GLI Practical Guide to TB Laboratory Strengthening

gli
global laboratory initiative
advancing TB diagnosis

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Contents

Acknowledgments

Abbreviations

AFB	Acid-fast bacilli
APHL	Association of Public Health Laboratories
ASLM	African Society for Laboratory Medicine
BSC	Biosafety cabinet
CLSI	Clinical & Laboratory Standards Institute
CSF	Cerebrospinal fluid
DST	Drug-susceptibility testing
EQA	External quality assessment
FL-LPA	Line probe assay for first-line drugs
FM	Fluorescence microscopy
FQ	Fluoroquinolone
GLI	Global Laboratory Initiative
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
HIV	Human immunodeficiency virus
INH	Isoniazid
ISO	International Organization for Standardization
IUALTD	International Union against Tuberculosis and Lung Disease
LAMP	Loop-mediated isothermal amplification
LED	Light-emitting diode
LF-LAM	Lateral flow lipoarabinomannan assay
LIMS	Laboratory information management system
LPA	Line probe assay
MDR-TB	Multidrug-resistant tuberculosis
MODS	Microscopic observation for drug susceptibility
MoH	Ministry of Health
MTB	*Mycobacterium tuberculosis* complex bacteria
NRA	Nitrate reductase assay
NSP	National strategic plan
NRL	National Tuberculosis Reference Laboratory
NTM	Non-tuberculous mycobacteria
NTP	National tuberculosis programme
PCR	Polymerase chain reaction
PLHIV	People living with HIV/AIDS
PT	Proficiency testing
QA	Quality assurance
QC	Quality control
QI	Quality improvement
QMS	Quality management system
QSE	Quality system essential
RIF	Rifampicin
RR-TB	Rifampicin-resistant TB
SLID	Second-line injectable drug
SLIPTA	Stepwise Laboratory Improvement Process Towards Accreditation
SL-LPA	Line probe assay for second-line drugs
SLMTA	Strengthening Laboratory Management Towards Accreditation
SOPs	Standard operating procedures
SRL	WHO TB Supranational Reference Laboratory
TB	Tuberculosis
WHO	World Health Organization
WRD	WHO-recommended rapid TB diagnostic
XDR-TB	Extensively drug-resistant tuberculosis

About the Global Laboratory Initiative

The Global Laboratory Initiative (GLI) is a network of international partners dedicated to accelerating and expanding access to quality assured tuberculosis (TB) laboratory services. GLI has been a Working Group of the Stop TB Partnership since 2007.

Coordinated by its core group with support from a secretariat at the World Health Organization (WHO) Global TB Programme, the mission of GLI is to serve as a collaborative platform for the development and uptake of practical guidance and tools for building and sustaining high-quality TB diagnostic networks, in the areas of:

- Implementation of WHO policy guidance on TB diagnostics and laboratory strengthening
- Health system solutions and innovations for ensuring rapid, accurate testing and linkage to appropriate patient management
- Continuous quality improvement at all levels of the laboratory network
- Integration of laboratory diagnostic networks
- Human resource capacity development
- Advocacy and resource mobilization

The GLI core group has representation from key constituencies including national and supranational reference laboratories, high TB and multidrug-resistant TB (MDR-TB) burden country programmes, technical partners, donors and civil society. For more information about GLI, visit its website at: www.stoptb.org/wg/gli or contact the secretariat at: gli_secretariat@who.int.

Purpose of the guide

This guide has been developed to provide practical guidance on implementation of WHO recommendations and international best practices for TB laboratory strengthening. The intended audience incudes TB laboratory managers and technicians, programme managers and other officials from Ministries of Health (MoHs), and their partners. Because an important function of GLI is the harmonization of technical assistance provided to TB laboratories by its many partners, providers of technical assistance may also use the guide as a reference for available resources and tools; the final chapter includes guidance specific for consultants before, during and after a mission.

The *GLI Practical Guide to TB Laboratory Strengthening* is available online at http://stoptb.org/wg/gli/gat.asp. Given the guide is not intended to be a comprehensive manual or to repeat information provided by other guidance documents, it contains hyperlinks to cited resources. Because many of these resources may be revised from time to time, the reader is advised to refer to the GLI or other websites where the latest versions of these resources will be available.

The most up-to-date WHO policy guidance on TB diagnostics and laboratory strengthening can be found on the WHO Global TB Programme website at http://www.who.int/tb/areas-of-work/laboratory/diagnostics.

Summary of changes in this update

Since publication of the first edition of this guide in November 2015, WHO has approved or updated guidance on several diagnostic tests for TB — specifically the loop-mediated isothermal amplification (TB-LAMP) test, line probe assays for first-line drugs (FL-LPA), LPA for second-line drugs (SL-LPA), and the lateral flow urine lipoarabinomannan (LF-LAM) assay. In addition, the End TB Strategy was adopted and a WHO *Framework of indicators and targets for laboratory strengthening under the End TB Strategy* developed. In this second edition, the guide has been updated to:

- Incorporate the goals of the End TB strategy and describe the new WHO indicators and targets for laboratory strengthening

- Incorporate the recent WHO recommendations for tests to detect *Mycobacterium tuberculosis* complex bacteria (MTB) including TB-LAMP and LF-LAM, and to detect drug resistance including FL-LPA and SL-LPA

- Describe recent advances in diagnostics connectivity solutions

- Describe the need to strengthen the entire diagnostic cascade including strengthening of pre-analytic and post-analytic laboratory testing steps as well as the clinical-laboratory interface

1. Background

1.1 WHO-recommended tests for detecting MTB and drug resistance

For decades, resource-constrained countries have relied on sputum smear microscopy as the primary method for detecting MTB. While inexpensive and requiring minimal biosafety precautions, microscopy is not a sensitive test particularly for people living with HIV/AIDS (PLHIV) and for children, and it provides no information on the drug resistance profile of the bacilli. Furthermore, microscopy is not able to distinguish between MTB and non-tuberculous mycobacteria (NTM). Bacteriological culture is considered the reference standard for detecting MTB, but suffers from the disadvantages that results take weeks to obtain and that testing requires a well-equipped laboratory, highly trained staff, and an efficient transport system to ensure specimens with viable bacteria. Phenotypic drug-susceptibility testing (DST) on cultured specimens is the conventional method used to detect resistance to first- and second-line TB drugs, and faster commercial liquid culture systems are now available. Building adequate culture capacity in many countries with a high burden of TB has been slow, given the cost and infrastructure requirements.

In recent years, rapid and sensitive tests based on molecular methods, including Xpert® MTB/RIF (Cepheid, Sunnyvale USA), TB-LAMP (Eiken Chemical, Tokyo Japan), and line probe assays, have become available to replace or complement existing conventional tests. A point-of-care rapid test using urine, LF-LAM, is now also available to assist with the diagnosis of TB among PLHIV who are seriously ill. Despite the advantages of these newer tests, conventional microscopy and culture remain necessary for monitoring the response of a patient to treatment. Conventional culture and DST is also needed to address gaps in the approved rapid test repertoire including DST for many important TB drugs, such as pyrazinamide, bedaquiline and delamanid, as well as for testing of a full-range of respiratory and non-respiratory specimens.

WHO's global strategy for TB prevention, care and control for 2015–2035 (known as the End TB Strategy) calls for the early diagnosis of TB and universal DST. The End TB Strategy highlights the critical role of laboratories in the post-2015 era and emphasizes that in order to meet the End TB Strategy targets, WHO-recommended rapid TB diagnostics (WRDs) should be available to all persons with signs or symptoms of TB, all bacteriologically confirmed TB patients should receive DST at least for rifampicin, and all patients with rifampicin-resistant TB should receive DST at least for fluoroquinolones (FQs) and second-line injectable drugs (SLIDs). Therefore all national TB control programmes (NTPs) need to prioritize the development of a network of TB laboratories that use modern diagnostics, have efficient referral systems, use standard

operating procedures (SOPs) and appropriate quality assurance (QA) processes, and have adequate biosafety and sufficient human resources. These priorities should be comprehensively addressed in national strategic plans and adequately funded.

WHO, in collaboration with GLI, has developed indicators and targets to assess a country's progress toward reaching the laboratory strengthening goals of the End TB Strategy (increase access to rapid and accurate detection of TB; reach universal access to DST; strengthen quality of laboratory services). To meet these goals, WHO recommends using modern methods, particularly more rapid and sensitive diagnostic methods that provide information on drug resistance in addition to detecting MTB, e.g., the Xpert MTB/RIF assay. Making the change to using such techniques requires a large-scale effort coordinated by MoHs and supported by local and international partner organizations.

Since 2007, WHO has issued recommendations on a wide range of tests including commercial liquid culture and DST systems, LED fluorescence microscopy, LPAs for first-line drugs, rapid TB identification tests, the Xpert MTB/RIF assay, the TB-LAMP test, the second-line LPA, and the LF-LAM assay, as well as updated guidance on first-line LPAs. Table 1 presents a summary of WHO-recommended methods for detecting MTB and drug resistance.

The following tests were evaluated but not recommended by WHO due to insufficient evidence to support the proposed uses:

- Sputum concentration and decontamination methods for AFB smear examinations

- Phage plaque method for rapid detection of rifampicin resistance

- Thin layer agar methods for rapid culture and DST

- Interferon γ release assays (IGRAs) to replace tuberculin skin testing for detecting latent TB in low-income and middle-income countries

The following tests were evaluated and recommended NOT to be used in low- and middle-income settings:

- Commercial sero-diagnostic tests for TB

- IGRAs for detecting active TB in all settings. The use of IGRAs to detect latent infection is discussed in the Policy on the *Use of tuberculosis interferon-gamma release assays (IGRAs) in low- and middle-income countries*.

In accordance with current WHO standards for evidence assessment in the formulation of policy recommendations on TB diagnostics, WHO engages in a systematic, transparent process using the GRADE approach. GRADE provides a structured framework for evaluating diagnostic test accuracy and patient and public health impact of new diagnostic tests. For more information, see the WHO *Implementing tuberculosis diagnostics: A policy framework*.
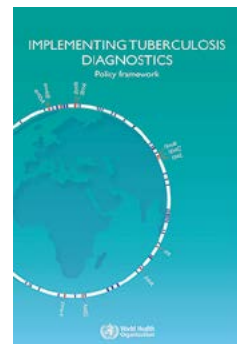
Table 1 Summary of WHO-recommended methods and their turnaround times[a]

TEST OR PROCEDURE	DESCRIPTION	LABORATORY TURNAROUND TIME[b]	COMMENTS
Smear microscopy	Conventional light microscopy with Ziehl–Neelsen staining	24 hours	Less sensitive than fluorescence microscopy.
	Conventional fluorescence microscopy (using mercury vapour lamps)		Requires a quartz halogen or mercury vapour lamp. Microscopes are expensive. Requires a dark room.
	LED fluorescence microscopy		LED microscopy is about 10% more sensitive and the observation time is significantly shorter than for conventional light microscopy. LED conversion kits for light microscopes are available. A dark room is not needed. LED fluorescence microscopy should be introduced using a phased-in approach and eventually replace examination of Ziehl–Neelsen stained smears by light microscopy. Direct smear microscopy may be done in a low-risk level TB laboratory (Table 14). The processing of samples for concentrated smear microscopy should be done in a moderate risk-level TB laboratory (Table 14).
Culture using solid media	Löwenstein–Jensen medium	3 weeks on average for smear-positive samples 4–8 weeks on average for smear-negative samples	Egg-based medium. Acceptable level of contamination 3–5%. Processing of samples for inoculating cultures should be done in a moderate risk-level TB laboratory (Table 14).
	Middlebrook 7H10 or 7H11 media		Agar-based medium. Acceptable level of contamination 3–5%. Processing of samples for inoculating cultures should be done in a moderate risk-level TB laboratory (Table 14).
Culture using liquid media	Commercial and non-commercial test systems[c]	8–10 days for smear-positive samples 2–6 weeks for smear-negative samples	Liquid TB culture methods are susceptible to contamination. Acceptable level of contamination 8–10%. Processing of samples for inoculating cultures should be done in a moderate risk-level TB laboratory (Table 14). A commercial example of an automated TB culture system is the BACTEC™ MGIT™ 960 TB System (Becton Dickinson Microbiology Systems, Sparks, USA).

TEST OR PROCEDURE	DESCRIPTION	LABORATORY TURNAROUND TIME[b]	COMMENTS
Immunochroma-tographic assay for rapid species identification	Commercial test systems to be performed on bacteria recovered from solid or liquid cultures	15 minutes (testing time)	Rapid identification of MTB isolated from solid or liquid cultures. Because of the need to process cultures, testing should be done in a high risk-level TB laboratory (Table 14). Commercial examples of this test include: • Capilia TB-Neo® (Tauns Laboratories, Numazu, Japan) • TB Ag MPT64 Rapid Test© (SD Bioline, Kyonggi-do, South Korea) • TBcID© (Becton Dickinson Microbiology Systems, Sparks, USA)
Phenotypic DST using solid media – 1st line	Löwenstein–Jensen or Middlebrook 7H10 or 7H11 media	3–4 weeks from positive culture (indirect DST)	Capacity to perform DST at least to rifampicin and isoniazid is needed. Recommended critical concentrations are found in the critical concentration table.[c]
Phenotypic DST using liquid media – 1st line	Commercial and non-commercial test systems[d]	1–3 weeks from positive culture (indirect DST)	Because of the need to process cultures, testing should be done in a high risk-level TB laboratory (Table 14).
Phenotypic DST using solid media – 2nd line	Löwenstein–Jensen or Middlebrook 7H10 or 7H11 media	3–4 weeks from positive culture (indirect DST)	Capacity to perform DST at least to a second-line injectable drug (SLID) and a fluoroquinolone (FQ) is needed.[e] Recommended critical concentrations are found in the critical concentration table.[c]
Phenotypic DST using liquid media – 2nd line	Commercial and non-commercial test systems[d]	1–3 weeks from positive culture (indirect DST)	Because of the need to process cultures, testing should be done in a high risk-level TB laboratory (Table 14).
Molecular testing	Xpert MTB/RIF assay Detects MTB and assesses resistance to rifampicin using real-time PCR	2 hours (testing time)	The Xpert MTB/RIF assay is suitable for all levels of the health system, although certain operational requirements apply, such as uninterrupted power supply and temperature controlled setting. Acceptable level of errors <3%. This test may be used rather than conventional microscopy and culture as the initial diagnostic test in all adults and children being evaluated for pulmonary TB. As a priority, the test should be used as the initial diagnostic test for in adults and children being evaluated for MDR-TB or HIV-associated TB.

TEST OR PROCEDURE	DESCRIPTION	LABORATORY TURNAROUND TIME[b]	COMMENTS
Molecular testing *(continued)*	Xpert MTB/RIF assay *(continued)*		The test should be used in preference to microscopy and culture as the initial diagnostic test using cerebrospinal fluid (CSF) specimens from patients being evaluated for TB meningitis, and may be used as a replacement test for usual practice (including microscopy, culture or histopathology) for testing specific non-respiratory specimens (lymph nodes and other tissues) from patients being evaluated for extrapulmonary TB.
			The test is suitable for use in a peripheral health centre level where microscopy is performed, given similar biosafety requirements (e.g., low risk, Table 14).
			The Xpert MTB/RIF® assay is commercially available (Cepheid, Sunnyvale, USA).
	First-line line probe assay (FL-LPA) Detects MTB and assesses resistance to rifampicin and isoniazid DNA targets are amplified by PCR and hybridized to immobilized oligonucleotide targets; results can be read visually or using an automated reader	1–2 days (testing time). Batching of samples may increase turnaround time	FL-LPA is suitable for use on culture isolates and AFB smear-positive sputum specimens
			Commercial FL-LPAs may be used as the initial test, instead of phenotypic culture-based DST, to detect resistance to rifampicin and isoniazid.
			Because of the need to process samples, direct testing of AFB smear-positive sputum specimens should be done in a moderate risk-level TB laboratory and testing of cultures done in a high risk-level TB laboratory (Table 14).
			Commercial examples of this test are the GenoType® MTBDRplus (Hain Lifescience, Nehren, Germany) and the NTM+MDRTB Detection Kit (NIPRO Corporation, Osaka, Japan) tests.

TEST OR PROCEDURE	DESCRIPTION	LABORATORY TURNAROUND TIME[b]	COMMENTS
Molecular testing *(continued)*	Second-line line probe assays (SL-LPA) Detects MTB and assesses resistance to FQs and SLIDs DNA targets are amplified by PCR and hybridized to immobilized oligonucleotide targets; results can be read visually or using an automated reader	1 to 2 days	For patients with confirmed rifampicin-resistant TB (RR-TB) or MDR-TB, SL-LPA may be used as the initial test, instead of phenotypic culture-based DST, to detect resistance to FQs and the SLIDs. SL-LPA is suitable for testing of cultured isolates of MTB and direct testing of sputum specimens from RR-TB or MDR-TB patients, irrespective of the smear status. The currently commercially available SL-LPA cannot be used to identify individual drugs to be used for treatment because of incomplete cross-resistance among individual drugs. Because of the need to process samples, direct testing of sputum specimens should be done in a moderate risk-level TB laboratory and testing of cultures done in a high risk-level TB laboratory (Table 14). Additional biosafety precautions may be warranted because the samples are at high risk of containing rifampicin-resistant MTB. The commercial example of this test is the GenoType® MTBDRsl test (Hain Lifescience, Nehren, Germany).
	TB-LAMP test Detects MTB in sputum specimens; it does not assess drug resistance DNA targets are amplified using loop-mediated isothermal amplification and results read visually under ultraviolet light	1.5 hours (testing time)	The TB-LAMP test may be used as a replacement for sputum smear microscopy for the detection of MTB in adults and children being evaluated for pulmonary TB. It may also be used as a follow-on test to smear microscopy when further testing of smear-negative sputum specimens is necessary. TB-LAMP should not replace the use of rapid molecular tests that detect MTB and resistance to rifampicin (e.g., Xpert MTB/RIF) especially among populations at risk of MDR-TB when there are sufficient resources and infrastructure to support their use. The TB-LAMP test is suitable for use in a peripheral health centre level where microscopy is performed, given similar biosafety requirements (e.g., low risk, Table 14). The commercial example of this test is the Loopamp™ MTBC Detection Kit (Eiken Chemical Company Ltd., Japan).

TEST OR PROCEDURE	DESCRIPTION	LABORATORY TURNAROUND TIME[b]	COMMENTS
Rapid antigen detection tests for TB	Urine-based lateral flow lipoarabino-mannan (LF-LAM) assay Based on the detection of mycobacterial LAM antigen in urine. It does not assess drug resistance.	30 minutes	LF-LAM may be used to assist in the diagnosis of TB in HIV-positive patients with signs and symptoms of TB (pulmonary or extrapulmonary) who have a CD4 cell count less than or equal to 100 cells/µl or HIV-positive patients who are seriously ill[f] regardless of CD4 count or with unknown CD4 count. Except as described above, LF-LAM should not be used for the diagnosis of TB or as a screening test for TB. The test is suitable for use at the point-of-care and has minimal infrastructure or biosafety requirements. The commercial example of this test is the Alere Determine™ TB LAM Ag test (Alere Inc, Waltham, USA).

[a] Tests not recommended by WHO are not included in the Table.

[b] Laboratory turnaround time refers to the time taken from receipt of a specimen at the laboratory to issuing a laboratory test result. The overall turnaround time (from specimen collection to receipt of the result by the clinician) may be much longer and is dependent on a number of factors including speed of referral of specimens to the laboratory and delivery of results to the clinician.

[c] WHO issued initial policy guidance on DST to second-line drugs in 2008 (WHO/HTM/TB/2008.392; http://whqlibdoc.who.int/hq/2008/WHO_HTM_TB_2008.392_eng.pdf). In 2012, WHO convened an Expert Group to review and update the critical concentrations for both first- and second-line anti-TB drugs. WHO did not proceed with formal policy guidance recommending the revised concentrations because they were based on limited evidence, but issued interim revised critical concentrations for first-line and second-line DST. Emerging evidence suggests that the revised concentrations may require further revision.

[d] WHO has conditionally recommended selected non-commercial liquid culture systems for detecting TB and for detecting rifampicin resistance as an interim solution pending the development of genotypic or automated liquid culture and DST capacity. These methods include MODS (microscopic observation of drug susceptibility), NRA (nitrate reductase assay), and CRI (colorimetric redox indicator). They are suitable for use at central-level or reference laboratories and require highly trained personnel. However, their use is not intended to replace conventional culture and DST. Their implementation should be phased and include validation against standard methods. Scaling-up the use of CRI, NRA, and MODS and decentralizing their use to lower-level laboratories are not recommended (WHO/HTM/TB/2011.9; http://www.who.int/tb/publications/2011/mdr_tb_diagnostics_9789241501620/en/)

[e] WHO recommends second line DST for each of the SLIDs and FQs available for use in each NTP.

[f] Seriously ill is defined based on 4 danger signs: respiratory rate > 30/min, temperature > 39 °C, heart rate > 120/min or unable to walk unaided.

Suggested reading

Framework of indicators and targets for laboratory strengthening under the End TB Strategy. Geneva, World Health Organization. 2016. (WHO/HTM/TB/2016.18).
http://www.who.int/tb/publications/labindicators/en/

Implementing tuberculosis diagnostics: A policy framework. Geneva, World Health Organization. 2015. (WHO/HTM/TB/2015.11).
http://www.who.int/tb/publications/implementing_TB_diagnostics

Non-commercial culture and drug-susceptibility testing methods for screening patients at risk for multidrug-resistant tuberculosis Policy statement. Geneva, World Health Organization. 2011. (WHO/HTM/TB/2011.9).
http://www.who.int/tb/publications/2011/mdr_tb_diagnostics_9789241501620/en/

The use of lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis and screening of active tuberculosis in people living with HIV: policy guidance. Geneva, World Health Organization. 2015. (WHO/HTM/TB/2015.25).
http://www.who.int/tb/publications/use-of-lf-lam-tb-hiv

The use of loop-mediated isothermal amplification (TB-LAMP) for the diagnosis of pulmonary tuberculosis: policy guidance. Geneva, World Health Organization. 2016. (WHO/HTM/TB/2016.07).
http://www.who.int/tb/publications/lamp-diagnosis-molecular

The use of molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs: policy guidance. Geneva, World Health Organization. 2016. (WHO/HTM/TB/2016.07).
http://www.who.int/tb/publications/lpa-mdr-diagnostics

The End TB Strategy – global strategy and targets for tuberculosis prevention, care and control after 2015.
http://www.who.int/tb/strategy/End_TB_Strategy.pdf

The use of molecular line probe assays for the detection of resistance to isoniazid and rifampicin. Policy update. Geneva, World Health Organization. 2016. (WHO/HTM/TB/2016.12).
http://www.who.int/tb/publications/molecular-test-resistance

Training packages on culture on solid and liquid medium; on DST by phenotypic and molecular methods; on line probe assays (LPAs). Global Laboratory Initiative. 2012.
http://www.stoptb.org/wg/gli/trainingpackages.asp

Training package on Xpert MTB/RIF. Global Laboratory Initiative. 2014.
http://www.stoptb.org/wg/gli/TrainingPackage_XPERT_MTB_RIF.asp

Use of tuberculosis interferon-gamma release assays (IGRAs) in low- and middle-income countries: policy statement. Geneva, World Health Organization. 2011. (WHO/HTM/TB/2011.18).
http://apps.who.int/iris/bitstream/10665/44759/1/9789241502672_eng.pdf?ua=1&ua=1

Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy update. Geneva, World Health Organization. 2013. (WHO/HTM/TB/2013.16).
http://www.who.int/tb/publications/xpert-mtb-rif-assay-diagnosis-policy-update/en/

1.2   The TB laboratory network

1.2.1   Country organisational structure for laboratories

TB laboratory services are typically managed through a national TB reference laboratory (NRL) that may or may not be under the NTP. When a NRL is managed separately from the NTP, coordination between both entities is essential to ensure that NTP priorities and strategies are reflected in the NRL activities and vice versa.

Countries vary widely with how they set up and manage laboratory services under their MoH. In some countries, laboratories do not fall under a specific unit of the MoH, in which case the management, coordination, and supervisory roles and responsibilities may not be clearly defined and may be spread out across different sections and levels of the MoH. When laboratories are part of a single unit of the MoH, they can fall within "public health", "disease control", "public health laboratory", or another equivalent section of the MoH. There may be a separate "clinical services" unit of the MoH through which certain clinical laboratory services are organized. Management of private sector laboratories can fall under the MoH, another ministry of the government, or it may not be specifically regulated or managed by any governmental unit.

Countries support a network of laboratories that provide services for TB diagnosis and treatment monitoring for patient care. The number and distribution of laboratories within the network will vary dramatically depending on several factors including geography, disease burden, economic setting, and political implications. The network is composed of laboratories with various testing capacity dependent on location, infrastructure, and the particular roles and responsibilities assigned to each specific laboratory. The first patient access point for diagnostic testing and treatment monitoring is often at the community or district level, while more sophisticated extensive testing is based at regional or central level facilities. The primary role of the network is to provide quality services within the population that will support the national programme for TB control.

Country capacity for diagnostic testing was previously monitored according to global targets that described numbers of microscopy centers per 100,000 population and culture/DST laboratories per 5 million (see *The Global Plan to Stop TB 2011–2015*). These global targets are no longer used because of advances in diagnostic technologies and the need for country-specific targets that take into account epidemiology and patient access (urban and rural populations, specimen referral systems, etc). A recommended method for calculating country-specific targets for numbers of tests and facilities for each of the main diagnostic technologies – microscopy, WRDs (including Xpert MTB/RIF), culture and DST – is provided in Annex 1 of the WHO *Framework of indicators and targets for laboratory strengthening under the End TB Strateg*y, and an Excel-based tool to assist in calculations is available online for download.[1]

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[1]   http://www.who.int/tb/publications/labindicators

1.2.2 Laboratory network structure

A network of TB laboratories within the public health system is typically organized in a tiered or pyramid structure illustrated in Figure 1: a large number of peripheral laboratories, called Level 1 laboratories, accessible to most individuals being evaluated for TB; a moderate number of intermediate laboratories, known as Level 2 laboratories, usually located in mid-sized population centres and health facilities; and a central Level 3 laboratory at the provincial, state or national level. In large countries there may be several Level 3 laboratories. Each level or tier has specific requirements for infrastructure and biosafety which are defined by the various activities and diagnostic methods being performed in the laboratories (see the WHO *Tuberculosis laboratory biosafety manual*). In addition, as the level of the laboratory increases from level 1 to level 3, the technologies become more advanced and as a result the necessary skills, proficiency, and training requirements for technicians increase. The organization and operations found at different levels of the laboratory network for TB services are described in publications listed at the end of this section. Figure 1 illustrates the general tiers associated with a conventional TB laboratory network. Table 2 summarizes the functions and responsibilities that often are attributed to each level.

