity can be assessed and modelled using this approach. Variability due to other sources e.g. patient characteristics (age), study quality and characteristics such as inclusion criteria and measurement of outcomes can also be explicitly modelled. The modelled DORs can be transformed back into paired sensitivities and specificities. In the unlikely case of sensitivity and specificity appearing independent (as judged by Spearman's rank correlation for example) then standard meta-analytic techniques will be applied. Heterogeneity can be assessed using the I^2 statistic (Higgins et al)).

Publication bias will be assessed using funnel plots of DORs. Galbraith plots will be used to identify outlying studies.

3.2. Mathematical modelling

Broad approach:
Mathematical modelling will translate the estimates of diagnostic accuracy into estimates of clinical impact, including the number of cases of infection, disease, treatment and death occurring under different molecular genetic testing strategies. This will also require additional parameters, such as the prevalence of infection/disease in different settings, patient adherence to treatment, infectivity of TB strains, and rates of progression from latent infection to disease. Estimates for these parameters will be derived through national surveillance and laboratory data curated by the applicants, as well as through additional literature reviews. Clinical and epidemiological collaborators will input into the design of the model – ensuring that it reflects current practice and understanding of the disease and its treatment – as well as advising on the identification and analysis of further information required for the transmission-dynamic and economic modelling

Detailed approach: We will use a compartmental (state transition) transmission-dynamic model (Anderson & May 1991); a type of model that we have experience of using in previous health-economic analyses (e.g. Jit et al. 2008, Baguelin et al. 2010). As numbers of MDR cases are relatively small, stochastic (random) effects become important in transmission, so we will use a stochastic compartmental model. The model population is divided up into compartments according to infection status (i.e. naive, latent infection, active disease, on treatment, recovered, etc - details are below). The model comprises a set of equations specifying rates of flow between compartments as individuals become infected, progress to disease, are diagnosed and placed on treatment, etc. The rates of flow depend upon per-capita rates and the number of individuals in the relevant compartment at the particular point in time. The rate of transmission in the population is a function of the number of infectious individuals (those with untreated / inappropriately-treated active disease) and the number susceptible. Isolation prevents transmission to others, as does appropriate treatment; inappropriate treatment for drug-resistant infection allows transmission to occur. HIV will be incorporated if it has a significant effect on the transmission dynamics (this is not the same as being important in the care of individual cases) and there are sufficient data to parameterise the model robustly.

The compartmental structure is based on that of Salomon et al. (2006), which was built on the work of Vynnycky and Fine (1997), Dye, Garnett et al (1998), and others (Blower et al. 1996; Murray & Salomon 1998). Several modifications were made, including inserting a pre-clinical disease stage between latent infection and active disease: i.e radiological abnormalities often predate clinical signs and symptoms so these individuals' disease is detectable by X-ray but is not yet clinically detectable (or infectious).

Those who acquire TB infection develop latent infection which may progress slowly or quickly. Progression from latent infection leads to pre-clinical disease (detectable by X-ray but without clinically-detectable signs or symptoms), followed by active disease. Active pulmonary disease may be smear-negative or smear-positive, with the latter being much more infectious. Self-cure returns some individuals with active disease to the latent state. Those with active disease who access health care are diagnosed and placed on treatment by passive case-finding, with a proportion destined to complete treatment successfully and the remainder destined to fail treatment. Those undergoing successful treatment are non-infectious and upon completion they enter the recovered compartment. Those who are destined to fail treatment are partially infectious, due to poor adherence, whilst on treatment and after failure, are returned to the compartment from which they commenced treatment. Those with untreated active disease are subject to additional TB associated mortality.

The model population is stratified into UK-born and non-UK-born individuals, reflecting differences in the probability of being MDR-TB-infected due to lifetime risk of exposure. This stratification could be further subdivided to represent immigrants from low- and high-MDR-TB-burden countries of origin based on the current WHO designation of high (eg Baltic states, Russia, Ukraine, China, Bangladesh) and low MDRTB-burden states (eg USA, UK, Western Europe etc)

3.3 Economic modelling

We will conduct an economic evaluation comparing a range of proprietary and in-house assays for genetic markers of antibiotic resistance in comparison with conventional culture and susceptibility testing for patients with smear-positive pulmonary tuberculosis and suspected multiple or extensive drug resistance. We will use modelling to estimate the clinical effects and costs for these individuals, and also to estimate potential savings and health benefits from the prevention of onward transmission. We will also compare alternative models of service provision (centralised versus disseminated) and assess the value of targeting rapid testing at various high risk subgroups. Different service configurations are represented by degrees of delay, geographical distance, local versus regional and national service configurations and their impact in obtaining the test result and the overall cost of testing. Our overall objective is to derive a single, coherent model that will integrate the results of the diagnostic accuracy review, the mathematical modelling and the economic analysis.

