

## Research articles

### THE ADDED VALUE OF A EUROPEAN UNION TUBERCULOSIS REFERENCE LABORATORY NETWORK – ANALYSIS OF THE NATIONAL REFERENCE LABORATORY ACTIVITIES

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National reference laboratories (NRL) and other laboratories are the cornerstones of well-functioning tuberculosis programmes and surveillance activities. However, the scope and activity of NRL services for mycobacterial identification and drug susceptibility testing (DST) has not been examined in detail across the European Union (EU), nor has the added value of cooperation and networking at the European level been explored with regard to strengthening laboratory services. Therefore, the European Centre for Disease Prevention and Control (ECDC) has commissioned a survey to explore these issues and to identify areas of work that could bring added value by supporting networking activities of tuberculosis (TB) reference laboratories in the EU. Structured questionnaires were sent to TB reference laboratory experts in the EU and European Economic Area (EEA) countries, and in three additional countries selected on the basis of their networking activities with EU projects and other initiatives (Switzerland, Croatia and Israel). The compiled results describe the activities and structure of 32 NRLs (29 countries replied, a response rate of 91%). The analysis of the survey led to the following recommendations for strengthening TB laboratory services: (1) implementing of the published European standards for TB laboratory services with respect to infrastructure, national reference functions, biosafety, human resources, quality assurance, operational research (including evaluation of new medical diagnostics), accuracy and speed, appropriately trained staff; (2) ensuring that laboratories only perform activities for which they have demonstrated proficiency; (3) implement validated and standardised second-line drug susceptibility testing (DST), including drugs used to define extensively drug-resistant tuberculosis (XDR TB); (4) aiming to identify *Mycobacterium tuberculosis* complex (MTBC) and rifampicin (RIF) resistance in over 90% of cultures and cases from smear-positive sputum directly within one to two working days. To realise some of the above recommendations and to strengthen links of TB surveillance and microbiology activities in the EU, a list of suggested generic areas of activities for an EU network of reference laboratories is presented. Such a network would build on and link to existing networks and initiatives at the European and global level.

#### Introduction

Tuberculosis (TB) remains a major cause of morbidity and mortality in Europe. In 2005, 51 of 53 countries in the World Health Organization (WHO) European region reported 426,717 cases (an overall notification rate of 48 TB cases per 100,000 population or 8% of the total number of cases reported globally) [1,2]. In the same year the countries of the current European Union

(EU) and European Economic Area (EEA) reported 93,129 cases (an average notification rate of 18/100,000) with notification rates and numbers significantly higher in the East than the West [2] (apart from Portugal). Higher rates were seen in the Baltic States, Romania, and Bulgaria with the latter two countries (EU accession states at the time) accounting for 35% of the cases. Even in low incidence countries [18] notification rates in vulnerable and high-risk populations can be as high as those reported in high burden countries globally [2].

In the context of the heterogeneous epidemiological setting in the EU, the situation of TB control is further complicated by the presence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis. High MDR TB rates are reported mainly in the Baltic States, but drug-resistant cases are found throughout the whole of the EU, with occasional outbreaks in countries with a low incidence of TB [2-8].

An integrated TB surveillance system already exists across the EU and European region, initially organised by the EuroTB project funded by the Directorate General for Health and Consumer Affairs (DG SANCO) and co-financed by the Institute de Veille Sanitaire, France (InVS) [2], and currently by a joint effort of the European Centre for Disease Prevention and Control (ECDC) and WHO European Region (WHO EURO). However, the scope and activity of national reference laboratory services for mycobacterial identification and drug susceptibility testing, on which much of this surveillance activity is based, has not been examined in detail across the EU Member States (MS), nor has the added value of cooperation and networking at EU level and with neighbouring countries been explored with regard to strengthening laboratory services.

In addition to its role in TB surveillance, the laboratory is the cornerstone of TB diagnosis, essential for both the management of individual patients and effective TB control. This requires access to accurate and timely laboratory diagnosis, including DST and, in particular, faster methods for the diagnosis of TB and MDR/XDR TB. Given this essential role, laboratory services, in the EU and globally, clearly need further strengthening and support in order to achieve the goals of national TB programmes and ensure quality diagnosis for patients [9,10].

