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An assessment of molecular diagnosis of tuberculosis and multi-drug resistant tuberculosis testing and quality assessment: findings of an international survey

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Abstract: Molecular '*in vitro* diagnostic' (IVD) tests are established for the diagnosis of tuberculosis (TB) and multi-drug resistant TB (MDR-TB). What is less clear is how the use of TB or MDR-TB molecular IVD results differ across regions, whether corroborative tests are conducted and what external quality assessment (EQA) infrastructure exists to underpin test confidence. This study investigated the current international status of molecular TB IVDs methods, application and quality assessment. An online survey was distributed by the IFCC's Committee for molecular diagnostics to TB diagnostic laboratories worldwide. 118 laboratories from 41 nations indicated a range of IVDs were used. ~75 % participated in EQA programs and 32 % reported this used the WHO International Standard. ~65 % also delivered MDR-TB results the majority of which were used to change therapy; 1/6 of these do so without EQA evaluation of the MDR-TB result. The study demonstrates a range of IVD solutions in use for TB diagnosis along with a high uptake of EQA in support of this global uptake of this test modality. However, we also reveal gaps in quality assurance for MDR-TB testing with 10 % of the laboratories using resistant results alone without participating MDR-TB EQA. This suggest additional work is required to build on established use of EQA to better support MDR-TB testing and better ensure confident when results are used to guide antibiotic use. Addressing these gaps will ensure the accuracy of future MDR-TB results, which is critical for effective disease management and help combat TB on a global scale.

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Introduction

Tuberculosis (TB) is described by the World Health Organization (WHO) as being the world's 'top infectious killer' infecting 10 million people a year leading to ~1.5 million global deaths per annum [1, 2]. TB, which is a disease of poverty, mainly occurs in low- and middle-income countries (LMIC). Accurate diagnostic tools aid in patient management, and this is especially important where treatment can be further complicated by the development and transmission of drug resistance. Multi-drug resistance TB (MDR-TB) is estimated to occur in >400,000 cases globally [3].

Diagnosis of TB and MDR-TB has changed over the last decade with increasing use of rapid molecular testing, with the WHO recommending that some molecular formats replace sputum smear microscopy as the primary method for the detection of TB (with culture as a reference standard) [4]. Rapid molecular tests detect DNA of the causative agent *Mycobacterium tuberculosis* within clinical specimens and many of the commercially available methods are also able to identify genetic markers of antibiotic resistance [5, 6] providing a route to guide choice of therapy.

The ability to quickly detect *M. tuberculosis* DNA, and identify genetic predictors of resistance, has the potential to revolutionise treatment by aiding clinical decision-making associated with patient more timely management. However, while molecular diagnostics solutions can complement clinical suspicion of a diagnosis of TB, because an MDR result is in cases provided automatically resistance will often be determined by the molecular method without an initial clinical suspicion of MDR. This will in turn require the clinical practitioner to decide whether to act on test alone or conduct corroborative action; in these situations, where the single test may be the only analytical source of evidence for MDR-TB, it is especially important that tests are performing within their specified performance criteria. Molecular test errors obtained from a test used in isolation leading to false negative results can lead to wider spread of the very condition the test is intended to identify [7] or in case of false positive results potentially lead to the use of unnecessary second line drugs; potentially further exacerbating the evolution and spread of resistance.

Given the potential significant impact of erroneous results, external quality assessment (EQA) has an important role to provide test confidence [8] and there are a number of EQA schemes available to demonstrate test and laboratory competency for TB molecular diagnostic methods. The reliability and comparability of test results between different laboratories and countries are important for effective TB control at the international level [9]. Quality measures include both external and internal controls within laboratories and independent EQA programs provided by third parties. In addition, the 1st WHO International Standard for *M. tuberculosis* was recently developed [10], which provides an opportunity to deliver traceability to performance metrics allowing nucleic acid analysis test manufacturers and end users to perform harmonized assay validation, test calibration and limit of detection studies while also supporting EQA harmonization.

To understand the current application and use of EQA of TB and MDR-TB molecular diagnostic tests at an international level, the Committee for Molecular Diagnostics of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC C-MD) conducted a voluntary web-based survey among molecular diagnostic laboratories conducting TB and MDR-TB testing. Questions sought to determine the range of molecular test modalities being deployed, the level of quality assurance available as well as how many tests also provided MDR-TB results, how are they used and what quality assurance measures are in place to support MDR-TB testing?