To estimate the value of rapid tests for antibiotic resistance, it is important to understand the context within which they are likely to be used. Current NICE guidance (NICE, 2006) recommends that patients with suspected MDR TB should be treated presumptively for TB, with initiation of appropriate infection control measures, including admission to a negative pressure room; the guideline further recommends that appropriate samples should be analysed for rifampicin resistance. For example, in an analysis of the first year (2000) of a new national molecular diagnostic service (Drobniewski et al 2000) in the UK, approximately 28 days were saved in the time to diagnosis by using a molecular rifampicin-resistance assay compared to conventional methods; at one London hospital potential annual savings of at least £50,000 were calculated based on reducing the cost of inappropriate isolation of patients with risk factors for MDRTB who were subsequently shown to have drug-sensitive tuberculosis.

Where there is overwhelming clinical suspicion of MDRTB (which is rare) treatment for drug sensitive disease with additional drugs to cover MDR TB (while waiting for test results) may be initiated. However, there are clear advantages in ruling out MDR TB in suspected cases as quickly as possible. These benefits include limiting a subject's exposure to second-line drugs, which have a higher risk of adverse effects, and avoiding unnecessary expense for the NHS, which can include prolonged hospital admission within a negative pressure facility. Rapid confirmation of drug resistance will directly benefit patients by correctly identifying those who are infected with MDRTB versus drug sensitive TB; patients will proceed down different and correct treatment paths. Smear positive MDRTB patients incorrectly treated would remain infectious for longer increasing the opportunity for onward transmission. Patients with MDRTB carry a higher mortality in general; those who are immunocompromised may die before standard methods of analysis are complete.

In addition to these direct costs and benefits for index cases, more rapid identification of MDR TB is likely to have significant public health benefits, preventing onward transmission. Indeed an essential component of the complete evaluation of cost-effectiveness of interventions against infectious diseases is calculation of infections averted by reducing onward transmission, using transmission-dynamic modelling. This has become a standard component of evidence considered for interventions, such as immunisation programmes (eg for human papillomavirus (Jit BMJ 2008) and swine flu vaccination (Baguelin et al 2010)) considered by the Joint Committee on Vaccination and Immunisation, and for studies of infectious disease interventions (such as Chlamydia screening (Roberts BMJ 2007) funded by the NHS Health Technology Assessment programme.

This is particularly important for investigating the potential effect of interventions against uncommon drug resistant strains such as MDR TB that may become more prevalent in the future in the absence of appropriate infection control strategies. Rapid diagnosis of drug-resistant TB and appropriate treatment is potentially important in minimising onward transmission, as it may enable faster initiation of more intensive contact tracing initiatives. Given the high cost of treatment of MDR TB even a small reduction in onward transmission through faster diagnosis is potentially cost-effective.

However, there are potential downsides to rapid molecular tests for antibiotic resistance in comparison with conventional susceptibility testing. In addition to cost, the accuracy of molecular tests is not perfect. False positive results could result in unnecessary continuation of infection control and drug treatment for MDRTB, and possibly unnecessarily extensive contact tracing. Conversely, false negatives could lead to a premature relaxation of precautions and a failure to initiate timely contact tracing. However this will not be completely open-ended as microbiological culture followed by bacteriological drug susceptibility would be performed in an optimal service. This partnership has access to a decade of data from the provision of a molecular diagnosis service by FD and colleagues measuring actual NAAT assay performance compared to the standard reference methods and the time saved by molecular NAAT method in compared to optimal bacteriological methods which can be fed into the model.

Cost-effectiveness will depend upon testing cost and speed, as well as sensitivity and specificity, which together with disease incidence and the proportion of cases who are drug resistant determine negative and positive predictive values of the tests. Therefore, we will consider different settings, including the general population and hard-to-reach groups in subgroup analyses.

We have previously developed a transmission-dynamic model of TB in hard to reach groups, which was used for the preliminary analysis of the Mobile X-Ray Unit (MXU) pilot study for TB Find and Treat services in London (Watson et al., 2007) and have funding from the Department of Health (DH) to perform a further, more-comprehensive, model-based health-economic evaluation of TB Find & Treat services in London, encompassing initiatives in addition to the MXU, and taking advantage of the additional data collected since that pilot-study evaluation. In addition we have funding from NICE for model-based economic analysis of interventions against TB in hard-to-reach groups in the UK.

