Report of the Second Meeting of the European Tuberculosis Laboratory Initiative

Copenhagen, Denmark
7–8 October 2013
ABSTRACT

With the support of the Governments of Belgium and the Netherlands and the United States Agency for International Development, the second meeting of the European Tuberculosis Laboratory Initiative was held in Copenhagen, Denmark on 7–8 October 2013, hosted and conducted by the WHO Regional Office for Europe. Key focuses of the event were providing a general overview of progress in developing and implementing TB laboratory development plans in the Region and exchanging experiences between countries; identifying challenges in scaling up rapid M/XDR-TB detection; and suggesting ways to address and overcome the challenges in scaling up the rapid detection of M/XDR-TB.

Keywords

EARLY DETECTION OF DISEASE
EXEMPLARY DRUG-RESISTANT TUBERCULOSIS
HEALTH POLICY
TUBERCULOSIS
XDR-TB
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### Abbreviations

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<tr>
<td>ELI</td>
<td>European Tuberculosis Laboratory Initiative</td>
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<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
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<td>IOM</td>
<td>International Organization for Migration</td>
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<td>M/XDR-TB</td>
<td>multidrug- and extensively drug-resistant tuberculosis</td>
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<td>MTB</td>
<td><em>Mycobacterium tuberculosis</em></td>
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<td>RIF</td>
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Summary

With the support of the Governments of Belgium and the Netherlands and the United States Agency for International Development, the second meeting of the European Tuberculosis Laboratory Initiative was held in Copenhagen, Denmark from 7 to 8 October 2013.

Representatives from 23 countries in the WHO European Region, mainly those in which TB is a high priority, joined the meeting and discussed issues including experiences with TB laboratory development plans, progress with implementing and scaling up the rapid diagnosis of multidrug- and extensively drug-resistant TB (M/XDR-TB) (including Xpert MTB/RIF and line probe assay) and quality management in TB laboratories. The participants also included representatives of WHO’s Stop TB Department, the Foundation for Innovative New Diagnostics, the KNCV Tuberculosis Foundation and the European Centre for Disease Prevention and Control.

Key outcomes of the meeting included:
- a general overview of progress in developing and implementing TB laboratory development plans in the Region and the exchange of experiences between countries;
- identifying challenges in scaling up rapid M/XDR-TB detection;
- suggesting ways to address and overcome the challenges in scaling up the rapid detection of M/XDR-TB; and
- initial work on developing standard algorithms for the modern laboratory diagnosis of TB in the countries of the Region.

Introduction

With the support of the Governments of Belgium and the Netherlands and the United States Agency for International Development, the second meeting of the European Tuberculosis Laboratory Initiative (ELI) was held in Copenhagen, Denmark from 7 to 8 October 2013.

ELI consists of a network of national and supranational TB laboratories in the Region and international partners dedicated to accelerating and expanding the access to quality-assured TB diagnostic laboratory services and to optimizing the laboratory-based surveillance of TB. ELI serves as a regional platform for discussion and communication on laboratory-related issues. The mission of ELI is to strengthen TB laboratory capacity in the Region with emphasis on the 18 countries in which TB is high priority. The aim of the ELI meeting was to strengthen the capacity of the TB laboratory network by updating countries on the latest developments in the laboratory diagnosis of TB and to review the progress made towards the Consolidated Action Plan to Prevent and Combat Multidrug- and Extensively Drug-Resistant Tuberculosis (M/XDR-TB) in the WHO European Region 2011–2015.

In line with the implementation of the Consolidated Action Plan, the WHO Regional Office for Europe established ELI in collaboration with the Global Laboratory Initiative to strengthen TB laboratory capacity for accurate diagnosis and early detection of drug-resistant TB in the Region. The first meeting of ELI was held in Bilthoven, Netherlands on 15–16 October 2012.
The second meeting was organized back to back with a workshop on anti-TB drug resistance surveillance for representatives of countries with a high burden of MDR-TB on 9–10 October 2013.

**Meeting objectives and expected outcomes**

The specific objectives of the meeting were:
- to update countries on the epidemiology of M/XDR-TB in the Region;
- to discuss the developments in the laboratory diagnosis of TB and WHO-endorsed rapid M/XDR-TB diagnostics, especially the Xpert MTB/RIF assay;
- to strengthen the capacity of the TB laboratory network by sharing information between countries and by informing countries on the new WHO biosafety guidelines and on how to manage a TB laboratory network; and
- to review the status of implementation of the laboratory components of the Action Plan and to discuss the challenges in implementing the Plan and the way forward.

The expected outcomes of the meeting were:
- updating participants on the recent developments in the laboratory diagnosis of TB, management of a TB laboratory network, rapid diagnosis of M/XDR-TB and the epidemiology of M/XDR-TB;
- reviewing progress towards implementing the laboratory components of the Action Plan and discussing the challenges and way forward;
- sharing experiences with using rapid diagnostic tests (especially the Xpert MTB/RIF and line probe assays) between the countries;
- presenting standard algorithms for the modern laboratory diagnosis of TB, including selection criteria for the individuals to be tested, for different settings in the Region; and
- discussing challenges in scaling up rapid M/XDR-TB detection and proposing ways to address these.