Materials and methods

The aim of the survey was to collect, analyze, and interpret data on the current practice of molecular genetic diagnosis of tuberculosis. The questions of the survey were developed through expert consultation with the members of the Committee on Molecular Diagnostics (C-MD), (of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and validated with stakeholders from the Foundation for Innovative New Diagnostics (FIND), UK Medicines and Healthcare products Regulatory Agency (MHRA) and University College London (UCL) prior to circulation. The invitation to participate in the survey was sent by email from the IFCC to all national societies that are members of the IFCC on 13 November 2023. The survey was offered in Spanish, French, and English to try to increase representation and was voluntary, with the possibility to participate between 13 November and 22 December 2023. The survey consisted of 15 questions, including both multiple-choice and open response formats open to all participants (Supplementary Information A). This survey covered the following sections: (1) laboratory demographics, (2) techniques used for tuberculosis molecular genetic diagnostics, (3) quality assurance, and (4) testing and quality assurance of MDR analysis and reporting. Surveymonkey.

com software was used to create and conduct the web-based survey open to any nation.

Results

Results from the questionnaire are provided in the Supplementary Information B.

Demographic characteristics of participating laboratories

A total of 118 laboratories participated with valid responses completing the full survey (Supplementary Table 1) in our international survey on molecular genetic diagnostics of tuberculosis. Three laboratories initiated the questioner but were excluded because they did not conduct molecular test of TB or did not fill in the form after selecting nation (Supplementary Table 1). Participation was geographically diverse (Supplementary Table 2A and B), with strong representation from Europe (n=57) and Asia (n=41). Africa and Latin America/South America were represented by eight and nine laboratories respectively. Within Europe, there was high participation from Germany (n=16) and Belgium (n=8). In Asia, the People's Republic of China dominated with 30 participating laboratories.

The distribution of laboratory types (Supplementary Table 3) showed a clear dominance of public institutions: 52 % were public health laboratories or affiliated with medical centers, followed by university institutions (30 %) and private laboratories (14 %). Large commercial laboratories defined as conducting more than 1,000 molecular tests per month accounted for only 4 % of participants. Most laboratories (93 %) rely on commercial kits for molecular TB diagnostics, either exclusively (79 %) or in combination with laboratory developed tests (LDTs, 14 %). Only 7 % of laboratories use exclusively LDTs (Supplementary Table 4).

Test volume and capacity

The test volume varies significantly among laboratories: 50 % perform 11–100 molecular tests weekly, 34 % perform 1–10 tests, and 12 % perform 101–1,000 tests (Supplementary Table 5).

Molecular diagnostic techniques used in TB

The Cepheid GeneXpert system was the most commonly used (although version was not disclosed) with 42 %, followed by Hain (15 %) and Roche Cobas systems (8 %) with all other solutions suggested by the questionnaire used by at least one participating laboratory (Figure 1 and Supplementary Table 6).

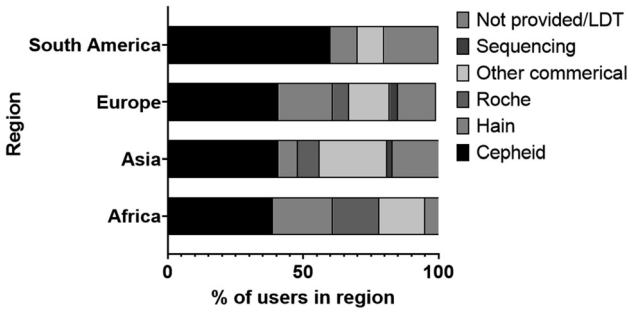

Figure 1: Breakdown of instrument use by region.

External quality assurance (EQA)/proficiency testing (PT) and alternative assessment procedures (AAP)

Three quarters (77 %) of laboratories participate in EQA/PT for TB detection (Figure 2A and Supplementary Table 7). 23 % did not participate in EQA/PT; this was because a program was either unavailable (14 %) or was available but not mandatory (9 %). INSTAND e.V. (20.0 %) and Quality Control for Molecular Diagnostics (QCMD) (14.2 %) are the most frequently used providers of EQA and PT with a wide range of alternative providers available (Supplementary Table 8).