So that the population impact of rapid testing scenarios can be estimated, we will combine transmission-dynamic (described in more detail above) and health-economic evaluation. This has the advantage over building separate transmission-dynamic and economic models, that sensitivity analyses can incorporate uncertainty in both epidemiological and economic parameters. The main epidemiological outputs of the transmission-dynamic part of model will be the number of cases of infection, disease, treatment and death occurring under different scenarios. Comparison of model scenarios of different service configurations will be performed, allowing calculation of numbers of averted cases of infection, disease (improving health) and treatment (saving treatment costs).

The epidemiological outputs will be combined with the estimated costs of different strategies and service configurations, and with estimates of the expected QALY loss attributable to early/late diagnosis of MDR TB to inform estimates of the cost effectiveness of these approaches. Cost-effectiveness analysis will be conducted according to the guidelines for developing NICE public health guidance (NICE, 2009), and following conventions on reporting economic studies (Drummond et al, 1997). In particular, we will be adopting a public sector perspective, considering discounting costs and benefits at 3.5% per annum in the base case. We will use sensitivity analyses to test the impact of alternative assumptions about the time horizon. Our involvement in related work will also allow us to also compare the cost-effectiveness of this intervention with that of other TB prevention and control measures such as different case finding and testing approaches.

The cost of alternative tests will be estimated under a range of feasible service configurations for the NHS, taking account of geographical variations in demand for tests, and the likely costs of laboratory staffing and skill mix, capital investment, consumables, wastage and storage, transport, communication and quality assurance procedures. This analysis will test the extent of likely economies of scale with more or less concentration of services. Resource use data will be obtained by direct laboratory observation within the Health Protection Agency National Mycobacterium Reference Laboratory, Barts and the London Microbiological Laboratory and the Royal Free/University College Microbiological Laboratory as well as selected general district hospital microbiology laboratories Unit cost data will be

based on actual national sources appropriate for the NHS, such as Agenda for Change salary scales, or local data adjusted for market forces.

We will also estimate the cost of treating MDR TB. White and Moore-Gillon (2000) estimated a tenfold difference in costs between MDR and drug sensitive TB (mean cost of managing a case of pulmonary MDR TB was in excess of £60,000 pounds compared with £6040 for drug- sensitive). However, this analysis is now over a decade old. We will obtain up-to-date estimates of the cost of treatment MDR TB, based on standard drug costings and actual treatment duration and drug used by auditing case records of patients treated at the Barts and the London NHS Trust by FD and colleagues (audit by FD and research fellow) and at the Royal Free Hospital by ML and colleagues over the last two years. This has a key advantage in that the original study was performed at Barts and the London NHS Trust. Preliminary data at the Royal Free site (unpublished) suggests that the cost ratio for patient management of MDRTB versus drug sensitive patients is comparable to that obtained by White and Moore-Gillon (2000) and we will extend and build on these analyses.

The service configurations that we will explore are part of a standard sensitivity analysis i.e. testing different costing/timing assumptions. In the economic model, the comparisons of different service configurations would form part of the overall sensitivity analysis. Scenarios will be created to reflect differences in cost and degree of delay arising from different ways of implementing the technology in routine practice. The rationale for this analysis is that that an appropriate service configuration may negate the overall economic benefits e.g. a highly centralized model might incur additional transport costs; conversely if a manufacturer's FDAS-approved test configuration is for a large number of tests a highly decentralized approach will lead to excessive waste as the test expiry and low usage means that many tests will be unused increasing the real cost per test.

Other model parameters will be obtained from the literature and from routine data sources. Appropriate utility weights for tuberculosis-related health states will be obtained from a systematic search of the literature. Wherever possible, utilities measured using the EuroQol EQ-5D will be used as recommended by the NICE guidelines for technology appraisal (NICE, 2008). Systematic methods will also be used selectively to identify, appraise and synthesise other key epidemiological and economic model parameters. A review protocol will be developed and agreed by the project team early in model development to specify sources for all model parameters, and to define formal search strategies where appropriate

The uncertainty around the results will be explored by conducting probabilistic sensitivity analysis on both epidemiological and economic parameters, with results presented by the use of cost-effectiveness acceptability curves. Key parameters driving results will also be presented using tornado graphs.

