AUDIT, RESEARCH AND GUIDELINE UPDATE

Rapid molecular detection of tuberculosis and rifampicin drug resistance: retrospective analysis of a national UK molecular service over the last decade

N Seoudi,1,2 S L Mitchell,1,3 T J Brown,1,3 F Dashti,2 A K Amin,2 F A Drobniewski1,2,3

ABSTRACT

Background Fast and reliable detection of Mycobacterium tuberculosis complex (MTBC) and drug resistance is crucial in establishing effective treatment and enforcing timely public health measures.

Methods The authors analysed the performance of a national UK molecular diagnostic service over a decade, based on the use of a line probe assay (Innolipa, LiPA) compared with conventional liquid and solid cultures with rapid molecular identification and culture-based drug resistance testing.

Findings Data were available for 7836 consecutive patient samples using LiPA and the reference microbiological technique (conventional liquid and solid cultures with rapid molecular identification and culture-based drug resistance testing). For all sputum specimens (n=3382) the sensitivity, specificity, positive predictive value, negative predictive value and accuracy for MTBC detection were 93.4%, 85.6%, 92.7%, 86.9% and 90.7%; the equivalent values for smear-positive sputum specimens (n=2606) were 94.7%, 80.9%, 93.9%, 83.3% and 91.3%. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy for detection of rifampicin resistance in all sputum samples (n=1667) were 92.1%, 99.3%, 89.4%, 99.5% and 98.9%, respectively; the equivalent values for smear-positive sputum specimens (n=1477) were 93.3%, 99.3%, 87.5%, 99.6% and 99%. Between January 2006 and December 2008, LiPA saved 25.3 and 32.2 days for TB diagnosis and rifampicin resistance of smear-positive sputum samples, respectively.

Interpretation A molecular diagnostic service, using a non-automated line probe assay approach, provides a rapid and reliable national service for diagnosing MTBC and rifampicin resistance.

INTRODUCTION

The rapid identification of multidrug resistant tuberculosis (MDRTB) (ie, tuberculosis (TB) isolates resistant to at least isoniazid and rifampicin) reduces the time for the instigation of appropriate treatment, helps to reduce the spread of drug-resistant TB and may improve survival.1–4

Conventional drug susceptibility testing (DST) can take 1–2 weeks once a positive culture has been obtained. In recent years, the use of assays for the genetic detection of mutations that confer resistance have been developed and evaluated. Among these, line probe assays (LPAs) are viewed as a rapid, very specific and sensitive tool for the detection of multidrug-resistant TB.5 Moreover, the WHO have recently endorsed a policy of the use of LPAs for the rapid screening of patients at risk of MDRTB6 and in 2010 recommended the use of the GeneXpert, XpertMTB/RIF following a successful multicentre analysis.7

In 1998, national and population-based services were proposed for the diagnosis of TB and rifampicin resistance directly from smear-positive patient specimens,8 and these were adopted in the UK and in other countries using LPAs. The UK Health Protection Agency National Mycobacterium Reference Laboratory (HPA NMRL) implemented this national molecular TB diagnostic service (branded as ‘Fasttrack’) in 1999–2000 with promising initial results.9 Rapid identification of rifampicin resistance and MDRTB with automated liquid culture is performed at the same time; specimens identified as MDRTB have any resulting cultures analysed for all first-line and second-line drugs simultaneously.

Using a different LPA, excellent sensitivity, specificity, positive predictive value (PPV) and negative predictive (NPV) were obtained when used directly on 536 smear-positive sputum specimens in South Africa,9 demonstrating that these techniques worked well in low and middle income countries.

The study evaluates the accuracy of results obtained for TB diagnosis and rifampicin detection compared with rapid culture-based methods in the context of a routine, non-trial national molecular diagnostic service. Sensitivity, specificity, PPV and NPV, analysis of discrepant results and turnaround times were obtained and compared with our previously published data to underline a decade of experience of these assays.

This study complements other published studies on the automated GeneXpert system and its XpertMTB/RIF assay9 by providing extensive evidence for an alternative system of diagnosis supporting WHO policy statements on the use of both LPAs and XpertMTB/RIF, and demonstrating the value of a national operational service.