At the lower levels of laboratory networks, services tend to be integrated, and TB-specific laboratories generally do not exist. Commonly, district level and lower laboratories will offer a range of basic diagnostic tests, including one or more of the following AFB smear microscopy, Xpert MTB/RIF, TB-LAMP, and LF-LAM. Patients
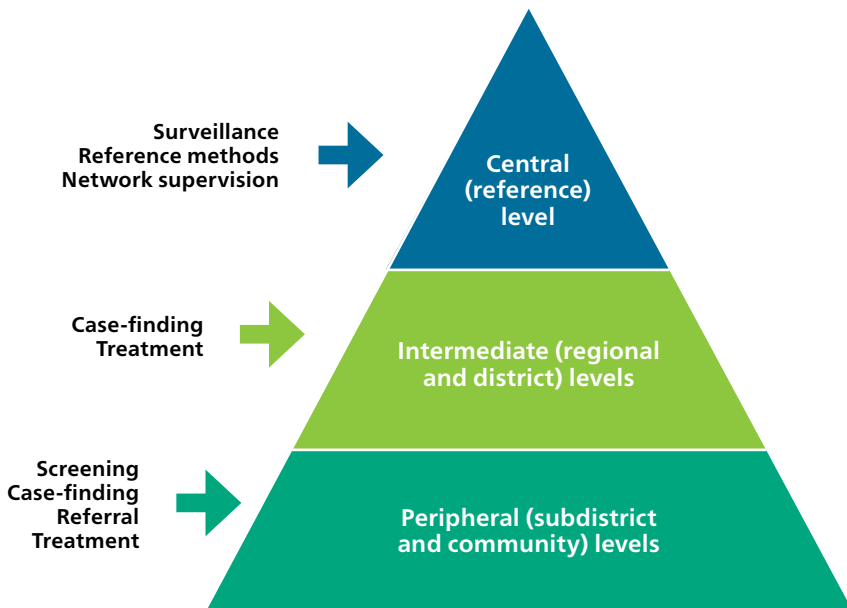
Fig. 1   The three tiers of the network of TB laboratories (from the 2015 WHO *Implementing tuberculosis diagnostics: A policy framework*)

may self-refer to these facilities or may be referred from rural health posts for initial testing. Further testing may be accomplished through referral of specimens to a higher level testing facility.

Many countries have regional, state, or provincial governance over laboratory services. These entities may not coordinate with central or national level laboratories, but develop services and practices essential for their province, state, or region. This situation makes the coordination and provision of services according to national guidelines challenging.

Table 2   Functions and Responsibilities

LEVEL 1. PERIPHERAL (OR COMMUNITY) LABORATORY – MICROSCOPY, XPERT MTB/RIF, TB-LAMP, LF-LAM

- Receives specimens
- Prepares, stains, and examines smears with Ziehl–Neelsen (ZN) or light emitting diode (LED) fluorescence microscopy (FM)
- May use Xpert MTB/RIF, according to national diagnostic algorithms
- May use TB-LAMP, according to national diagnostic algorithms
- May use LF-LAM, according to national diagnostic algorithms
- Records and reports results, according to national guidelines
- Maintains laboratory registers
- Cleans and maintains equipment
- Manages reagents and laboratory supplies
- Uses appropriate quality control (QC) and quality assurance (QA) procedures
- Participates in external quality assessment (EQA) programmes (e.g., blinded rechecking, panel testing, supervisory visits)
- Has appropriate biosafety measures in place

LEVEL 2. INTERMEDIATE (OR REGIONAL) LABORATORY – LEVEL 1 PLUS CULTURE AND LPA

- Performs all of the functions of a Level 1 laboratory
- May use FL-LPA with smear-positive sputum specimens, according to national diagnostic algorithms
- May use SL-LPA with sputum specimens from patients that are detected with rifampicin-resistant TB using Xpert MTB/RIF, according to national diagnostic algorithms
- Performs digestion and decontamination of specimens, inoculates cultures
- Uses culture to isolate and identify MTB
- Refers positive cultures to appropriate reference laboratory for DST
- Trains microscopists and supervises peripheral-level staff in microscopy and the use of WHO-recommended rapid diagnostic tests (e.g., Xpert MTB/RIF, TB LAMP) and LF-LAM.[a]
- Prepares and distributes reagents for microscopy to peripheral laboratories
- Engages in proficiency testing (PT) and quality improvement (QI) activities for peripheral laboratories

LEVEL 3. CENTRAL (OR NATIONAL) LABORATORY – LEVEL 2 PLUS PERFORMS IDENTIFICATION OF MTB, FIRST- AND SECOND-LINE DST

- Performs all of the functions of Level 1 and Level 2 laboratories

- Collaborates closely with the central level of the national TB programme

- Provides strategic oversight to ensure the effective management of laboratories in the network, the quality of the testing, and the efficient use of the network's services and TB diagnostics

- Performs DST of *M. tuberculosis* isolates to determine resistance to first-line and second-line anti-TB agents

- Performs molecular testing for rifampicin resistance on positive cultures (alone or in combination with testing for resistance to isoniazid)

- May use SL-LPA with positive cultures from rifampicin-resistant TB or MDR-TB patients, according to national diagnostic algorithms

- Identifies non-tuberculous mycobacteria (NTM)

- Arranges for a specialist to periodically check, calibrate, and repair laboratory equipment

- Updates and disseminates laboratory manuals, including guidelines on diagnostic methods, equipment maintenance, training and supervision, and QA

- May distribute reagents and consumables when requested by intermediate-level or peripheral-level TB laboratories

- Supervises intermediate-level laboratories' implementation and use of bacteriological methods, as well as the laboratories' performance monitoring of peripheral laboratories

- Undertakes QA of all procedures performed at intermediate-level laboratories including microscopy, culture, and DST

- Ensures an appropriate human resources development programme is in place, including training, re-training, and competency assessment

- Conducts drug resistance surveillance

- Undertakes operational and applied research relating to the laboratory network and coordinates this with the requirements and needs of the NTP

- Establishes a formal collaboration agreement with a TB Supranational Reference Laboratory (SRL) for panel testing, for support in implementing and validating new diagnostics, assistance with laboratory development and expansion strategies, and referral for challenging cases who need specialized testing

[a] WRD testing (e.g., Xpert MTB/RIF) may be placed at higher level laboratories for diagnostic purposes as well as for proficiency of reference level staff responsible for supervision.

The private sector also plays a significant and increasing role in TB control and laboratory services in many low- and middle-income countries in parallel to the public health laboratory system. Private sector facilities may directly inform the NTP of new TB cases, but in many countries private laboratories are not linked with the NTP, and thus may not follow national guidelines or quality standards or report TB case data. This scenario causes substantial challenges with the "quality" of diagnostic services and the accuracy of testing as they are not under national QA programmes. In addition, these facilities often are not reporting cases or resistance data, which limits the NTP's ability to accurately assess the true burden of TB disease as well as define the levels of drug resistance within the population. Initiatives to develop links between public and private sector laboratories are important to facilitate higher quality services and to provide necessary reporting and data sharing to optimize TB control.

1.2.3 Network development: capacity building and strengthening

Generally, resource limitations restrict the ability to rapidly establish complete networks of TB laboratories that will meet all of a country's needs during the early stages of development. Thus, it is best to implement a network or build capacity in stages during a timeframe agreed by consensus among the programme's managers and knowledgeable laboratory personnel.

As a general rule, rather than establishing full national capacity at the beginning of implementation, countries and territories with small populations of TB patients may find it more practical to outsource specific services to neighbouring countries or territories, while building their own capacity, expertise and proficiency.

Several considerations will guide the placement and the expansion of services when implementing new technologies within the current laboratory network structure. When technologies are being positioned, one must consider the following:

- Available resources for implementation

- Infrastructure requirements

- Biosafety requirements

- Projected testing volumes

- Trained human resource capacity

- Links to other laboratories for further testing

- Specimen referral and result reporting mechanisms

Generally, microscopy is found at the lower levels, or in smaller testing facilities, due to the minimal biosafety and infrastructure requirements for performing the test and the need for community level access to ensure rapid screening. The Xpert MTB/RIF test and TB-LAMP test may be implemented at this level in facilities that are able to meet infrastructure requirements for the test (e.g., uninterrupted power and temperature-controlled storage areas for Xpert MTB/RIF). Nevertheless, these technologies are also suitable for implementation at the intermediate and central levels provided suitable sample referral mechanisms from lower level laboratories or community health services are in place. The other technologies placed at intermediate- and higher-level laboratories cannot be pushed to the lower levels of the network because of infrastructure requirements, biosafety concerns, test complexity, and the need for trained staff.

The priority for the use of culture is usually to perform second-line DST and to monitor the response to treatment of patients with MDR-TB and extensively drug-resistant TB (XDR-TB). Cultures are required monthly during the intensive phase of treatment and less frequently (according to country guidelines) during the continuation phase. At a minimum, quality-assured culture must be established at the central TB laboratory with the appropriate equipment, biosafety measures, infrastructure, and referral mechanisms in place. If no central level laboratory exists with culture capacity, then mechanisms for transporting specimens to an SRL or to a neighbouring country's NRL for culture-based testing and drug resistance evaluations should be in place.

A strategic process with measurable sequential objectives to carefully implement or build capacity to a network of TB laboratories is less likely to result in wasted resources. Past experiences can guide an effective and efficient approach for gradual expansion of a network. The process of designing an overall strategic plan for laboratory strengthening, capacity building and expansion is discussed in Section 2.10.

1.2.4 TB networks and human resources

As networks are developed and capacity strengthened, it is essential to build human resources on site. Each laboratory will have specific requirements for trained and competent staff needed to perform the various tests they run. Higher levels of skill and training are needed to perform advanced testing for DST and surveillance at central and intermediate level laboratories. Limitations on the number of tests performed by technicians in order to reduce errors and ensure quality performance have been recommended by WHO. It is important to ensure that each level has enough trained staff to efficiently perform daily routine workloads. Further support staff are also required to assist with non-testing activities such as media and reagent preparation, housekeeping and maintenance, waste management, data management, quality management, QA activities and various administrative work. It is essential that laboratories at all levels are well staffed to support the necessary demands for testing in order to have a successful system for patient management and care.

Table 3 provides information that may be helpful in determining the number of personnel needed to perform various tests in a TB laboratory. During some phases of the testing processes, personnel may be able to perform additional tasks. In addition, it may take almost the same amount of time to test one or two specimens as to test several specimens depending on the experience of the technician. The numbers provided below are estimated assuming proficient and well-trained staff. Testing is often batched in smaller units throughout the workday. Daily workload and testing will depend on the availability of equipment and biosafety cabinets. Often laboratories have routine daily and weekly schedules for cabinet use, which allows for the efficient management of routine activities.

Section 2.7 covers in more detail the practical considerations TB laboratories face when it comes to human resources.

Suggested reading

Tuberculosis laboratory biosafety manual. Geneva, World Health Organization. 2012. (WHO/HTM/TB/2012.11). http://www.who.int/tb/publications/2012/tb_biosafety/en/index.html

Laboratory Diagnosis of Tuberculosis by Sputum Microscopy: The Handbook. Global Edition. Global Laboratory Initiative. 2013. http://www.stoptb.org/wg/gli/gat.asp

The End TB Strategy – global strategy and targets for tuberculosis prevention, care and control after 2015. Geneva, World Health Organization.
http://www.who.int/tb/strategy/End_TB_Strategy.pdf

Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 and 2016 updates. Geneva, World Health Organization. 2011 (WHO/HTM/TB/2011.6) and 2016 (WHO/HTM/TB/2016.04).
http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/resources

Table 3   Estimated number of tests that can be performed during an 8-hour workday

PROCEDURE	No. OF TESTS PER DAY[a]	
AFB light microscopy	20–25[b]	per technician
AFB fluorescence microscopy	40–50[b]	per technician
Culture (liquid/solid media, including specimen processing)	20–40[c]	per technician
DST (using liquid media)	10–20	per technician
DST (using solid media)	10–20	per technician
FL LPA (manual method)	12–24	per instrument
SL-LPA (manual method)	12–24	per instrument
TB-LAMP test	Up to 70[d]	per instrument
Xpert MTB/RIF assay (using four-module instrument)	12–16[e]	per instrument

[a] The number of tests that can be performed in a day is given as an indication. The number will vary according to local conditions. The ranges provided were estimated assuming that a technician would work on all parts of the given procedure.

[b] The recommendations provided for the maximum number of AFB smear examinations that can be performed by a single, competent laboratory worker are based on staining a maximum of 12 smears per batch, and examining smears stained with Ziehl–Neelsen (light microscopy) for five minutes each and smears stained with Auramine O (fluorescence microscopy) for two minutes each; these specifications have been taken from the *GLI Laboratory Diagnosis of Tuberculosis by Sputum Microscopy: The Handbook*. Additional time will be required to engage in QA activities and to prepare reagents and reports. As a general rule, the maximum number of Ziehl–Neelsen smears that can be examined by a microscopist in a single day should not exceed 25 because beyond that, eye fatigue may lead to a deterioration in reading quality. However, proficiency in reading Ziehl–Neelsen smears should be maintained through regular examination of at least 10–15 smears per week.

[c] To maintain overall laboratory proficiency in culture, laboratories should process a minimum of 20 specimens per week with a minimum of 5 cultures per person. The same minimum requirements hold for maintaining proficiency in culture-based DST.

[d] The maximum number of patient samples that can be run per cycle is 14. Each cycle takes 1.5 hours. The proposed number is for 5 cycles per day.

[e] One technician could perform more than 12 Xpert MTB/RIF tests per day (up to 24) assuming more than one instrument was available in the laboratory. Where one instrument is available, a single technician may have time to perform other duties, such as reading smears.

Companion handbook to the WHO guidelines to the PMDT. Geneva, World Health Organization. 2014. (WHO/HTM/TB/2014.11).
http://www.who.int/tb/publications/pmdt_companionhandbook/en/

Laboratory services in tuberculosis control. Geneva, World Health Organization. 1998. (WHO/TB/98.258). http://www.who.int/tb/publications/who_tb_98_258/en/index.html

The Public Health Service National Tuberculosis Reference Laboratory and the National Laboratory Network: minimum requirements, role and operation in a low-income country. 1998.
http://www.uphs.upenn.edu/bugdrug/antibiotic_manual/iuatld_natTBreflabmanual.pdf

Policy framework for implementing new tuberculosis diagnostics. Geneva, World Health Organization. 2015. (WHO/HTM/TB/2015.11).
http://www.who.int/tb/publications/implementing_TB_diagnostics/en/

Framework of indicators and targets for laboratory strengthening under the End TB Strategy. Geneva, World Health Organization. 2016. (WHO/HTM/TB/2016.18).
http://www.who.int/tb/publications/labindicators/en/

1.3   Diagnostic algorithms

As a region's laboratory capacity improves or new diagnostic tests are implemented, algorithms will need to be modified. Modifications to algorithms must be put in place only after a formal evaluation, review, and approval by officials within the MoH and the NTP. Often nationally appointed thematic working groups are used to evaluate new technologies and develop implementation plans, which typically include revising current algorithms. These groups consist of local ministry officials and professionals (laboratory and medical) who will decide the most optimal utilization and placement of the new technology within the current network structure. A technical consultant may be a part of this working group either formally or informally as an expert adviser to assist with evaluation, training, implementation, or expansion activities.

The following points should be considered when designing or reviewing algorithms for testing at different levels of the laboratory network:

- The specific diagnostic tests in use or being considered for use;
- Whether, and for what purposes, the tests are recommended by WHO;
- The current and planned capacity of the country's laboratories, the laboratory infrastructure, and the availability of competent personnel to conduct the tests;
- The adequacy of systems for specimen collection and transport, and the average turnaround time between sites;
- The capacity of clinical services to offer diagnosis and treatment;
- Which drugs are used for the treatment of TB; and
- Characteristics (risk groups) of the population being served, which should be derived from population-based studies (if available), including the proportion with drug-resistant TB, the proportion that is HIV-positive, the proportion with extrapulmonary TB, and the proportion that is among children.

Algorithms should be designed to use existing laboratory services so that specimens can be referred to the appropriate level for tests that are not available at the peripheral level laboratories. Such referrals are particularly important when persons are being evaluated for drug-resistant TB or HIV-associated TB, when children are being evaluated for TB, or when persons are being evaluated for extrapulmonary disease.

The WHO *Policy framework for Implementing Tuberculosis Diagnostics* and the *GLI Guide for providing technical support to TB laboratories in low- and middle-income countries* provided sample algorithms using WHO-recommended diagnostics as of early 2015. Since the publication of these documents, WHO has approved or updated guidance on several diagnostic tests for TB including LF-LAM, TB-LAMP, FL-LPA and SL-LPA.

Four updated model algorithms are presented that incorporate the goals of the End TB Strategy that emphasize that WHO-endorsed rapid TB diagnostics should be available to all persons with signs or symptoms of TB and that all bacteriologically confirmed TB cases should receive DST. The algorithms are illustrative and must be adapted by countries to the local situation. They were originally published in the *GLI Model TB Diagnostic Algorithms*.

1.3.1 Algorithm 1: Preferred algorithm for universal patient access to rapid testing to detect MTB and rifampicin resistance

Persons to be evaluated for TB[1]

↓

Collect 1 specimen and perform Xpert MTB/RIF[2]

MTB not detected

- Re-evaluate the patient clinically[6]
- Conduct additional testing in accord with national guidelines
- Consider repeat Xpert MTB/RIF testing
- Use clinical judgment for treatment decisions

MTB detected, rifampicin resistance not detected

- Treat with first line regimen[4]

MTB detected, rifampicin resistance detected

- Evaluate patient for MDR-TB risk factors

Patient at high risk of MDR-TB[3]

- Refer patient to DR-TB treatment Initiation Site
- Treat with second line regimen
- Follow *Algorithm 3* for further testing and assessment

Patient at low risk of MDR-TB

- Repeat Xpert MTB/RIF[5]

MTB detected, rifampicin resistance detected

MTB detected, rifampicin resistance not detected

- Treat with first line regimen[4]

MTB not detected

- Re-evaluate the patient clinically[6]
- Conduct additional testing in accordance with national guidelines
- Consider repeat Xpert MTB/RIF testing
- Use clinical judgment for treatment decisions

MTB detected, rifampicin indeterminate

- Treat with first line regimen[4]
- Repeat Xpert MTB/RIF[7]
- Follow algorithm 1 to interpret

No result, error, or invalid test

- Repeat Xpert MTB/RIF[5]
- Follow *Algorithm 1* to interpret

[1] Persons to be evaluated for TB include adults and children with signs or symptoms suggestive of TB or with a chest X-ray with abnormalities suggestive of TB. This algorithm may also be followed for the detection of MTB using CSF, lymph node and other tissue specimen from persons being evaluated for extrapulmonary TB. For persons being evaluated for TB who are HIV positive and have CD4 counts ≤100 cells/μl or are seriously ill, see Algorithm 4.

[2] Programmes may consider collecting two specimens upfront. The first specimen should be promptly tested using the Xpert MTB/RIF test. The second specimen may be used for the additional testing described in this algorithm. For persons being evaluated for pulmonary TB, sputum is the preferred specimen.

[3] Patients at high risk for multidrug-resistant TB (MDR-TB) include previously treated patients including those who had been lost to follow-up, relapsed, and failed a treatment regimen; non-converters (smear positive at end of intensive phase); MDR-TB contacts; and any other MDR-TB risk groups identified in the country.

[4] Patients should be initiated on a first-line regimen according to national guidelines. A sample may be sent for molecular or phenotypic DST for isoniazid if the patient has been previously treated with isoniazid or if there is a high prevalence of isoniazid resistance not associated with rifampicin resistance (i.e., isoniazid mono- or poly-resistance) in this setting or for DST for rifampicin if rifampicin resistance is still suspected.

[5] Repeat Xpert MTB/RIF test at the same testing site with a fresh specimen. Interpret the result of the repeat test as shown in this algorithm. Use the result of the second Xpert MTB/RIF test for clinical decisions.

[6] Further investigations for TB may include chest X-ray, additional clinical assessments, clinical response following treatment with broad-spectrum antimicrobial agents, repeat Xpert MTB/RIF testing, or culture.

[7] Repeat Xpert MTB/RIF test at the same testing site with a fresh specimen. Use the rifampicin result of the second Xpert MTB/RIF test in this algorithm for a decision(s) regarding choice of regimen (first line or second line regimen).

Algorithm 1 is the preferred algorithm for testing to detect MTB in individuals being evaluated for pulmonary TB and incorporates the goals of the End TB Strategy for the use of WRDs and universal DST. This algorithm is feasible when a GeneXpert instrument is available on site or when Xpert MTB/RIF testing can be accessed through a reliable referral system with short turnaround time. This algorithm may also be used for the detection of MTB using CSF, lymph nodes and other tissue types from persons being evaluated for extrapulmonary TB.

Decision Tree for Algorithm 1 in which the Xpert MTB/RIF test is used as the initial diagnostic test for all adults and children (regardless of HIV status) with signs or symptoms of pulmonary TB or with a chest X-ray with abnormalities suggestive of TB

- The Xpert MTB/RIF test is recommended as the initial diagnostic test for persons being evaluated for TB. This includes all newly presenting symptomatic persons and may also include patients who are on therapy or have been previously treated if the patient is being evaluated for possible rifampicin-resistant TB (e.g., non-converters at the end of the intensive phase of treatment) or for a new or continuing episode of TB (e.g., relapse cases or previously treated patients including those who had been lost to follow-up).

- The Xpert MTB/RIF test is also recommended for use in persons being evaluated for extrapulmonary TB, although the test is not recommended for use with all types of extrapulmonary specimens. It is recommended for use with CSF, lymph nodes and other tissue samples. However, the test has low sensitivity for pleural fluid specimens and data are limited for its sensitivity with stool, urine or blood specimens. See the WHO *Policy Update: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children* for a discussion of the use of the Xpert MTB/RIF assay with extrapulmonary specimens.

- The Xpert MTB/RIF test is not recommended as a test to monitor treatment; instead microscopy and culture should be used according to national guidelines.

- The algorithm describes the collection of one initial specimen to be used for Xpert MTB/RIF testing and the collection of additional specimens as needed. Operationally, it may be easier to collect two specimens (e.g., spot and morning sputum samples or two spot specimens) from each patient routinely instead of only collecting a second specimen when additional testing is needed. The first specimen should be promptly tested using the Xpert MTB/RIF test. The second specimen may be used for the additional testing described in the algorithm (e.g., repeat Xpert MTB/RIF testing) or for smear microscopy as a baseline for treatment monitoring.

  — If more than one specimen cannot be collected (e.g., only one lymph node biopsy can be collected), the algorithm should be modified to prioritize testing using the Xpert MTB/RIF test and consider using any portions of the sample remaining after the Xpert MTB/RIF test for other testing. Clinical decisions should be made based on clinical judgement and the results of available laboratory tests.

- The GeneXpert software provides Xpert MTB/RIF assay results as 'MTB not detected'; 'MTB detected (high, medium, low, or very low), rifampicin resistance detected, not detected, or indeterminate'; 'no result'; 'error'; or 'invalid'. In this document, each of the semi-quantitative categories of MTB detected is considered as bacteriological confirmation of TB.

- For persons being evaluated for TB who are HIV positive and seriously ill with danger signs or have CD4 counts ≤100 cells/μl, a urine LF-LAM assay may also be used (See Algorithm 4).

1. Collect a good quality specimen and transport it to the testing laboratory. Conduct the Xpert MTB/RIF test. For persons being evaluated for pulmonary TB, induced or expectorated sputum (preferred), bronchoalveolar lavage, gastric lavage, and gastric aspirate specimens may be used. Data are limited for the sensitivity of the Xpert MTB/RIF with other samples such as nasopharyngeal aspirates, string test samples, or stool samples.

2. If the Xpert MTB/RIF test result is MTB detected, rifampicin resistance not detected:

   a. The patient should be initiated on an appropriate regimen using first-line TB drugs according to national guidelines.

   b. Some programmes may request additional DST in some situations:

      i. Programmes may request molecular (e.g., FL-LPA) or phenotypic DST for isoniazid if the patient has been previously treated with isoniazid or if there is a high prevalence of isoniazid resistance that is not associated with rifampicin resistance (i.e., isoniazid mono-resistance or poly-resistance, but not MDR-TB) in this setting.

         1. Note that current treatment guidelines do not recommend a specific regimen for isoniazid-resistant TB. A regimen with first-line TB drugs is currently recommended. See WHO *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis*.

         2. However, a recent systematic review suggests that treatment of isoniazid-resistant TB with a first-line regimen may be suboptimal and may result in higher rates of treatment failure, relapse and acquisition of multidrug resistance.[2] Evidence will be reviewed by WHO in 2017.

      ii. Additional molecular or phenotypic DST for resistance to rifampicin may be requested if the patient is considered to be at risk of having MDR-TB despite the initial Xpert MTB/RIF result. False rifampicin-susceptible Xpert MTB/RIF results are rare but have been observed in 1–5% of TB cases tested in various epidemiologic settings. In contrast, phenotypic DST for rifampicin, especially using liquid culture, is associated with a higher proportion of false-susceptible results.[3]

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[2] M. Gegia et al. 2016. Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis. *Lancet Infect Dis* (2016) published online Nov 16. DOI: http://dx.doi.org/10.1016/S1473-3099(16)30407-8

[3] A. Van Deun et al. Rifampin drug resistance tests for tuberculosis: Challenging the gold standard. *J Clin Microbiol*. August 2013; 51 (8): 2633-2640. DOI: http://dx.doi.org/10.1128/JCM.00553-13

c. If additional molecular or phenotypic testing is done:

   i.   The molecular and phenotypic testing may be done in different laboratories. These tests should be initiated in parallel; do not wait for the results of one test before initiating the other test.

   ii. The molecular and phenotypic DST may be done using the specimen (direct DST) or using bacteria recovered by culture (indirect DST). While direct DST has a much shorter turnaround time, indirect phenotypic DST may be preferred because of technical issues.

   iii. A rapid molecular test is preferred. Currently, FL-LPA is the only WHO-approved rapid molecular test for isoniazid resistance. DNA sequencing has proven useful in many cases but has not yet been evaluated by WHO.

   iv. Culture-based phenotypic DST for isoniazid and rifampicin requires 3 to 8 weeks to produce a result. Phenotypic DST may be useful for the evaluation of patients with a negative FL-LPA result, particularly in populations with a high pre-test probability for resistance to isoniazid.

3. If the Xpert MTB/RIF test result is MTB detected, rifampicin resistance detected, an MDR-TB risk assessment is needed. Patients at high risk for MDR-TB include previously treated patients including those who had been lost to follow-up, relapsed, or failed a treatment regimen; non-converters (smear positive at end of intensive phase); contacts of MDR-TB patients; and any other MDR-TB risk groups identified in the country.

   a. If the patient is at high risk of having MDR-TB, the rifampicin-resistant test result is definitive and the patient should be initiated on a regimen for rifampicin-resistant (RR-TB) or MDR-TB according to national guidelines and follow Algorithm 3 for additional testing.

   b. If the patient is at low risk of having MDR-TB, repeat the Xpert MTB/RIF test with a second sample. If FL-LPA is available at the site and the sputum specimen is smear positive, FL-LPA can be used for confirming the rifampicin-resistant result.

      i.   Initiate an MDR-TB regimen according to national guidelines if the second test also indicates rifampicin resistance and follow Algorithm 3 for additional testing.

      ii. Initiate treatment with a first-line regimen according to national guidelines if the Xpert MTB/RIF result for the second sample is MTB detected, rifampicin resistance not detected. While in most situations false-positive rifampicin-resistant results due to technical performance of the assay are rare, false-positive rifampicin-resistant results due to laboratory or clerical errors may be more likely. Therefore it may be assumed that the result of the second test is correct and the result of the first test may have been due to a laboratory or clerical error.

   c. For all patients with RR-TB or MDR-TB follow Algorithm 3.

4. If the Xpert MTB/RIF test gives a result of MTB detected, rifampicin indeterminate, the Xpert MTB/RIF test should be retested at the same testing site with a second specimen.

    a. The initial Xpert MTB/RIF result of MTB detected should be considered as bacteriological confirmation of TB. The patient should be initiated on an appropriate regimen using first-line TB drugs according to national guidelines.

    b. If the result of the second Xpert MTB/RIF test is MTB detected, rifampicin resistance not detected, follow step 2. If it is MTB detected, rifampicin resistance detected, follow step 3.

    c. An Xpert MTB/RIF result of MTB detected, rifampicin indeterminate often occurs when there are very few bacteria in the specimen. Testing of a second sample, which also may contain very few bacteria, may, in some cases, generate a result of MTB detected, rifampicin indeterminate or a result of MTB not detected. In this situation, additional investigations such as culture and phenotypic DST may be needed to confirm or exclude resistance to rifampicin because the indeterminate result provides no information on resistance.