Alternative assessment procedures (AAP) are conducted by 46 % of the laboratories surveyed if EQA was not available (27 %) or in addition to EQA scheme availability (19 %) (Supplementary Table 9). Strategies for AAPs are outlined in the Supplementary Table 10.

Of the laboratories participating in EQA, 35 % stated that the scheme used the WHO International Standard for *M. tuberculosis* for NAT-based assays to provide methodological traceability (Figure 2B and Supplementary Table 11).

Resistance testing

Multidrug-resistant tuberculosis (MDR-TB), quality assurance and handling of MDR-TB results

Two thirds (76 laboratories) of the molecular tests also provide a result for MDR-TB (Figure 3A and Supplementary Table 12) with 30 % of them also providing additional resistance predictors in addition to those used for MDR-TB management (Supplementary Table 13). When asked about how the MDR-TB

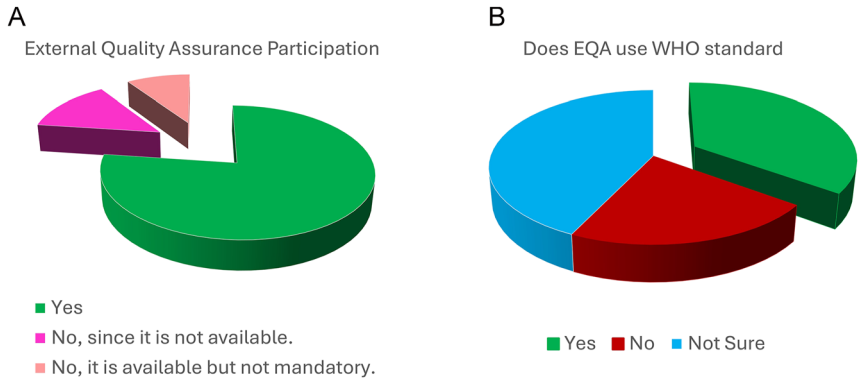

Figure 2: Participation of laboratories in EQA. Proportion of laboratories participating in EQA in support of TB molecular IVD (A) and whether the EQA providers uses the WHO standard to support traceability (B).