**Welcome and introduction**

Guénaël Rodier, Director of the Division of Communicable Diseases, Health Security and Environment, WHO Regional Office for Europe and Dara Masoud, Programme Manager, Tuberculosis and M/XDR-TB Control Programme, WHO Regional Office for Europe, welcomed the participants to the meeting and to the recently opened UN City in Copenhagen, Denmark. They encouraged the participants to discuss and exchange experiences and information. Despite progress on implementing the Action Plan, much still needs to be achieved. The WHO European Region has the lowest treatment success rate worldwide, two thirds of the people with MDR-TB are not yet detected and rapid molecular diagnosis should be further improved. Laboratory work plays a key role in all these.

Based on the latest surveillance data, Andrei Dadu, Technical Officer, Tuberculosis and M/XDR-TB Control Programme, WHO Regional Office for Europe, provided the participants with a general overview of the current burden of M/XDR in the Region. This shows that, despite a decrease in TB notification, drug-resistant TB continues to be a major concern, and the root
causes of its emergence and transmission urgently need to be addressed. In addition, shortcomings in health systems and social determinants of health in relation to TB should be addressed in every country; finally, early detection of TB, particularly drug-resistant TB, and adequate treatment with patient-friendly services need to be ensured across the Region.

**Genetic characterization of M/ XDR-TB in the European Region**

Genetic aspects of M/XDR-TB were discussed based on presentations of three studies from the Region.

**Origin and spread of a TB clone from the Russian Federation**

Igor Mokrousov, St Petersburg Pasteur Institute, presented the results of a study on the origin, emergence and current spread of the successful TB strain Beijing B0/W148. Based on a systematic review of studies on the Beijing B0/W148, the strain most likely originated in Siberia, and due to massive population outflow from Siberia to the European part of the Russian Federation in the 1960s to 1980s was spread. The study indicates that the successful spread of the strain may be ascribed to the introduction and wide use of modern anti-TB drugs and the strain’s remarkable capacity to acquire drug resistance. The presentation evoked lively discussions among the participants about the implications of the study’s findings in terms of preventing further transmission and of how the Beijing B0/W148 strain differs from other strains that have not been studied in as much detail.

**Reinfection with MDR-TB in hospitals demonstrated by DNA fingerprinting**

Elena Romancenco, head of the Moldova National Reference Laboratory, presented a study from the Republic of Moldova on reinfection with MDR-TB strains in hospitals. The aim of the study was to evaluate the phenomenon of reinfection with MDR-TB strains in hospitals by using DNA fingerprinting. The retrospective study (2009–2011) included 103 new and previously treated people with pulmonary TB from four hospitals. The study demonstrated that, among people with sensitive TB and an intensive treatment phase in hospitals, reinfection with new MDR-TB strains was common (69% of these people were reinfected). This can in part be explained by nosocomial (hospital-acquired) transmission of MDR-TB. Strains of the Beijing and Ural genotypes of *Mycobacterium tuberculosis* were most frequently isolated from people during inpatient treatment. In addition, the Ural genotype was strongly associated with the pathogenicity and transmissibility of MDR-TB infection during inpatient treatment in the hospitals. The study shows how DNA fingerprinting, in combination with conventional epidemiological investigations, can contribute greatly to understanding the pathogenesis and transmission of TB and, as a result, to investigate contact and outbreaks effectively and in a timely manner. In the Republic of Moldova, the study trigged considerable discussion between physicians and other specialists and gave rise to re-evaluating the situation of infection control in TB hospitals and contributed to moving towards more outpatient treatment. In the discussion, the participants highlighted the importance of these research studies focusing on application in practice and convincing policy-makers of the necessary changes and not just for the sake of publication.

**Quality of the different types of rifampicin resistance**

Finally, Evgeni Sahalchyk, Supranational TB Reference Laboratory in Germany, presented the findings from a study on mutations associated with anti-TB drug resistance in central Asia and
the use of various methods for detecting rifampicin resistance. The study showed that rifampicin resistance is clinically and epidemiologically highly relevant. The study also showed that the HAIN line probe assay will most likely detect 98% of the cases of high-level resistance and 50% of low-level resistance, while the Xpert MTB/RIF assay will probably detect less. Xpert mainly misses resistance in mixed populations because the wild-type strain is present in such mixtures. Xpert MTB/RIF and the HAIN line probe assay misidentify about 3% of all phenotypically susceptible isolates as resistant. The mycobacteria growth indicator tube misses most low-level resistance. Molecular tests can detect half of such cases of resistance. During the discussion, the implication of the findings for practice was brought up again. Low-level resistance presents a complex problem for clinicians, but it is important to raise the issue and try to understand how much it affects treatment outcome and whether knowledge about low-level resistance can be used in choosing treatment regimens. In addition, it is important to show that resistance detection is complicated and that inconsistent results between tests do not just arise because of poor laboratory performance.