5. If the Xpert MTB/RIF test result is MTB not detected, re-evaluate the patient and conduct additional testing in accordance with national guidelines.

    a. Further investigations for TB may include chest X-ray, additional clinical assessments, clinical response following treatment with broad-spectrum antimicrobial agents (fluoroquinolones should not be used), additional Xpert MTB/RIF testing, or culture.

    b. Consider the possibility of clinically defined TB (i.e., no bacteriological confirmation). Use clinical judgement for treatment decisions.

6. If the Xpert MTB/RIF test does not give a result or gives a result of error or invalid, the Xpert MTB/RIF test should be retested at the same testing site with a second specimen. If FL-LPA is available at the site and the second specimen is smear positive, FL-LPA can be used for the repeat testing; although repeat Xpert MTB/RIF testing is preferred.

This algorithm relies on testing of a sample with the Xpert MTB/RIF test for the detection of MTB and assessment of susceptibility to rifampicin. On occasion follow-up testing is recommended to ensure that clinical decisions are well informed. However, discordant results may happen, usually when comparing culture-based results with molecular results. Each discordant result will need to be investigated, on a case-by-case basis. General considerations are:

1. Xpert MTB/RIF MTB detected, culture negative.

    a. The Xpert MTB/RIF result should be used to guide treatment decision pending additional testing.

    b. The Xpert MTB/RIF result should be considered as bacteriological confirmation of TB if the sample was collected from a person who was not recently receiving treatment with anti-TB drugs. Cultures from persons with pulmonary TB may be negative for a variety of reasons including the patient being treated for TB,

transport or processing problems that inactivated the tubercle bacilli, cultures lost to contamination, or inadequate testing volume, or the discrepancy may be due to laboratory or clerical error.

    c. Follow-up actions may include re-evaluate the patient for TB, reassess possibility of prior or current treatment with anti-TB drugs (including fluoroquinolone use), evaluate the possibility of laboratory or clerical error, and repeat culture.

2. Xpert MTB/RIF MTB not detected, culture positive.

    a. Treatment decision should be based on the culture result.

    b. The culture-positive result should be considered as bacteriological confirmation of TB because culture is the current gold standard for the laboratory confirmation of TB. Using a sputum specimen, Xpert MTB/RIF has a pooled sensitivity of 89% for detecting MTB compared to culture.[4] Its sensitivity is lower in PLHIV, children, and other specimen types such as CSF.

    c. False-positive cultures can result from a variety of causes such as cross-contamination in the laboratory or from sample labelling problems. In well-function laboratories, such errors are rare.

    d. Follow-up actions may include re-evaluation of the patient for TB and response to anti-TB therapy; conduct additional testing using Xpert MTB/RIF; process and culture additional samples; and evaluate the possibility of laboratory or clerical error.

3. Xpert MTB/RIF MTB detected, rifampicin resistance detected; rifampicin susceptible by phenotypic DST.

    a. The Xpert MTB/RIF result should be used to guide treatment decisions pending additional testing.

    b. Certain mutations are known to generate this discordant result, particularly in the BACTEC™ MGIT™ system (i.e., a false-susceptible phenotypic result). Patients infected with strains carrying these mutations often fail treatment with rifampicin-based first-line regimens.[5]

    c. In some low MDR-TB prevalence settings, silent mutations have been observed that generate a false-resistant Xpert MTB/RIF result but these tend to be very rare.

    d. Follow-up actions may include DNA sequencing, phenotypic DST using solid media, and evaluating the possibility of laboratory or clerical error.

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[4] K.R. Steingart et al. Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. *Cochrane Database Syst Rev.* 2014 Jan 21;(1):CD009593. DOI: http://dx.doi.org/10.1002/14651858.CD009593.pub3

[5] A. Van Deun et al. Rifampin drug resistance tests for tuberculosis: Challenging the gold standard. *J Clin Microbiol.* August 2013; 51 (8): 2633-2640. DOI: http://dx.doi.org/10.1128/JCM.00553-13

4. Xpert MTB/RIF MTB detected, rifampicin resistance not detected; rifampicin resistant by phenotypic DST.

    a. Treatment decisions should be based on the phenotypic DST result.

    b. False rifampicin-susceptible Xpert MTB/RIF results are rare but have been observed in 1–5% of TB cases tested in various epidemiologic settings. Mutations in the region of the rpoB gene sampled by the Xpert MTB/RIF tests have been shown to account for 95–99% of rifampicin resistance. The remainder of rifampicin resistance arises from mutations outside the sampled region, which produce an Xpert MTB/RIF result of rifampicin resistance not detected.

    c. Follow-up actions may include DNA sequencing, repeating the phenotypic DST, and evaluating the possibility of laboratory or clerical error.

Suggested Reading

GLI Model TB Diagnostic Algorithms. Global Laboratory Initiative. 2017.
http://www.stoptb.org/wg/gli/gat.asp

Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy update. Geneva, World Health Organization. 2013. (WHO/HTM/TB/2013.16).
http://www.who.int/tb/publications/xpert-mtb-rif-assay-diagnosis-policy-update/en/

Guidance for national tuberculosis programmes on the management of tuberculosis in children – 2nd ed. Geneva, World Health Organization. 2014. (WHO/HTM/TB/2014.03).
http://www.who.int/tb/publications/childtb_guidelines

The use of molecular line probe assays for the detection of resistance to isoniazid and rifampicin. Policy update. Geneva, World Health Organization. 2016. (WHO/HTM/TB/2016.12).
http://www.who.int/tb/publications/molecular-test-resistance

Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 and 2016 updates. Geneva, World Health Organization. 2011 (WHO/HTM/TB/2011.6) and 2016 (WHO/HTM/TB/2016.04).
http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/resources

Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, World Health Organization. 2014 (WHO/HTM/TB/2014.11).
http://www.who.int/tb/publications/pmdt_companionhandbook/en/

Training package on Xpert MTB/RIF. Global Laboratory Initiative. 2014.
http://www.stoptb.org/wg/gli/TrainingPackage_XPERT_MTB_RIF.asp

1.3.2 Algorithm 2: Interim algorithm moving towards universal access, with rapid testing for priority populations

Persons to be evaluated for TB[1]

⬇

Evaluate patient for TB, HIV[2] and MDR-TB risk factors

Priority patients for Xpert MTB/RIF testing:
PLHIV,[3] high MDR-TB risk,[4] children

⬇

- Collect 2 sputum samples
- Perform 2 sputum smears[5] on site
- Refer 1 sputum for Xpert MTB/RIF[8]

Other patient categories

⬇

- Collect 2 sputum samples
- Perform 2 sputum smears[5]

Smear positive

- Treat with first line regimen[6]
- Review treatment based on Xpert MTB/RIF result (*Algorithm 1*)

Smear negative

- Re-evaluate the patient clinically[7]
- Conduct additional testing in accordance with national guidelines
- Use clinical judgment for treatment decisions
- Review clinical decisions based on Xpert MTB/RIF result (*Algorithm 1*)

Both smear negative

- Re-evaluate the patient clinically[7]
- Conduct additional testing in accordance with national guidelines
- Consider Xpert MTB/RIF testing
- Use clinical judgment for treatment decisions

One or both smear positive

- Treat with first line regimen[6]
- Refer 1 sputum for Xpert MTB/RIF testing or other molecular DST
- Follow *Algorithm 1* for interpretation and further testing

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[1] Persons being evaluated for TB include all persons with signs or symptoms suggestive of TB or persons with a chest X-ray with abnormalities suggestive with TB. This algorithm may also be used for persons being evaluated for extrapulmonary TB. See footnotes to Algorithm 1.

[2] For persons being evaluated for TB who are HIV positive and have CD4 counts ≤100 cells/µl or are seriously ill, see Algorithm 4.

[3] PLHIV include persons who are HIV positive or whose HIV status is unknown, but who present with strong clinical evidence of HIV infection in settings where there is a high prevalence of HIV or among members of a risk group for HIV. For all people with unknown HIV status, HIV testing should be performed according to national guidelines.

[4] Patients at high risk for MDR-TB include previously treated patients including those who had been lost to follow-up, relapsed, and failed a treatment regimen; non-converters (smear positive at end of the intensive phase of treatment); MDR-TB contacts; and any other MDR-TB risk groups identified in the country.

[5] TB-LAMP may be used as a replacement test for sputum smear microscopy.

[6] Patients should be initiated on a regimen with first-line TB drugs according to national guidelines unless the patient is at very high risk of having MDR-TB. In that case, treat according to national guidelines while awaiting the Xpert MTB/RIF result.

[7] Further investigations for TB may include chest X-ray, additional clinical assessments, clinical response following treatment with broad-spectrum antimicrobial agents, or culture if available.

[8] A third sample should be collected if neither of the original two samples collected has sufficient volume for both microscopy and Xpert MTB/RIF testing, or according to national guidelines.

Algorithm 2 is an interim measure towards meeting the goals of the End TB Strategy, in which Xpert MTB/RIF testing is used primarily for priority populations (adults being evaluated for HIV-associated TB or MDR-TB, and children) as described in the WHO *Policy Update: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children*. This algorithm is suitable when there is no GeneXpert instrument on site and when Xpert MTB/RIF testing cannot be accessed through a reliable referral system with short turnaround time or when resources do not permit testing of all samples with the Xpert MTB/RIF test. As countries move toward the goals of access to rapid diagnostics and universal drug-susceptibility testing and as access to prompt Xpert MTB/RIF testing becomes available at a site (either through phased implementation of additional instruments or strengthening of the sample referral system), Algorithm 1 should be implemented.

Decision Tree for Algorithm 2 in which the Xpert MTB/RIF test is not available for all persons being evaluated for TB but is only available for priority populations because of resource limitations or lack of testing capacity, and smear microscopy is used for other patients being evaluated for TB

- Algorithm 1 (not Algorithm 2) should be followed in any setting where Xpert MTB/RIF testing is available on site or when Xpert MTB/RIF testing can be accessed through a reliable referral system with short turnaround time.

- Many countries have not yet built the capacity to conduct Xpert MTB/RIF testing for all persons being evaluated for TB. In such situations, Xpert MTB/RIF testing often initially focuses on testing the priority populations identified in the WHO *Policy Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children* and builds towards universal access. The priority populations are adults being evaluated for HIV-associated TB and MDR-TB, and children.

- This algorithm may also be used for persons being evaluated for extrapulmonary TB. See Decision Tree for Algorithm 1 for sample types and considerations.

- See Annexes 14 and 15 of the WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach – Second edition* for detailed algorithms for the management of persons being evaluated for HIV-associated TB.

- The TB-LAMP test may be used as a replacement for smear microscopy for the detection of pulmonary MTB in adults and children with signs or symptoms suggestive of TB. However, TB-LAMP should not replace the use of rapid molecular tests that detect MTB and resistance to rifampicin (e.g., Xpert MTB/RIF) especially among populations at risk of MDR-TB when there are sufficient resources and infrastructure to support their use. TB-LAMP should also not replace the use of rapid molecular tests that have a higher sensitivity for detection of MTB among PLHIV.

1. Evaluate the person for TB, determine HIV status, and assess risk factors for having MDR-TB.

    a. As Xpert MTB/RIF testing becomes available, expand access to include testing of all adults and children being evaluated for TB (i.e., Algorithm 1).

b. PLHIV include persons who are HIV positive or whose HIV status is unknown, but who present with strong clinical evidence of HIV infection in settings where there is a high prevalence of HIV or among members of a risk group for HIV. For all persons with unknown HIV status, HIV testing should be performed according to national guidelines.

c. For PLHIV who have CD4 counts ≤100 cells/μl or are seriously ill with one or more danger signs, a urine LF-LAM assay may also be used (See Algorithm 4).

2. For PLHIV, persons at risk of having MDR-TB, and children, collect two or three good quality sputum specimens. Conduct smear microscopy or TB-LAMP test on site and transport a sample to the testing laboratory for the Xpert MTB/RIF test.

a. Because of a potential delay in receiving the Xpert MTB/RIF result, programmes may prefer having smear microscopy results from two specimens.

i. If only two specimens are collected, smear microscopy may be done on both specimens if at least one of the samples has adequate volume for conducting both microscopy and Xpert MTB/RIF. The Xpert MTB/RIF test should be given priority. If not, a third sample should be collected.

ii. In some settings, collecting three specimens (two for smear microscopy and one for Xpert MTB/RIF testing) may be preferred.

b. If one or both samples are positive by smear microscopy or the TB-LAMP test, treat with TB drugs while awaiting the result of the Xpert MTB/RIF test.

i. The patient should be initiated on a regimen with first-line TB drugs according to national guidelines unless the patient is at very high risk of having MDR-TB. For patients at very high risk of having MDR-TB (e.g., household contacts of MDR-TB patients), an MDR-TB regimen should be initiated according to national guidelines.

ii. Follow Algorithm 1 for the interpretation of the Xpert MTB/RIF test results.

c. If both samples are negative by smear microscopy or the TB-LAMP test, use clinical judgement for further evaluation or treatment while awaiting the Xpert MTB/RIF result.

i. If Xpert MTB/RIF positive, follow the decision tree for Algorithm 1.

ii. If Xpert MTB/RIF negative (MTB not detected), use clinical judgement and conduct additional testing as described in Algorithm 1.

3. For patients not in the priority populations, collect two good quality sputum specimens and conduct smear microscopy or TB-LAMP examinations on both. Follow national guidelines for the detection of MTB based on smear microscopy.

a. If one or both samples are positive, treat with a regimen of first-line TB drugs according to national guidelines.

i. If resources allow, collect an additional specimen and refer for Xpert MTB/RIF testing and follow Algorithm 1 for interpretation and additional testing. One of the already collected specimens may be referred for Xpert MTB/RIF testing if sufficient volume is available.

    ii. If Xpert MTB/RIF testing is not available and if the infrastructure and resources for FL-LPA have been developed, a specimen may be referred for testing with FL-LPA to detect MTB and to assess resistance to isoniazid and rifampicin. Note that FL-LPA is recommended for use with smear-positive sputum samples only. FL-LPA results are interpreted as described in the WHO *Policy Update: use of molecular line probe assay for the detection of resistance to isoniazid and rifampicin.*

b. If both samples are negative, re-evaluate the patient and conduct additional testing in accordance with national guidelines.

    i. Further investigations for TB may include chest X-ray, Xpert MTB/RIF test, additional clinical assessments, clinical response following treatment with broad-spectrum antimicrobials (fluoroquinolones should not be used), or culture.

    ii. Consider the possibility of clinically defined TB (i.e., no bacteriological confirmation). Use clinical judgement for treatment decisions.

Suggested Reading

Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy update. Geneva, World Health Organization. 2013. (WHO/HTM/TB/2013.16)
http://www.who.int/tb/publications/xpert-mtb-rif-assay-diagnosis-policy-update/en/

The use of loop-mediated isothermal amplification (TB-LAMP) for the diagnosis of pulmonary tuberculosis: policy guidance. Geneva, World Health Organization. 2016. (WHO/HTM/TB/2016.07).
http://www.who.int/tb/publications/lamp-diagnosis-molecular

Guidance for national tuberculosis programmes on the management of tuberculosis in children – 2nd ed. Geneva, World Health Organization. 2014. (WHO/HTM/TB/2014.03).
http://www.who.int/tb/publications/childtb_guidelines/en/

Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 and 2016 updates. Geneva, World Health Organization. 2011 (WHO/HTM/TB/2011.6) and 2016 (WHO/HTM/TB/2016.04).
http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/resources

The use of molecular line probe assays for the detection of resistance to isoniazid and rifampicin. Policy update. Geneva, World Health Organization. 2016. (WHO/HTM/TB/2016.12).
http://www.who.int/tb/publications/molecular-test-resistance

Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, World Health Organization. 2014. (WHO/HTM/TB/2014.11).
http://www.who.int/tb/publications/pmdt_companionhandbook/en/

1.3.3 Algorithm 3: Algorithm for testing for second-line drug resistance among rifampicin-resistant TB or MDR-TB patients

All patients with rifampicin-resistant TB or MDR-TB

↓

- Initiate treatment with second-line regimen[1]
- Refer a specimen for SL-LPA[2]

SL-LPA: Resistance to FQ, SLID, or both detected

↓

- Initiate individualised MDR-TB treatment based on SL-LPA results and considering use of new drugs and later generation fluoroquinolone
- During treatment monitoring, any positive culture suggestive of treatment failure should undergo phenotypic 2nd line DST, if available. Review treatment regimen based on phenotypic DST results

SL-LPA: Resistance NOT detected to both FQ and SLID

↓

- Initiate patient on the shorter MDR-TB treatment regimen if patient meets criteria[3]
- If not eligible, initiate an individualised MDR-TB regimen in accordance with national guidelines
- In settings with high underlying prevalence of resistance to FQs or SLIDs or for patients considered at high risk of resistance, refer a specimen for culture and phenotypic 2nd line DST
- During treatment monitoring, any positive culture suggestive of treatment failure should undergo phenotypic 2nd line DST, if available. Review treatment regimen based on phenotypic DST results

SL-LPA indeterminate

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[1] Patients may be initiated on the shorter MDR-TB regimen if the patient is assessed as being at low risk of having resistance to FQs and to SLIDs and meets the eligibility requirements. In patients at high risk of resistance or in settings with high underlying prevalence of resistance to FQs or SLIDs, selection or design of the treatment regimen to initiate may be guided by SL-LPA if the results can be obtained rapidly. See WHO Guidelines for the programmatic management of drug-resistant tuberculosis, 2016 update.

[2] Diagnostic accuracy is similar when SL-LPA is performed directly on sputum or from cultured isolates. SL-LPA can be used on smear-positive or smear-negative specimens although a higher indeterminate rate will occur when testing smear-negative specimens.

[3] The shorter MDR-TB regimen may be used in MDR-TB patients who do not have the following conditions: 1) confirmed resistance, or suspected ineffectiveness, to a medicine (except isoniazid) in the shorter MDR-TB regimen for which there is reliable DST, 2) previous exposure for >one month to a second-line medicine included in the shorter MDR-TB regimen, 3) intolerance to one or more medicines in the shorter MDR-TB regimen or increased risk of toxicity, 4) pregnancy, or 5) extrapulmonary disease.

Algorithm 3 is for further evaluation of patients with RR-TB or MDR-TB. All patients with RR-TB or MDR-TB should be started on a second-line regimen. The results of DST for FQs and SLIDs should ideally be known for all RR-TB and MDR-TB patients before starting treatment, although this testing should not delay the start of treatment (see the WHO *Guidelines for the programmatic management of drug-resistant tuberculosis, 2016 update* for more details on choice of regimen).

Decision Tree for Algorithm 3 in which SL-LPA is used as the initial diagnostic test for resistance to FQs and SLIDs for patients with RR-TB or MDR-TB

- The diagnostic accuracy SL-LPA is similar when it is performed directly on sputum or from cultured isolates. SL-LPA can be used on smear-positive or smear-negative specimens although a higher indeterminate rate will occur when testing smear-negative specimens.

- SL-LPA is only recommended for use with sputum specimens or MTB isolates. The laboratory testing of other specimen types should rely on culture and phenotypic DST.

- SL-LPA is suitable for use at the central or national reference laboratory level and may be used at the regional level if the appropriate infrastructure and human resources are available. Implementation of SL-LPA testing must ensure the availability of a reliable specimen transport system and efficient result reporting mechanism.

Note: If SL-LPA is not available, patients should be treated according to national guidelines. Patients may be evaluated for the use of a shorter MDR-TB regimen using criteria such as country drug-resistance patterns and the patient's treatment history. Algorithms that rely on culture and phenotypic DST are described in the WHO *Policy Framework for Implementing Tuberculosis Diagnostics*. Phenotypic DST, if done, should include at a minimum testing for resistance to the FQs and SLIDs used in the country. If phenotypic DST to second-line drugs is not available in-country, specimens or isolates may be shipped to an external laboratory for testing (e.g., a WHO Supranational Reference Laboratory).

1. The patient should be promptly initiated on a MDR-TB regimen in accordance with national guidelines. Patients may be initiated on the shorter MDR-TB regimen if the patient is assessed as being at low risk of having resistance to FQs and to SLIDs and meets the eligibility requirements. In patients at high risk of resistance or in settings with high underlying prevalence of resistance to FQs or SLIDs, selection or design of the treatment regimen to initiate may be guided by SL-LPA if the results can be obtained rapidly.

2. Transport a sputum specimen or isolate to the appropriate laboratory for testing by SL-LPA.

3. If SL-LPA detects a mutation(s) associated with resistance to an FQ, SLID, or both, the patient should be initiated on an individualised MDR-TB treatment regimen considering use of new drugs and later generation fluoroquinolones. Note that cross-resistance between individual FQs or between individual SLIDs is complex and not fully understood; there are limited data on the ability of SL-LPA to assess the cross-resistance.

4. If SL-LPA is negative for mutations associated with resistance to FQs and to SLIDs, the patient should be assessed for eligibility for the shorter MDR-TB regimen.

   a. The shorter MDR-TB regimen may be used in MDR-TB patients who do not have the following conditions 1) confirmed resistance, or suspected ineffectiveness, to a medicine (except isoniazid) in the shorter MDR-TB regimen for which there is reliable DST, 2) previous exposure for >one month to a second-line medicine included in the shorter MDR-TB regimen, 3) intolerance to one or more medicines in the shorter MDR-TB regimen or increased risk of toxicity, 4) pregnancy, or 5) extrapulmonary disease.

      i. Eligible patients should be placed on a shorter MDR-TB regimen according to national guidelines.

      ii. For eligible patients at risk of having FQ-resistant or SLID-resistant TB (e.g., based on the country drug-resistance patterns), a specimen should be referred for culture and phenotypic DST, if such testing capacity is available. At a minimum, the phenotypic DST should include testing for resistance to the FQs and SLIDs used in the country.

      iii. Reliable DST is available for the FQs and SLIDs. Although technically difficult, reliable DST for pyrazinamide is available, and resistance to pyrazinamide at the start of treatment may also be considered a criterion for exclusion. Reliable DST for ethambutol and the other drugs in the regimen (i.e., prothionamide, clofazimine) are not available and WHO does not recommend basing treatment decisions on the DST for these drugs. See WHO *Frequently asked questions about the implementation of the new WHO recommendation on the use of the shorter MDR-TB regimen under programmatic conditions, Version: 20 December 2016* and WHO *Guidelines for the programmatic management of drug-resistant tuberculosis: 2016 update* for a detailed discussion.

   b. If the patient is not eligible for the shorter regimen, the patient should be started on a MDR-TB regimen in accordance with national guidelines.

   c. In settings with high underlying prevalence of resistance to FQs or SLIDS or for patients considered at high risk of resistance, a specimen should be referred for culture and phenotypic DST, if such testing capacity is available. If phenotypic DST to FQs and SLIDs is not available in-country, specimens or isolates may be shipped to an external laboratory for testing (e.g., a WHO Supranational Reference Laboratory). At a minimum, the phenotypic DST should include testing for resistance to the FQs and SLIDs used in the country. The regimen should be modified as needed based on the results of the phenotypic DST.

5. For all patients, treatment monitoring should include the collection of samples for culturing as described in the WHO *Guidelines for the programmatic management of drug-resistant tuberculosis, 2016 update*. Any positive culture suggestive of treatment failure should undergo phenotypic DST, if available. At a minimum, the phenotypic DST should include testing for resistance to the FQs and SLIDs used in the country. The regimen should be modified as needed based on the results of the DST.

Considerations for the use of SL-LPA:

When used to test directly sputum specimens from patients RR-TB or MDR-TB, SL-LPA will detect 86% of patients with FQ resistance and 87% of patients with SLID resistance and rarely give a positive result for patients without resistance, as described in the 2016 WHO policy guidance *The use of molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs*. Because of this, WHO recommends that treatment decisions be made on the basis of the SL-LPA results with the following considerations:

- Despite good specificity and sensitivity of SL-LPA for the detection of FQ resistance (pooled sensitivity of 86% and specificity of 99% compared to phenotypic DST) and SLID resistance (pooled sensitivity of 87% and specificity of 99% compared to phenotypic DST), culture and phenotypic DST is required to completely exclude resistance to the individual drugs in these drug classes as well as to other second-line drugs. Phenotypic DST may be particularly needed in settings with a high pre-test probability for resistance to either FQs or SLIDs or both drugs to exclude resistance when the SL-LPA does not detect mutations associated with resistance.

- SL-LPA cannot determine resistance to individual drugs in the class of FQs. Resistance conferring mutations detected by SL-LPA are highly correlated with phenotypic resistance to ofloxacin and levofloxacin. However, the correlation of these mutations with phenotypic resistance or clinically significant resistance to moxifloxacin and gatifloxacin is unclear. The inclusion of moxifloxacin or gatifloxacin in a MDR-TB regimen is best guided by phenotypic DST results.

- SL-LPA has high specificity for the detection of resistance conferring mutations in the rrs gene and these mutations are highly correlated with phenotypic resistance to each of the SLIDs (kanamycin, amikacin and capreomycin). However, mutations in the eis promoter region correlate with phenotypic resistance to kanamycin only. These mutations also confer an increase in the minimum inhibitory concentration (MIC) for amikacin, but the clinical significance of the increase in amikacin MIC is unknown.