We therefore conducted a situation analysis of national TB reference laboratory (NRL) services across the member states of the EU/EEA countries (including Norway and Iceland), and selected

non-EU countries (Switzerland, Croatia and Israel) that were linked to EU projects. It was aimed at determining the range and availability of primary and reference diagnostic services that offer identification of mycobacterial cultures as *Mycobacterium tuberculosis* complex (MTBC; usually *M. tuberculosis*, or *M. bovis*) and first- and second-line drug susceptibility testing. Information on the existence of standard operating procedures (SOPs), standardisation and quality control of procedures was sought and respondents were asked what they believed the NRL service should do and whether they thought these activities were currently being undertaken.

### Materials and Methods

A structured questionnaire was sent electronically to TB reference laboratory experts within the EU/EEA countries as well as to Switzerland, Croatia and Israel, countries that are involved in other EU-supported initiatives relevant to this survey. These experts were identified through the following sources or criteria: (1) They were included on lists of directors of NRLs held by EuroTB and WHO EURO; (2) They were the recipients of specimen panels which are sent to NRLs globally by the WHO Global Project on TB Drug Resistance. Within the EU, the identity of the director of the NRL and whether they were qualified to comment on the national TB reference service was additionally confirmed, wherever possible, by the recently established forum of ECDC National Microbiological Focal Points (a consultation group of microbiologists, appointed by the MS, who know the systems and structures of public health microbiology services in their countries well and can support ECDC in strategic and technical issues) [11].

A pilot survey was conducted that involved only a small number of EU and non-EU countries (Croatia, Denmark, Germany, Italy, Latvia, Sweden and the United Kingdom). The questionnaire was subsequently modified for clarity and precision to produce a final questionnaire that was made available in English, French and Russian. These final questionnaires were completed electronically and contained a total of 83 questions. Most questions required choosing between "Yes", "No", "Don't know", and "Not applicable" from a drop-down menu, and some required entering numerical data *and/or* additional comments.

A list of all activities typically performed by TB laboratories was compiled and the respondents were asked whether they believed the activity was appropriate for an NRL ("ideal" activity). They were then asked if their NRL performed this activity ("actual" activity). The responses were graded on a five-point scale with a maximum score of 160 points per activity in case all laboratories agreed that this activity should be performed (32 laboratories x 5 points).

Those aspects of the survey that referred to functions expected of the NRL services and to areas of added value from networking of NRLs at EU level, were discussed in working groups and plenary sessions at a meeting of TB surveillance correspondents in Stockholm, September 2007 ["ECDC - WHO EURO - EuroTB: Annual Meeting on Tuberculosis Surveillance in Europe"]. The participants were TB microbiology experts, including those who had received and responded to the questionnaire and those from other TB microbiological centres, as well as TB surveillance experts.

### Results

Responses were received from 32 TB reference laboratory experts, situated in laboratories in the cities indicated below, and representing 27 EU/EEA countries as well as two countries outside the EU (29 countries overall, a response rate of 91%):

- EU: Belgium (Brussels and Antwerp), Bulgaria (Sofia), Cyprus (Nicosia), Czech Republic (Prague), Denmark (Copenhagen), Estonia (Tartu), Finland (Turku), France (Paris), Germany (Borstel), Hungary (Budapest), Ireland (Dublin), Italy (Rome and Milan), Latvia (Riga), Lithuania (Vilnius), Luxembourg (Luxembourg), Malta (Valetta), Netherlands (Bilthoven), Poland (Warsaw), Portugal (Lisbon and Oporto), Romania (Bucharest), Slovakia (Nitra), Slovenia (Golnik), Spain (Zaragoza), Sweden (Stockholm), United Kingdom (London);
- EEA: Iceland (Reykjavik), Norway (Oslo);
- non-EU/EEA: Croatia (Zagreb), Israel (Tel Aviv).

### Laboratory activities

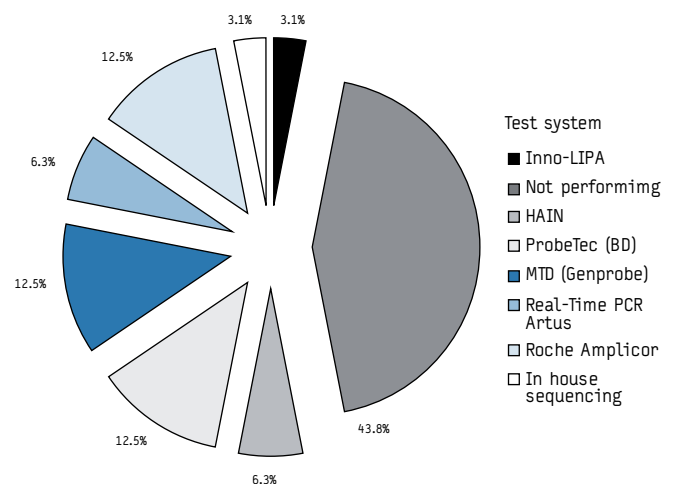
The respondents provided data on cultural and molecular diagnostic methods used in their laboratories for the isolation, detection and speciation of *Mycobacteria*, and for DST.