MATERIALS AND METHODS

Clinical specimens

A total of 8501 consecutive primary specimens were referred to the UK HPA NMRL at the request of National Health Service (NHS) physicians over a 7-year period (January 2003–December 2009) for molecular ‘Fasttrack’ analysis. A single specimen from each patient was analysed in any one year. The reference assay was conventional culture-based diagnosis and rifampicin resistance (see below).
Out of the 7836 samples with both molecular and comparative culture-based results, 4420 were respiratory samples, including 3382 sputum samples, 753 bronchoalveolar lavage (BAL) samples, 269 pleural fluid aspirates and 36 other respiratory samples such as lung biopsy; 5406 samples were non-respiratory, including 1638 cerebrospinal fluid (CSF) samples.

**Microscopy, culture and susceptibility testing**

All samples were decontaminated and processed according to the NMRL standard operating procedure, which has previously been described.\(^5\) NaOH/N-acetyl-L-cysteine (NaOH/NALC) (6 ml) was added to each sample in a 50 ml Falcon tube. The sample was allowed to be incubated with the NaOH/NALC for 30 min with periodic gentle mixing. Subsequently, each sample was diluted (1:40 dilution) with phosphate buffer (pH 6.8) followed by centrifugation at 5000 × g for 30 min. The supernatant was discarded and 2 ml of sterile phosphate buffer was added to resuspend the pellet. Half of the suspension was used for the molecular assay, 0.25 ml of each decontaminated sample was cultured on Lowenstein-Jensen (LJ) slopes and 0.5 ml was inoculated into mycobacterial growth indicator tubes (MGIT) (Becton, Dickinson and Company, New Jersey, USA). Suitable samples for microscopy examination were investigated by fluorescent auramine phenol staining according to the NMRL standard operating procedure.

First-line DST was carried out on all culture-positive MTBC isolates using the resistance ratio method on LJ slopes\(^10\) and including rifampicin, isoniazid, ethambutol and pyrazinamide. Second-line (reserve) DST was performed using the MGIT system. The isolated microorganism was identified by using GenoType-Series molecular assay (Hain Lifescience GmbH, Nehren, Germany).

**LiPA**

DNA was extracted from 1 ml of each decontaminated sample and a commercial and validated LiPA assay (Innolipa, LiPA; Innogenetics, Ghent, Belgium) was performed for all samples included in the analyses (7836 specimens) according to the manufacturer’s instructions and as previously described.\(^5\)

**Standardisation and blinding**

Staff performing molecular analyses were blind to the culture-based reference methods. Bacteriological staff usually had no prior experience of molecular diagnostic assays but were appropriately trained to perform the LiPA over a 1-week period using written standard operating procedures. A PhD grade molecular scientist oversaw the service. Culture-based internal and external quality assurance and proficiency systems were in place throughout and were introduced in 2003 for molecular assays.

**Statistical analysis**

Data were entered into a Microsoft Excel spreadsheet (Microsoft Corporation, Washington, USA) and analysed by Prism (GraphPad, USA). The accuracy of the LiPA assay for detecting MTRBC and rifampicin resistance was compared with the accepted standards of culture (ie, one MGIT plus one LJ slope), and phenotypic DST.\(^11\)\(^\text{12}\) Sensitivity, specificity, PPV, NPV and diagnostic accuracy were calculated as follows: sensitivity (%) = (true positive/true positive + false negative) × 100; specificity (%) = (true negative/false positive + true negative) × 100; PPV (%) = (true positive/true positive + false positive) × 100; NPV (%) = (true negative/false negative + true negative) × 100; and diagnostic accuracy (%) = (true positive + true negative/total number) × 100. An increase in sensitivity indicated a decrease in false-negative cases, while an increase in specificity indicated a decrease in false-positive cases. PPV is defined as the probability that a person has the disease and their test was positive, while NPV is defined as the probability that a person does not have the disease and their test was negative. CIs were calculated using the method of Vollset.\(^13\) The sensitivity, specificity, PPV and NPV were compared (using the χ² test) with our previously published data.\(^5\) Statistical significance was determined using a p value ≤0.05.

Detailed turnaround times were calculated for a recent 3-year period (2006–8). The time to diagnosis was calculated from the date of receiving the sample in the NMRL to the date of issuing the results to the clinician. The time to diagnosis was based on direct LiPA testing of patient specimens compared with the time taken for culture growth and identification of the isolated mycobacterium. The NMRL use GenoType-Series molecular assays for rapid identification of mycobacterial cultures (performed daily, Monday–Friday).