Suggested Reading

The use of molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs: policy guidance. Geneva, World Health Organization. 2016. (WHO/HTM/TB/2016.07).
http://www.who.int/tb/publications/lpa-mdr-diagnostics

The use of molecular line probe assays for the detection of resistance to isoniazid and rifampicin. Policy update. Geneva, World Health Organization. 2016. (WHO/HTM/TB/2016.12).
http://www.who.int/tb/publications/molecular-test-resistance

Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 and 2016 updates. Geneva, World Health Organization. 2011 (WHO/HTM/TB/2011.6) and 2016 (WHO/HTM/TB/2016.04).
http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/resources

Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, World Health Organization. 2014. (WHO/HTM/TB/2014.11).
http://www.who.int/tb/publications/pmdt_companionhandbook/en/

Frequently asked questions about the implementation of the new WHO recommendation on the use of the shorter MDR-TB regimen under programmatic conditions, Version: 20 December 2016. Geneva, World Health Organization. 2016.
http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/FAQshorter_MDR_regimen.pdf

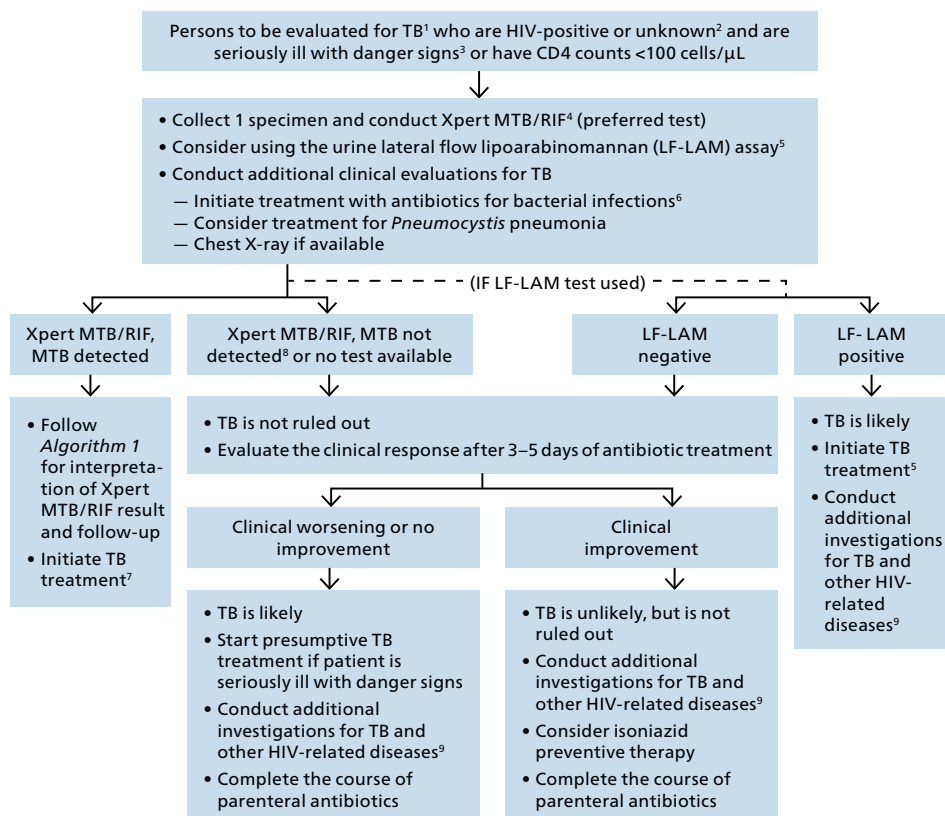*Policy framework for implementing new tuberculosis diagnostics.* Geneva, World Health Organization. 2015. (WHO/HTM/TB/2015.11).
http://www.who.int/tb/publications/implementing_TB_diagnostics/en/

Training packages on culture on solid and liquid medium; on DST by phenotypic and molecular methods; on line probe assays (LPAs). Global Laboratory Initiative. 2012.
http://www.stoptb.org/wg/gli/trainingpackages.asp

1.3.4 Algorithm 4: Algorithm for evaluating persons for TB, among PLHIV who are seriously ill with danger signs or have CD4 counts ≤ 100 cells/μl

Persons to be evaluated for TB[1] who are HIV-positive or unknown[2] and are seriously ill with danger signs[3] or have CD4 counts <100 cells/μL

- Collect 1 specimen and conduct Xpert MTB/RIF[4] (preferred test)
- Consider using the urine lateral flow lipoarabinomannan (LF-LAM) assay[5]
- Conduct additional clinical evaluations for TB
  - Initiate treatment with antibiotics for bacterial infections[6]
  - Consider treatment for *Pneumocystis* pneumonia
  - Chest X-ray if available

– – – – – – – – – (IF LF-LAM test used) – – – – – – – –

Xpert MTB/RIF, MTB detected

- Follow *Algorithm 1* for interpretation of Xpert MTB/RIF result and follow-up
- Initiate TB treatment[7]

Xpert MTB/RIF, MTB not detected[8] or no test available

- TB is not ruled out
- Evaluate the clinical response after 3–5 days of antibiotic treatment

Clinical worsening or no improvement

- TB is likely
- Start presumptive TB treatment if patient is seriously ill with danger signs
- Conduct additional investigations for TB and other HIV-related diseases[9]
- Complete the course of parenteral antibiotics

Clinical improvement

- TB is unlikely, but is not ruled out
- Conduct additional investigations for TB and other HIV-related diseases[9]
- Consider isoniazid preventive therapy
- Complete the course of parenteral antibiotics

LF-LAM negative

LF- LAM positive

- TB is likely
- Initiate TB treatment[5]
- Conduct additional investigations for TB and other HIV-related diseases[9]

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[1] Persons to be evaluated for TB include adults and children with signs or symptoms suggestive of TB or with a chest X-ray with abnormalities suggestive of TB. This algorithm may also be followed for the detection of MTB using CSF, lymph node and other tissue specimen from persons being evaluated for extrapulmonary TB.

[2] PLHIV (People living with HIV/AIDS) include persons who are HIV positive or whose HIV status is unknown, but who present with strong clinical evidence of HIV infection in settings where there is a high prevalence of HIV or among members of a risk group for HIV. For all people with unknown HIV status, HIV testing should be performed according to national guidelines. For all adults living with HIV/AIDS regardless of CD4 cell count or clinical stage, ART should be recommended and initiating co-trimoxazole preventive therapy should be considered.

[3] Danger signs include any one of the following: respiratory rate >30 per minute, temperature >39°C, heart rate >120 beats per minute, or unable to walk unaided.

[4] The Xpert MTB/RIF test is the preferred initial diagnostic test. For persons being evaluated for pulmonary TB, sputum is the preferred specimen.

[5] The LF-LAM assay may be used to assist in diagnosing active TB in both in-and out-patients who are seriously ill with danger signs, regardless of CD4 count. Testing with the LF-LAM assay may be especially useful for patients unable to produce a sputum specimen. Whenever possible, a positive LF-LAM should be followed up with other tests such as Xpert MTB/RIF. While awaiting results of other tests, clinicians could consider initiating TB treatment immediately based on the positive LF-LAM and their clinical judgment.

[6] Antibiotics with broad-spectrum antibacterial activity (except do not use fluoroquinolones) should be used.

[7] Initiate a treatment with first-line or second-line TB drugs based on the Xpert MTB/RIF result. See Algorithm 1.

[8] If the Xpert MTB/RIF test does not detect MTB, the test can be repeated using a fresh specimen. See Algorithm 1 for a discussion of possible follow-up testing for an Xpert MTB/RIF result of MTB not detected.

[9] Further investigations for TB may include chest X-ray, additional clinical assessments, a repeat Xpert MTB/RIF using a fresh specimen, or culture. If the patient is being evaluated for extrapulmonary TB, extrapulmonary specimens should be obtained and sent for culture and abdominal ultrasound may be performed.

Algorithm 4 is used for PLHIV being evaluated for TB (pulmonary or extrapulmonary) who have a CD4 cell count less than or equal to 100 cells/µl or who are seriously ill regardless of CD4 count. This algorithm is based on Annex 15 of the WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach – Second edition.*

Decision Tree for Algorithm 4 is used for testing PLHIV being evaluated for TB who have a CD4 cell count less than or equal to 100 cells/µl or who are seriously ill regardless of CD4 count.

- Follow Algorithm 1 or 2 for all persons being evaluated for TB except PLHIV who have a CD4 cell count less than or equal to 100 cells/µl or who are seriously ill regardless of CD4 count.

- Algorithm 4 may be used for persons being evaluated for pulmonary or extrapulmonary TB.

- The Xpert MTB/RIF test is the preferred initial diagnostic test for Algorithm 4.

- The urine LF-LAM assay may also be used to assist in the diagnosis of TB in these individuals and may be especially useful in persons who cannot produce a good quality sputum specimen or when the Xpert MTB/RIF test is not available.

- Testing using the approved rapid methods should be given priority. Smear microscopy and culture may be useful, particularly when the rapid tests do not detect MTB.

1. Evaluate the patient for TB, determine HIV status, and assess presence of danger signs for being seriously ill. In PLHIV who are not seriously ill, it may also be necessary to measure CD4 cell counts to assess eligibility for testing with the LF-LAM assay.

    a. Persons to be evaluated for TB include adults and children with signs or symptoms suggestive of TB (pulmonary or extrapulmonary) or with a chest X-ray with abnormalities suggestive of TB.

    b. PLHIV include persons who are HIV positive or whose HIV status is unknown, but who present with strong clinical evidence of HIV infection in settings where there is a high prevalence of HIV or among members of a risk group for HIV. For all people with unknown HIV status, HIV testing should be performed according to national guidelines.

    c. Seriously ill is defined as presenting with any one of the following danger signs: respiratory rate >30 per minute, temperature >39 °C, heart rate >120 beats per minute, or unable to walk unaided.

2. For PLHIV being evaluated for TB who have a CD4 cell count less than or equal to 100 cells/µl or who are seriously ill regardless of CD4 count:

    a. Collect a specimen and conduct the Xpert MTB/RIF test. Follow Algorithm 1 for result interpretation and follow-up testing.

        i. For persons being evaluated for pulmonary TB, induced or expectorated sputum (preferred), bronchoalveolar lavage, gastric lavage, and gastric aspirate specimens may be used. Data are limited for the sensitivity of the

Xpert MTB/RIF with other samples such as nasopharyngeal aspirates, string test samples, or stool samples.

ii. For persons being evaluated for extrapulmonary TB, the Xpert MTB/RIF test is recommended for use with CSF, lymph nodes and other tissue samples. However, the test has low sensitivity for pleural fluid specimens and data are limited for its sensitivity with stool, urine or blood specimens.

b. Collect a urine specimen and conduct the LF-LAM assay.

i. If the Xpert MTB test is available on site, the LF-LAM testing should be done in parallel to the Xpert MTB/RIF test.

ii. A positive LF-LAM result should be interpreted in the context of clinical judgment, chest X-ray findings (if available), and bacteriological results including Xpert MTB/RIF testing. While awaiting results of other tests, clinicians could consider initiating TB treatment immediately based on the positive result of the LF-LAM test and their clinical judgment.

iii. If the LF-LAM result is negative, re-evaluate the patient and conduct additional testing in accordance with national guidelines. Further investigations for TB may include chest X-ray, repeat Xpert MTB/RIF test, additional clinical assessments, or culture.

c. Conduct additional clinical evaluations for TB such as initiating treatment for bacterial infections using antibiotics with broad-spectrum antibacterial activity (except do not use fluoroquinolones). Consider treatment for Pneumocystis pneumonia. Evaluate clinical response after 3–5 days of treatment.

i. If clinical worsening or no improvement after 3–5 days of treatment, initiate further investigations for TB and other diseases and, if patient is seriously ill with danger signs, start presumptive TB treatment.

ii. If clinical improvement, reassess for TB and other HIV-related diseases.

1. Consider that clinical improvement may occur if the patient has TB and a bacterial infection, i.e., TB may not be ruled out.

2. If there is high clinical suspicion of TB (clinical history and physical exam, history of previous TB that can be reactivated, chest ray suggestive) in the patient, use clinical judgement as to whether to initiate TB treatment.

iii. All patients should complete the course of treatment for bacterial or Pneumocystis infections.

Considerations when using the LF-LAM test:

- The LF-LAM test should not be used to assist in the diagnosis of TB in populations other than described in Algorithm 4 and should not be used as a screening test for TB.

- LF-LAM is designed for use with urine samples. Other samples (e.g., sputum, serum, CSF or other body fluids) should not be used.

- LF-LAM does not differentiate between the various species of the genus *Mycobacterium*. However, in areas with a high prevalence of TB, the LAM antigen detected in a clinical sample is likely to be attributed to MTB.

- The use of the LF-LAM assay does not eliminate the need for other diagnostic tests for TB such as Xpert MTB/RIF or culture. These tests exceed the LF-LAM test in diagnostic accuracy and provide information on drug susceptibility. Whenever possible, a positive LF-LAM should be followed up with other tests such as Xpert MTB/RIF, WRD, or bacteriological culture and drug-susceptibility testing.

- Published studies revealed that the LF-LAM test may give a different result than the Xpert MTB/RIF test or culture (e.g., LF-LAM positive, Xpert MTB/RIF MTB not detected). This is not unexpected because the tests have different sensitivities and measure different analytes. Treatment decisions should rely on clinical judgement and all available information.

Suggested Reading

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach – Second edition. Geneva, World Health Organization. 2016.
http://www.who.int/hiv/pub/arv/arv-2016/

The use of lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis and screening of active tuberculosis in people living with HIV: policy guidance. Geneva, World Health Organization. 2015. (WHO/HTM/TB/2015.25).
http://www.who.int/tb/publications/use-of-lf-lam-tb-hiv

Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy update. Geneva, World Health Organization. 2013. (WHO/HTM/TB/2013.16)
http://www.who.int/tb/publications/xpert-mtb-rif-assay-diagnosis-policy-update/en/

Training package on Xpert MTB/RIF. Global Laboratory Initiative. 2014.
http://www.stoptb.org/wg/gli/TrainingPackage_XPERT_MTB_RIF.asp

1.4 Targets and indicators for TB laboratory strengthening

The WHO End TB Strategy calls for the early diagnosis of TB including universal DST, currently defined as DST for at least rifampicin, among all patients with bacteriologically confirmed TB, and further DST for at least FQs and SLIDs among all TB patients with rifampicin resistance. A prerequisite for any NTP to reach this goal is a quality-assured laboratory network equipped with rapid diagnostics. The WHO *Framework of indicators and targets for laboratory strengthening under the End TB Strategy* serves as a guide for all countries in the development of plans for laboratory strengthening in 2016–2025. The indicators measure the programme's capacity to detect patients accurately and rapidly using new diagnostics (i.e., WRDs), provide universal DST, and ensure quality of testing. The twelve core indicators grouped under three objectives (increase access to rapid and accurate detection of TB; reach universal access to DST, strengthen quality of laboratory services) will be monitored

at the global level by WHO to assess a country's progress towards reaching targets; additional stratified indicators are also included for monitoring at country-level when recording and reporting systems allow.

Laboratory strengthening efforts in country must be aware of these indicators and prioritize activities that address the accomplishment of the goals of the End TB strategy.

Table 4   Indicators for laboratory strengthening under the End TB Strategy[a]

OBJECTIVE 1: INCREASE ACCESS TO RAPID AND ACCURATE DETECTION OF TB	
Indicator 1.	Does the national diagnostic algorithm indicate a WHO-recommended rapid diagnostic (WRD[b]) is the initial diagnostic test for all people with signs and symptoms of TB?
Indicator 2.	Percentage of notified new and relapse TB cases tested with a WRD as the initial diagnostic test
Indicator 3.	Percentage of notified new and relapse TB cases with bacteriological confirmation[c]
Indicator 4.	Percentage of testing sites using a WRD at which a data connectivity system has been established that transmits results electronically to clinicians and to an information management system
Indicator 5.	Does national policy indicate that TB diagnostic and follow-up tests provided through the national TB programme are free-of-charge, and/or that fees can be fully reimbursed through health insurance, for all people with signs and symptoms of TB?
OBJECTIVE 2: REACH UNIVERSAL ACCESS TO DST[d]	
Indicator 6.	Does the national policy and diagnostic algorithm indicate there is universal access to DST?
Indicator 7.	Percentage of notified, bacteriologically confirmed TB cases with DST results for rifampicin
Indicator 8.	Percentage of notified, rifampicin-resistant TB (RR-TB) cases with DST results for fluoroquinolones and second-line injectable agents
OBJECTIVE 3: STRENGTHEN THE QUALITY OF LABORATORY SERVICES	
Indicator 9.	Percentage of diagnostic testing sites that monitor performance indicators and are enrolled in an external quality assessment (EQA) system for all diagnostic methods performed
Indicator 10.	Percentage of DST sites that have demonstrated proficiency by EQA panel testing for all DST methods performed
Indicator 11.	Percentage of laboratories conducting either culture, LPA and/or phenotypic DST, in which a formal quality management system (QMS) is being implemented that aims to achieve accreditation according to international standards
Indicator 12.	Is the National Reference Laboratory currently accredited according to the ISO15189 standard?

[a] Indicators are not listed in order of priority.

[b] WHO-recommended rapid diagnostics (WRDs) employ molecular techniques for the detection of TB.

[c] A bacteriologically confirmed TB case is one from whom a biological specimen is positive by smear microscopy, culture, or WRD.

[d] Universal access to DST is currently defined as DST for at least rifampicin among all patients with bacteriologically confirmed TB and further DST for at least FQs and SLIDs among all TB patients with rifampicin resistance. DST methods include genotypic (molecular) and phenotypic methods.

Suggested reading

Framework of indicators and targets for laboratory strengthening under the End TB Strategy. Geneva, World Health Organization. 2016. (WHO/HTM/TB/2016.18). http://www.who.int/tb/publications/labindicators/en/

2. Key technical areas

2.1   Procurement and supply-chain management

Effective care and treatment of TB requires support from fully functioning laboratory services that provide accurate, reliable, and timely results. To be fully functional, laboratory services require a continuous uninterrupted supply of commodities. These commodities include equipment and supplies, such as reagents, diagnostic kits, and various consumables.

Effective supply chain management is a complex process that includes:

- product specification
- product selection
- forecasting of needs (based on past and projected consumption)
- procurement
- customs clearance, if applicable
- distribution
- storage and use

However, in the majority of low- and middle-income countries, provision of uninterrupted supplies at laboratories continues to be a significant challenge. This may be for several reasons, including heavy reliance on direct donor procurement; lack of coordination and standard procedures for procurement and distribution of supplies by government, donors, and other partners; lack of accurate consumption data on which to estimate actual supply needs; lack of up-to-date guidance with regard to the necessary technical specifications, international ISO regulations, or essential quality parameters; and long and bureaucratic procedures for procurement within the government, involving several government ministries and levels of approval.

Consequently, this has led to:

- Frequent stock-outs leading to interruptions in service delivery and delays in treatment or patient management decisions
- Waste due to expiry of reagents
- Poor quality of materials or reagents which in turn can lead to inaccuracy of testing or test failure
- Equipment which is inappropriate or non-functional

An inadequately managed supply chain may result in either under- or over-stocking supplies, both of which have serious detrimental effects. If access to supplies is

interrupted, a laboratory may have to suspend services and/or divert patients to other testing sites. This may result in delayed diagnosis of patients, added cost and inconvenience to patients who are referred to other sites, and confusion and lack of confidence in the laboratory by clinicians. Over-stocking also has negative consequences, including waste of resources when stock reaches its expiry date before being consumed. Furthermore, poor selection of equipment and supplies leads to inadequate or poor quality goods being used.

Effective management of laboratory equipment and supplies is essential at every level of the network. It requires planning, understanding the routine consumption rates of supplies, and anticipating changes in the workload (e.g., due to seasonal or annual trends). Donors and partners who are procuring laboratory supplies directly must also be coordinated. Thus the NTP, NRL, and others involved in commodities decision making, forecasting, and procurement must work together to ensure a continuous flow of supplies to support testing. Some countries have instituted a central pooled procurement process in order to better manage procurement of certain supplies, e.g., Xpert MTB/RIF cartridges. Such a system ensures the needs of all laboratories are met while reducing waste due to reagents expiring before they are used. Other countries have implemented a logistics strategy to ensure that sufficient numbers of within expiry cartridges are available; when a laboratory has accumulated excess stock, it is reallocated to other laboratories within the network.

The NRL, NTP or other central institution, working with national medical supply services or procurement agencies, usually sets standards for commodities management, and also provides QA and reporting mechanisms. They should also evaluate the quality, accuracy, and performance of equipment and supplies. More specifically the NRL, NTP, and supportive commodities management organizations should be responsible for:

- Selecting equipment and supplies, and setting specifications and quantities

- Participating in budgeting and planning – including verifying tenders, bids, and contracts

- Working with local and national procurement organizations

- Arranging and training laboratory managers and staff in commodity management activities

Managing a laboratory's commodities involves careful planning and coordination, and should follow the well-recognized cycles of selection, procurement, distribution, and use. General guidance can be obtained from various sources, including *USAID/Deliver: Guidelines for Managing the Laboratory Supply Chain*.

WHO has developed guidelines and specifications which provide standard guidance on procuring TB laboratory equipment, consumables and supplies for TB microscopy, culture, and DST equipment and supplies; see WHO *Guidance for countries on the specifications for managing TB laboratory equipments and supplies*.

Fig. 2 Flow of information and supplies in a laboratory network from *Guidelines for Managing the Laboratory Supply Chain: Version 2*. Arlington, Va.: USAID | DELIVER PROJECT, Task Order 1.

Commodity flow — Information flow
NPHLS = National Public Health Laboratory Services
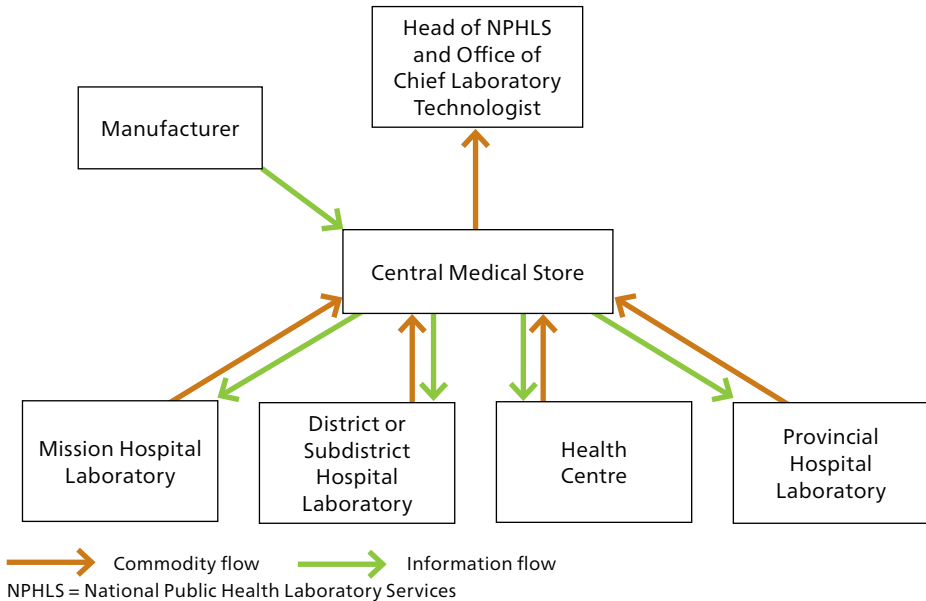
In well-functioning TB programmes, forecasting, procurement, and distribution are under regulation by a national system and well documented using electronic data systems which monitor both distribution and consumption rates for all laboratories. In addition, materials and supplies are stored in well-organized national warehouses with proper climate control conditions. Distribution is then provided on a schedule which correlates to usage rates. Shipments to laboratories are organized on a central calendar to ensure timely delivery. Often regional hubs are established to facilitate local transit or pickups. These systems are rare in most limited resource settings, but their presence is increasing due to the increased use of molecular testing technologies which have specific storage specifications for reagents and materials necessary for quality testing. Countries are encouraged to develop commodities management guidelines and national distribution systems to limit issues of expiry, stock-out, or wastage due to inappropriate storage, poor forecasting, and inefficient shipment. Factors influencing procedures for storage and distribution include expiry dates and storage requirements.

Each laboratory (at all levels) should have a comprehensive list of equipment, reagents, and consumables for the tests being performed. This list should include detailed specifications with catalogue and lot numbers for each item in stock. These specifications are required if the laboratory goods need to be procured by tender. In order to maintain a consistent record, this data should be managed by a single person in the laboratory. While the data can be kept in a paper register, it is better to have this information in a database or excel register if possible (see references for

supply chain management tools). Any materials or equipment provided directly to a laboratory by a donor or partner organization should be placed in this inventory and reported to the national programme or national procurement systems services. It is important that all commodities be registered with the national authorities in order to maintain equity within the system and avoid over-stocking or materials expiring.

Product lead time (i.e., the time from the placing of an order to the delivery of the goods) may be long and involve complex procedures, contributing to stock outs and service interruption. This time may be further extended by customs clearance procedures for imported products. These procedures often require special knowledge and skills, and may lead to unanticipated costs and incorrect storage conditions. Delays in clearing customs may result in supplies being unfit for use. In some countries customs clearance is handled by specialised public or private entities; in others, TB laboratory or MoH staff may dedicate considerable time to ensuring supplies are cleared from customs in a timely fashion.

KEY ACTIVITY AREAS FOR TECHNICAL SUPPORT

- **Advise on developing specifications for TB laboratory supplies and equipment and product selection criteria**
- **Review existing supplies management practices and advise on improvements**
- **Assist with measuring consumption and establishing inventories**
- **Develop technical specification for equipment, consumables, and reagents**
- **Assist with developing forecasting strategies**
- **Support development of internal commodities registers**
- **Implement laboratory information management systems (LIMS) to assist with commodities management**
- **Provide training on various aspects of supply chain management**
- **Support establishment and management of the laboratory storage and distribution system**
- **Help develop national guidelines for commodities management**

Suggested reading

Logistics supply management tool. TB CARE I.
http://www.tbcare1.org/publications/toolbox/lsm/

Guidance for countries on the specifications for managing TB laboratory equipments and supplies. Geneva, World Health Organisation. 2011.
http://whqlibdoc.who.int/publications/2011/9789241503068_eng.pdf

Guidelines for Managing the Laboratory Supply Chain: Version 2. Arlington, Va.: USAID | DELIVER PROJECT, Task Order 1 2008.
http://deliver.jsi.com/dlvr_content/resources/allpubs/guidelines/GuidManaLabSC_v2.pdf

2.2 Specimen collection, transport and registration

Proper steps for sputum collection are important to obtain specimens of good quality in order to ensure accurate and reliable test results. Use of good quality specimen containers is critical, and specifications should be clearly defined to ensure good quality specimen containers are available at all sites. Specimen containers must always be labelled before the specimen is collected from the patient.

Having a well-functioning sample reception unit that checks the quality of each sample and rejects those that are of inadequate quality is an essential step in ensuring that the testing process runs correctly and produces a quality result. The reception unit must check each sample for compliance with quality criteria and completed documentation. Once accepted, each specimen must be recorded in the laboratory register with all the necessary information. If the sample doesn't completely comply with the criteria it must be rejected and a request should be made for a new sample. If documentation is incomplete, efforts must be taken to contact the sending physician or clinic to acquire all the necessary information to complete the register.

When testing cannot be conducted at the site of collection, collected specimens must be properly labelled and efficiently and safely transported using a specimen referral system to the nearest laboratory for testing. Lower level health centres and laboratories must be linked to higher level laboratories to be able to provide universal patient access to testing as stipulated in national diagnostic algorithms, ensure efficient patient management and optimize use of different technologies at different levels of a tiered network. Optimization of the specimen referral network requires careful consideration to balance access, costs and turnaround time. Transporting sputa must be done according to recommended protocols, taking into account the distance and transit time, in order to ensure integrity. All efforts should be made to integrate TB specimen transport and referral systems with systems used for other specimens and testing purposes.

The NTP and NRL should determine the information to be included on the specimen container and requisition (examination request) form, drawing on WHO recommendations as described in *Guidance on regulations for the Transport of Infectious Substances 2015–2016*. It is critical that the NTP and NRL train and monitor provincial health units and other referring facilities to ensure proper and safe collection practices are in place, proper transit protocols are utilized, and documentation is complete. Laboratories should develop a laboratory handbook that includes information relating to collection, labelling, and transporting of specimens, with target turnaround times and specimen rejection criteria; this handbook should be distributed to all referring facilities.

Important considerations for collection, labelling, transporting, and registering specimens can be found in GLI-approved training programmes for Xpert MTB/RIF, culture, and DST.[1] Target turnaround times should be set locally and monitored for adherence. For more information, see *General Quality Indicators* in Section 2.3.2.

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[1] http://stoptb.org/wg/gli/trainingpackages.asp

2.2.1 Collection

Good quality specimens are necessary to ensure proper laboratory diagnosis of TB. Non-salivary sputum specimens of approximately 3–5 ml are optimal. However, collecting sputum represents a significant hazard since coughing produces potentially infectious aerosols. Therefore, specific measures must be taken to minimize the health worker's exposure to these aerosols. Wherever possible, sputum specimens should be collected outdoors where infectious droplets will be rapidly diluted and ultraviolet light can rapidly inactivate TB bacilli. Specimens should never be collected in laboratories, toilets or washrooms, waiting areas, reception rooms, or any other enclosed space where people congregate. When ventilated sputum collection rooms (or booths) are correctly used and maintained, they are a safe alternative to outdoor collection. Maintenance of these rooms or booths requires proper modes of ventilation during expectoration and appropriate decontamination and disinfection procedures.

Staff must be trained to provide patients with proper instructions about how to collect a quality specimen. Instructions on posters and leaflets in designated sputum collection areas are helpful. Nevertheless, it is necessary to supervise the first specimen collection process to help the patient understand the protocol. While supervising, the health care worker must stand behind the patient away from any possible exposure to aerosolized droplets. Detailed guidance on safe collection of good quality sputum specimens is provided in *Laboratory Diagnosis of Tuberculosis by Sputum Microscopy: The Handbook, Global Edition*.