#### Detection of MTBC and drug susceptibility analysis in clinical specimens

Twenty-seven of 32 laboratories perform smear microscopy and microbiological culture of primary clinical specimens. Laboratories that do not analyse clinical specimens routinely include Bilthoven, Brussels, Oslo, Stockholm, and Turku. Eighteen of 31 laboratories of those testing primary specimens) use rapid methods for detection of MTBC in direct specimens (Figure 1). Most laboratories (14/18) used commercially available assays including reverse-phase hybridisation of labelled PCR products with DNA probes immobilised on membranes (Inno-LiPA, Innogenetics, Belgium and HAIN, Germany) or microplates (Roche Amplicor *Mycobacteria*), strand displacement amplification (BD ProbeTec ET), amplification and detection of specific rRNA fragments (MTD Genprobe), and real-time PCR (Artus).

Commercial molecular assays used for the diagnosis of drug resistance are all based on the detection of mutations in specific genes associated with drug resistance. Rapid identification of RIF *and/or* isoniazid (INH) resistance in clinical specimens is particularly important for early detection of MDR TB. These tests are performed by 13 (RIF) and 11 (INH) laboratories, using commercial reverse-

**FIGURE 1**  
Rapid detection of *Mycobacterium tuberculosis* in direct clinical specimens



hybridisation assays such as Inno-LIPA RifTB assay for detection of RIF resistance only, and the HAIN MTBDR and MTBDR+ assays for detection of resistance to RIF and INH together.

A non-commercial reverse hybridisation assay (microarray) for detection of both RIF and INH resistance is in use in the laboratory in London, six laboratories (Antwerp, Bilthoven, Brussels, London, Milan and Paris) use in-house DNA-sequencing (rpoB gene) for detection of RIF resistance only, and one laboratory (Milan) uses multiplex PCR for the detection of mutations in genes associated with INH resistance (katG and inhA).

### Reference culture identification

Identification of isolates can be performed either by using conventional phenotypic methods based on isolation of bacterial cultures on liquid or solid media followed by biochemical tests, or by using molecular methods based on detection of highly specific nucleotide sequences in certain genes (e.g. 16S RNA or rpoB).

Identification of cultures as MTBC with conventional methods is performed by 30 of the 32 laboratories (Reykjavik submits their isolates for identification to Copenhagen and Valetta to London). Five laboratories do not differentiate isolates further to species level within the MTBC (Riga, Vilnius, Antwerp, Rome, and Reykjavik). Rapid identification of MTBC isolates is performed by all but four laboratories (Sofia, and Bucharest do not identify isolates rapidly; cultures from Reykjavik and Valetta are rapidly identified in Copenhagen and London, respectively), using a variety of commercial (Accuprobe, HAIN, Inno-LiPA) and non-commercial molecular assays (DNA sequencing and in house PCR) with most laboratories (16/28) using more than one method: as a first choice method, 13, 11, two, and two laboratories used Accuprobe, HAIN, Innolipa, and in-house molecular methods, respectively.

Non-tuberculous mycobacteria from cultures are identified at all but three laboratories (Vilnius does not perform identification of non-tuberculous mycobacteria; cultures from Reykjavik and Valetta are identified in Copenhagen and London, respectively).

### Drug susceptibility testing on cultures

Conventional phenotypical drug susceptibility tests for first-line drugs isoniazid, rifampicin, streptomycin, and ethambutol are performed by all laboratories, and for pyrazinamide by all but four laboratories (first and second-line DST of cultures from Reykjavik, Valetta and Nicosia are performed in Copenhagen, London and Borstel, respectively). The range of second-line (and "third-line") drugs tested for resistance is more limited (Figure 2): Most laboratories test (or submit isolates for testing) for susceptibility to ofloxacin (27 laboratories), cycloserine, para-aminosalicylic acid (PAS) and capreomycin (26 laboratories each), amikacin (25 laboratories), ethionamide (23 laboratories), kanamycin (19 laboratories), and ciprofloxacin (17 laboratories).