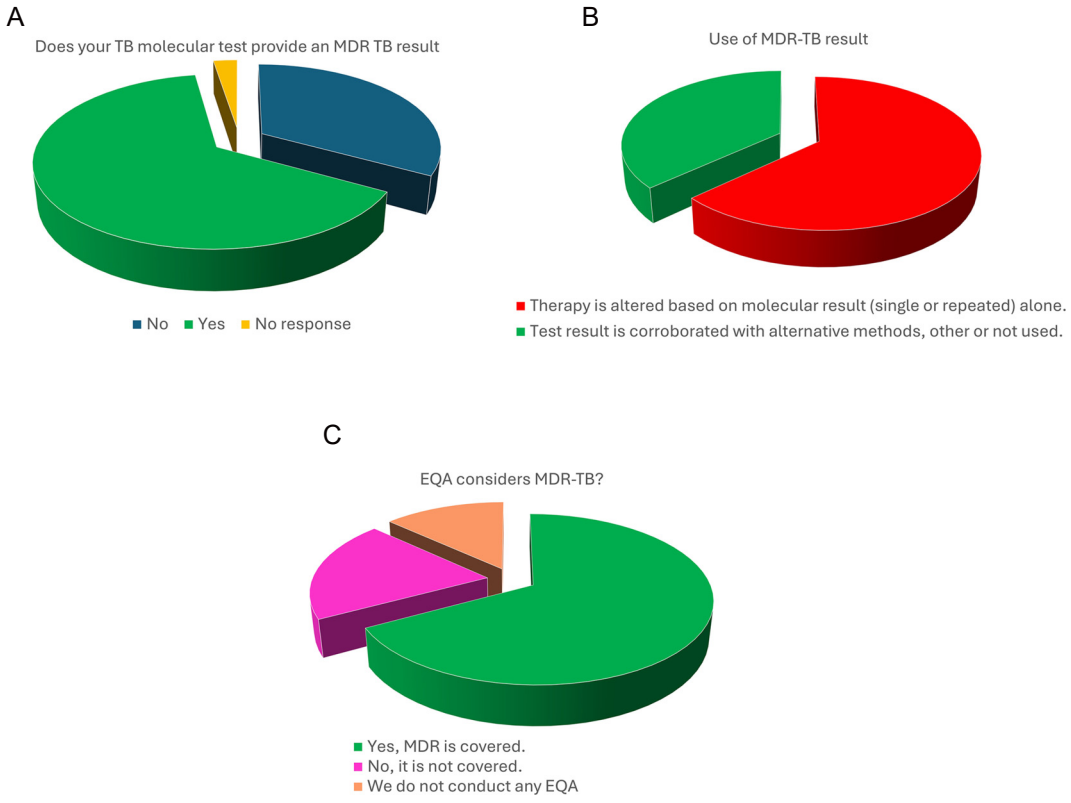

Figure 3: Drug resistance testing. Proportion of tests which provide an MDR result as part of the test output (A), whether or not alternative method is used to corroborate the molecular MDR result following alternation of therapy (B) and whether the MDR aspect of the test is evaluated by the respective EQA schemes (C).

result was acted upon 37 % of 76 laboratories relied on the molecular test as the only analytical result to change therapy with 26 % repeating the molecular test for corroboration (Supplementary Table 14). Consequently, 48 out of the 76 laboratories that used the MDR molecular result without corroboration from an alternative format (Figure 3B). Of the 76 laboratories reported, 21 % corroborate the findings with culture prior to altering therapy. The remaining 16 % either did not respond, did not use MDR result or stated other with responses stating unknown or that the decision on therapy was the duty of the clinical team.

Sixty seven percent of the 76 laboratories who reported that they used the MDR results reported that the EQA scheme provided an evaluation of the MDR prediction aspect of the assay (Figure 3C and Supplementary Table 15). Based on this question we identified that 12 of the 48 laboratories that used the molecular result for MDR detection (either alone or with repeat) to alter therapy did not participate in any EQA for MDR-TB testing.

Discussion

Tuberculosis (TB) remains a leading cause of global morbidity and mortality on which, as a disease of poverty, the majority of the burden falls on those living in the developing world. While treatment for TB is available it has been complicated by challenges associated with diagnosis and the rise of antibiotic resistance leading to drug resistance tuberculosis which is a World Health Organization priority [3]. Tuberculosis is also an example of a disease where molecular IVDs, that detect the DNA of the causative pathogen *M. tuberculosis*, have had considerable success leading the WHO to recommend one instrument format, the Xpert MTB/RIF from Cepheid, be used "*as an initial test for TB and rifampicin resistance in all adults and children with signs and symptoms of pulmonary TB*" [3].

Furthermore, because these molecular methods can identify specific pathogen sequences within clinical specimens, they are often also designed to also determine the sequence of genes that may confer antimicrobial resistance which can be used to guide therapeutic choice [11]. The success and wider global uptake of these molecular IVD solutions for TB and MDR-TB raises the question of how these results are used, what instruments are available and what systems are in place to provide manufacturers, users and patients with the confidence that the results from a given instrument/laboratory are accurate. In clinical testing ranging from clinical chemistry to microbiology, as well as in many areas of molecular diagnosis, such confidence can be provided through participating in external quality assessment (EQA) or proficiency testing (PT) schemes.

To address some of these questions we present the results of an international survey from 118 laboratories exploring the use of on molecular diagnosis of TB and MDR-TB. Most of the results were from Asia and Europe and this geographic distribution must be considered when interpreting the results as it may reflect regional differences in resources and practices. The majority of laboratories conduct <100 tests a week and were from public health laboratories or affiliated with medical centers and university institutions reflecting the important role of public institutions in TB diagnostics. Within the cohort represented here only 14 % were private laboratories.

While public health laboratories where prominent in conducting testing the private sector had more prominent role in the manufacturer of the tests with over 90 % of tests from commercial providers. This strong preference for commercial diagnostic solutions can aid in standardization because manufacturers must comply with regulatory requirements specified by region and/or nation. The adherence to regulations can necessitate internal quality control, batch verification, etc. which in turn can be advantageous for the comparability and reliability of results. Using commercial IVDs can also reduce the need for individual laboratories to have expertise in molecular test design and validation required where laboratory developed tests are used.

The Cepheid Xpert TB/RIF was the most popular format used by 42 % of laboratories, which reflects its first to market status and widely cited use within WHO documentation. However, the fact that the Xpert TB/RIF only represented two fifths of the tests suggests a range of alternative molecular IVDs for TB and MDR-TB are not only available (Figure 1), but in use, which is important to encourage test development, innovation and to ensure redundancy for testing across regions.