**RESULTS**

Of the 8501 consecutive samples received by the NMRL for LiPA assay during the period between January 2003 and December 2009, comparison with bacteriological culture was possible for 7836 samples (culture could not be performed or was contaminated in 290 (3.4%) samples; PCR was not performed for 140 (1.6%) samples (see below); PCR was inhibited or not interpretable in 285 (3.4%) samples (including 50 specimens which also had contaminated cultures); hence these were excluded from the analysis) (figure 1).

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**Figure 1** Flow chart of samples received in the National Mycobacterium Reference Laboratory (NMRL) in the period between January 2003 and December 2009. AFB, acid fast bacilli; +ve, positive; –ve, negative.
Specimens were analysed by sample type and sub-divided by microscopy result if known. Specimens were also analysed as ‘respiratory’ (sputum, BAL, pleural fluid and other respiratory samples such as lung biopsy) and ‘non-respiratory’ (CSF, lymph node biopsy, aspirate, pus, blood, pericardial fluid and others) and included with urine and others) and sub-divided by microscopy result if known (tables 1, 2 and supplementary online tables A1–A2).

The acid-fast bacilli smear microscopy was positive for 3656 of 7836 primary specimens (46.4%), negative for 3076 (39.5%) and unknown for 1124 (14.3%). These 1124 specimens that did not have microscopy performed routinely or did not have a microscopy result included in the main analysis but excluded from the specific sub-analysis described in tables 1–2 and online supplementary tables A1–A2. A total of 3299 MTBC and 520 non-tuberculosis mycobacteria (NTM) were cultured in the 7-year study period.

LiPA

LiPA was not performed in 140 of 8501 (1.6%) specimens as a culture had been sent previously and the MTBC and rifampicin results were already known. For the 8361 processed samples, the results of LiPA analysis for MTBC were negative for 4745 (56.8%), positive for 3381 (39.8%), and 285 (3.4%) were inhibited or not interpretable. Of the 3381 PCR-positive cases, 146 (4.4%) were reported as rifampicin resistant, 3173 (95.2%) were reported as rifampicin resistant using the standard resistance ratio drug susceptibility method (phenotypic contrast), 132 (5.7%) specimens were reported as rifampicin resistant only using the LiPA assay, 249 (7.4%) were reported as rifampicin resistant and 12 (0.4%) gave equivocal results.

The overall sensitivity, specificity, PPV, NPV and diagnostic accuracy of LiPA assay for MTBC detection were analysed using different sample types in relation to the standard culture-based technique as shown in table 1 and online supplementary tables A1 and A2. Overall sensitivity, specificity, PPV, NPV and diagnostic accuracy of rifampicin resistance in comparison to the standard resistance ratio drug susceptibility method (phenotypic sensitivity) are shown in table 2 and online supplementary table A2.

A single molecular test performed against liquid and solid culture for all specimens had an overall sensitivity of 87.3%, specificity of 91.1%, PPV of 87.7%, NPV of 90.8% and overall accuracy of 89.5% for MTBC detection (table 1). For all sputum specimens (n=3382), the results of LiPA analysis for MTBC were 92.1%, 92.6%, 92.7% and 90.8% respectively. The equivalent figures for smear-positive specimens (n=2606) were 94.7%, 80.9%, 93.9%, 85.6%, and 90.7% respectively. The results for non-sputum samples were good (with the exception of CSF), although with lower sensitivity, for example, BAL smear-positive sensitivity was 86.8% (online supplementary table A1).

The DST data were available for 2306 specimens for both techniques (LiPA and the standard resistance ratio susceptibility method). A total of 136 (5.9%) specimens were reported as rifampicin resistant by LiPA and 2170 (94.1%) were sensitive. In contrast, 152 (5.7%) specimens were reported as rifampicin resistant using the standard resistance ratio susceptibility method and 2174 (94.3%) were sensitive.