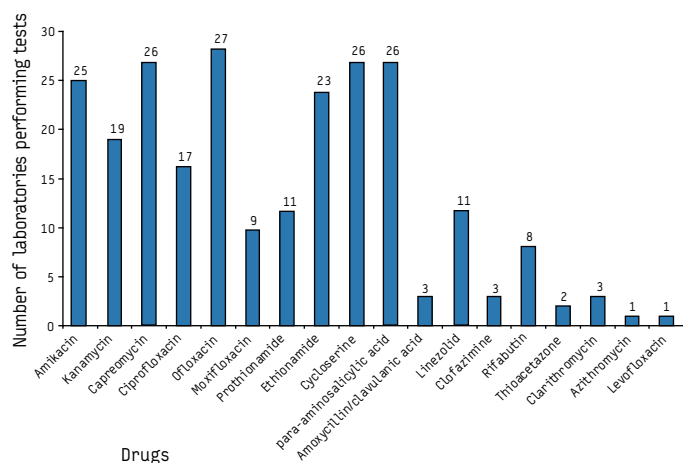
Susceptibility tests for 10 other drugs are performed by between one and 11 laboratories (Figure 2). As a consequence, seventeen laboratories are unable to identify all potential XDR TB isolates. However, taking into account recent findings on molecular mechanisms of cross-resistance between aminoglycosides (e.g. kanamycin and amikacin) and cyclic peptides (capreomycin) [12], those laboratories that do not perform tests for all injectable second-line drugs may still be able to detect most XDR TB cases.

Rapid identification of RIF resistance is performed by 19 laboratories and of INH resistance by 15 laboratories, using molecular methods including the Inno-LIPA (RIF), HAIN (RIF and INH), and pyrosequencing commercial assays, or in-house sequencing (rpoB, katG, inhA genes) as the principal molecular method for the detection of drug resistance.

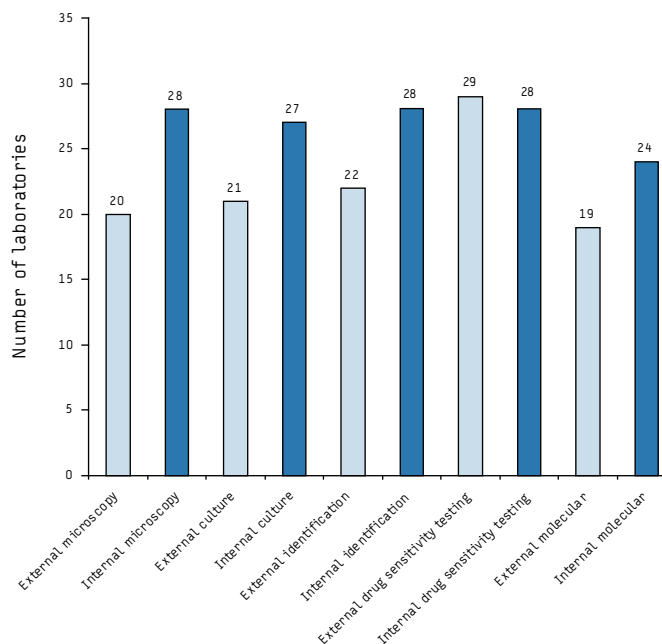
### Quality issues

The respondents were requested to provide information on their accreditation, links to WHO supranational reference laboratories

**FIGURE 2**  
Laboratories performing (or submitting isolates for) second- and third-line drug susceptibility testing



**FIGURE 3**  
External and internal quality control in tuberculosis reference laboratories (n=31)



(SNRL), availability of written SOPs, and their participation in external and internal quality control programmes.

Fifteen laboratories received accreditation from their authorised national bodies. The remaining laboratories did not report formal accreditation (Brussels, Budapest, Dublin, Lisbon, Luxembourg, Nicosia, Nitra, Oporto, Reykjavik, Riga, Golnik, Sofia, Tel-Aviv, Turku, Valetta, Warsaw, and Zagreb. Nine laboratories (Antwerp, Bilthoven, Borstel, London, Oporto, Paris, Prague, Rome (with Milan), and Stockholm) have WHO SNRL status. Of the remaining 23 laboratories, 19 are connected to a defined SNRL (with three laboratories collaborating with Borstel, seven with Stockholm, five with London, one with Barcelona, one with Prague, one with Paris, and one with Bilthoven).