The LF-LAM test is a unique WHO-approved test for detecting TB in that it uses urine as the patient sample. Guidance on collecting and storing of urine samples for the LF-LAM can be found in the Alere Determine™ TB LAM Ag Package insert.[2]

2.2.2 Transport and packaging

The use of triple packaging is required to safely transport infectious material – that is, the container should be wrapped in absorbent material (cotton or paper towels), protected by secondary packaging (e.g., ziploc bag) and then placed in shock-resistant outer packaging. Special requirements for local and international transit are illustrated below.

Local Transit

Local transit may be done by various means – by courier, health facility vehicles, other means of transport such as motorcycles, or "hand delivery" by district TB officers or other cadres. All persons transporting specimens should be provided with training on biosafety and have spill kits accessible in case of accidents. All transporters should follow local regulations where applicable. Use of specimen transport logs is recommended in order to provide adequate budgeting for a sustainable system and to identify high service areas that may need an additional laboratory or referral hub.

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[2] https://ensur.invmed.com/ensur/broker/ensurbroker.aspx?code=I-DET-7D2740&cs=28935940

International Transit

International transportation requires proper packaging according to carrier specifications for shipping infectious materials and must comply with international regulations. The diagram below (Figure 3) illustrates the elements required for packaging and shipping through international postal carriers. The package should be labelled according to regulations for the transport of infectious materials and logged into a transportation register by the carrier, with a copy given to the referring centre for tracking. International organizations such as the Universal Postal Union (UPU), the International Civil Aviation Organization (ICAO), and the International Air Transport Association (IATA) follow specific guidelines to facilitate the safe shipment of infectious materials. Shipping *M. tuberculosis* cultures internationally (for example, for diagnostic DST, retesting, or proficiency testing) is subject to international regulations as well as to specific national import and export regulations. International protocols and guidelines for safe transit are well established and described in the WHO *Guidance on regulations for the transport of infectious substances*.
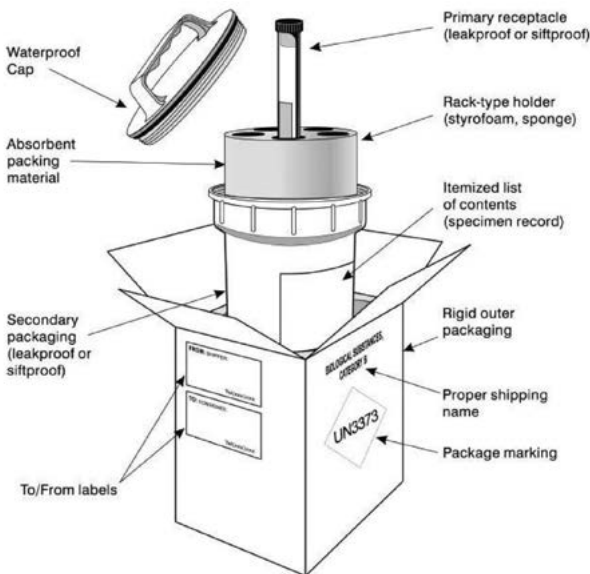
If delays in transport are anticipated, specimens should be transported to the laboratory in a cool box. This is especially relevant for specimens for TB culture. Sample contamination due to inappropriate storage and long transport times is less of a concern with smear or rapid molecular tests than with conventional culture-based approaches.

Fig. 3 Example of triple packaging for Category B infectious substances (IATA) from *Guidance on regulations for the transport of infectious substances* 2015. World Health Organization.

Shipment of infectious materials is an expensive process and it is critical to ensure that shipments are not delayed by bureaucratic or packaging errors; shipments may be rejected or suffer excessive delays that render the samples useless for subsequent laboratory investigations.

2.2.3 Specimen logs, registers and examination request forms

Proper documentation of samples being transported and received is critical to tracking and managing referral activities, while also providing a structure for collecting essential patient information. Primary forms of documentation include referral logs or registries, specimen registries, and test request forms. All forms and registers need to be complete and well maintained. While some laboratories may utilize electronic registries, most settings still rely on paper-based systems.

The following documentation is generally needed for shipments outside the country (e.g., to a SRL) and should be checked prior to initiating a shipment:

- Customs declarations

- Evidence that staff have a current IATA certification (if air shipment is required)

- Current import permits

- Contact details of person to whom shipment is being sent

All copies of paperwork should be sent to consignee in advance (e.g., airway bill, customs, quarantine, Dangerous Goods declaration).

Transport registers or logs may or may not exist; however, it is important to encourage programmes to develop these within their systems. Transport registers help provide a tracking system and should record the name of the referring clinic, the date of transport, the number of specimens being transported, type of specimens transported if the transport system is integrated (e.g., containing blood, urine, or extrapulmonary tissue or fluids in addition to sputum specimens for TB testing), distance (km) transported (to assist with budgeting for fuel and manage efficient travel routes), and incidents or accidents during transport that cause delays or promote contamination. A sample log is provided in Figure 4.

Specimen registers are required for all laboratories. The register contains the information from the specimen examination request form for each patient and queues the specimen into the laboratory testing schedule. Each specimen is assigned a number which is then used as the identifier throughout all testing processes. The specimen identification number ensures patient confidentiality and eliminates preferential queuing for certain clients. The identification number is linked to patient TB registration or identification numbers and therefore the patient's internal records. Registers will vary depending on the level of the laboratory and the tests performed at the facility. A sample register for a peripheral laboratory using microscopy and Xpert MTB/RIF is provided in Figure 5.

Specimen examination request forms contain information about the patient and the tests requested by the physician. These forms identify the patient as a new case for diagnosis or a patient requiring follow-up testing to manage treatment. This form

Fig. 4   Specimen transport log

Daily Specimen Transport Register Date: _____	Driver/Carrier:				Odometer Start: _____	
Location (facility/city)	No. of specimens	Specimen Types*	Time of Pick-up	Time of Drop-off	Odometer (Km)	Incidents or delays

Odometer End: _____   Total Km: _____

* Specimen Types: S=Sputum, B=Blood (including DBS), U=Urine, O= Other

Driver signature: _____

Courier Supervisor: _____   Date: _____

Fig. 5   Sample register for a peripheral laboratory

LABORATORY REGISTER FOR SMEAR MICROSCOPY AND XPERT MTB/RIF

Lab serial no.	Date specimen received[a]	Patient Name	Sex M/F	Age / Date of birth	Patient address	Treat-ment unit	BMU* and TB register no.	HIV infection (Y/N/ Unk)[b]	Patient previ-ously treated for TB[c]	Examination type (tick one option)		Examination result				Remarks[g]
										Diagnosis	Follow-up	Xpert[e]	Smear microscopy[f]			
													1	2	3	
											Month[d]	Date	Date	Date	Date	

[a] For diagnostic testing employing serial sputa or other specimens, this is the date of receipt of the first set of specimens.

[b] Y = Yes; N = No; Unk = unknown

[c] Y = previously treated; N = not previously treated; Unk = unknown

[d] Patient on TB treatment; indicate month of treatment at which follow-up examination is performed.

[e] Xpert MTB/RIF test result reported as follows: T = MTB detected, rifampicin resistance not detected
RR = MTB detected, rifampicin resistance detected
TI = MTB detected, rifampicin resistance indeterminate
N = MTB not detected
I = invalid / no result / error

[f] Smear results reported as follows: 0 = no AFB
(1–9) = exact number if 1–9 AFB/100 HPF (scanty)
+ = 10-99 AFB/100 HPF
++ = 1-10 AFB/HPF
+++ = >10 AFB/HPF

[g] If Xpert MTB/RIF indeterminate result, indicate error code or "invalid"

* BMU = Basic management unit

is the most critical form and must be complete in order to capture data for routine surveillance activities and proper patient record management. A sample form is shown in Figure 6.

Fig. 6 Specimen examination request form

Request for examination of biological specimen for TB

Treatment unit: _____   Date of request: _____

Patient name: _____

Age (years): _____   Date of birth: _____   Sex: ☐ Male   ☐ Female

Patient address: _____

_____   Telephone: _____

Reason for examination:

    ☐ Diagnosis. If diagnosis, presumptive RR-TB/MDR-TB?: ☐ Yes ☐ No

  OR ☐ Follow-up. If follow-up, month of treatment: _____

HIV infection?　　　　　　☐ Yes ☐ No ☐ Unknown

Previously treated for TB?　☐ Yes ☐ No ☐ Unknown

Specimen type:　　　　　　☐ Sputum　　☐ Other (specify):_____

Test(s) requested:　　　　☐ Microscopy ☐ Xpert MTB/RIF

　　　　　　　　　　　　☐ Culture　　☐ Drug susceptibility　☐ Line probe assay

Requested by (Name and signature): _____

_____

Microscopy results (to be completed in the laboratory)

Date sample collected (filled by requestor)	Specimen type	Laboratory serial number(s)	Visual appearance (blood-stained, mucopurulent or saliva)	Result (tick one)				
				Negative (0 AFB/ 100 HPF)	1–9/100 HPF (scanty; report no. of AFB)	+ (10–99 AFB /100 HPF)	++ (1–10 AFB/ HPF)	+++ (>10 AFB/ HPF)

Examined by (name and signature): _____

Date of result: _____

Fig. 6 *(continued)*

Xpert MTB/RIF test result *(to be completed in the laboratory)*

Date sample collected: _____

| M. tuberculosis: | ☐ Detected | ☐ Not detected | ☐ Invalid / No result / Error |
| Rifampicin resistance: | ☐ Detected | ☐ Not detected | ☐ Indeterminate result |

Examined by (name and signature): _____

Date of result: _____

Culture results *(to be completed in the laboratory)*

Date sample collected (filled by requestor)	Media used (liquid or solid)	Laboratory serial number(s)	Result (tick one)						
			Negative (0 colonies)	1–9 (<10 colonies)	+ (10–100 colonies)	++ (>100 colonies)	+++ (Innumerable/ confluent growth)	NTM[1]	Contaminated

Examined by (name and signature): _____

Date of result: _____

Drug susceptibility test (DST) and line probe assay (LPA) results *(to be completed in the laboratory)*

Date sample collected (filled by requestor)	Method[a]	Laboratory serial number(s)	Results[b] (mark for each drug)											
			H	R	E	S	Amk	Km	Cm	FQ:	Other:	Other:	Other:	Other:

[a] Specify: solid media DST; liquid media DST; direct LPA; indirect LPA

[b] Results codes: R = Resistant   S = Susceptible   C = Contaminated   — = Not done

Examined by (name and signature): _____

Date of result: _____

The *Definitions and reporting framework for tuberculosis – 2013 revision* should be used as a template for devising request and report forms for referring specimens and reporting results from smear microscopy, culture, Xpert MTB/RIF testing, or DST (including LPA). Countries are encouraged to modify these forms to include additional tests such as TB-LAMP or SL-LPA. For example, the form shown in Figure 6 could be modified to add TB-LAMP to the Xpert MTB/RIF column and a set of TB-LAMP reporting values added to the footnotes.
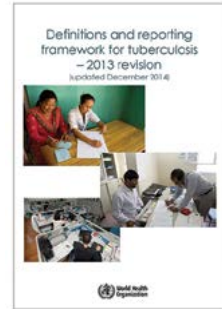
KEY ACTIVITY AREAS FOR TECHNICAL SUPPORT:

- ■ **Offer training on proper collection for quality specimens**
- ■ **Develop aids for patients on specimen collection and safe practices**
- ■ **Offer training on specimen packaging and transportation**
- ■ **Develop specimen referral systems with proper tracking systems**
- ■ **Analyse recent shipments to determine cost, efficiency, and service received**
- ■ **Establish a data system to record referral activities to assess the process; allow adequate budgeting for materials, personnel and fuel; identify limitations to access; and stratify referral to define access for risk groups**
- ■ **Develop and updates templates of logs, registers and specimen examination request forms**

Suggested reading

Laboratory Diagnosis of Tuberculosis by Sputum Microscopy. The Handbook: Global Edition. Global Laboratory Initiative. 2013.
http://stoptb.org/wg/gli/gat.asp

Tuberculosis laboratory biosafety manual. Geneva, World Health Organization. 2012. (WHO/HTM/TB/2012.11).
http://www.who.int/tb/publications/2012/tb_biosafety/

Definitions and reporting framework for tuberculosis – 2013 revision. Geneva, World Health Organization. 2013. (WHO/HTM/TB/2013.2).
http://www.who.int/tb/publications/definitions

TB diagnostics and laboratory strengthening: WHO policy. Definition of a new sputum smear-positive TB case, 2007. Geneva, World Health Organization. 2007.
http://www.who.int/tb/laboratory/policy_sputum_smearpositive_tb_case/

Guidance on regulations for the Transport of Infectious Substances 2015–2016. Geneva, World Health Organization. 2015. (WHO/HSE/GCR/2015.2).
http://www.who.int/ihr/publications/who_hse_ihr_2015.2/

2.3 Quality assurance (QA)

2.3.1 Introduction to QA

A comprehensive and systematic QA programme should be implemented to enable laboratories to achieve and maintain high levels of accuracy and proficiency in testing, to ensure the reliability and reproducibility of results, and thus to inspire confidence in clinicians and patients who are users of the laboratory's services.

QA may be defined as follows:

"Planned and systematic activities to provide confidence that an organization fulfils requirements for quality." [CLSI GP26-A4]

"Encompasses a range of activities that enable laboratories to achieve and maintain high levels of accuracy and proficiency despite changes in test methods and the volume of specimens tested." [www.cdc.gov/labstandards]

In many resource-limited settings, comprehensive QA for TB diagnostic tests is limited or absent, may be performed sporadically, and is often poorly documented. Routine monitoring of laboratory indicators is often not done, and quality control (QC) and external quality assessment (EQA) may only be performed in a limited way or only on certain tests. Even when such procedures are in place, it is common that the results of QA activities are not reported back to the laboratories in a timely fashion, or support for corrective actions is not available, leading to missed opportunities for quality improvement. The content and quality of training provided in a country may vary widely, and training participants are often not assessed for competency. Implementation of a holistic QA programme can significantly improve TB laboratory services.

Figure 7 illustrates the essential elements of a QA programme applied to any technology. Some requirements are general to all technologies and others have test-specific requirements or definitions.

QA activities should be seen as an integral part of the routine workload and not as a separate activity. All QA activities must be documented. Feedback to testing sites and

Fig. 7   Essential elements of a comprehensive QA programme

Environment	Personnel	Equipment	Supplies	Specimens	Internal quality monitoring	External Quality Assessment (EQA)	Accurate and timely reporting
Safe and functional Temperature control	Trained and competent staff Test user is documented Current SOPs readily available	Maintained and serviced	Uninterrupted supplies Appropriate transport and storage condition	Good quality Labelled with unique ID Completed request form	Test working properly	Lab's work checked by another lab	Turnaround time Results review

Accurate, reliable and timely results

implementing corrective and preventive measures are the most critical aspects of any QA programme and also those aspects which are often poorly implemented.

QA is, however, just one part of a laboratory quality management system (QMS), which is required to ensure the quality of all a laboratory's processes.

2.3.2 Key QA activities

Specific QA activities can be defined beyond the general elements already mentioned. The following are considered to be essential QA activities for any TB laboratory. They are also ISO 15189 requirements.

Key QA activities:

a. Training and competence assessment

b. Instrument verification

c. Equipment maintenance

d. Method validation

e. Quality control (QC)

f. Lot testing (also known as incoming quality control or new batch testing)

g. External quality assessment (EQA)

h. Quality indicator monitoring

i. Continuous quality improvement (QI)

a. Training and competence assessment

Training materials have been developed and are freely available for most WHO-recommended TB diagnostics, including smear microscopy (light and fluorescence), solid and liquid culture, DST, LPA, and Xpert MTB/RIF. They may be downloaded from the training packages on the GLI website.[3] QA procedures associated with each technology are included in each package and should be part of any trainings. Some specific training materials have also been developed which deal exclusively with QA in more detail, for example the *External quality assessment for AFB smear microscopy*.

Such materials may require customization based on the country situation, resources and existing policies and guidelines. Such customization should be done, wherever possible, in close collaboration with the NRL and NTP, often through a laboratory technical working group, to ensure local ownership and country relevance. A standardized training package and tools should be implemented in all laboratories in a given country. Where it exists, a process for national approval of the training materials should be followed, and all organizations providing training in the country should follow the approved training materials, ensuring consistent quality and content.

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[3] http://stoptb.org/wg/gli/trainingpackages.asp

At the country level, one of the most common approaches is "training the trainers", in which selected participants (usually from the NRL or regional referral laboratories) are provided intensive content training as well as being coached in how to deliver the training to other personnel. This may be done regionally or by country. These participants, once deemed competent, then provide training to staff in peripheral laboratories within the country.

When planning to conduct training, you should liaise with the NRL to ensure that the appropriate personnel are invited to the training. For example, for laboratory training in DST, personnel who will conduct the testing on a routine basis should be trained, rather than managers or non-laboratory personnel.

All trainings should include a competence assessment of the participants. Competence is defined as a *demonstrated ability to apply knowledge and skills*, and clear criteria for competence should be set in advance. Staff competence should be monitored on a regular basis, and refresher training provided.

b. Instrument verification

Instruments should be evaluated as being "fit for purpose" through verification with known positive and negative material prior to commencing testing of clinical specimens, and after calibration or repair of instruments. Verification testing should be repeated in case of any deviation from expected results, and suppliers contacted in case of repeated errors for troubleshooting.

c. Equipment maintenance

A schedule of preventive maintenance and calibration should be designed for each piece of equipment. If calibration and maintenance are easy to perform, then a staff member or a designated equipment officer may perform the tasks, with or without additional technical training. If the equipment is sensitive and maintenance or calibration is complex, it is better to hire an external, specialized company to perform these tasks. In some cases, manufacturers offer maintenance and calibration services.

d. Method validation

All tests used in the laboratory must be validated for their intended use. For commercial tests, in which the test is used according to the manufacturer's intended use, additional large scale laboratory evaluations are not necessary. Rather, small scale method validations, or verifications, in line with requirements for national or international accreditation schemes, may be warranted. However, some laboratories do conduct such large scale evaluation studies to confirm performance if they believe country-specific factors, such as the prevalence of different mutations, may cause performance to deviate substantially from results of the manufacturer's or other evaluation studies. However, if laboratories perform non-standard or modified methods, use tests outside their intended scope (e.g., specimens for which the test has not been validated), or use methods developed in-house, then more extensive method validation is required prior to commencing testing of clinical specimens.

This usually consists of testing either a well-characterized panel of known positive and negative samples (in a blinded fashion) or prospectively testing the current gold standard and new test in parallel on clinical specimens.

e. Quality control

Quality control (QC) monitors activities related to the examination, i.e., analytical phase of testing. The goal of QC is to detect, evaluate, and correct errors due to test system failure, environmental conditions, or operator performance before patient results are reported. QC involves examination of control materials or known substances at the same time and in the same manner as patient specimens to monitor the accuracy and precision of the complete analytical process. If QC results are not acceptable, patient results must not be reported.

QC materials are most commonly the following: well-characterized strains of MTB or NTM, water or decontamination solutions (negative QC samples), known positive or negative clinical samples, or aliquots of DNA extracts from known strains. Controls may also be built-in to the test device (sometimes referred to as an *Internal control*) and are performed automatically with each test, e.g., Xpert MTB/RIF assay. However, internal controls may only monitor a portion of the procedure, and additional traditional QC may be needed from time to time.

QC is one element of process control, which refers to control of the activities employed in the handling and examination of samples. QC ensures accurate and reliable testing, and it is a requirement for all testing for accreditation. Other aspects of process control apply to the other stages of testing, i.e., pre-analytical and post-analytical.

In TB laboratories in resource-limited settings, you may encounter limited use of QCs, or their use only with certain tests. One of the commonly cited reasons for the absence of QCs is a lack of funding. However, local solutions can be found to fulfil QC requirements, and reliance on expensive commercial solutions is not usually necessary. Other barriers include the cost of additional reagents and supplies needed to perform the QC testing. Technical support may be needed to develop local solutions using available resources, e.g., strains obtained from well-characterised panels received as part of EQA programme from SRLs.

QC in a TB laboratory can, for example, include monitoring the following activities (see Table 5 for more examples of general quality indicators): preparation of stains and media, staining and examining AFB microscopy slides, decontamination and inoculation of culture, DNA extraction and LPA procedure, sample processing control and probe check control in the Xpert MTB/RIF assay.

f. Lot testing

QC testing should be performed on new kits or lots of reagents prior to their use for testing patient samples to ensure that they perform as expected. Incoming QC testing is a requirement of ISO 15189. If kits are centrally procured and then distributed to peripheral sites (e.g., Xpert MTB/RIF cartridges), the incoming QC testing requirement may be fulfilled by centralised testing before distribution to outlying sites. However, caution is required since transportation of reagents and kits to an end user site may

damage or inactivate the products; QC testing is strongly advised at the end user site before being used on clinical samples.

In addition to new lot QC testing, continuous monitoring at site level of the performance indicators of tests, including error rates, is important for the early detection of any problems with different lots due to local storage conditions or other factors.

g. *External quality assessment*

External quality assessment (assurance) is defined as follows:

"Inter-laboratory comparisons and other performance evaluations that may extend throughout all phases of the testing cycle, including interpretation of results; determination of individual and collective laboratory performance characteristics of examination procedures by means of inter-laboratory comparison; NOTE: the primary objectives of EQA are educational and may be supported by additional elements." [CLSI GP27-A2]

EQA for TB laboratories may include the following components:

- On-site supervision
- Proficiency testing
- Blinded re-checking

While all laboratories should ensure that all tests are part of an EQA programme, monitoring performance using laboratory quality indicators (also known as performance indicators) is the most effective way to assure the quality of the laboratory results and identify areas for improvement. Quality indicator monitoring should always be implemented in conjunction with an EQA programme. See the next section for more information on quality indicators.

i) On-site supervision

Site visits should be planned at regular intervals to assess the laboratory and testing site practices and adherence to protocols. Usually conducted by the NRL, NTP, or partners, they may be conducted by national, regional, or district level staff and should be integrated with other on-site supervision where possible (e.g., quarterly NTP site visits). A standardized checklist must be utilized for consistency and completeness of information. On-site supervision should form part of the EQA processes for all TB diagnostic technologies. On-site visits provide motivation and support to staff, especially in peripheral settings. Establishing strong relationships with staff encourages rapid reporting of any problems, allowing rapid troubleshooting, re-training and corrective actions. When planning on-site visits, sufficient time should be allocated, making sure to include travel time. The extent of the evaluation during each visit will depend on the frequency of the visits, the capacity of the staff, and the performance of the laboratory, with more extensive evaluation needed in poorly performing sites. During the visit, all components of testing and laboratory workflow should be evaluated, including pre- and post-analytical stages (i.e., specimen collection, recording and reporting results, and confirmatory testing), and a review

and analysis of trends in quality indicators should always be conducted. Supervision visits are an opportunity to discuss concerns and solve problems, as well as mentor staff on troubleshooting.

A schedule for site visits should be drawn up in advance, preferably integrated with other supervision activities. Responsibilities for on-site supervision may be de-centralized to regional or district staff where sufficient capacity exists. All staff conducting supervision visits need appropriate training and should use standardized checklists. Reports should be shared with the testing site and the NRL or NTP according to local practices.

Failed proficiency testing (PT, see below) or out-of-range quality indicators can help identify testing sites which are performing poorly, and they should then be prioritized for on-site visits. However, PT and monitoring of quality indicators do not negate the need for on-site supervision. On-site visits are especially critical during the early stages of implementation of a new technology.

ii) Proficiency testing

Proficiency testing (PT) is defined as:

"A programme in which multiple specimens are periodically sent to members of a group of laboratories for analysis and/or identification, in which each laboratory's results are compared with those of other laboratories in the group and/or with an assigned value, and reported to the participating laboratory and others." [CLSI GP27-A2]

Ideally, a PT programme checks key pre-analytical, analytical, and post-analytical processes occurring at the testing site. A number of samples are sent to the laboratory or testing site several times per year. Testing is performed as it would be with patient specimens, and results are compared to expected results and across several testing sites. Results are monitored for trends over time. While PT does not measure routine laboratory performance, it may identify laboratories with major deficiencies. PT is recommended at least once per year, and is an ISO 15189 requirement. Feedback regarding PT results should be provided in a timely manner to the testing sites and to supervisory staff. Rapid feedback is needed to enable prompt initiation of corrective actions. While on-site supervision and routine monitoring of quality indicators are the most critical components of QA, PT helps to identify major non-conformities, allowing supervisors to target the most poorly performing laboratories for on-site supervision.

PT may be used, in conjunction with quality indicator monitoring, where inadequate human or financial resources are available to implement a regular on-site supervision programme. PT panels may also be used to evaluate post-training performance of technicians.

iii) Blinded re-checking

Blinded re-checking, usually applied to AFB smear microscopy, involves the re-examination of a sample of routine smears at a higher level laboratory. Slides are usually sampled on a quarterly or monthly basis. The technician re-checking the slides does so in a blinded fashion, i.e., not knowing the original diagnostic results, and the percentage of agreement is calculated. Extensive information on establishing a blinded re-checking programme as well as other EQA elements is given in the resource *External quality assessment for AFB smear microscopy*.

Since blinded re-checking actually assesses the routine performance of microscopy, it is an important component of an EQA programme. However, it is resource intensive, since it requires sampling slides and re-reading, and many countries face challenges with wide scale implementation. Furthermore, collecting the necessary data and providing timely feedback to sites for corrective actions remains challenging in many settings.

NTPs should have data on the following performance indicators which provide an insight into the participation of laboratories in the network, both regionally and nationally:

- Proportion of laboratories participating in the blinded smear re-checking activity

- Proportion of participating laboratories participating in all quarters for a given year

- Proportion of laboratories with <5% error rate and no high false errors

h. *Quality performance indicator monitoring*

Routine monitoring of quality indicators, also known as performance indicators, is a critical element of QA for any diagnostic test as well as an ISO requirement. All laboratories should collect and analyse testing data on at least a monthly basis, using a standardised format. Targets should be set for all indicators monitored, and any unexplained change in quality indicators, such as increase in error rates, a change in MTB positivity rate or rifampicin resistance rate, or a significant change in volume of tests conducted, should be documented and investigated. A standard set of quality indicators should be used for all sites conducting a particular test to allow for comparison. Quality performance indicators should be reviewed by the laboratory manager and must always be linked to corrective actions if any unexpected results or trends are observed. Documentation of corrective actions and subsequent improvement and normalization of laboratory indicators following the corrective actions are critical.

A system should be in place for centralized reporting of monthly quality indicators to the NRL or NTP. For newer diagnostics that product electronic data, including GeneXpert®, Bactec™ MGIT™, and LPAs with automated readers, use of diagnostics connectivity solutions (see Section 2.6.1) allow for real-time remote monitoring of sites within a network and provide the capacity to easily and accurately stratify data as needed for analysis of performance.

The indicators provided in this section focus on laboratory testing. It is important for laboratories to work with clinicians and programme managers to develop and monitor quality indicators that reflect the whole diagnostic process, such as the proportion of patients started on treatment or the turnaround time from collection of specimen to treatment initiation. This is discussed further in Section 2.8 Linking laboratory services to TB care and treatment and Section 1.4. Targets and Indicators for TB Laboratory Strengthening.

i) General quality indicators

The following set of quality indicators apply to all technologies and should be collected, analysed on a monthly basis, and disaggregated according to tests. These indicators are provided as a guide, and laboratories should review and set locally appropriate targets.