The overall sensitivity, specificity, PPV, NPV and accuracy for the detection of rifampicin resistance for all specimens which became culture positive and for which a phenotypic DST data were available (n=2306), was as follows: 92.4%, 99.4%, 99.7%, 99.5% and 99.0%, respectively. Out of the 2306 samples analysed; the acid-fast bacilli smear microscopy was

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**Table 1** Results of LiPA compared with culture in detecting Mycobacterium tuberculosis complex (2003–2009)

<table>
<thead>
<tr>
<th>Sample type</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All*</td>
<td>87.3</td>
<td>91.1</td>
<td>87.7</td>
<td>90.8</td>
<td>89.5</td>
</tr>
<tr>
<td>Respiratory+ve</td>
<td>93.8</td>
<td>93.8</td>
<td>93.8</td>
<td>93.8</td>
<td>93.8</td>
</tr>
<tr>
<td>Respiratory-ve</td>
<td>87.3</td>
<td>91.1</td>
<td>87.7</td>
<td>90.8</td>
<td>89.5</td>
</tr>
<tr>
<td>Non-respiratory*</td>
<td>91.1</td>
<td>91.1</td>
<td>91.1</td>
<td>91.1</td>
<td>91.1</td>
</tr>
<tr>
<td>Sputum*</td>
<td>93.4</td>
<td>93.4</td>
<td>93.4</td>
<td>93.4</td>
<td>93.4</td>
</tr>
<tr>
<td>Chest clinic</td>
<td>77.8</td>
<td>92.7</td>
<td>77.2</td>
<td>92.9</td>
<td>89.1</td>
</tr>
</tbody>
</table>

*Respiratory samples + non-respiratory samples + unclassified samples.

PPV, positive predictive value; NPV, negative predictive value; AFB, acid-fast bacilli; BAL, bronchoalveolar lavage; NPV, negative predictive value; PPV, positive predictive value; CSF, cerebrospinal fluid; MTBC, Mycobacterium tuberculosis complex.
positive for 1922 primary specimens (1922/2306) (83.3%), negative for 213 (213/2306) (9.2%) and unknown for 171 (171/2306) (7.4%); table 2 and online supplementary table A2).

In the period between January 2006 and December 2008, implementation of molecular techniques enabled an earlier diagnosis for all samples and saved a mean of 35.9 days compared with culture. Focusing on all smear-positive samples only, the assay consistently helped to reach an earlier diagnosis of MTBC and rifampicin resistance (25.3±19.4 and 32.2±16.9 days saved, respectively) (table 3).

**Discrepant results**

In the period 2003—2009, there were 420 false-negative results for MTBC; these samples were found to be negative using LiPA but culture positive for MTBC. Of these 420 false-negative results, 220 (52.3%) specimens were respiratory and 200 (47.7%) were non-respiratory. Of 403 false-positive MTBC results (specimens positive using PCR but failing to grow on microbiological culture), 197 (48.9%) were respiratory samples and 206 (51.1%) were non-respiratory samples. Interestingly, only eight cases out of the total of 520 NTM (2.5%) cultured using standard techniques were positive using LiPA and accounted for <2% of the false-positive cases. We believe that these eight cases were mixed MTBC and NTM or contaminated cultures but no MTBC was cultured probably due to overgrowth by more rapid NTM growth.

For sputum samples, there were 148 false-negative results; these samples were found to be negative using LiPA for MTBC detection but culture positive. Of these, 104 (70.2%) specimens were smear positive representing 4% (104 of 2606) of the total smear-positive sputum samples analysed, 28 (18.9%) were smear positive representing 5.4% (28/523) of the total smear-negative sputum samples analysed and 16 (10.8%) were unknown. There were 165 cases which appeared to be false-positive MTBC results using LiPA; these specimens were positive by PCR but failed to grow MTBC using standard culture techniques. Of the 165 false-positive results, 122 (73.9%) specimens were smear positive representing 4.7% (122/2606) of the total smear-positive sputum samples analysed, 29 (17.6%) were smear negative representing 5.8% (29/523) of the total smear-negative sputum samples analysed and 14 (8.5%) were unknown.

There were 10 false-negative rifampicin sensitive results; 10 cases were reported as sensitive to rifampicin by PCR but the standard phenotypic sensitivity showed resistance. However, there were 14 false-positive results using LiPA. These 14 cases were reported as resistant to rifampicin using PCR but were subsequently considered to be sensitive to rifampicin using the standard phenotypic sensitivity. Of the 14 false-positive cases, 12 (85.7%) were from respiratory specimens (table 2).