#### **Availability of SOPs, biosafety and participation in Quality Control programmes**

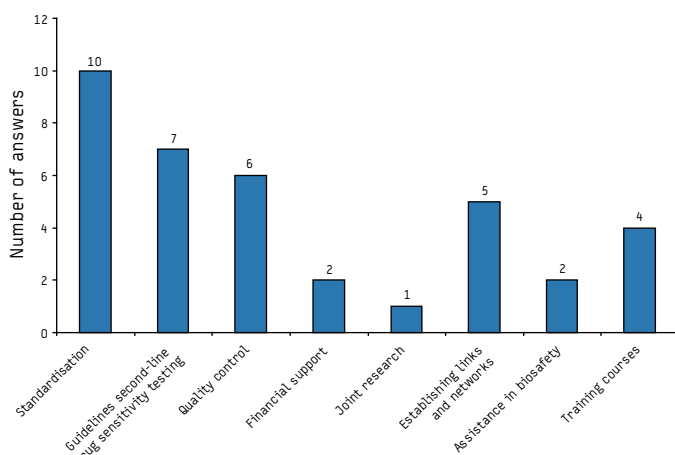
Written SOPs for microscopy, culture, species identification, DST, and molecular methods are available at all laboratories performing these tests, except Tel-Aviv (which does not have SOPs for DST and molecular methods). Most laboratories participate in external quality control systems and have appropriate policies for internal quality control for the different methods they use (Figure 3).

External quality control systems for DST cover all 29 laboratories performing these tests, whereas coverage for other techniques, especially microscopy, molecular methods, and culture is poorer, with 20, 19, and 21 laboratories, respectively (n=32) (Figure 3). Internal quality control policies for microscopy, identification and DST are available at almost all laboratories performing these tests, with fewer laboratories having these policies for culture, and molecular methods (27 and 24, respectively, of a total of 32 laboratories.) (Figure 3).

Written biosafety protocols are available at all but one laboratory (Oporto). Nevertheless, staff working on TB is at risk from being exposed, and seven active TB cases from six laboratories were reported within the last five years. Five of those cases were laboratory-acquired.

**FIGURE 4**

#### **Most frequently voiced opinions on how ECDC could assist in improving tuberculosis reference services across Europe (more than one answer possible)**



Service continuity *and/or* disaster recovery plans are available in 24 laboratories.

#### **Role of ECDC**

All respondents but one believed that ECDC could assist in improving laboratory services across Europe by assisting in the development of standards of laboratory practice, and of DST in particular, assisting in the implementation of quality control systems, establishing links between laboratories across Europe, organising training courses, implementing joint research activities and providing financial support (Figure 4). Most laboratories (24/31) reported that they conduct research with just over a quarter of staff (93 persons) being active in research. One respondent felt that assistance with research implementation could be facilitated by ECDC.

#### **TB National reference laboratory – status, primary functions and activities**

In this section of the questionnaire, the respondents were asked whether NRLs existed in their country and whether their laboratory was the NRL, how the NRL in their country was selected, and what types of activities the respondents believed should be performed by NRL.

Of the 32 laboratories that participated in the survey, 29 indicated they considered themselves as the NRL, and 25 of the 32 were formally recognised as the NRL.

The principles of NRL selection (n=16) differed significantly between countries, with six laboratories appointed directly by the Ministry of Health, four by a national committee of clinical bacteriologists or other governmental bodies, and six laboratories selected on the basis of quality assessment, formal review *and/or* tendering processes.

National (regional) TB laboratory networks exist in 22 countries (Cyprus, Denmark, Iceland, Israel, Luxembourg, Malta, and Portugal do not have a network, but in most of these cases this is because a single laboratory performs all primary and reference mycobacterial work). Twenty-one laboratories do not have a specific budget for reference activities. Twenty-three laboratories participate in the implementation of the National TB Programme (NTP) and in the provision of formal training/supervision within the laboratory network.

The respondents were asked about the obstacles in performing reference functions. Budget constraints were considered by the majority of respondents (27 of the 32) as the major obstacle to performing the reference functions of a NRL. Other problems such as lack of equipment, poor infrastructure, and human resources issues, were mentioned by 13, 13, and 17 laboratories, respectively. Some laboratories mentioned additional obstacles to performing reference functions, for instance the absence of formal national recognition, poor administrative support (four laboratories), decentralised TB services (one laboratory), and poor cooperation with the epidemiology service (one laboratory).