**Molecular diagnostics for M/ XDR-TB**

Two presentations on molecular diagnosis of MDR-TB provided the background for discussing developments in the molecular diagnosis of TB in the Region.

**Molecular diagnosis of MDR-TB by using the Xpert MTB/ RIF assay**

Alexei Korobitsyn of the Foundation for Innovative New Diagnostics provided the participants with an overview of the developments in and role of molecular diagnosis using the Xpert MRB/RIF assay three years after it was endorsed by WHO. GeneXpert has become routine for many countries: it enhances case detection, rapidly identifies drug resistance, reduces time to treatment and decreases initial default – but there are still many unanswered questions. A recently published systematic review confirms its high accuracy for pulmonary TB and WHO recommendations for using Xpert MTB/RIF in extrapulmonary TB. There is also promising evidence for its performance in TB among children, but more evidence is needed. Regarding its role, Alexei Korobitsyn shared the plans on moving towards remote calibration so that models will no longer need to be replaced annually in the future. A remote Internet-based monitoring tool was being tested and was expected to be ready soon. The packaging is also being changed to reduce waste and shipping costs. For validating the machines, the validation panel of the Global Laboratory Initiative is most broadly used. Progress on integrating HIV viral load testing in the GeneXpert system was reported. The first steps are being taken, and this test is expected to be released in 2014. Currently, the major unmet needs remain: (i) screening at the first point of contact; (ii) work-up and choice of treatment at a dedicated region; and (iii) support surveillance, with quality assurance at a specialized unit. The presentation ended with an encouragement to continue sharing and collecting experiences on how to use molecular tools optimally.

**Line probe assays and anti-TB drug resistance**

Sabine Rüsch-Gerdes of the National Reference Laboratory for Mycobacteria in Germany gave a technical talk on the use of line probe assays for detecting drug resistance and described some of its restriction for predicting resistance to second-line drugs. Molecular tests should not be used for monitoring treatment because even the DNA of dead bacteria might still be detected; microscopy and culture are still needed for monitoring. The manufacturer has recently evaluated a new version of the line probe assay for detecting resistance to second-line drugs that can more reliably detect resistance to fluoroquinolones and no longer detects resistance to ethambutol. In
addition, advice was provided on how to avoid different kinds of contamination. The importance of developing a diagnostic algorithm when implementing rapid diagnostic tools was highlighted, and it was stressed that discussing this with all people involved in TB diagnostics is essential for successful implementation. Finally, the participants were strongly encouraged to perform analysis on their own data to identify which strains are circulating in their country and communities. After the presentation, the participants had the opportunity to ask clarifying questions about the use of line probe assays, criteria for their use at which laboratory levels they should be used and advice on the development of country-specific diagnostic algorithms.

TB laboratory strengthening

The last session of the day was dedicated to issues around biosafety, TB laboratory network management and opportunities for financial support from the Global Fund to Fight AIDS, Tuberculosis and Malaria for strengthening TB laboratories.

New biosafety guidelines

Diego Zallocco of the WHO Stop TB Department presented the WHO *Tuberculosis laboratory biosafety manual*. The new edition is developed on a risk-based approach that does not use the risk group classification or the containment levels. Instead it is based on assessing the risk associated with the various technical procedures performed in the different types of TB laboratories.

The WHO manual describes the minimum requirements for facilities and practices that can be adopted by local regulations as a result of a risk assessment. Countries are, however, free to apply stricter biosafety rules than those described in the WHO manual.

Substantial time was dedicated to present WHO’s advice on the steps in conducting risk assessment, risk precaution levels and their associated laboratory activities. In addition, basic definitions of biosafety were provided, and basic administrative activities to secure biosafety in the TB laboratory as well as good laboratory practices were highlighted.

Management of a TB laboratory network

Alexei Korobitsyn of the Foundation for Innovative New Diagnostics gave a presentation on managing a TB laboratory network. Following a general overview of health system management, some of the challenges specific to TB laboratory networks were defined. The main focus of the presentation was, however, on the experiences of the EXPAND-TB project, focused on strengthening the capacity of central and regional laboratories with new TB diagnostics. Using the example of Kyrgyzstan, the process of implementation was described, including some of the major problems encountered during the implementation of the project. These included the need for costly infrastructure and biosafety upgrades; scarcity of human resources and high turnover; and lack of a system for transporting samples. During the subsequent discussion the challenge of the lack of human resources was extensively discussed. It was the experience of most countries that a solution to the human resource gap in laboratory services is very much needed, partly because of a rapidly increasing workload. A main problem is that the policy level poorly understands the need to give priority to human resources in laboratory services. It was requested

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that WHO or ELI develop guidelines on the human resources required for national reference laboratories. In addition, training and postgraduate education are essential to ensure that the right personnel and not just enough personnel.