**Comparative analysis between 1999—2002 and 2003—2009 data**

The specificity, PPV and NPV were compared with our previously published data using the $\chi^2$ test. Data from the

<table>
<thead>
<tr>
<th>Table 3: Days saved to reach earlier diagnosis by implementing the Innolipa LiPA Rif assay</th>
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<tbody>
<tr>
<td><strong>All samples</strong></td>
</tr>
<tr>
<td>Days saved before culture</td>
</tr>
<tr>
<td>(mean±standard deviation)</td>
</tr>
<tr>
<td>Days saved before rifampicin</td>
</tr>
<tr>
<td>sensitivity results (mean±standard deviation)</td>
</tr>
</tbody>
</table>

Tuberculosis assay in comparison to the standard culture and sensitivity techniques (2006—2009).
MDRTB are injectable drugs that are also resistant to a quinolone and one or more of the extensively drug-resistant TB (XDRTB) (ie, MDRTB isolates non-compliance, which can increase the likelihood of developing toxicity and the length of treatment often contribute to administered for a long time, and drugs can be toxic. Drug groups (table 4). The improvement in sensitivity highlights the and their subgroups, namely respiratory and non-respiratory line and reserve drugs simultaneously.


We have had the ability to rapidly and accurately diagnose TB and their subgroups, namely respiratory and non-respiratory sensitivity of the test-2002 to detect a significant increase in current study (2003–2009) were in line with previously and improving patient outcomes2

Table 4 Results of LiPA compared with culture in detecting Mycobacterium tuberculosis complex (2003–2009 in comparison to 1999–2002) (χ² test)

<table>
<thead>
<tr>
<th></th>
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</tr>
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<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>Specificity (%)</td>
<td>PPV (%)</td>
<td>NPV (%)</td>
</tr>
<tr>
<td>All† ‡</td>
<td>782/918 (85.2)</td>
<td>886/1004 (88.2)</td>
<td>782/900 (86.9)</td>
</tr>
<tr>
<td>All smear +ve</td>
<td>747/796 (93.6)</td>
<td>231/301 (70.8)</td>
<td>747/835 (89.5)</td>
</tr>
<tr>
<td>All smear –ve</td>
<td>35/119 (29.4)*</td>
<td>644/673 (95.7)</td>
<td>35/64 (54.7)</td>
</tr>
<tr>
<td>Respiratory†</td>
<td>672/738 (91.1)</td>
<td>496/560 (86.8)</td>
<td>672/736 (91.3)</td>
</tr>
<tr>
<td>Respiratory smear +ve</td>
<td>657/696 (94.4)</td>
<td>170/219 (77.6)</td>
<td>657/706 (93.1)</td>
</tr>
<tr>
<td>Respiratory smear –ve</td>
<td>15/42 (35.7)**</td>
<td>313/327 (95.7)</td>
<td>15/29 (51.7)</td>
</tr>
<tr>
<td>Non-respiratory†</td>
<td>110/180 (61.1)</td>
<td>390/444 (87.6)</td>
<td>110/164 (67.1)</td>
</tr>
<tr>
<td>Non-respiratory smear +ve</td>
<td>90/102 (88.2)</td>
<td>43/52 (52.4)</td>
<td>90/129 (68.8)</td>
</tr>
<tr>
<td>Non-respiratory smear –ve</td>
<td>2077/282 (73.0)**</td>
<td>331/346 (95.7)</td>
<td>20/35 (57.1)</td>
</tr>
</tbody>
</table>

* There is a statistically significant increase in the sensitivity of the LiPA testing of all smear positive samples by time (p<0.005).
** There is a statistically significant increase in the sensitivity of the LiPA testing of smear negative respiratory samples by time (p<0.05).
*** There is statistically significant increase in the sensitivity of the LiPA testing smear negative non-respiratory samples by time (p<0.019).
† Smear negative + smear positive + smear unknown.
‡ Respiratory samples + non-respiratory samples + unclassified samples.
AFB, acid-fast bacilli; NPV, negative predictive value; PPV, positive predictive value; +ve, positive; †+, positive; **+, positive; ***+, positive; "+, positive.