#### **Core functions and activities of NRL**

Figure 5 summarises the core, or primary, functions and activities of NRLs from two perspectives: the participants' opinion regarding the activities that their NRLs actually perform; and their opinion regarding the "ideal" core functions of NRLs. The responses were graded on a five-point scale. Overall, there was good agreement between current activity at NRLs and ideal activity, i.e. agreement on the importance of accurate and timely identification of MTBC,

drug susceptibility testing, appropriate infrastructure and staffing, involvement and control of laboratory budgets, and supporting the national TB programme in laboratory areas. However, there were some differences: fewer respondents agreed, for example, that NRLs should perform microscopy and culture of clinical specimens.

### Discussion and conclusion

In the EU, and in Europe in general, the strengthening of laboratory services will include the development of an appropriate infrastructure, methodology, training and quality assurance controls for laboratories, providing both conventional (i.e. smear microscopy, culture and drug susceptibility testing) and rapid diagnostic tests. High quality diagnosis is the first priority, however emphasis on more wide-spread introduction of existing, high quality, rapid tests for TB and RIF resistance/MDR TB identification would greatly facilitate earlier identification of MDR TB patients and their enrolment on appropriate treatment. Implementation of such rapid diagnostic tests will need investment in infrastructure, equipment, training, reagents, supplies, and adequate biosafety measures. [7,13]. Given the circumstances described above, there was a need to carefully assess the current mycobacterial laboratory services and quality control practices throughout the EU. A situational analysis of this

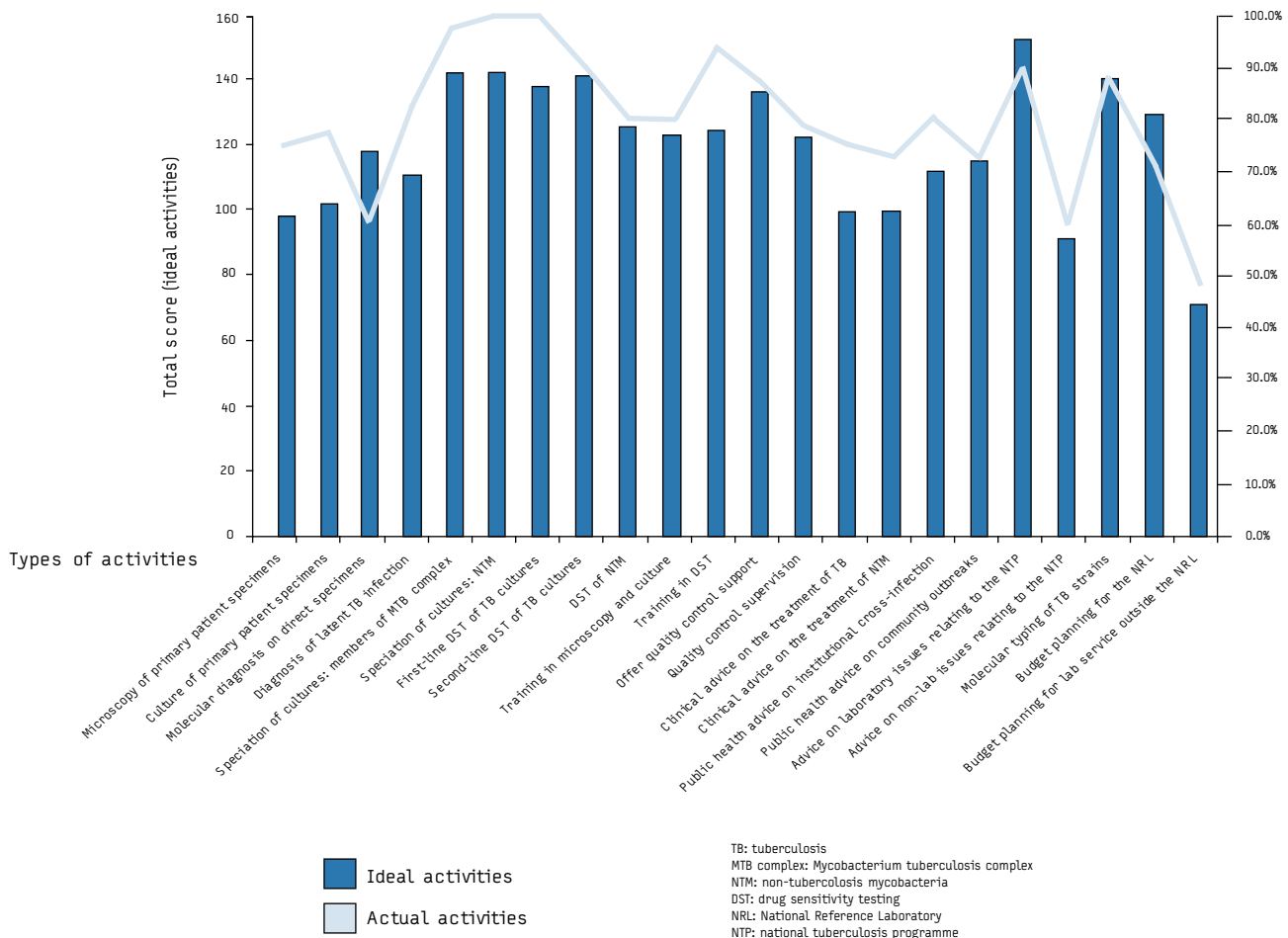
kind provides a starting point for identifying needs and gaps in laboratory methods/services and for exploring the added value of EU reference laboratory networking activities.