**The Global Fund’s new funding mechanism and how it could support TB laboratories**

As the final presentation of the day, Martin van den Boom of the WHO Regional Office for Europe presented the participants with a glimpse of the Global Fund’s new funding mechanism and its possible practical implications. One of the main novelties in the Global Fund’s funding mechanisms is a focus on investing in national strategic plans, described in a concept note, which is developed through country dialogue (partner involvement) involving government, civil society, partners, donors and the Global Fund Secretariat. In addition, greater alignment with country schedules and contexts is given priority, since the concept note replaces the previous mechanism based on rounds. The Global Fund will focus on countries with the highest burden of disease and lowest ability to pay, while keeping the portfolio global. The aim is to have a shorter and more predictable application processes and more predictable funding levels. Another change is the establishment of an “early” technical review panel to provide feedback on the draft concept note and enhance the engagement of the Global Fund. Martin van den Boom also presented some practical steps for countries and key lessons learned from the application process by Kazakhstan. Finally, laboratory involvement in the Global Fund process was suggested.

**Country experiences: progress towards implementing the Consolidated Action Plan**

Substantial time was allocated to country presentations on progress towards and experiences with implementing the laboratory components of the Consolidated Action Plan to Prevent and Combat Multidrug- and Extensively Drug-Resistant Tuberculosis (M/XDR-TB) in the WHO European Region 2011–2015. The presentations and discussions were divided into three main topics: (i) developing a TB laboratory development plan; (ii) scaling up rapid M/XDR-TB diagnostics; and (iii) implementing quality management in TB laboratories.

**Progress towards implementing the Consolidated Action Plan and update on ELI activities**

Kristin Kremer of WHO gave an update on the progress towards implementing the Consolidated Action Plan and on the latest ELI activities. After a brief reminder about the targets of the Consolidated Action Plan and the current burden of M/XDR-TB in the Region, an overview was provided on reaching the targets and indicators of the Consolidated Action Plan in the Member States.

Of 18 high-priority countries, only the Baltic states and Kazakhstan have reached the target of an MDR-TB detection rate of at least 85%. The data show that there are still great differences between the countries in the eastern and western parts of the Region, both in laboratory capacity and availability of services in the region and the level of laboratory confirmation of TB. For example, in the non-EU countries, the availability of culture, drug susceptibility testing and rapid diagnosis tests and cases is much lower than in EU countries. Looking at countries reporting on laboratory practices and external quality assurance, the 18 high-priority countries are, however, doing well and have the highest reporting level in the Region. Huge steps have also been taken in
national and international external quality control of microscopy, with great improvement during the past few years. In addition, the quality of lower-level laboratories in drug susceptibility testing in 2012 (57%) has improved compared with 2010 (29%) and 2011 (44%).

During the presentation, the participants were asked to indicate whether they had a TB laboratory development plan in place in 2013. Nine countries reported positively on this. Nevertheless, many countries have a general strategic plan that covers components of TB laboratory services as well. For quality assurance schemes and minimum biosafety in place most countries indicated positively on this.

The suggested next steps for ELI include: (i) developing guidance on new diagnostic algorithms; (ii) scaling up rapid new diagnostic tools to detect MDR-TB; and (iii) strengthening laboratory capacity to detect XDR-TB.

Country experiences with a TB laboratory development plan

Seven countries (Armenia, Azerbaijan, Georgia, Kyrgyzstan, Russian Federation, Serbia and Tajikistan) presented their experiences with national TB development plans. Common experiences and topics discussed among the participants were:

- successful reorganization of the laboratory networks towards centralizing laboratory TB services;
- problems associated with the transport system for sputum specimens, causing delay in diagnosis and contamination;
- human resource problems, exemplified by a profound lack of qualified personnel, both for maintaining new equipment but also general laboratory personnel, which is related both to lack of motivation and training offered to current staff and challenges in making policy-makers understand the importance of budgeting for TB laboratory personnel and services;
- experiences and challenges in developing national diagnostic algorithms; and
- discussion among the participants about the level at which rapid diagnostic tests (such as Xpert MTB/RIF) are needed compared with the availability of other tests.

Armenia

Armenia has optimized its laboratory network since 2010. The optimization process includes establishing regional laboratories, improving the sputum transport mechanism to the national reference laboratory and reducing the number of peripheral microscopy laboratories. In 2012, a laboratory supervisory group was founded and a new monitoring and evaluation database was developed, including questions on activities performed by supervisory laboratory staff. From 2013, the national reference laboratory has performed quarterly monitoring and external quality assurance of peripheral and regional TB laboratories in Armenia. In 2013, Xpert MTB/RIF was implemented at the national reference laboratory and at TB dispensaries at the regional level. Implementation at the national HIV prevention centre is in progress. A laboratory diagnosis algorithm is under development as well as the introduction of an advanced electronic database programme for laboratory data management. Strengthening initiatives include: procurement support services (voluntary pooled procurement); further changes in the sputum transport system; organized maintenance for biosafety cabinets in the national reference laboratory and the City TB Dispensary; and a second mycobacteria growth indication tube system and the Epicenter software implemented at the national reference laboratory. Feedback of laboratory results is
being implemented. The plans for 2014 include implementing a polymerase chain reaction method for diagnosing nontuberculous mycobacteria, Xpert MTB/RIF for extrapulmonary TB cases and drug susceptibility testing for pyrazinamide in the mycobacteria growth indication tube system. In addition, training for sputum microscopy laboratory specialists is planned as well as renovation of the national reference laboratory, continuing the renovation of sputum microscopy laboratories and sputum collection points and creating regional pharmacy centres.