Table 4 Results of LiPA compared with culture in detecting Mycobacterium tuberculosis complex (2003–2009 in comparison to 1999–2002)
group the free text section indicated that the patient was on treatment. It is well documented that PCR-based techniques would detect DNA for dead bacteria but these bacteria would not be cultivable. This study was not designed to measure the actual impact on clinical management but supports other studies that suggest earlier diagnosis of MDRTB is advantageous.\textsuperscript{2} 20–22

The recent study by Boehme\textit{et al.} demonstrated a high sensitivity even for smear-negative sputum samples (72.5\% for single automated XpertMTB/RIF compared with culture) but we were able to show a comparable level of sensitivity for LPA, indicating that this remains a highly sensitive and specific tool in appropriate laboratories. The XpertMTB/RIF assay is simple to perform requiring limited training to achieve quality results but at a higher cost. LPA requires less proprietary equipment but a more appropriate PCR-suite infrastructure, longer training and greater operator expertise than XpertMTB/RIF. Having effective competitor assays will support cost reduction for XpertMTB/RIF, LPA and other assays under development.

As most parts of the world have a low prevalence of MDRTB this will lead to a low PPV. Globally, confirmation of positive XpertMTB/RIF (and/or LPA) results using another molecular method or with microbiological DST is needed to be in line with WHO policy recommendations. For maximum benefit, there should be rapid identification of TB cultures with phenotypic analysis of first-line and second-line DST once a molecular test has identified drug resistance mutations associated with rifampicin (and possibly isoniazid) resistance. This will significantly reduce the time between sputum collection and full susceptibility testing for MDRTB cases. Addressing timeliness in technological improvement should go in tandem with minimising organisational delay. Clinicians need to make prompt therapeutic changes following rapid DST.

Assays with higher sensitivities are needed to address paucibacillary samples from patients who are HIV positive (despite the significant improvement demonstrated for the XpertMTB/RIF assay in this patient group), children especially the very young who produce little or no sputum, and extrapulmonary material, particularly dilutional fluids such as CSF, ascites and pleural fluid.

CONCLUSION

A national molecular diagnostic service for TB and drug-resistant TB (using a non-automated LPA) provides a rapid and reliable national service for diagnosing MTBC and rifampicin resistance.

Acknowledgements We thank Dr Richard Hooper, Barts and the London School of Medicine, for valuable statistical advice. We would like to thank all the staff at the HPA NMRL for their assistance.

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Competing interests We declare that we have no conflict of interest. Specifically all the LPA molecular and culture assays described were purchased at the normal price. All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

Patient consent Uses routine data submitted on request form for TB diagnosis sent to our centre. Samples part of standard of care.

Ethics approval Uses routine data submitted on request form for TB diagnosis sent to our centre.

Contributors FAD, NS, SM and TB contributed to study design. NS, SM, TB, FD, AKA and FAD participated in data collection and NS, SM, TB and FAD in data management. NS, SM, TB, FD, AKA and FAD contributed to data analysis. NS, SM and FAD wrote the manuscript; all other authors critically reviewed it and approved the final version.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES


What is already known on this topic

A recent study described the performance of a new automated diagnostic system (Cepheid, California, USA GeneXpert, XpertMTB/RIF) for tuberculosis (TB) and multidrug resistant TB (MDRTB). In that study the two features that stood out were the high sensitivity of the assay in patients who were sputum smear negative and the ease of use with minimal technical training required.

What this study adds

The authors describe the performance of a national UK diagnostic service for TB and rifampicin resistance in a non-trial context using another WHO-endorsed non-automated approach based on line probe assays over the last decade. The authors feel this study complements other studies on the XpertMTB/RIF system, demonstrating a comparable sensitivity and clearly indicating that there is an alternative (and potentially cheaper) strategy for sensitive TB diagnosis. The study also demonstrates the real-world performance of such a diagnostic service which will assist policy makers and TB programme managers in determining the optimum configuration and roll-out of services. For example, the line probe assay requires much less (and mostly generic) laboratory equipment but is technically more demanding. For centres that have the technical skills, there is an effective alternative to the XpertMTB/RIF system and the resulting competition will support competitive pricing in low and middle income countries (and probably industrialised countries where TB services are part of the public sector).

Limitations of the study

Ideally additional clinical information would have been useful. However, it was previously shown that smear-positive specimens from patients who remained persistently positive on treatment (arousing suspicion that the patient has drug-resistant \textit{Mycobacterium tuberculosis} complex or was not adherent to therapy) were frequently culture positive on therapy as the bacilli were viable because of resistance or due to patients’ non-adherence to treatment.\textsuperscript{23} Therefore, not excluding patients currently on treatment might have reduced the specificity but not as much as might be expected.


REFERENCES


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