3.4 Expected output

A comprehensive report will be prepared in which the phases above fit together as follows:

- **The systematic literature review** (section 3.1 of the proposal)

This will provide comprehensive estimates of the diagnostic accuracy of each assay, as measured by sensitivity and specificity, positive and negative predictive values. These are essential parameters to estimate the clinical impact and cost-effectiveness of rapid testing for MDR or XDR TB, and will feed directly into the mathematical model.

- **The mathematical model** (section 3.2)

This will translate the estimates of diagnostic accuracy into estimates of clinical impact, including the number of cases of infection, disease, treatment and death occurring under different molecular genetic testing strategies. This will also require additional parameters, such as the prevalence of infection/disease in different settings, patient adherence to treatment, infectivity of TB strains, and rates of progression from latent infection to disease.

Estimates for these parameters will be derived through national surveillance and laboratory data curated by the applicants, as well as through additional literature reviews.

- **The economic model** (section 3.3)

This will extend the mathematical model to estimate the economic impacts of different genetic testing strategies, including the effect on population health (QALYs) and the cost to the clinical and public health system (£). This will require additional information about quality of life, mortality and costs, which will be obtained through further literature reviews and costing studies accessed through the laboratory and clinical members.

Our overall objective is to derive a single, coherent model that will integrate the results of the diagnostic accuracy review, the mathematical modelling and the economic analysis.

The literature review is vital to inform the modelling and will be closely linked with both elements of the modelling (including the involvement of the modellers in the literature review steering group) to ensure that search terms find appropriate papers, and providing their expertise in the assessment of specific papers where required. Further, the clinical and epidemiological collaborators will input into the design of the model - ensuring that it reflects current practice and understanding of the disease and its treatment - as well as advising on the identification and analysis of further information required for the transmission-dynamic and economic modelling.

The population reviewed:
(i) We will consider the general population and hard to reach groups, as in our previous work. (ii) We will use an ordinary differential equation model as cited in the proposal); as is standard in these models the rate of transmission in the population is a function of the number of infectious individuals (those with untreated / inappropriately-treated active disease) and the number susceptible.
(iii) Using a standard approach, interaction between UK- and foreign-born individuals can be varied on a continuous scale from homogeneous mixing to no mixing at all between the groups. (iv) Isolation prevents transmission to others, as does appropriate treatment; inappropriate treatment for drug-resistant infection allows transmission to occur. (v) The process of delay in diagnosis of MDR TB is modelled thus: if treatment for presumed drug-sensitive TB is started then the individual enters a state of inappropriate treatment if MDR TB is diagnosed and treatment changed, when the individual moves to a state of appropriate treatment; if no treatment is started prior to MDR TB diagnosis then the individual remains in the untreated (and infectious, unless isolated) state until treatment starts, when they enter a state of appropriate treatment. The effects of false positive and false negative test results are incorporated: the former results in unnecessary treatment for resistant infection, which would still be effective; the latter results in inappropriate treatment until resistance is detected and the regimen changed. (vi) HIV will be incorporated if it has a significant effect on the transmission dynamics (this is not the same as being important in the care of individual cases) and there are sufficient data to parameterise the model robustly.

Report contents: The final report will include recommendations to the NIHR HTA regarding evidence for the implementation of a comprehensive rapid molecular diagnostic service for MDRTB and/or XDRTB in sputum smear positive TB patients and the advantages of different service delivery models. In addition to a formal report to the HTA, the research will be disseminated through peer reviewed publications, conference presentations and engagement with policy makers (Department of Health, Health Protection Agency, Commissioning Consortia), patients and the public (via local clinical networks in London, professional organisations including the British Thoracic Society, British Infection Society, the medical and nursing Royal Colleges, community-based programmes working with at-risk for TB populations and voluntary sector agencies such as TB Alert).

The report will also assist in the development of policy in determining which of the following expected clinical and public health benefits derived from routine screening are realised. Putative benefits include:

1. Earlier identification of TB and MDRTB patients
2. Earlier implementation of appropriate infection control procedures limiting/reducing staff and patient exposure to MDR cases, ‘look-back’ exercises etc.
3. Correct prioritisation of cases for negative pressure rooms
4. Earlier analysis of first and second line drug susceptibility results by the MRU (we would know ahead of time that resulting cultures from patients were likely to be MDR)

5. Reduced scope of and cost of contact training investigations both in institutions and the community.

We will compare alternative assays, providing estimates of the incremental cost and health impact of the available assays. We will also examine whether by elimination of cost at point of care delivery (in favour of a centralised/commissioned single provider contract or similar) is a likely factor in deciding whether to examine a patient specimen and to what extent this limits the value of these systems by introducing diagnostic delay.

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