When considering routes for ensure quality assurance 77 % of laboratories participated in EQA or PT (Figure 2A and Supplementary table 7) of which 35 % are reported as using the WHO standard to underpin traceability (Figure 2B and Supplementary Table 11). EQA was available from a wide variety of providers (Supplementary Table 8) which is also promising as it reflects a response to a clearly identified need. This is also a promising finding when compared to other similar assessments studied by this team for other molecular IVD testing [12–14]. However, this does illustrate that a quarter of laboratories either do not have access to, or do not participate, in EQA. If these findings are reflective of a more widespread global picture, then this is of concern as these tests may not be independently evaluated to ensure they are performing within specified performance criteria. Alternative assessment procedures provide some measure of test performance [13] that complement, but cannot replace EQA in terms of independent evaluation. A variety of AAP were reported as being conducted instead of, or alongside, EQA including the use of internal specimens, externally sourced control materials and sharing samples with other laboratories (Supplementary Table 11).

Two thirds of the molecular tests also provide a result for MDR-TB (Figure 3A and Supplementary Table 12) with a quarter also providing resistance predictors in addition to those used for MDR-TB management (Supplementary Table 13). One of the more significant findings associated with those participating in this survey is linked to the apparent use, and quality assurance, of the drug resistance results. Half the laboratories using the MDR result reported that anti-TB therapy was altered following the result of molecular testing with two thirds of those reporting that this is based on a single result alone (Figure 3B and Supplementary Table 14).

Where the use of MDR results becomes especially significant is when we consider EQA for MDR testing. Two thirds of the laboratories who depend on the molecular result alone, report that their EQA scheme allows for drug resistance evaluation (Figure 3C and Supplementary Table 15) leaving 25 laboratories either using EQA that does not include MDR-TB or not participating in EQA at all. Of these, 12 report that they use the MDR-TB result without corroboration of the MDR result using another approach such as culture. Consequently approximately 10 % of the laboratories report that their MDR-TB results are used to alter therapy without corroboration and that they do not participate in EQA.

The issue of EQA for MDR TB molecular diagnosis represents a limitation of this study as the answers immediately raise further questions. Further granularity is required to determine how the EQAs are structured across regions to account for the respective MRD resistance genotypes and how testing for extensively drug-resistant TB (XDR-TB) is also supported. Furthermore, whether the EQA is setup to evaluate heteroresistance [15] which can influence the sensitivity of a test for drug resistance and potentially the success of the treatment which the test is used to guide [16] must also be considered if molecular tests for MDR and XDR-TB become increasingly relied upon. An assessment of EQA provision for MDR TB testing is required to better understand the current state-of-the-art, limitations and best practices. This could ultimately foster an agreed standardized format for EQA scheme materials and laboratory evaluation criteria would be developed as it contributes towards tests are working within specified parameters. This is arguably as important as the development and uptake of the initial molecular tests themselves as it will aid in maximizing impact and reduce the incorrect treatment of MDR and XDR-TB.

Conclusions

The results of this survey are intended to help identify best practices, uncover potential weaknesses, and formulate recommendations for the further development and standardization of molecular TB diagnostics on an international level [17] and serve as a basis for developing targeted training programs and improving existing quality assurance systems [18]. The response from 118 laboratories across 48 nations suggests a wide variety of IVD formats are available for the molecular diagnosis of TB and MDR-TB and that EQA is established in support of their use. Furthermore, the WHO international standard is being used to support a 1/3 of these schemes. A concerning finding was the suggestion that 1/3 of laboratories use MDR-TB results, but are not supported by appropriate EQA for this part of the tests. Further studies of this type would benefit from consulting the EQA providers to understand how they differ regionally; this would be especially relevant for MDR-TB EQA provision. A wider suggestion from this study would be for regions to increase EQA availability or, where available, make it mandatory for TB, and where used, MDR-TB molecular testing. Notwithstanding the EQA findings RE MDR-TB this work indicates considerable support and application of EQA for TB molecular diagnosis suggesting a more established framework than in previous IFCC studies considering molecular testing for SARS-CoV-2 [14] or circulating tumor DNA [12]. These findings suggest molecular diagnosis for TB, and the systems to support its quality, are in a good position to further support combating the disease more effectively worldwide and achieving the goals set by the WHO for TB elimination [19, 20].

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Data availability: The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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