Table 5   General quality indicators

INDICATOR	TARGET
Number of tests performed, by type of test	–
Service interruptions	No interruptions
(a) Stock outs	No stock outs leading to service interruption
(b) Equipment down time	No equipment downtime leading to service interruption
Turnaround time (TAT)	90% of results meet test-specific TAT
Test statistics (quality indicator) report	100% reports completed by defined due date
EQA results	>90% EQA panels are passed
QC results	>90% QC results meet expected criteria
Specimen rejection	<1% specimens rejected[a]
Customer satisfaction	>80% surveyed customers are satisfied
Technician productivity	Report average number of tests performed per month per technician

[a]   Where resources allow, additional secondary indicators may be collected by some laboratories, such as volume and quality of sputum specimens. This may be important for certain tests (e.g., >1ml sputum is required for Xpert MTB/RIF test). Specimen rejection criteria related to quality of specimen, or incompletely labelled or leaking specimens are applied in some laboratories.

ii) Test-specific quality indicators

This section provides recommended quality indicators for each WHO-approved method, which are in addition to the general quality indicators listed in Table 5. Targets provided in the tables below are intended as a guide, and laboratories should determine their own targets. These targets, and especially isolation rates, will vary based on local situation, patient population tested, and other relevant factors. Deviations from the usual rates should be investigated.

Smear microscopy

Table 6 lists quality indicators recommended for AFB smear microscopy. They should be collected, analysed on a monthly basis, and disaggregated by type of microscopy (light, FM) where more than one method is employed.

Table 6   Quality indicators for smear microscopy

INDICATOR	DESCRIPTION	TARGET[a]	REFERENCE
Smear positivity rate for diagnostic smears (new and relapse cases)	Total number AFB-positive diagnostic smears / Total number of diagnostic smears	Approximately 10%	*Laboratory Diagnosis of Tuberculosis by Sputum Microscopy. The Handbook*. Global Edition. GLI. 2014.
Proportion of low grade AFB-positive smears among diagnostic smears (new and relapse cases)	Number of scanty and 1+ diagnostic smears / Total number of diagnostic smears	30–50%	
Smear positivity rate for follow-up smears	Number of AFB-positive follow-up smears / Total number of follow-up smears	5–10%	
Laboratory turnaround time	Time between receipt of specimens for smear at the laboratory and result reporting (mean, range and 90th centile)	24–48 hours	

[a] Targets are setting-specific. Laboratories should monitor indicators and establish local targets and acceptable ranges. Deviations from expected values should be investigated.

Culture

Table 7 lists quality indicators recommended for culture. They should be collected and analysed on a monthly basis in addition to the general quality indicators. Indicators should be disaggregated by type of culture medium if more than one type is used. For laboratories processing a range of specimen types for MTB culture further disaggregation is recommended.

Table 7   Quality indicators for culture

INDICATOR	DESCRIPTION	TARGET	REFERENCE
Number and proportion of diagnostic specimens (new and relapse) that were culture positive (MTB and NTM combined)	Number of diagnostic specimens that were culture positive for MTB or NTM / Number of diagnostic specimens processed for culture	15–20%	Siddiqi SH, and Rüsch-Gerdes S. *MGIT procedure manual*. Geneva, FIND, 2006.
Number and proportion of diagnostic specimens (new and relapse) that were MTB positive	Number of diagnostic specimens culture positive for MTB / Number of diagnostic specimens processed for culture	10–15%	
Number and proportion of diagnostic AFB smear positive specimens (new and relapse) that were culture positive for MTB	Number of AFB smear positive specimens culture positive for MTB / Number of smear positive diagnostic specimens processed for culture	95–98% (liquid) 85–90% (solid)	
Number and proportion of diagnostic AFB smear negative specimens that were culture positive for MTB	Number of AFB smear negative specimens culture positive for MTB / Number of smear negative diagnostic specimens processed for culture	20–30%	
Number and proportion of contaminated cultures leading to uninterpretable results[a]	Number of inoculated culture tubes or plates discarded due to contamination / Total number of inoculated tubes or plates inoculated for culture	3–5% (solid) 8–10% (liquid)	
Laboratory turnaround time	Time between receipt of specimens for culture at the laboratory and result reporting (mean, range and 90th centile)	Solid culture: On average, 3 weeks for smear- positive samples and 4–8 weeks for smear-negative samples Liquid culture: 8–10 days for smear-positive samples and 2–6 weeks for smear-negative samples	

[a]   For solid culture, some results may be interpretable in the presence of low-level contamination. Some laboratories may also reprocess contaminated cultures and the results of the repeat testing may be reportable.

Phenotypic DST

Table 8 lists quality indicators recommended for use with phenotypic DST methods. These indicators should be collected and analysed on a monthly basis in addition to the general quality indicators. Other secondary indicators may be collected on a less frequent basis (e.g., quarterly), such as the number and proportion of unusual drug resistance patterns.

Table 8   Quality indicators for DST

INDICATOR	DESCRIPTION	TARGET	REFERENCE
Number and proportion of isolates with mono-resistance and multidrug resistance to all combinations of drugs tested (e.g., isoniazid monoresistance, rifampicin mono-resistance, MDR)	Number of isolates resistant to single or multiple drug combination/ Total number of isolates tested	Dependent on population tested and country drug resistance prevalence and patterns	Siddiqi SH, and Rüsch-Gerdes S. *MGIT procedure manual*. Geneva, FIND, 2006.
Number and proportion of isolates inoculated for DST that were discarded due to contamination	Number of isolates discarded due to contamination / Total number of isolates inoculated for DST	<3%	
Number and proportion of isolates inoculated for DST that were uninterpretable due to lack of growth of control (drug-free) tubes/plates	Number of isolates discarded due to lack of growth on drug-free media / Total number of isolates inoculated for DST	<3%	
Laboratory turnaround time	Time between inoculation of DST and result reporting (mean, range and 90th centile)	Solid media: 3–4 weeks Liquid media: 2–3 weeks	
	Total DST turnaround time including time for primary culture to produce inoculum	Solid media: 8–16 weeks Liquid media: 4–6 weeks	

Line probe assay (first-line and second-line drugs)

Table 9 lists indicators recommended for use with LPAs for the detection of TB and rifampicin resistance or of resistance to FQs or SLIDs. They should be collected and analysed on a monthly basis in addition to the general quality indicators. A critical component of monitoring good performance of LPA testing is noticing when the indicators fall outside expected values. For example, positive results obtained on negative controls will require investigation regarding concerns for cross contamination.

If LPA testing is performed both directly from clinical specimens and from isolates, quality indicators should be disaggregated according to sample. Additional secondary indicators, including breakdown of mutations (*inhA*, *katG*) and unusual

banding patterns, may be collected on a less frequent basis (e.g., quarterly). SL-LPA is monitored similarly except one assesses FQ- and SLID-resistance among rifampicin-resistant specimens or cultures.

Table 9   Quality indicators for first-line and second-line LPA

INDICATOR	DESCRIPTION	TARGET	REFERENCE
Number and proportion of samples with mono-resistance and multidrug resistance (i.e., isoniazid monoresistance, rifampicin monoresistance, MDR)	Number of samples with mono- or multidrug resistance / Total number of samples tested	Dependent on population tested and country drug resistance prevalence and patterns	*Training package on LPA* (MTBDRplus, v.2) – October 2012 http://www. stoptb.org/wg/gli/ trainingpackages. asp
Number and proportion of samples with mono-resistance and XDR (i.e., rifampicin-resistance plus FQ-resistance, rifampicin-resistance plus SLID-resistance, rifampicin-resistance plus SLID and FQ-resistance)	Number of isolates with mono- or dual-drug resistance / Total number of rifampicin-resistant isolates tested	Dependent on population tested and country drug resistance prevalence and patterns	
Number and proportion of samples with un-interpretable results	Number of samples with uninterpretable results / Total number of samples set up for LPA	<5%	
Laboratory turnaround time	Time between receipt of specimens for LPA at the laboratory and result reporting (mean, range and 90th percentile). For indirect LPA, add the culture turnaround time for total turnaround time	1–2 days (longer if batching of tests)	

Xpert MTB/RIF

Table 10 lists indicators recommended for Xpert MTB/RIF testing. They should be collected and analysed on a monthly basis, in addition to the general quality indicators. Where possible, countries should collect disaggregated data according to the population group tested (e.g., HIV positive, MDR-TB risk, extrapulmonary TB). If the quality indicator for error rates exceeds the target value, it should be further disaggregated to identify common error codes, in order to assist with corrective and preventive actions. The GeneXpert platform produces electronic data, and therefore a data connectivity solution should be established to allow remote monitoring of quality indicators. More information on the advantages of remote monitoring can be found in Section 2.6.1.

Table 10 Quality indicators for Xpert MTB/RIF

INDICATOR	DESCRIPTION	TARGET	REFERENCE
Number and proportion of specimens with MTB detected, rifampicin resistance not detected	Number of specimens with MTB detected rifampicin resistance not detected / Total number of specimens tested	Dependent on population tested and country drug-resistance prevalence and patterns	*Xpert MTB/RIF training package*. Global Laboratory Initiative. http://stoptb.org/wg/gli/TrainingPackage_XPERT_MTB_RIF.asp
Number and proportion of specimens with MTB detected, rifampicin resistance detected	Number of specimens with MTB detected rifampicin resistance detected / Total number of specimens tested	Dependent on population tested and country drug-resistance prevalence and patterns	*Xpert MTB/RIF implementation manual*. World Health Organization. http://www.who.int/tb/laboratory/xpert_launchupdate/en/
Number and proportion of specimens with MTB detected rifampicin indeterminate	Number of specimens with MTB detected rifampicin indeterminate / Total number of specimens tested	Dependent on population tested and country drug-resistance prevalence and patterns	
Number and proportion of specimens with MTB not detected	Number of specimens with MTB not detected / Total number of specimens tested	Dependent on population tested and country drug resistance prevalence and patterns	
Number and proportion of specimens with errors	Number of specimens with errors / Total number of specimens tested	<3%	
Number and proportion of specimens with invalid results	Number of specimens with invalid results / Total number of specimens tested	<1%	
Number and proportion of specimens with no results	Number of specimens with no results / Total number of specimens tested	<1%	
Laboratory turnaround time	Time between receipt of specimen for Xpert MTB/RIF at the laboratory and result reporting	2–24hrs	

TB-LAMP

The following indicators (Table 11) are recommended for TB-LAMP testing, and should be collected and analysed on a monthly basis, in addition to the general quality indicators. Where possible, countries should collect disaggregated data according to the population group tested (HIV positive, extrapulmonary TB).

Table 11 Quality indicators for TB-LAMP

INDICATOR	DESCRIPTION	TARGET
Number and proportion of specimens with MTB detected	Number of specimens with MTB detected/ Total number of specimens tested	Dependent on population tested and TB and HIV prevalence
Number and proportion of specimens with invalid results or no results	Number of specimens with invalid or no results / Total number of specimens tested	<1%
Laboratory turnaround time	Time between receipt of specimen for TB LAMP at the laboratory and result reporting	2–24hrs

LF-LAM

The following indicators (Table 12) are recommended for LF-LAM testing and should be collected and analysed on a monthly basis, in addition to the general quality indicators. Where possible, countries should collect disaggregated data according to the population group tested (pulmonary, extrapulmonary TB).

Table 12 Quality indicators for LF-LAM

INDICATOR	DESCRIPTION	TARGET
Number and proportion of specimens with MTB detected	Number of specimens with MTB detected/ Total number of specimens tested	Dependent on population tested and TB prevalence among HIV-positive patients
Number and proportion of specimens with invalid results or no results	Number of specimens with invalid or no results / Total number of specimens tested	Not enough evidence for global guidance
Laboratory turnaround time	Time between receipt of specimen for LF-LAM at the laboratory and result reporting	1–24hrs

i. *Continuous quality improvement*

Quality improvement (QI) is a critical and often neglected part of the quality assurance process. The identification of non-conformities through data collection, subsequent data analysis, and creative problem solving are key components of the QI process, which involves not only continual monitoring but also identifying and analysing actual and potential defects. Non-conformities may be identified in many ways, including PT, reviewing quality indicators, reporting of issues identified by staff members, and audits.

The QI cycle in Figure 8 involves four steps: Plan, Do, Check, and Act. Non-conformities identified during routine testing and QA activities should be analysed, corrective actions implemented, and the results monitored over time. These four steps should

**Monitoring
and evaluation**
Customer satisfaction
Quality control
Proficiency
Testing
Audit

**Quality
improvement
plan**

**Continuous
quality
improvement**

Corrective action
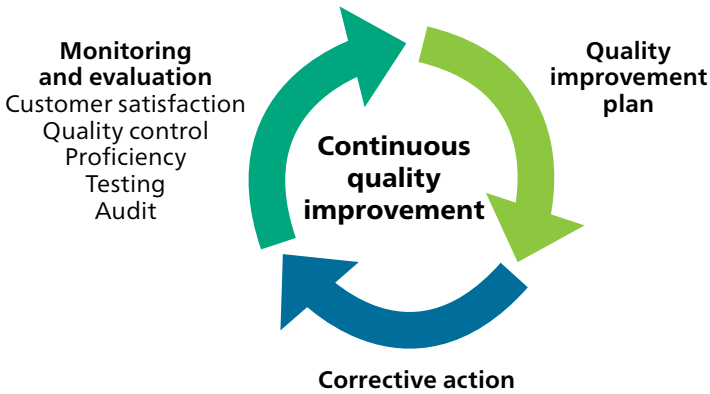
Fig. 8   Continuous QI cycle from *WHO LQMS Handbook*

be repeated regularly to ensure continuous improvements in laboratory processes. For many laboratories, this process is the most difficult to implement in a routine and systematic way, but it is an essential part of implementing quality services. This is a key area in which technical assistance may be required.

Procedures for identifying non-conformities, determining responsibility, recalling the results associated with the non-conformities, and resuming routine testing following corrective actions must be clearly defined. Follow up actions to prevent the same non-conformity from occurring in the future must also be put in place.

Table 13 QA components for TB diagnostics

TEST	QUALITY INDICATOR MONITORING	QUALITY CONTROL	PROFICIENCY TESTING	ON-SITE SUPERVISION	BLINDED RE-CHECKING	SOURCE OF TRAINING MATERIALS / REFERENCE
Smear microscopy, light	Monthly Refer to list of indicators (general and test specific) in section 2.3.2.h above	• QC of in-house prepared stains • Incoming QC of new batches of commercial stains • One positive and one negative slide tested with each batch of slides stained and examined • Cross-check results with a second reader before releasing report (on all or portion of results)	• Recommended at least once per year • Provided by NICD South Africa, SRLs	• Usually quarterly with NTP site visits for data collection	• Recommended • Slide sampling usually quarterly • Re-staining of slides may be considered	*External Quality Assessment for AFB Smear Microscopy.* Geneva, APHL, CDC, IUATLD, KNCV, RIT, WHO, 2002. https://www.aphl.org/aboutAPHL/publications/Documents/External_Quality_Assessment_for_AFB_Smear_Microscopy.pdf
Smear microscopy, FM	Monthly Refer to list of indicators (general and test specific) in section 2.3.2.h above	• QC of in-house prepared stains • Incoming QC of new batches of commercial stains • One positive and one negative slide tested with each batch of slides stained and examined • Cross-check results with a second reader before releasing report (on all or portion of results)	• Recommended at least once per year • Provided by NICD South Africa, SRLs	• Usually quarterly with NTP site visits for data collection	• Recommended • Slide sampling may be monthly or quarterly • Re-staining of slides may be considered	*External Quality Assessment for AFB Smear Microscopy.* Geneva, APHL, CDC, IUATLD, KNCV, RIT, WHO, 2002. https://www.aphl.org/aboutAPHL/publications/Documents/External_Quality_Assessment_for_AFB_Smear_Microscopy.pdf

Test	Frequency / indicators	QC activities	PT	External support		References
Solid culture	Monthly Refer to list of indicators (general and test specific) in section 2.3.2.h above	• QC of in-house prepared media and reagents • Incoming QC of new batches of commercial media • Process one well-characterised known positive (drug susceptible MTB) and one negative (decontamination solution, water, or PBS) with each batch of specimens processed for culture • Cross-check results with a second reader before releasing report (on all or portion of results)	• PT for culture is not recommended • PT for identification may be done using MTB and NTM isolates. (provided by CAP)	• For NRL, may be provided by SRLs or other partners providing technical assistance • NRL or other experienced referral laboratory should provide at least annual site visits to other TB culture laboratories in the country	• Not recommended	*Training Package on Culture in solid and liquid media* – October 2012. http://www.stoptb.org/wg/gli/trainingpackages.asp
Liquid culture	Monthly Refer to list of indicators (general and test specific) in section 2.3.2.h above	• QC of in-house prepared reagents (e.g., decontamination solutions) • Incoming QC of new batches of commercial media • Process one well-characterised known positive (drug susceptible MTB) and one negative (decontamination solution, water or other bacteria e.g., *E.coli*) with each batch of specimens processed for culture • *Internal QC*: Cross-check results with a second reader before releasing report (on all or portion of results)	• PT for culture is not recommended • PT for identification may be done using TB and non-TB isolates (provided by CAP)	• For NRL, may be provided by SRLs or other partners providing technical assistance • NRL or other experienced referral laboratory should provide at least annual site visits to other TB culture laboratories in the country	• Not recommended	*Training Package on Culture in solid and liquid media* – October 2012. http://www.stoptb.org/wg/gli/trainingpackages.asp *MGIT Manual.* http://www.finddx.org/wp-content/uploads/2016/02/mgit_manual_nov2006.pdf

TEST	QUALITY INDICATOR MONITORING	QUALITY CONTROL	PROFICIENCY TESTING	ON-SITE SUPERVISION	BLINDED RE-CHECKING	SOURCE OF TRAINING MATERIALS / REFERENCE
Species identifica-tion tests	Monthly Refer to list of indicators (general and test specific) in section 2.3.2.h above	• Incoming QC of new batch • Process positive culture controls included in batch, and add positive (MTB) and negative (NTM – *M. avium*, *M. intracellulare*, or *M. kansasii*) to Immunochromatographic assays • Cross-check results with a second reader before releasing report (on all or portion of results)	• Species identification is included in culture and DST PT	• Provided as part of liquid culture supervision	• Not recommended	*Training Package on Culture in solid and liquid media –* October 2012. http://www.stoptb.org/wg/gli/trainingpackages.asp
Culture-based DST for first line drugs	Monthly Refer to list of indicators (general and test specific) in section 2.3.2.h above	• QC of in-house prepared media and reagents • Incoming QC of new batches of commercial media • Process one well-characterised known positive (drug susceptible MTB) and one negative (decontamination solution, water or other bacteria) with each batch of specimens processed for culture • *Internal QC*: Cross-check results by second reader before releasing report (on all or portion of results)	• Recommended at least once per year • Provided by SRLs, once per year. • Other providers available: e.g., UK NEQAS, NICD South Africa, CDC	• For NRL, may be provided by SRLs or other partners providing technical assistance • NRL or other experienced referral laboratory should provide at least annual site visits to other TB culture laboratories in the country	• Lab should establish formal link with SRL. SRLs may re-check a proportion of isolates for DST • Expected levels of agreement for rifampicin and isoniazid DST are >95%, and acceptable agreement for other drugs should be established	*Training Package on DST by phenotypic and molecular methods.* http://www.stoptb.org/wg/gli/trainingpackages.asp *MGIT Manual.* http://www.finddx.org/wpcontent/uploads/2016/02/mgit_manual_nov2006.pdf

| Culture-based DST for second-line drugs | Monthly

Refer to list of indicators (general and test specific) in section 2.3.2.h above | • QC of in-house prepared media and reagents
• Incoming QC of new batches of commercial media
• Process one well-characterised known drug-susceptible MTB and a well-characterised drug-resistant MTB
• Internal QC: Cross-check results with a second reader before releasing report (on all or portion of results) | • Recommended at least once per year
• Provided by SRLs | • May be provided to NRL by SRL experienced in SL DST | • Lab should establish formal link with SRL. SRLs may re-check a proportion of isolates for second-line DST
• Expected level of agreement for each drug should be established | *Training Package on DST by phenotypic and molecular methods.* http://www.stoptb.org/wg/gli/trainingpackages.asp |

TEST	QUALITY INDICATOR MONITORING	QUALITY CONTROL	PROFICIENCY TESTING	ON-SITE SUPERVISION	BLINDED RE-CHECKING	SOURCE OF TRAINING MATERIALS / REFERENCE
FL-LPA for rifampic-in, and isoniazid resistance SL-LPA, for FQs and SLIDs	Monthly Refer to list of indicators (general and test specific) in section 2.3.2.h above	• Incoming QC of new batches • Process a positive control using an aliquot of a previously extracted DNA from a well characterized drug susceptible MTB strain and a blank with PBS as sample (negative control) • Include a negative PCR control in every batch using molecular grade water • Internal QC: check each strip for the presence of the CC, AC controls (must be present in ALL including negatives) to ensure quality of hybridization and PCR reagents • Check strip from patient and positive control for the presence of the TUB band to ensure presence of MTB • Cross-check results with a second reader before releasing report (on all or portion of results)	• Recommended at least once per year • Provided by SRLs	• For NRL, may be provided by SRLs or other partners providing technical assistance • NRL or other experienced referral laboratory should provide at least annual site visits to other TB laboratories in the country	• Not recommended	*Training package on first-line LPA (MTBDRplus v2) – October 2012* http://www.stoptb.org/wg/gli/trainingpackages.asp

TB-LAMP	Monthly Refer to list of indicators (general and test specific) in section 2.3.2.h above	• Incoming QC of new batches • Process a positive control using an aliquot of a previously extracted DNA from a well characterized drug susceptible MTB and a blank with molecular grade water as sample (negative control) • Cross-check results with a second reader before releasing report (on all or portion of results)	• Recommended at least once per year	• NRL or other experienced referral laboratory should provide at least annual site visits to other TB laboratories in the country	• Not recommended	
Xpert MTB/RIF	Monthly Refer to list of indicators (general and test specific) in section 2.3.2.h above Remote monitoring using a diagnostics connectivity solution is recommended	• Incoming QC of new batch • Internal QC: Cross-check results for transcription errors on manually reported results (on all or portion of results)	• Recommended at least once per year	• NRL or experienced regional referral laboratories should undertake regular on-site supervision visits of Xpert MTB/RIF testing sites	• Not recommended due to insufficient sample remaining after testing	*Xpert MTB/RIF training package*. Global Laboratory Initiative. http://www.stoptb.org/wg/gli/TrainingPackage_XPERT_MTB_RIF.asp
LF-LAM	Monthly Refer to list of indicators (general and test specific) in section 2.3.2.h above	• Incoming QC of new batch • Internal QC: check each strip for the presence of the control bar. If the control bar does not turn purple/gray by assay completion, the test result is invalid • Cross-check results with a second reader before releasing report (on all or portion of results)	• Recommended at least once per year	• NRL or experienced regional referral laboratories should undertake regular on-site supervision visits	• Not recommended	http://www.alere.com/en/home/product-details/determine-tb-lam.html

KEY ACTIVITY AREAS FOR TECHNICAL SUPPORT

- ■ Provide guidance on implementing international best practises for TB laboratory quality assurance
- ■ Provide training and mentoring in establishing QA practices
- ■ Assess QA procedures and practises in individual laboratories, and provide recommendations for improvement
- ■ Review criteria for on-site supervisory visits and assist with planning an on-site supervisory programme to be established in conjunction with other QA activities
- ■ Support EQA programme for smear microscopy and Xpert MTB/RIF, including establishing processes for provision of timely feedback to sites on performance and corrective actions
- ■ Provide support to establish systems for quality indicator monitoring, in order to identify non-conformities and implement corrective and preventive actions

Suggested reading, including quality assurance tools

External quality assessment for AFB smear microscopy. Geneva, APHL, CDC, IUATLD, KNCV, RIT, WHO, 2002.
https://www.aphl.org/aboutAPHL/publications/Documents/External_Quality_Assessment_for_AFB_Smear_Microscopy.pdf

GLI laboratory toolbox. Global Laboratory Initiative, 2014.
http://stoptb.org/wg/gli/gat.asp

Laboratory services in tuberculosis control. Part I: organization and management. Geneva, World Health Organization. 1998. (WHO/TB/98.258).
http://whqlibdoc.who.int/hq/1998/WHO_TB_98.258_(part1).pdf

Laboratory services in tuberculosis control. Part II: microscopy. Geneva, World Health Organization. 1998. (WHO/TB/98.258).
http://whqlibdoc.who.int/hq/1998/WHO_TB_98.258_(part2).pdf

Laboratory services in tuberculosis control. Part III: culture. Geneva, World Health Organization. 1998, (WHO/TB/98.258).
http://whqlibdoc.who.int/hq/1998/WHO_TB_98.258_%28part3%29.pdf?ua=1

Laszlo A et al. "Quality assurance programme for drug susceptibility testing of Mycobacterium tuberculosis in the WHO/IUATLD Supranational Reference Laboratory Network: five rounds of proficiency testing", 1994–1998. *International Journal of Tuberculosis and Lung Disease*, 2002, 6:748–756.

MGIT procedure manual. Siddiqi SH, Rüsch-Gerdes S. Geneva, FIND, 2006.
http://www.finddx.org/wp-content/uploads/2016/02/mgit_manual_nov2006.pdf

TB Laboratory Standard Operating Procedures. FIND.
https://www.finddx.org/implementation-resources/

The use of molecular line probe assays for the detection of resistance to isoniazid and rifampicin. Policy update. Geneva, World Health Organization. 2016. (WHO/HTM/TB/2016.12).
http://www.who.int/tb/publications/molecular-test-resistance

The Public Health Service National Tuberculosis Reference Laboratory and the National Laboratory Network: Minimum Requirements, Role and Operation in a Low-Income Country. Paris, International Union Against Tuberculosis and Lung Disease. 1998.
http://www.uphs.upenn.edu/bugdrug/antibiotic_manual/iuatld_natTBreflabmanual.pdf

The use of lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis and screening of active tuberculosis in people living with HIV: policy guidance. Geneva, World Health Organization. 2015. (WHO/HTM/TB/2015.25).
http://www.who.int/tb/publications/use-of-lf-lam-tb-hiv/en/

The use of loop-mediated isothermal amplification (TB-LAMP) for the diagnosis of pulmonary tuberculosis: policy guidance. Geneva, World Health Organization. 2016. (WHO/HTM/TB/2016.07).
http://www.who.int/tb/publications/lamp-diagnosis-molecular/

The use of molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs: policy guidance. Geneva, World Health Organization. 2016. (WHO/HTM/TB/2016.07).
http://www.who.int/tb/publications/lpa-mdr-diagnostics/en/

Xpert MTB/RIF implementation manual. Technical and operational 'how to': practical considerations. Geneva, World Health Organization. 2014.
http://www.who.int/tb/publications/xpert_implem_manual

Xpert MTB/RIF training package. Global Laboratory Initiative. Available in English, French, Portuguese, and Russian.
http://www.stoptb.org/wg/gli/TrainingPackage_XPERT_MTB_RIF.asp
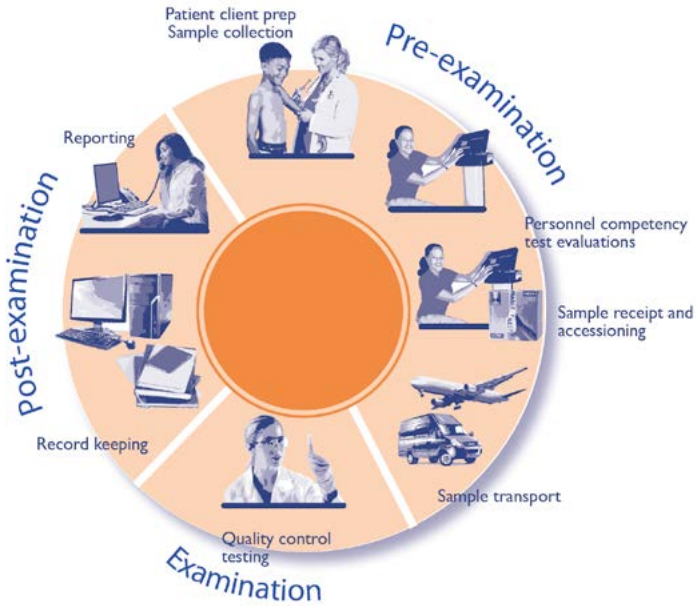
2.4 Implementing a quality management system (QMS)

2.4.1 Introduction to QMS

A QMS is defined as "*coordinated activities to direct and control an organization with regard to quality*". This definition is used by the International Organization for Standardization (ISO) and by the Clinical and Laboratory Standards Institute (CLSI), both of which are internationally recognized laboratory standards organizations. In a QMS, all aspects of the laboratory operation, from the organizational structure to the processes and procedures, need to be addressed to ensure quality. The whole workflow must be considered, from the patient through to the reporting of results. For a laboratory QMS handbook and associated training toolkit, go to http://www.who.int/ihr/training/laboratory_quality/. This training toolkit can be customised to fit local needs.