**Azerbaijan**

A major problem in Azerbaijan’s TB laboratory services is related to human resources. There is a shortage of both specialists for maintaining laboratory equipment and general workforce capacity. Qualified personnel leave the field, and finding and training appropriate replacements is difficult. Another problem is the lack of a common work algorithm and standardization of diagnostic test methods in level II laboratories. For regional laboratories, it is not possible to implement a unique algorithm since not all laboratories have GeneXpert. Finally, experience shows difficulties with sputum collection and filling in the request forms for the sputum examination. Proposed solutions include introducing new technologies and training for regional laboratories; continued support from WHO and supranational reference laboratory experts; improved quality control, effective and systematic monitoring of level I and II laboratories; formal feedback between laboratories and introduction of a common electronic database; adaptation and approval of standard operating procedures for level I and II laboratories; and training personnel (TB specialists and laboratory technicians) on a new work algorithm.

**Georgia**

Georgia has set four goals for its TB laboratory network. These include:

- improving TB laboratory diagnostics by introducing modern test methods;
- ensuring the accomplishment of the main task of TB diagnosis and treatment;
- ensuring timely and adequate treatment by providing high-quality and timely diagnostics; and
- establishing a laboratory infrastructure in accordance with WHO’s biosafety standards.

The planned activities include introducing four GeneXpert MTB/RIF systems in 2013 and an additional 12 in 2014 in all level I laboratories. Because of the malfunctioning transport system, Georgia has started a pilot project in two regions to use the postal services for transporting sputum specimens. The first preliminary results show improvement in culture growth rate because of faster delivery. It is planned to continue the pilot project. Objectives for the future include increasing the number of detected and treated cases of TB and MDR-TB; renovating and upgrading the national reference laboratory for the use of new diagnostic methods; introducing GeneXpert; providing technical support for ensuring the correct and adequate use of the diagnostic tools; providing training; and improving the biosafety system.

**Kyrgyzstan**

Kyrgyzstan’s national plan for developing TB laboratory services is a part of the National TB Programme IV, a component of the National Consolidated M/XDR-TB Action Plan and will also be a part of the national plan for optimizing laboratory services. In recent years, reviews of laboratory services have been conducted as well as an anti-TB drug resistance survey. In 2012, Xpert MTB/RIF was implemented, and guidelines have been developed for managing and maintaining laboratory equipment and a quality management system in TB laboratories. Finally,
a biosafety level III national reference laboratory has been constructed with support from the German Development Bank (KfW). Future activities include reorganizing the laboratory network, with increased centralization. In addition, an analysis of the current and future human resources situation is planned, including developing measures for improving the motivation of employees. Other challenges that need to be addressed are maintaining laboratory equipment (especially for the new biosafety level III laboratory), transport and logistics. Finally, issues around supply, reporting and recording and securing future funding need to be addressed.

**Russian Federation**

Key components of the development plan for TB laboratory services in the Russian Federation include implementing standard algorithms and schemes of examinations for diagnosis and control, improving laboratory documentation and standardizing accounting and reporting forms. In accordance with other countries in the Region, there is a need to strengthen the human resource capacity of laboratories, including creating standards for the workload of staff members and reviewing the staffing of laboratories to meet modern standards of working time and increasing knowledge of laboratory personnel in laboratory biosafety to improve infection control measures.

**Serbia**

A major activity of the TB laboratory network in Serbia has been centralizing TB laboratory services by reducing the number of laboratories. Despite a reduction in the number of TB cases in Serbia, the number of specimens has not fallen at an equal rate. The country has a unified recording and reporting system, and national guidelines are available on biosafety. The rapid diagnosis of TB in Serbia is based on an automated liquid culture system (BACTEC mycobacteria growth indication tube and BacT/Alert) and line probe assay.

**Tajikistan**

Tajikistan conducted a drug resistance survey in two regions, which gave rise to a pilot project with a treatment scheme of people with MDR-TB. The project has been expanded to include more regions during the past five years. As part of Project HOPE, rapid diagnostic tests have been introduced with the purchase of polymerase chain reaction and GeneXpert and training of laboratory specialists. In addition, standard operating procedures have been developed as well as diagnostic algorithms, laboratory forms and a log register for culture laboratories. Guidelines were developed and launched as part of the pilot implementation of quality management systems for laboratories. Finally, a study on external quality assurance was implemented.