There was general agreement that the key roles of a NRL and service were: (1) to identify of mycobacterial cultures as *M. tuberculosis* or non-tuberculous mycobacteria; (2) to analyse first- and second-line drug resistance of TB cultures; (3) to perform rapid identification and detection of at least RIF resistance in patient specimens; (4) to develop protocols and SOPs; (5) to set standards and to run external quality control and assurance schemes (with partners); (6) to be involved in operational research such as the validation of new diagnostics; (7) to provide clinical and relevant public health advice on the treatment of TB; (8) to advise on laboratory issues relating to national TB programmes; and (9) to perform molecular typing of *M. tuberculosis* strains in support of public health actions, *and/or* in geographically *and/or* time defined settings, for example a city, *and/or* to answer specific focused questions on transmission.

Achieving the above requires the use of good laboratory practice and a commitment to: (1) meeting or developing adequate standards

FIGURE 5

### Ideal and actual activities performed by National Reference Laboratories across Europe



for laboratory diagnosis, be it microscopy, bacterial culture, DST or molecular diagnosis [13,14]; (2) ensuring appropriate and safe laboratory infrastructures; and (3) providing adequate numbers of sufficiently trained staff to perform the work.

In addition to strengthening TB reference laboratory services, an increased effort is required to increase the TB case detection rate and to improve the speed of TB and MDR TB diagnosis (especially in individuals co-infected with human immunodeficiency virus (HIV)) and the proper management of multidrug-resistant (MDR and XDR) TB cases. Therefore, both basic diagnostic and specialised reference laboratories will need to be significantly upgraded, and quality laboratory maintenance and management sustained thereafter.

The extent of the necessary improvements varies considerably among the EU Member States, and the small number of non-EU countries invited to participate in this current survey. It would be beneficial to extend this analysis across the whole European region in order to obtain a consistent picture of the national reference services across Europe and of how larger centres may be able to support smaller ones.

Biosafety continues to be an issue seeing as several laboratory staff have developed active TB during their employment. Human resources also remain a significant problem and will be presented and discussed in a separate analysis of data obtained in the current survey.

Several countries, in particular those of the former Soviet Union, have high rates of drug resistance amongst their TB patients [1,3,4,7]. Many of these countries, for example the Baltic States, are now part of or bordering the EU.

Measuring resistance to first- and second-line drugs is complex and for many second-line drugs lacks standardisation. Most countries have few MDR TB cases and maintaining the technical expertise needed for accurate analysis is difficult.

There remains a need to standardise second-line drug resistance testing across the EU and beyond, using agreed and standardised methodology [15-17], and such testing should only be performed at NRLs due to the relatively small number of cases and the difficulty

## Box 1

### General recommendations and principles to improve the access to and performance of mycobacterial laboratories with the aim to ensure reliable and timely diagnostic services

- Implement the European standards for TB laboratory services [13] with respect to infrastructure, national reference functions, biosafety, human resources, quality assurance, accreditation, operational research including evaluation of new medical devices, accuracy and speed;
- Ensure safe, secure and adequate laboratory infrastructures and sufficiently trained staff to perform the work;
- Recognise that high quality laboratory services are an integral part of the surveillance chain;
- Support surveillance systems in routine reporting, optimising case detection and identification of antimicrobial resistance, and understanding the spread of the resistance in various settings;
- Support the application of appropriate national and international quality assurance schemes with agreed testing panels;
- Ensure political commitment and investment in infrastructure and human resources to improve and sustain laboratory services in the long term, through the training of sufficient numbers of staff in appropriate TB laboratory procedures with forward planning for the replacement of retired staff or staff who have resigned.