2.4.2 Accreditation

Accreditation is defined as a procedure by which an independent, authorised body gives formal recognition that a laboratory is competent to perform specific tasks. Laboratory accreditation recognizes a laboratory's technical capability and is usually specific the systems, products, components, or materials for which the laboratory claims proficiency. Accreditation allows a laboratory to determine whether it is performing its work correctly and according to appropriate standards. This does not guarantee that a given analytical result is correct, but it does establish standards that must be met and a framework within which non-conformities are identified and addressed.

Fig. 8 A QMS incorporates pre-examination, examination, and post-examination phases of testing (*WHO LQMS Handbook*)
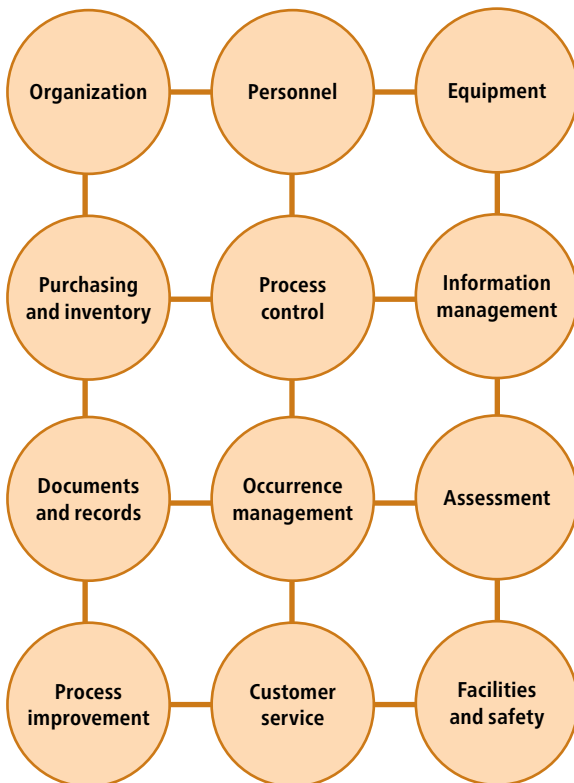
Quality system essentials (QSEs) are a set of coordinated activities that form the building blocks of a quality management system. In order to have a functioning QMS, all QSEs must be in place.

The accreditation of clinical or medical laboratories is achieved by measuring performance against ISO 15189, which addresses the 12 QSEs. These QSEs are described in *Application of a quality management system model for laboratory services*, published by CLSI.

The accreditation of clinical or medical laboratories is provided by an independent organization that has achieved the standards of ISO 17021 (*Conformity assessment: requirements for bodies providing audit and certification of management systems*) and that is affiliated with or a member of the International Laboratory Accreditation Cooperation (http://ilac.org). Some of the organizations that provide accreditation to medical laboratories include:

- the College of American Pathologists (http://www.cap.org/)

- the Kenya Accreditation Service (http://www.kenyaaccreditation.org/)

- the South African National Accreditation System (http://www.sanas.co.za)

Accredited laboratories are recognized as meeting certain quality standards and having the necessary technical processes and administrative systems in place to ensure high-quality results. A strong laboratory QMS is critical to ensuring the quality of testing, and weak laboratory systems have a direct impact on patient care. For example, laboratory errors may lead to over- or under-diagnosis of TB; poor stock management or lack of equipment maintenance systems may lead to interruptions in service; and failure to meet biosafety standards put laboratory workers, patients, and the community at risk of infection. Appropriate turnaround times for results are critical for optimal patient management, while a strong reporting system and referral network ensures results reach clinicians in time to deliver appropriate care and treatment. Such requirements can only be consistently met by concerted efforts to develop and maintain a QMS within the TB laboratory.

Every NRL should be engaged in implementing a QMS towards national or international accreditation. National laboratory strategic plans should articulate the goals for accreditation of NRLs and regional referral laboratories, where applicable. Working to achieve international accreditation standards is a complex and time-consuming task for any laboratory, especially when starting from a low baseline with limited resources and staff with limited capacity. Plans to work towards accreditation should be realistic and budgeted for appropriately in order to be successful. The first step towards strengthening a country's TB laboratory network is to improve the quality management of the NRL so that they have the capacity to support the other laboratories in the network. Regional referral laboratories should then be targeted for quality improvement initiatives, since they provide culture and DST services, in addition to supervising peripheral laboratories in their region.

In most resource-limited settings it is not realistic for peripheral laboratories to meet the quality standards required for international accreditation. However, meeting minimum standards to ensure accurate and reliable testing is still important, and quality improvement plans should be developed, documented, and monitored over time to ensure minimum quality standards can be consistently achieved. GLI has developed an *AFB microscopy network accreditation tool* that can be used to assess

and improve the quality of the whole laboratory network. This tool applies only to microscopy laboratory networks, but it can be adapted for use in laboratory networks performing tests other than microscopy, such as Xpert MTB/RIF. This tool has been developed for self-assessment, and it is not currently linked to a formal accreditation programme.

The WHO *Framework of indicators and targets for laboratory strengthening under the End TB Strategy* includes an indicator for accreditation of NRLs with a target of 100% of NRLs in high TB burden countries being accredited by 2020. While progress is already being made in a number of resource-limited countries, in other countries there is limited awareness or implementation of QMS.

Implementing a QMS is a complex process, and requires committed laboratory and facility management; appropriate infrastructure, personnel, equipment, and supplies; and putting in place standardised procedures and documentation of all processes. All stages of the diagnostic process must be monitored, from specimen handling to testing and reporting. Good management practices are essential to ensuring that the quality of a laboratory's services remains high and that improvements are made as deficiencies are identified. At the national level, regulations and accreditation programmes that outline standards and guarantee accountability are necessary factors for ensuring that high quality services are maintained.

2.4.3 Approaches and tools for implementing a QMS

Factors to consider when selecting an approach or tool include what is already being done on QMS in the country, in both TB and non-TB laboratories; which national organizations and people are responsible for the accreditation; and the country's current capacity to support TB laboratories in training and mentoring. Local ownership of the programme will be a critical factor for success, since working towards accreditation is a long process that may outlive any individual person or organization providing support. A laboratory's goal may be formal national or international accreditation, or it may simply be implementing or strengthening a QMS to improve the quality of results without intending to become formally accredited.

There are several frameworks that can be used to help laboratories preparing for accreditation, or simply wishing to implement or improve their QMS without the ultimate goal of accreditation. This section briefly describes these tools. It may be prudent to decide to follow one overall framework in order to avoid confusion. However, because each framework has different strengths and may offer different activities and tools, consultants should be aware of what each package or approach has to offer and use components from each accordingly. This decision-making process should be led by the country authorities, with technical input from partners and consultants. The guidance document, *ISO 15189 Quality Management System Implementation: Look Before You Leap – Best practice guidance document*, (http://www.challengetb.org/publications/tools/lab/ISO15189_QMS_Implementation.pdf) describes the deployment of QMS in three NRLs in Africa and recommends best practices.

Tools

There are a number of key resources that can be used to assist TB laboratories in developing and maintaining a QMS:

- ISO 15189:2012. Medical laboratories – particular requirements for quality and competence
- WHO Laboratory Quality System Handbook and Training package
- GLI tool: Stepwise approach towards TB laboratory accreditation
- SLIPTA: Stepwise Laboratory Improvement Process Toward Accreditation
- SLMTA: Strengthening Laboratory Management Toward Accreditation

ISO 15189:2012. Medical laboratories – particular requirements for quality and competence

This International Standard is for use by medical laboratories in developing their QMSs and assessing their competence. Laboratory customers, regulating authorities, and accreditation bodies may also use it for confirming or recognizing the competence of medical laboratories. It is not intended to be used as the basis for certification of laboratories. ISO standards are copyrighted and should not be reproduced without permission, and therefore may be difficult for individual laboratories to purchase. The latest version of the standard was issued in 2012, although many laboratories may still use the version from 2007.

WHO Laboratory Quality Management System (LQMS) Handbook and toolkit

This training toolkit was developed by the WHO Lyon Office for National Epidemic Preparedness and Response, the United States Centers for Disease Control and Prevention (CDC) – Division of Laboratory Systems, and CLSI. It provides an introduction to QMS and is applicable to all medical laboratories.

The toolkit includes a manual and training modules. It is based on CDC and WHO field experience and CLSI guidelines for ISO 15189 implementation. Trainers can customize the materials to meet the local training needs.
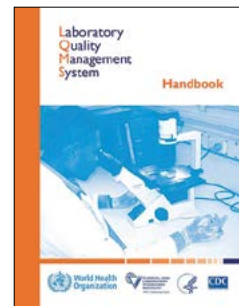
### GLI Stepwise Process Towards TB Laboratory Accreditation

The Global Laboratory Initiative has developed the GLI stepwise process towards TB laboratory accreditation, an online tool available at http://gliquality.org. This tool can help national reference TB laboratories gradually implement all the requirements of a properly functioning QMS in compliance with the ISO 15189:2012 standard.

The GLI tool covers technical, managerial, and TB specific requirements. It provides implementation guidance and user-friendly guidelines, roadmaps, checklists, and links to support materials to address each requirement of the ISO15189 standard. Within the tool, the ISO15189 requirements are translated into specific activities in a TB laboratory context. These activities are grouped along the 12 QSEs as defined by CLSI.

Activities are divided into four phases, with each phase having a specific focus. Laboratories are encouraged to complete one phase before proceeding to the next. However, the tool is constructed so that even if a laboratory does not fully implement a QMS, it will nonetheless improve the quality of its services. The four phases of implementation are:

- Phase 1: ensuring that the primary processes of the laboratory are operating correctly and safely. During this phase the basic elements necessary to enable safe and adequate laboratory practices are established. These are procedures that all laboratories should have in place regardless of their size or location.

- Phase 2: quality control and assurance, and creating traceability. The fundamentals of the QMS are established – that is, QC and QA.

- Phase 3: ensuring that the laboratory is properly managed, well organized and with strong leadership. Effective organizational systems, management practices, and leadership are implemented.

- Phase 4: creating continual improvements over time and preparing for accreditation. Systems are implemented that enable passive and active identification of needs for improvement; these are used to optimize the quality of services.

Fig. 10 Sample roadmap for the implementation of elements of a QMS
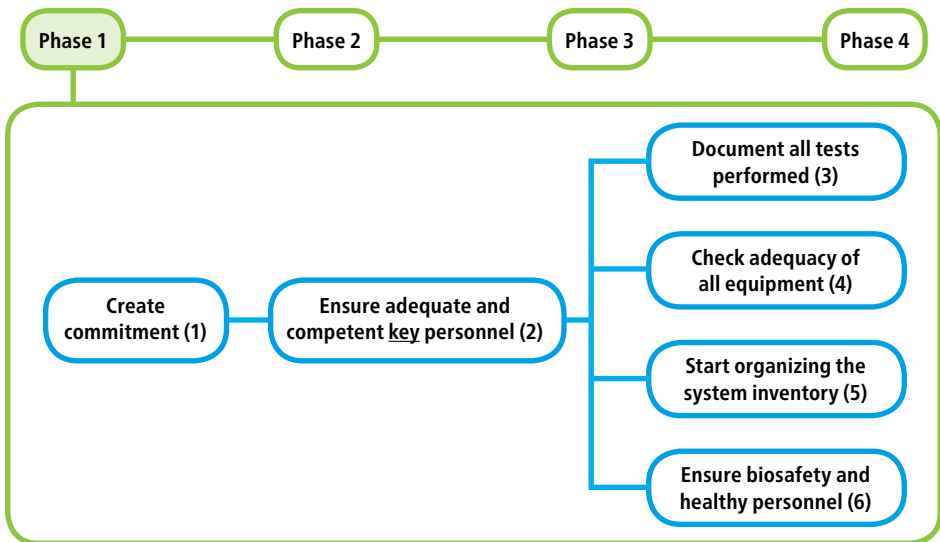
Because the GLI tool does not incorporate a training programme for country-wide implementation, it may be used in conjunction with other approaches, e.g., SLMTA, below, or used as a technical resource for mentoring by experienced laboratory mentors supporting individual laboratories.

SLIPTA: Stepwise Laboratory Improvement Process Toward Accreditation

SLIPTA is a monitoring and auditing framework that was originally developed by WHO's Regional Office for Africa. A SLIPTA certification programme is administered in Africa by the African Society for Laboratory Medicine (ASLM). ASLM is not an accreditation body; this is a stepwise certification process. SLIPTA is based on ISO 15189:2007 and CLSI Quality Management System: Approved Guideline (GP26-A4: 2011). The checklist was developed to monitor the progress and improvement of laboratory quality system. It is directly applicable to all laboratory settings and disciplines. SLIPTA is based on the 12 QSEs identified by CLSI and the assessment is scored and rated on a scale of 1 to 5 stars. It is considered an indicator of readiness for international accreditation. SLIPTA has been implemented in 160 laboratories in 18 African countries, and numerous other countries are also using SLIPTA as the basis of quality improvement initiatives (with or without the SLMTA programme, see below). ASLM has a training programme for certified SLIPTA auditors, and a number of African countries have local capacity for certified SLIPTA audits. The SLIPTA checklist is available in English, French and Portuguese.

SLMTA: Strengthening Laboratory Quality Management Toward Accreditation

Developed by the US Centers for Disease Control and Prevention, in collaboration with the American Society for Clinical Pathology, the Clinton Health Access Initiative, and WHO AFRO, SLMTA[4] is a task-based training and mentoring tool kit provided to laboratory personnel in a multi-workshop implementation model.

The foundation of this programme is a framework that defines the tasks a laboratory must perform in order to deliver quality laboratory service, which support optimal patient care. Training activities are designed to enable laboratory managers to accomplish those tasks using tools and job aids to enhance their management routines. It empowers laboratory managers to initiate immediate laboratory improvement measures, even without additional resources.

The framework consists of two stages: a Training of Trainers workshop (10 days), followed by country-wide implementation. This may be done in two ways: (1) three interactive workshops that last one week each or (2) a facility-based approach in which the modules are taught in blocks at each facility. Between each of the workshops or blocks, the trainer or consultant conducts site visits, and improvement projects are completed by the laboratory's staff. A baseline and final assessment of the laboratory is conducted by auditors, and improvement projects are developed based on the findings of the baseline assessment. Baseline and exit assessments are conducted using the SLIPTA checklist to document improvement and impact of SLMTA.

FIND has developed a TB specific programme, TB SLMTA, incorporating the GLI tool into the SLMTA programme, including a TB Laboratory QMS Towards Accreditation Harmonized checklist,[5] specific training modules and tools that meet the differing requirements of TB laboratories, for example with regard to QA and biosafety. The

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4 http://slmta.org

5 https://www.finddx.org/wp-content/uploads/2016/07/NEW-TB-Harmonized-Checklist-v2.1-2-2016.pdf

harmonised checklist incorporates GLI checklist clauses within the SLIPTA checklist and results in the same SLIPTA score as with the official SLIPTA checklist.

All the above-mentioned tools help laboratories to meet the requirements of ISO15189:2012. All three can be used individually as well as in combination.

GLI recommends that the NRL undertake a baseline assessment, using the SLIPTA checklist or the TB Harmonized checklist, and develop action plans based on any non-conformities identified. Several possibilities exist for implementing quality improvements, depending on the resources and support available. TB laboratories may work through activities provided in the GLI online tool, often with external consultant support. Alternatively, where the SLMTA programme is being implemented in a whole country, TB laboratories may be integrated into a general SLMTA programmes in a country, and may complement this programme with TB specific elements from the GLI tool. A number of countries are following the specific TB SLMTA programme with or without additional on-site mentoring.

2.4.4 Mentoring

Structured mentoring has been demonstrated to accelerate a laboratory's progress towards accreditation. Different models of mentoring have been used depending on available resources, the availability of mentors, and the number of laboratories being supported. The scope of mentoring should be clearly defined, and early engagement of facility and laboratory managers is critical to ensuring that the mentor has the necessary authority to conduct the agreed upon scope of work. A clear mentoring schedule should be drawn up in advance and agreed to by all parties. Mentoring should always be conducted in a standardised way, with clear action plans and well-delineated responsibilities. Mentors should be experienced and receive training not only in the technical aspects of assessment and the use of a structured mentoring approach, but also in "soft" skills, such as effective presentation, negotiation, and conflict resolution. The mentor's role is to work alongside the laboratory staff and to help them implement the various activities and improvements. While it may lead to more rapid results in the short term for the mentor to conduct activities on their own, this seldom leads to sustainable improvements and it does not help to foster a sense of ownership by the laboratory staff.

2.4.5 Assessment

Assessment is a process for examining laboratory performance and comparing it to standards, benchmarks, or the performance of other laboratories. Assessments can be internal, performed by the laboratory's own staff, or they may be external, conducted by a group or person outside the laboratory.

The above-mentioned checklists may be used for QMS assessments. Alternatively, shorter checklists may be used more frequently or to audit specific technical areas, such as biosafety. Since properly auditing a laboratory takes a minimum of one to two days, it may be more efficient to use abbreviated checklists for more frequent internal audits. Audit reports, including non-conformities and recommendations for

improvement, should be shared with the laboratory manager and staff, and support should be provided for planning how to act on them.

In addition to the checklists mentioned above, other checklists may be in use in the country, such as the 2012 WHO *Laboratory Assessment Tool* or the 2013 GLI *TB Microscopy Network Accreditation Assessment Tool*. When providing technical support, consultants may be asked to review local checklists to assess that they are comprehensive and conform to international standards. Alternatively, countries may wish to customise these standard checklists to make them more directly relevant to their setting.

KEY ACTIVITY AREAS FOR TECHNICAL SUPPORT

- ■ Advocate within appropriate MoH structures for the need for NRL accreditation and QMS
- ■ Prepare plans and budget for implementing QMS in TB laboratories and assist in liaising with partners for funding and technical support
- ■ Conduct laboratory QMS assessments, make recommendations for quality improvements, and work with laboratory personnel to develop action plans
- ■ Conduct basic QMS training (e.g., using WHO LQMS package)
- ■ Conduct training and mentoring programme for TB laboratories working towards accreditation
- ■ Conduct laboratory assessment (auditing) training
- ■ In conjunction with regional bodies, such as ASLM, conduct formal external audits (e.g., WHO AFRO SLIPTA) – if appropriately qualified
- ■ Coordinate with other partners providing support to TB laboratories in the country to ensure a harmonized approach
- ■ Provide support for country customisation of checklists used for laboratory assessments
- ■ Review local checklists for conformance to international standards

Suggested reading

GLI stepwise process towards TB laboratory accreditation.
http://gliquality.org

ISO 15189 Quality Management System Implementation: Look Before You Leap. TB CARE I.
http://www.challengetb.org/publications/tools/lab/ISO15189_QMS_Implementation.pdf

Laboratory Quality Management System Training Toolkit. Geneva, World Health Organization. 2014.
http://www.who.int/ihr/training/laboratory_quality/doc/en/

Maruta T, Motebang D, Wanyoike J, Peter T, Rotz PJ. *Impact of mentorship on WHO-AFRO Strengthening Laboratory Quality Improvement Process Towards Accreditation (SLIPTA).* Afr J laboratory Med. 2012;1(1), Art. #6, 8 pages.
http://dx.doi.org/10.4102/ajlm.v1i1.6

QMS: a model for laboratory services GP26-A4. Wayne, PA, Clinical Laboratory Standards Institute. 2011.
http://labmed.ascpjournals.org/content/43/1/26.short

TB Microscopy Network Accreditation. An assessment tool. Global Laboratory Initiative. 2013.
http://www.stoptb.org/wg/gli/assets/documents/TBMicroscopy_Network_Accreditation_Web.pdf

Yao K, McKinney B, Murphy A et al. *Improving Quality Management Systems of Laboratories in Developing Countries: An Innovative Training Approach to Accelerate Laboratory Accreditation.* Am J Clin Pathol (2010) 134 (3): 401–409.
http://ajcp.oxfordjournals.org/content/134/3/401.long

WHO Guide for the Stepwise Laboratory Improvement Process Towards Accreditation in the African Region (with checklist). World Health Organization. 2012.
http://www.stoptb.org/wg/gli/assets/documents/slipta-guide050813.pdf

15189:2012: Medical laboratories – requirements for quality and competence. Geneva, International Organization for Standardization. 2012.
http://www.iso.org/iso/catalogue_detail?csnumber=56115

2.5 TB laboratory biosafety

2.5.1 Introduction to biosafety

In many countries there are severe gaps in the provision of safe working environments for TB laboratories. Even where infrastructure has been upgraded, challenges remain in ensuring adequate servicing and maintenance of safety equipment (biosafety cabinets [BSCs], air handling systems), and un-interrupted supply of personal protective equipment (respirators, gloves, etc.).

Establishing and maintaining a safe working environment with best practices in a TB laboratory is essential. Administrative, environmental, and personal protective controls must be in place to ensure the safety of workers and guarantee quality performance.

The WHO *Tuberculosis laboratory biosafety manual* should be consulted for the latest detailed recommendations for biosafety.
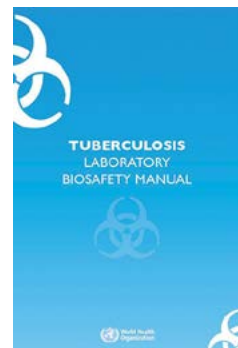
2.5.2 Assessing risk

In order to understand the level or risk involved in a laboratory, a formal assessment must be performed. A risk assessment is simply a careful examination of what in the laboratory's work could cause harm to people within the facility.

There are different identifiable risks according to the methods and activities being performed. In TB laboratories there are three established risk levels (low, moderate,

and high risk) for performing different standard procedures required for various testing: see Table 14. The risk level refers to how likely it is that someone in the laboratory will become infected with TB as a result of procedures performed in the laboratory.

Table 14 Risk precaution levels associated laboratory activities and risk assessment for tuberculosis (TB) laboratories (WHO Tuberculosis laboratory biosafety manual, 2012)

RISK LEVEL OF TB LABORATORY	LABORATORY ACTIVITIES	ASSESSMENT OF RISK
Low risk	Direct sputum-smear microscopy; preparation of specimens for use in an automated nucleic acid amplification test cartridge (such as the Xpert MTB/RIF assay)	Low risk of generating infectious aerosols from specimens; low concentration of infectious particles
Moderate risk	Processing and concentration of specimens for inoculation on primary culture media; direct DST (for example, line-probe assays on processed sputum)	Moderate risk of generating infectious aerosols from specimens; low concentration of infectious particles
High risk (TB-containment laboratory)	Culture manipulation for identification; DST or line-probe assays on cultured isolates	High risk of generating infectious aerosols from specimens; high concentration of infectious particles

TB-LAMP is considered suitable for use in low risk TB laboratory with biosafety precautions similar to that for direct smear microscopy. SL-LPA is similar to FL-LPA in that direct testing of sputum specimens is considered moderate risk and testing of cultures is considered high risk. Laboratories may consider using additional precautions against airborne transmission because the samples for SL-LPA are from patients with known or presumed rifampicin-resistant TB or MDR-TB. The manipulation of urine for LF-LAM is considered to have minimal risk for the transmission of TB, and universal precautions are recommended for the handling of urine.

Low Risk: These procedures should be performed in an adequately ventilated area or room (that is, one with unidirectional airflow and 6–12 air changes per hour). If appropriate microbiological techniques are used, testing can be performed on an open laboratory bench or counter. If laboratory ventilation is inadequate, a ventilated work station or a BSC should be used.

Moderate Risk: Procedures that have a moderate risk of generating aerosols include processing and concentrating sputum specimens for inoculation onto primary culture media or for performing direct DST (for example, LPA testing on processed sputum). These procedures must be performed in a BSC because of their inherent risks. A separate laboratory area is required for moderate-risk procedures. The laboratory should have a sink for hand washing, and adequate ventilation (that is, unidirectional air flow into the laboratory with 6–12 air changes per hour). Infectious wastes should be sterilized before disposal. Centrifuges used for processing specimens must have sealed buckets that prevent leaks. Work with specimens must be carried out in a BSC of either class I or class IIA2.

High-risk (TB-containment laboratories): High-risk procedures must be performed in a TB-containment laboratory. These procedures include manipulating cultures or suspensions of MTB for identification, indirect DST, or molecular assays. Cultures contain large numbers of TB bacilli and constitute a high level of risk for laboratory staff who manipulate them. Essential features of a high-risk facility include restricted access to essential personnel, controlled ventilation system providing at least 6-12 air changes per hour, and on-site autoclaving for waste management. Further details on requirements are provided in the WHO *Tuberculosis laboratory biosafety manual*.

2.5.3 Infrastructure

Countries often require infrastructure development or upgrades in order to reach minimum standards of safety for conducting culture and DST. With the support of donors and partners, many NRLs are undergoing such upgrades. Technical assistance may be required on how to design laboratories to ensure safe and efficient workflow. Upgrading infrastructure is a long process, and interim interventions may be conducted to improve the safety of the laboratory staff and the public. Sometimes simple changes can contribute towards improved safety, before or in the absence of large capital investment, such as re-positioning equipment, dividing rooms, and de-cluttering workstations. Where safety is seriously compromised, safety concerns and proposed solutions should be clearly articulated in written reports to management and donors and partners, and advocate for immediate action. In some circumstances, where the safety of staff or the public is put at risk, it may be that the only option available is to recommend that testing be interrupted until corrective actions can be implemented.

2.5.4 Personal protection

As with all laboratories, personal protection begins with an individual's understanding of laboratory policies and guidelines on safety, and the use of best practices while working in the laboratory. Additional protection can be obtained through proper use of recommended personal protective equipment. The particular types of equipment used in TB laboratories depend on the risks associated with the procedures being performed. For example, gloves and laboratory coats or gowns should be used for any work that involves handling specimens (sputum, blood, and body fluids) and other potentially infectious materials (especially waste), manipulating cultures, or preparing reagents using hazardous materials. Gowns that open in the back, are seamless in front, and have long sleeves with elastic cuffs should be worn in moderate-risk and high-risk laboratories where cultures are being prepared or used for advanced testing. Shoe covers or shoe changes are recommended in entry and exit protocols designed for TB containment laboratories. Protective eyewear should also be used during procedures where there is the risk of eyes being splashed by hazardous or infectious materials, such as preparing acid or basic solutions, cleaning glassware that previously contained infectious materials, or incinerating waste.