**Country experiences with surveys and scaling up rapid M/ XDR-TB diagnostics**

**Armenia: scaling up rapid diagnostics**

In Armenia, culture is the gold standard for diagnosing TB, and other methods are considered and interpreted as complementary diagnostic methods. Communication between clinicians and microbiologists is imperative. The future of TB diagnosis is the application of new molecular techniques, but more accurate evaluation of these tests is still required. Molecular detection of rifampicin and isoniazid works well, but phenotypic resistance is still needed for confirming resistance to first-line drugs and second-line drugs. The Xpert MTB/RIF assay is highly promising, but how it will influence the diagnosis algorithm is still unclear. Molecular typing is needed to investigate nosocomial infection and the spread of TB among contacts.
**Azerbaijan: anti-TB drug resistance survey**

Azerbaijan conducted a second drug resistance survey in 2012–2013. Experiences from the first drug resistance survey (2005–2007) had revealed difficulties with case definition for clinicians at inpatient facilities and problems with the timely delivery of specimens for shipment (resulting in a high level of contamination). These experiences were taken into account in planning the second drug resistance survey. Thus, training was provided to physicians and laboratory specialists in case definition, and a sputum transport system was developed with special training of drivers. In addition, mechanisms of work supervision (questionnaires, logbooks and supervisory visits) were developed to confirm that all data were recorded. Challenges encountered included incorrect identification of patients’ type and errors in filling in the registry forms. Duplication of sputum samples was an additional problem as well as an unexpectedly high workload for the laboratory. Preliminary results based on national reference laboratory data shows a culture positivity rate of 53% and a contamination rate of less than 1%, but based on the aggregated laboratory data, it is about 10%. Issues to be resolved include methods to confirm TB early in the process; the concordance of the drug susceptibility testing results at the national reference laboratory and supranational reference laboratory; developing a national reference laboratory work algorithm; and continuing drug resistance surveillance.

**Latvia: early diagnostics algorithm for MDR-TB**

In Latvia, the Xpert MTB/RIF assay is available at the national level (Centre for Tuberculosis and Lung Diseases), while regional levels offer culture laboratories and microscopy centres. A TB laboratory diagnosis algorithm has been developed and implemented. The specimens of everyone suspected of having TB are tested by microscopy and culture on solid media. When the culture is positive, drug susceptibility testing is performed for first-line drugs. If MDR is detected, drug susceptibility testing is also performed for second-line drugs. For people with a higher risk of MDR-TB (relapses, re-treatment or MDR-TB contacts) whose microscopy is positive, a line probe assay is used to detect mutations associated with resistance to rifampicin and isoniazid within the first days of admission to the Centre for Tuberculosis and Lung Diseases. If MDR-TB is suspected, drug susceptibility testing for first- and second-line drugs is performed on a mycobacteria growth indication tube when the culture is positive. The experience so far is that early molecular TB diagnosis methods have: (i) reduced the duration of TB and MDR-TB diagnosis; (ii) improved the treatment results of people with MDR-T; (iii) reduced intrahospital MDR-TB transmission; and (iv) reduced treatment costs for TB.

**Republic of Moldova: scaling up rapid diagnostics**

The Republic of Moldova is one of the countries with the highest burden of MDR-TB. Despite a well-developed TB laboratory network and universal coverage of culture and drug susceptibility testing, the Republic of Moldova still experiences substantial delays in full diagnosis and in initiation of correct treatment. A priority has been rapid implementation of the Xpert MTB/RIF assay at the peripheral (district) level. It is now available in civilian TB services, in penitentiary institutions and in AIDS centres. So far, experiences have shown that Xpert MTB/RIF is a precise and reliable technology that is fully relevant to the country context and that it has been a big step forward in timely diagnosis and treatment. However, substantial lead time is required to start (logistics), taking into account the number and specifics of project sites. A problem at the initial stages has been slow uptake of the new technology by clinical staff at all level. Currently, however, there is full acceptance and use of the technology, and the productivity has reached the set targets. Future challenges include securing continued funding for these expensive methods,
continued implementation, ensuring appropriate application of the new diagnostic algorithm and alignment with treatment pathways at all levels and changes in the model of care delivery.

**Romania: scaling up rapid diagnostics**

Molecular testing is being implemented in Romania. Two line probe assay systems have been implemented at the national reference laboratory, and training was conducted. In addition, manuals for drug resistance TB case management and manuals for rapid tests for MDR-TB case detection and diagnosis (standard operating procedures and forms) have been developed and distributed. Despite progress, much remains to be done. There is a need to reorganize and centralize the laboratory services; reorganize the transport system for specimens; continue training of staff; and sustain national reference laboratory and regional reference laboratories with equipment and supply for rapid tests (including mycobacteria growth indication tubes). In addition, ensuring quality assurance for the tests performed, including line probe assays and acquisition of two Xpert RIF/TB systems in 2014 and maintaining the accreditation of TB laboratories, are necessary next steps.

**Russian Federation: performance of the Xpert MTB/ RIF test**

The results of testing unconcentrated and concentrated portions of the same sputum specimen with the Xpert MTB/RIF assay were compared with results from conventional smear, culture and drug susceptibility testing. In a setting with a high prevalence of MDR-TB, the Xpert test reliably detected 95% of TB cases, including 51% smear-negative cases, and identified 94% of MDR-TB cases within hours of specimen collection.

**Tajikistan: anti-TB drug resistance survey**

The results of the second drug resistance survey conducted were presented. Challenges encountered during the survey included problems with registering people with TB; problems with specimen transport; the cultures of samples; and international transport of cultures.