## Box 2

### Recommendations for the development of a well functioning EU reference laboratory network with added pan-European value

Create an EU reference laboratory network, with the capacity to serve and support the EU Member States and the European Region. Such a network should build on, synergise with, and not duplicate activities covered by other supranational/global initiatives with a special focus on the challenges of TB control and elimination in the EU setting. The network would add pan-European value by supporting the following types of activities:

- international laboratory technical support and access to diagnostic services (i.e. access to drug susceptibility testing through twinning or other contractual arrangements);
- strengthened routine and enhanced surveillance initiatives and links to microbiological laboratories;
- training opportunities through workshops, staff exchanges, access to training material;
- possibilities for peer-review of laboratory performance and implementation of standards;
- development and/or maintenance of standardised and harmonised methods (n.b. while this is a particularly high priority for second-line drug testing, it is relevant for the whole spectrum of new and traditional diagnostic methods);
- promotion of the implementation of existing WHO and other external quality assurance systems;
- development of new external quality assurance systems (e.g. typing and rapid molecular diagnosis);
- development of an infrastructure for operational research (e.g. development and/or validation of new diagnostic methods or devices).

## Box 3

### Recommendations to ensure access to culture methods and drug susceptibility testing (DST) for first- and second-line drugs with proper implementation of new diagnostic tools

- Improve universal access to mycobacterial culture and use of routine drug susceptibility analysis;
- Perform accurate, timely, high quality drug resistance analysis for all new TB cases for first-line drugs on specimens taken before initiating treatment, if the patient continues to be culture-positive after two to three months and if there is a history of prior TB treatment (a major risk factor for drug resistance);
- As a minimum for laboratories supplying DST data from reference cultures to clinicians, governments, the WHO, and for surveys or surveillance, correctly identify resistance to isoniazid and rifampicin in over 90% of quality control samples in two out of the last three quality control rounds;
- Rapidly identify mycobacterial cultures as *M. tuberculosis* complex (mainly *M. tuberculosis* and *M. bovis*) and identify rifampicin resistance as the first priority within one or two working days; Modern molecular techniques allow the successful identification of isoniazid resistance in at least 75% of *M. tuberculosis* complex isolates within one or two working days; It is now technically possible to rapidly (1-2 days) identify MDR-TB;
- Implement validated and standardised second-line drug DST (including drugs used to define XDR-TB);
- Develop and implement appropriate quality assurance for second-line drugs and determine the underlying reasons for programmatic failures leading to the need for DST for second-line drugs;
- Accelerate the development and implementation of techniques for the rapid diagnosis of TB, rifampicin resistance, and MDR/XDR-TB in primary patient specimens, in particular for the most infectious cases; aim, as a minimum, to identify MTBC and rifampicin resistance in over 90% of cases from smear positive sputum directly, where logistic resources are available, within one or two working days;
- Support appropriate operational and translational research (clinical research, programme management in the context of laboratory services, barriers to the implementation of appropriate therapy), development, and application of new tools, i.e. of diagnostic methods (particularly for children or individuals co-infected with HIV and meningitis), new treatments, proof of cure in patients with drug resistant TB, and prevention tools.

of maintaining testing proficiency in a setting where multiple centres perform this activity.

Box 1 shows general principles and recommendations to improve the access and performance of mycobacterial laboratories to ensure reliable and timely diagnostic services.

Box 2 and 3 provide detailed recommendations drawing on the participants' responses, a round table discussion focussing on drug resistance, the specific European Standards for mycobacterial laboratories [13] that need to be achieved, and the implementation of new tools which will help to achieve them.

The laboratory remains at the centre of TB control activities, and laboratory activities in Europe could be further developed and strengthened through the creation of an EU reference laboratory network (Box 2) with the capacity to serve and support the EU Member States and the European Region, demonstrated proficiency in their activities, and appropriate links with other relevant technical and scientific support bodies in the EU as well as Europe in general.

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