The survey revealed a high level of MDR-TB. A high level of drug resistance was detected for all first-line drugs, with 17.5% among new cases and 57.2% MDR among previously treated cases, respectively. The level of resistance to second-line drugs was also high, with the highest levels being kanamycin (23.4%) and ciprofloxacin (21.3%). XDR-TB was detected among 15.3% of previously treated people with TB and 2.6% of new cases.

**Country experiences with implementing quality management in laboratories**

**Kazakhstan: blinded rechecking of acid-fast bacillus smear microscopy**

Since 2006 a pilot project of the United States Agency for International Development on blinded rechecking of slides based on lot quality assessment sampling has been implemented in a pilot region of Kazakhstan. One of the objectives was to determine an optimum sample size that allows statistically acceptable samples, to assess the quality of work by the laboratory technicians. The project showed that reducing the sample size leads to significant time saving and to increased motivation and performance of staff. Implementing the blinded rechecking method reduced the workload at higher-level laboratories and provided additional information on smear quality. In addition, good practical training of laboratory staff was essential to overcome difficulties related to the shift to the new external quality assurance method.
Optimal results in quality improvement could be achieved by regularly analysing the rechecking of results and feedback provided to laboratories. Based on the experiences from the pilot project, the National TB Programme has decided to expand the blinded method of external quality assurance to the whole country.

**Tajikistan: implementing a quality management system**

As part of the Quality Health Care Project of the United States Agency for International Development, laboratory services in Tajikistan have been strengthened. The strategic approach in implementing a laboratory quality management system included situation analysis; selection of a pilot site; quality management system training; development of quality management system guidelines and monitoring and evaluation tools; and technical support for the implementation process. In addition, a quality management system e-tool is being developed.

**Laboratory component of a quality management system of TB screening in migrants**

The International Organization for Migration (IOM) shared experiences with managing the quality of TB screening in migrants. The aim of the IOM is to provide quality control and quality assurance of outsourced laboratories to ensure that the quality standards of laboratory services are in accordance with the requirements of the destination country. IOM services in TB diagnosis include identifying people suspected of having TB based on abnormalities detected during physical and X-ray examinations, sputum collection for smear microscopy and culture tests and identification and drug susceptibility testing of culture-positive specimens. Based on their experiences, the potential benefits of a quality management system include:

- improved laboratory performance, with enhancement of all procedures and increased consistency of laboratory tests;
- improved record keeping and data collection, leading to increased ability to identify efficiency through data analysis;
- increased accountability through compliance with internationally recognized standards;
- strengthened structure of TB laboratory services; and
- closer integration within the collaboration between the IOM and the Central TB Research Institute and with partners.

**The way forward for implementing the Consolidated Action Plan**

The participants split into two working groups to discuss the way forward for implementing the Consolidated Action Plan. The results of the two groups’ work was then presented and discussed in plenary.

**Working group on diagnostic algorithms**

The working group had extensive discussions on developing a model diagnostic algorithm. Based on algorithms already in use in countries in the Region, the group did, however, reach agreement on the components of a standard algorithm to be applied for modern laboratory diagnosis of TB, including selection criteria for the individuals to be tested, for different settings in the Region.
It was, however, also agreed that a standard algorithm must vary according to whether the
country is a high-priority country or has a high prevalence of MDR-TB, a high-priority country
without a high prevalence of MDR-TB or a country in western Europe. In addition, the algorithm
will vary depending on the level of laboratory at which it is to be applied (low level, intermediate
level and national reference laboratory).

**Working group on scaling up rapid M/XDR-TB detection**

The working group focused their discussion on identifying challenges in scaling up rapid
M/XDR-TB detection and ways to address them.

The challenges include the following:

- discordance between line probe assay, Xpert and drug susceptibility testing;
- cultures;
- invalid results;
- shortage of GeneXpert cartridges;
- false-positive rifampicin resistance in the line probe assay;
- link between laboratory results and change in treatment;
- reorganization of the laboratory network;
- official recognition of regional laboratories;
- transport of samples;
- sustainability of supplies;
- funding limitations;
- in-country validation of new test;
- cost-efficiency of tests;
- technical assistance and maintenance of equipment;
- external quality assurance of Xpert MTB/RIF;
- availability of drugs for detected cases and infection control;
- mycobacteria growth indication tube does not detect all resistance;
- added new drugs in cartridge;
- higher rates of discrepancies between molecular and conventional drug susceptibility
testing (and other tests) reported suggests limitation of the tests, insufficient quality of drug
susceptibility testing and/or insufficient quality of the quality management system in
laboratories; and
- human resources: increased knowledge needed and increased human resources capacity.

The way forward includes:

- implementation following a systematic approach (for example, TB care eight-step plan)
  and with the support of the health ministry and national TB programme;
- TB and HIV integration: ensure rapid tests for people living with HIV and vice versa;
• training of national TB programme and clinicians together with laboratory specialists;
• increasing complexity of laboratory tests requires increased knowledge and thus training of laboratory staff;
• clear standard operating procedures and guidance on test discordance (guidance from the KNCV Tuberculosis Foundation in collaboration with WHO – March 2014 evaluated);
• strengthen the capacity of external quality assurance for drug susceptibility testing;
• following new case definitions – improve country reporting;
• strengthen the quality management system in laboratories;
• for external quality assurance of Xpert: inactivated bacteria suspension in artificial sputum;
• customs clearance;
• continued support of supranational reference laboratories to confirm discrepant results and/or to implement rapid methods in national reference laboratories so they can confirm;
• standardized monitoring tool for reporting (preferably to WHO) to harmonize reporting on molecular tools and avoid double reporting on results; and
• continue to advocate financial support at higher levels for laboratory diagnosis of TB.
Annex 1

PROGRAMME

Monday, 7 October 2013

Session 1: Introduction and M/XDR-TB in the European Region  
Chairperson: Kristin Kremer

09:00–09:20 Opening and welcome  
Guénaël Rodier, Masoud Dara

09:20–10:00 M/XDR-TB in the WHO European Region  
Andrei Dadu

10:00–10:30 Anti-TB drug resistance survey in Azerbaijan  
Natavan Alikhanova

Session 2: Genetic characterization of M/XDR-TB in the European Region  
Chairperson: Larisa Chernousova

11:00–11:30 Origin, emergence and current spread of a successful  
Russian TB clone  
Igor Mokrousov

11:30–11:50 Nosocomial transmission of MDR-TB demonstrated by  
DNA fingerprinting  
Elena Romancenco

11:50–12:20 M. tuberculosis rpoB gene variability in central Asia and  
its correlation with rifampicin resistance phenotypes  
Evgeni Sahalchyk

Session 3: Molecular diagnostics for M/XDR-T  
Chairperson: Diego Zallocco

13:30–14:15 Recent developments in the molecular diagnosis of  
MDR-TB by using the Xpert MTB/RIF assay  
Alexei Korobitsyn

14:15–15:00 Line probe assays for the detection of anti-TB drug  
resistance and restrictions of line probe assays for the  
prediction of second-line drug resistance  
Sabine Rüsch-Gerdes

Session 4: TB laboratory strengthening  
Chairperson: Andrei Dadu

15:30–16:15 New biosafety guidelines  
Diego Zallocco

16:15–17:00 Management of a TB laboratory network  
Alexei Korobitsyn

17:00–17:30 Update on the Global Fund’s new funding mechanism  
and how this could support TB laboratory strengthening  
Martin van den Boom

Tuesday, 8 October 2013

Session 5: Progress towards the implementation of the Consolidated Action Plan  
Chairpersons: Marija Joncevska and Sabine Rüsch-Gerdes

09:00–09:30 Progress towards the implementation of the laboratory  
components of the Consolidated Action Plan to Prevent  
and Combat Multidrug- and Extensively Drug-Resistant  
Tuberculosis (M/XDR-TB) in the WHO European  
Region 2011–2015 and update on ELI activities  
Kristin Kremer
09:30–11:00 Country experiences on the development of a TB laboratory development plan (10-minute presentations)
- TB laboratory network in Armenia
  Hasmik Margaryan
- Azerbaijan: challenges and next steps in the laboratory
  Mehriban Seyfaddinova
- TB laboratory network in Georgia
  Rusudan Aspindzelashvili
- Kyrgyzstan: development of the national TB plan
  Gulmira Kalmambetova
- Perspective plan for the laboratory services for TB diagnosis in the Russian Federation
  Larisa Chernousova
- TB laboratory network plan and action plan for Serbia
  Branislava Savic
- Experiences and problems in the laboratory services in Tajikistan
  Guljamol Kasymova

11:30–13:00 Country experiences with the scale-up of rapid M/XDR-TB diagnostics (10-minute presentations)
- Moldovan experiences with the scaling up of rapid M/XDR-TB diagnostics
  Elena Romancenco
- Experience of Romania in scaling up rapid M/XDR-TB diagnostics
  Daniela Homorodean
- MDR-TB: early diagnostics in Latvia
  Andra Cirule
- Performance of the Xpert MTB/RIF test for detection of M. tuberculosis and rifampicin resistance in sputum specimens in two regions of the Russian Federation
  Larisa Chernousova
- Armenian experiences with the rapid M/XDR-TB diagnostics test
  Hasmik Margaryan
- Anti-TB drug resistance survey in Tajikistan
  Farangiz Mirzoeva

13:45–14:30 Country experiences with implementing quality management in laboratories
- Implementation of a quality management system in the TB laboratory network in Tajikistan
  Marija Joncevska
- Blinded rechecking of acid-fast bacillus smear microscopy in primary health care laboratories in Kazakhstan
  Bekzat Toxanbayeva
- Laboratory component of quality management of International Organization for Migration TB screening in migrants
  Olga Irtouganova

Session 6: The way forward for implementing the Consolidated Action Plan
Chairperson: Kristin Kreme
14:30–15:30 Working group discussions
16:00–16:45 Feedback to plenary on the working group discussions
16:45–17:00 Closing
17:00–18:00 ELI Core Group meeting
Annex 2

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