Respiratory equipment, either N95 (US standard) or FFP2 (European standard), may be used to provide additional protection during high-risk procedures that generate aerosols with high concentrations of infectious particles, such as manipulating cultures

for identification and DST. Staff required to use respirators must undergo proper fit testing and understand proper donning and doffing procedures[6]. Reuse of respirators is not recommended; however, due to resource limitations, some laboratories may implement a reuse policy. If reuse of respirators is necessary, laboratory administrators must ensure adherence to administrative and engineering controls in order to limit potential N95 respirator surface contamination (e.g., properly certified BSCs and adequate ventilation). In addition, frequent training or the use of posters regarding strict adherence to hand hygiene practices, proper personal protective equipment donning and doffing technique, physical inspection, and performing a user seal check should be in place to reinforce the need to minimize unnecessary contact with the respirator surface. Unfortunately, there is no way of determining the maximum number of safe reuses. Safe N95 reuse is affected by a number of variables, such as exposure time and atmospheric bacterial load. Protective respiratory equipment is not a substitute for a poorly functioning BSC or an uncertified BSC. In all cases, the use of good microbiological technique is essential to prevent aerosol production and minimize the risk of laboratory-acquired infections.

2.5.5 Emergency preparedness and response

Safety procedures must include emergency preparedness and response. Staff must be trained and practice responding appropriately to accidents or incidents such as fires or power outages, accidental spill exposures, and the need for emergency medical treatment and evacuation. Emergency preparedness plans should be devised following a risk assessment that evaluates which laboratory areas are considered to be high risk; which personnel are at risk and which personnel should be involved in responding to incidents; what medical treatment and emergency transport is available; and which equipment and supplies are needed for each specific response. Safety procedures and emergency preparedness plans should be written, readily available, and even displayed at locations visible and easily accessible to all staff. At a minimum, annual trainings on emergency procedures should be implemented, including practical spill exercises. All staff, including drivers transporting specimens, clerks, and other support staff need biosafety training.

2.5.6 Occupational health

The goal of occupational health programmes is to provide a safe workplace. For TB laboratories, occupational health programmes include taking measures to minimize employees' risk of exposure to infectious aerosols and other materials, making certain that employees know the signs and symptoms of TB, and ensuring that competent medical diagnosis and treatment are available if laboratory-acquired infections occur.

Employee medical evaluations should be obtained prior to employment to ascertain both the risk level and baseline of health for each staff member. Additional health surveillance strategies should be implemented to monitor staff on a regular basis. Strategies may include personal consultations with staff regarding their current health status or the use of medical surveys. If possible and applicable, regular follow-

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6 http://www.cdc.gov/niosh/npptl/respusers.html

up with available diagnostic tests (X-ray, tuberculin skin test) can be implemented. In order provide a supportive working environment for staff, ensure their health, and promote retention of well-trained human resources, a mechanism for occupational health surveillance is recommended.

2.5.7 Waste management

The appropriate management of laboratory waste is important to ensure safety for the laboratory personnel, prevent contamination of the environment, and eliminate the risk of exposing the community to harmful materials. Waste-management procedures must comply with all pertinent local and national requirements and regulations, though in some countries, these regulations may be non-existent or ill-defined.

In many countries there are limited options for waste disposal, especially for sharps (lancets, blades, syringes, or hypodermic needles), broken glass (such as Pasteur pipettes and contaminated vials), or hazardous chemicals. Resources for proper disinfection or sterilization procedures are often limited, especially in remote areas. Consequently, burial or open pit burning practices are still widely used. These practices are problematic because they often result in incomplete disinfection or destruction of the waste, and in addition they produce emissions which contribute to local air pollution. In extremely poor settings materials from these sites may be scavenged by locals and sold to buyers who wash, repackage, and recirculate items for reuse without proper sterilization. These unethical practices lead to the transmission of infectious diseases and are extremely problematic for public health programmes. It is the responsibility of the consultant to educate and train national programme officials and laboratory personnel on how best to manage waste given the constraints of the local setting.

TB laboratories can produce various types of waste, from non-infectious general waste to hazardous chemical or biological infectious materials.

Infectious waste is all waste that has been in contact with infectious materials. This includes infected body tissues or fluids; used needles; personal protective equipment used in protocols handling infectious materials; and any instruments or consumables that have come in contact with infectious materials which cannot be sterilized and recycled. The overriding principle in minimizing risks from infectious waste is to decontaminate, sterilize by autoclave, or incinerate all items.

Chemical waste in TB laboratories is reagents and solutions used for various protocols such as specimen processing, microscopy, media preparation, and decontamination. Sometimes chemical waste may need additional segregation depending on the type or category. Chemical waste should be neutralized (in the case of an acid or base) or sent off to a collection facility with the appropriate knowledge and training on disposal (for organic solvents).

Non-infectious general waste consists of basic materials that can be disposed of in the general facility's trash (e.g., paper, boxes, containers).

All waste must be segregated according by category into appropriate disposable bags or containers with proper markings and disposed of using appropriate protocols.

Again, burial and open-pit burning should be avoided, and proper methods of decontamination and sterilization should be adopted. At lower level facilities in rural areas, access to equipment or disinfectants essential for proper disposal may be limited and thus burial or open-pit burning may be the only options. However, in these instances, it is important to design waste segregation and pick-up strategies, provide proper decontaminating agents, or construct small incinerators to facilitate proper waste management practices.

Some materials such as glassware, instruments, and laboratory clothing can be reused or recycled after proper sterilization. However, sometimes there may be attempts at recycling other items by boiling and washing them, such as microscope slides and sputum cups (among others); these practices should be avoided.

Often cost and sustainability are the primary limitations to implementing proper waste management practices. Expensive equipment such as sterilizers or the construction of incinerators for each facility may not be possible within the current programme budget. Under these circumstances, strategies for waste pick-up and transportation to larger waste management facilities may be an option. Having centralized facilities at regional or provincial levels with larger incinerators to handle the increased demand and volume should be considered. In this scenario, each laboratory would have waste accumulation and holding areas with restricted access and regular pick-ups would be scheduled. Depending on the local terrain and available infrastructure this may or may not be more cost-effective for the programme.

As previously stated, it is important for programmes to establish policies, guidelines and protocols at the national level for laboratory waste disposal. Implementing waste management programmes for TB laboratories is an essential step in providing QMSs that are essential for accreditation. Specific information on waste management in TB laboratories can also be found in the *WHO tuberculosis laboratory biosafety manual* listed in the reference section. A free online training programme based on the WHO Manual is available via FIND website.

KEY ACTIVITY AREAS FOR TECHNICAL SUPPORT

- **Review working practices within the laboratory and advise on improvement in safety**
- **Offer training on biosafety for all level laboratories**
- **Develop biosafety guidelines for TB laboratories**
- **Perform a risk assessment**
- **Develop guidelines for and establish waste management practices**
- **Assist with development of SOPs**
- **Assist with development of occupational health programme**
- **Assist with laboratory design and workflow for safe operations**
- **Assist with developing an emergency preparedness plan**

Suggested reading

Tuberculosis laboratory biosafety manual. Geneva, World Health Organization. 2012. (WHO/HTM/TB/2012.11).
http://www.who.int/tb/publications/2012/tb_biosafety/en/

Biosafety in Microbiological and Biomedical Laboratories, 5th ed. Atlanta, GA, United States, Centers for Disease Control and Prevention, 2009 (CDC 21-1112).
http://www.cdc.gov/biosafety/publications/bmbl5/

Laboratory Safety Chemical Hygiene Plan. Washington, DC. United States Occupational Safety and Health Administration. 2011. (OSHA FS-3461 8/2011).
http://www.osha.gov/Publications/laboratory/OSHAfactsheet-laboratory-safety-chemical-hygiene-plan.pdf

TB Laboratory Biosafety Online Training. FIND.
http://finddiagnostics-training.org/find-biosafety-training.html

Ventilated Workstation Manual for AFB Smear Microscopy: manufacturing, validation and user guide. DHHS, CDC, GLI, IUATLD, APHL.
http://stoptb.org/wg/gli/assets/documents/vwm4afbsm.pdf

2.6 Implementing systems to manage laboratory data

All laboratories need a system for managing their data, be it manual or electronic. In recent years, there has been increased interest and progress in implementing electronic data management systems, particularly in reference and referral laboratories. However, the norm in many countries' peripheral laboratories remains a manual recording and reporting system.

A Laboratory Information Management System (LIMS), also known as a Laboratory Information System (LIS) or Laboratory Management System (LMS), whether paper-based or electronic, usually includes the following features:

- requisition, receipt, and scheduling of tests

- collection and management of samples, including chain of custody

- reporting of test results to clinicians

- other reporting, such as billing

- workload statistics and laboratory performance

- QC and EQA processes

- inventory management

Additional functionalities may include audit management, a bar code reader, instrument calibration and maintenance, and time tracking to calculate laboratory turnaround times.

There are several benefits to electronic data management over paper-based reporting, such as improved data quality (e.g., by highlighting values that are outside the normal limits); decreased workload by removing duplicate data entry; facilitated access to data, data analysis and reporting; allowing flexibility to modify reporting format; as well as linking multiple test results performed on a single patient. LIMS may be open-

source applications, proprietary products, or they may be developed by individual developers for a particular laboratory. Open-source applications can more readily be integrated with other electronic databases such as electronic TB registers and electronic medical records, allowing laboratory data to be loaded directly into the application. Proprietary products may deliver the required set of features and come with set up and maintenance support; however, changing or adding features once the system is installed requires additional fees that may be difficult for some laboratories once initial partner support for the installation is over. Self-developed or open-source applications do require sufficient local information technology support to ensure upgradability and sustainability, as well as to make subsequent revisions to the system. Additional information can be found in the WHO publication *Electronic recording and reporting for tuberculosis care and control*.
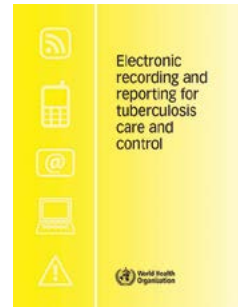
LIMS may be implemented within an individual facility, or a number of sites in a country may be networked. Several partners are involved in improving the networking capabilities of laboratory networks.

2.6.1 Diagnostics connectivity

By taking advantage of opportunities to connect diagnostic test devices that produce results in a digital format such as Xpert MTB/RIF, liquid culture (e.g., MGIT), and LPAs with automated readers, electronic data can be transmitted reliably to a variety of users and can provide a highly cost-effective way to ensure proper functioning of a diagnostic device network. The adoption of diagnostics connectivity solutions will be monitored as a core indicator for laboratory strengthening under the End TB Strategy.

As described in the *GLI Quick Guide to Diagnostics Connectivity Solutions*, diagnostics connectivity solutions typically comprise: 1) a connectable diagnostic device that produces electronic data, 2) a software platform that receives and interprets data, and 3) a means to transmit data from the device to the software platform and to a server. Systems have been developed by Cepheid, USA (C360), SystemOne (GxAlert™/Aspect™), Savics (DataToCare™) and FIND (Connected Diagnostics Platform). Importantly, the developers are collaborating to ensure the compatibility of the systems. The software can usually be configured so that subsets of data can be securely made available to those that need access to it. Security protocols also protect the privacy of the patient.
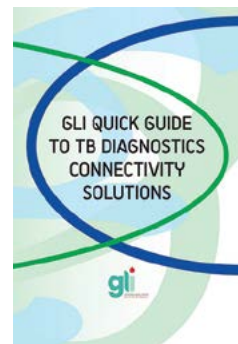
Key features of the systems are the ability to remotely monitoring performance, conduct QA and manage inventory. With remote monitoring, designated persons can use any internet-enabled computer to access the software platform, providing them with an overview of the facilities, devices and commodities in their network. For, example, the head of an NRL or other authority can easily see how many tests are being performed and where; what are the results; and which sites are underperforming or experiencing

abnormal results or errors, which may highlight a need for troubleshooting, device repairs, targeted on-site supervision, or retraining of technicians. Software can track consumption and inventory to avoid stock outs and expiring cartridges as well as potentially identify commodity lots or specific instruments with poor performance and abnormal error rates for QA purposes.

Test results can be sent to the NTPs as real-time data to assist with surveillance of trends on disease or resistance patterns as well as enhance the capacity of NTPs to generate performance indicators and to provide the data needed for several of the top 10 indicators of the End TB Strategy.

Another key feature of the system is to send results automatically to clinicians and automatically into LIMSs and electronic registers. (see section 2.8. Linking laboratory services to TB care and treatment).

Whether laboratories are using paper-based or electronic data management systems, it is important for countries to have standardised recording and reporting formats, and to use a standard set of quality indicators to measure laboratory performance. Furthermore, laboratory information needs to be integrated into data management systems used by the NTP.

The Association of Public Health Laboratories (APHL) has developed a series of documents to guide countries in the selection and implementation of a LIMS, including a *Guidebook for Implementation of Laboratory Information Systems in Resource-Poor Settings*, a detailed toolkit for implementation, and a software provider report.

KEY ACTIVITY AREAS FOR TECHNICAL SUPPORT

- **Provide guidance to laboratories to strengthen and standardise paper-based and electronic LIMS**
- **Assist laboratories to implement paper-based and electronic LIMS**
- **Provide guidance on addition of new features or upgrades to existing LIMS**
- **Provide guidance on diagnostic connectivity solutions**
- **Advise on integration of LIMS data into national data management systems, including electronic databases, e.g., electronic TB registers**

Suggested reading

Electronic recording and reporting for tuberculosis care and control. World Health Organization. 2012. (WHO/HTM/TB/2011.22).
http://who.int/tb/publications/electronic_recording_reporting/en/

Guidebook for Implementation of Laboratory Information Systems in Resource-Poor Settings. Association for Public Health Laboratories.
http://www.aphl.org/MRC/Documents/GH_2005October_LIS-Guidebook.pdf

Laboratory Information System (LIS) High Level Requirements. Association for Public Health Laboratories.
http://www.aphl.org/MRC/Documents/GH_2005October_LIS-High-Level-Requirements.pdf

Toolkit to Accompany the LIS High Level Requirements. Association for Public Health Laboratories.
http://www.aphl.org/MRC/Documents/GH_2005October_LIS-Toolkit.pdf

LIS Software Provider Report. Association for Public Health Laboratories.
http://www.aphl.org/MRC/Documents/GH_2005October_LIS-Software-Provider-Report.pdf

GLI Quick Guide to TB Diagnostics Connectivity Solutions. Global Laboratory Initiative. 2016.
http://stoptb.org/wg/gli/assets/documents/gli_connectivity_guide.pdf

2.7   Human resources

One of the greatest challenges for TB programmes in resource-limited settings is the development and maintenance of well-trained laboratory staff. Qualified personnel who have extensive training, experience, and advanced technical skills often take positions in the private sector or in other countries where they can earn higher salaries than in the public health sector. As a result, public sector laboratories have high staff turn-over. In some places, personnel are rotated on a systematic basis from laboratory to laboratory in order to cover the staffing shortages. While this may seem practical, rotation policies are detrimental to consistent and reliable routine testing as newly cycled staff need training on the laboratory's methods and technologies. Under these circumstance laboratories cannot establish the proper level of proficiency to provide continuous quality testing. Finally, as more MDR-TB and XDR-TB samples come to the laboratory, awareness of personal risk is rising, which may mean that staff prefer to work in other laboratory areas.

The issue of insufficient staffing is very serious and it will be not resolved unless government health programmes provide better wages, well-defined paths for career progression, and safe working environments. Proper planning for human resource capacity building should be included in national strategic plans. Without sufficient adequately trained, motivated, skilled, readily available, well distributed, and supported human resources for laboratories, national TB control targets will not be met.

2.7.1 Human resource capacity and development

As networks are built or expanded and technical capacity increased, human resources should also be expanded. When a laboratory is being developed or technologies are being implemented, it is important to assess the human resource situation and the current and predicted workload. As noted in section 1.1, there are limitations on daily workload for laboratory testing. For example, it is recommended that microscopists performing ZN staining read only 25 smears per day. In laboratories where multiple methods are performed, staff may be assigned to one type of test, or they may perform parts of different test procedures (e.g., decontamination for culture, reading of smears, etc.). Alternately, technicians can perform a variety of tasks throughout the day or week. Having a routine schedule of activities with defined roles and

responsibilities for staff will improve the quality and efficiency of the work. To have efficient testing and reach recommended turnaround times, laboratories must have enough staff to perform the work. Laboratories also need support staff for preparing materials for testing; waste management; housekeeping and facilities maintenance; and data recording and reporting. Proper time management is crucial to timely results.

In light of a proper assessment of the human resources situation, areas of weakness can be addressed, such as the absence of consistent routine training programmes or the need for systems to manage human resources.

2.7.2 Training programmes

For many countries, a human resources crisis limits laboratory services at all levels. At the peripheral level, the shortage of laboratory technicians forces countries to train a new cadre of individuals with little or no formal education. For AFB microscopy and even Xpert MTB/RIF testing, individuals with no formal background are trained "on the job". In these scenarios, training programmes must be well thought out and include competency assessment at the end of training, supported by some combination of regular review of quality indicators (broken down by operator), routine supervision, and proficiency testing to monitor performance.

In other settings, formal training for laboratory technicians (or technologists) may require a 2 or 3-year certification, diploma, or bachelor's degree from a university. With the increased focus on skills for culture methods and DST, more attention needs to be given to the curriculum and requirements of laboratory technology to ensure that their graduates have the competencies required for increasingly specialized work.

Perhaps one of the most glaring human resource deficiencies is the lack of programmes for laboratory managers and leaders. Management of laboratory personnel requires highly skilled laboratory scientists who understand the complexity and details associated with each testing platform and with quality systems, while also having the skills to manage people. Whereas in many high-resource countries doctorates are required to direct a laboratory, in many limited resource countries the majority of laboratory managers, even at the national level, do not have a graduate degree or any specific management training. Furthermore, many post-graduate qualifications focus on research, with little or no training in laboratory management. Laboratory management and network management are underestimated capacities that require mentoring and training in order to develop the next generation of leaders who will implement new technologies and programmes. Therefore, it is important to facilitate technical assistance in a manner that will transfer knowledge and build internal national capacity in order to allow programmes to gain independence and become sustainable. Some organisations and institutions offer post-graduate training opportunities and in-service training focused on laboratory management.

It may be important to assess and review current country level training programmes for laboratory staff and managers. An assessment of the availability and quality of training provided; procedures for the evaluation of competency and proficiency; and refresher training should be included. Proper documentation of trainings conducted and feedback from participants are also critical.

A primary responsibility of management is to maintain and upgrade staff training programmes as new staff are hired and testing programmes expand. Often this is performed by Training-of-Trainers programmes that specifically train a cadre of personnel to lead the implementation and training for new technologies or methods throughout the network. Training curriculum development is a critical component of a consultant's work and should involve country officials and designated NRL staff to guide the development according to the country situation, programme strategies, or national guidelines. The primary purpose of training from an external consultant is to build capacity and provide modes for sustainability.

It is essential that appropriate persons are selected to attend training courses: technical staff who will perform tests should be trained on new techniques, while staff who will oversee or supervise implementation may be selected to attend programmatic level trainings or workshops. Those organizing training courses should work closely with laboratory or facility management and programme managers to ensure that the purpose of the training is well communicated and that staff can be appropriately selected. Various factors need to be considered when planning trainings, including location (on-site versus regional or central trainings); transportation costs; accommodation and per diems; facilitators (local and external); as well as the content and format of the training.

2.7.3 Roles and responsibilities

Laboratories should have job descriptions for each position within the laboratory, encompassing specific requirements for education, experience, theoretical and practical background, and demonstrated skills required for each position. In addition, each individual should have a personal job description that outlines work activities, employer expectations, the mode for competency assessment, and in-service training requirements. Establishing clear roles and responsibilities for all staff members alleviates confusion and promotes a systematic strategy for daily work.

2.7.4 Leveraging resources

In countries with a weak TB laboratory network, it is critical to optimize all available technical resources. All countries should cast a wide net to identify the best technical base possible, both inside and outside their NTP and MoH. For TB diagnostics and related clinical services, expertise can be greatly increased by collaborating with national academic and research laboratories in both the public and private sectors. It is imperative that the nature and scope of the partnerships be established from the beginning, with formally defined roles and responsibilities. It is also important to establish links with international laboratory networks. Ideally, each NRL should be connected to a WHO SRL, from which it receives training and to which the NRL is accountable in terms of technical proficiency.

KEY ACTIVITY AREAS FOR TECHNICAL SUPPORT

- Assist with programmes that enhance human resource capacity building
- Assist with training programmes for laboratory technicians on methods and protocols
- Assess competency and proficiency of staff
- Help establish a guideline for human resource development for laboratories
- Assist with the development of incentive programmes

Suggested reading

Towards comprehensive TB control: HRD vision, goal, key strategies and implementation approaches. Geneva, World Health Organization.
http://www.who.int/tb/health_systems/human_resources/hrh_action_framework/en/

Assessing human resources development. Geneva, World Health Organization.
www.who.int/tb/publications/tb_framework_checklist17.doc

2.8   Linking laboratory services to TB care and treatment

A laboratory test is just one part of the diagnostic cascade that starts with a clinician evaluating a patient and ordering of a test and continues through the receipt and interpretation of the results and initiation of appropriate TB treatment. Delays in any of the steps from specimen collection to transport to the laboratory to the laboratory testing to reporting the results back to the clinician to the clinician receiving and acting on the laboratory result can reduce the clinical and public health impact of a laboratory test.

Too often, improvements in laboratory services or the introduction of a new laboratory tests focuses only on improving testing in the laboratory (the examination phase). Efforts must also be made to improve the pre-examination (pre-analytic) and post-examination (post-analytic) phases of testing. Furthermore, the clinical-laboratory interface must be strengthened to improve the linkage to care. Not only must laboratory staff be trained in conducting the entire diagnostic testing process, but health care workers must also be trained in selecting persons to be tested; ordering the most appropriate tests; collecting and shipping samples to the laboratory; and receiving, interpreting, and acting upon results.

Effectively addressing the gaps in the diagnostic cascade requires a comprehensive approach including identifying the gaps in the diagnostic process; systematic evaluation of technologies, diagnostic networks, test quality, linkage to care-related challenges, and barriers to patient and programmatic impact; and development and introduction of innovative solutions and models to address barriers and reduce TB-associated morbidity and mortality.

To strengthen the entire diagnostic cascade, a systems approach should be used which identifies gaps in the diagnostic cascade, emphasizes access to quality-assured

laboratory services, and uses quality management principles to ensure prompt and reliable flow of specimens and information. This can dramatically reduce the time from the ordering a test to making a treatment decision as well as increase access to laboratory services for all patients.

Clinical and public health impact is increased when timely and accurate diagnosis of TB is quickly be followed by appropriate, quality treatment and care; the diagnosis alone will not cure the patient nor will it prevent further transmission of TB within the community.

The steps necessary for linking diagnosis and treatment include:

- Reporting the results back to the client and provider. Because TB laboratory testing is not usually completed at the moment the client submits the specimen, the laboratory needs to ensure they have a mechanism in place to report the result back to both the client and the provider. In some cases, this will be a paper form that is transported back to the provider; in other cases, it will be by telephone or text message. The laboratory should ensure that the results are actually received by the intended recipient.

- Notifying positive TB results to the appropriate TB programme staff or office

- Registering the person with positive TB results for treatment

- Having the person with positive TB results begin appropriate treatment

- Completing additional laboratory tests at the initial laboratory, or sending a portion or second specimen to another laboratory for confirmatory testing, DST, or other testing when indicated

- Monitoring treatment response through routine collection and testing of patient specimens as per the national guidelines, and timely reporting back of results back to the provider

There are separate registers at the laboratory and treatment site which should be reviewed regularly to ensure that persons with positive TB results are registered for and started on treatment. Treatment registers should be reviewed to ensure that follow-up laboratory testing is completed and recorded to monitor treatment response.

The diagnostics connectivity solutions described in section 2.6.1 can facilitate the automatic transmission of electronic data and improve linkage to care and patient management. For example, test results can be automatically integrated into LIMSs or electronic registers, reducing staff time and the chance of transcription errors, and greatly facilitating monitoring and evaluation processes. A text message could be sent to a patient informing when their test results are ready and instructing them to visit the clinician to receive them and perhaps reducing loss-to-follow-up. Test results can automatically and instantly upon result availability be sent to a clinician's phone or email, SMS printer or other clinical results reporting mechanism, allowing for faster patient follow-up and improving linkage to care. Access to specialty care such as MDR-TB treatment can be facilitated by including automatic transmission of the detection of a patient with RR-TB to the local MDR-TB treatment focal point.

Coordination between the TB laboratory services and the TB programme and treatment facilities is essential at all levels to ensure that all diagnosed cases are treated, and all treated cases are bacteriologically monitored to ensure they are cured. This can be monitored through routine reporting, routine meetings, or other communication between the laboratories and the programme.

KEY ACTIVITY AREAS FOR TECHNICAL SUPPORT

■ Support sensitisation of clinicians to new diagnostic tools, the importance of referral of specimens for testing, and the interpretation of results

■ Participate in joint laboratory-clinical planning and review meetings

■ Participate in revisions to laboratory and TB registers for new diagnostics

■ Support assessment and improvement of the diagnostic cascade

Suggested Reading

International Standards for Tuberculosis Care. 3rd Edition. TB CARE I, The Hague, 2014.
http://www.who.int/tb/publications/ISTC_3rdEd.pdf

National plan for reliable tuberculosis laboratory services using a systems approach: recommendations from CDC and the Association of Public Health Laboratories Task Force on Tuberculosis Laboratory Services. Centers for Disease Control and Prevention. 2005. MMWR (RR-6) 54, 1–12.

The future of TB laboratory services – a framework for integration, collaboration, leadership. Washington, DC, Association of Public Health Laboratories. 2004. Available at
https://www.aphl.org/programs/infectious_disease/tuberculosis/Documents/ID_2004_TB-Task-Force-Future.pdf

GLI Quick Guide to TB Diagnostics Connectivity Solutions. Global Laboratory Initiative. 2016.
http://stoptb.org/wg/gli/assets/documents/gli_connectivity_guide.pdf

2.9 Strengthening the role of private laboratories in national TB programmes

Private sector laboratories play an important role in many countries. People with signs and symptoms of TB often first access diagnostic services in the private sector. Private laboratories are often better resourced (with more funding and staff) and may have testing capacity that exceeds that of the public sector laboratory network. It is therefore critical that private sector TB laboratory services be linked to the NTP and the NRL at several points in the diagnostic and treatment pathway. The nature of such collaborations will be agreed on between the NTP and private laboratories, but may include the following areas:

• **TB diagnostic reporting and treatment follow-up:** private-sector laboratories should be required to report results to the TB control programme that identifies new TB patients and DST results. NTPs should make national laboratory request

forms and registries available to private laboratories and be part of the referral and feedback mechanisms to ensure that all TB cases are promptly registered with the NTP and linked to appropriate treatment.

- **TB laboratory testing:** private-sector laboratories should be advised to follow WHO laboratory policies and recommended tests. For example, private laboratories should be encouraged NOT to use serological methods or interferon-gamma release assays to diagnose TB. Private laboratories should also adhere to WHO- and internationally-recommended biosafety policies and procedures. When available, private laboratories should also have access to established specimen transportation and referral mechanisms used by the NTP.

- **Training and supervision:** private sector laboratories should be included in national training workshops and provided with NRL-developed SOPs and other guidelines. Private laboratories should also be included in national and sub-national supervision schedules and have mechanisms for performance monitoring and feedback in place.

- **Supply management and equipment validation and maintenance:** where needed and possible, private laboratories should have access to quality-assured reagents and supplies, either free from NTP or through access to approved procurement agents and distributors. Private laboratories should also benefit from NTP- or NRL-recommended equipment validation and maintenance agreements for TB diagnostic instruments.

- **QA and management** – private laboratories should be required to participate in an EQA programme, which may include site visits, panel PT, and blinded rechecking of their results.

KEY ACTIVITY AREAS FOR TECHNICAL SUPPORT

- ■ Advise on engagement of private sector laboratories with the NTP
- ■ Participate in planning and implementation of projects aimed at engaging private laboratories in improving quality of services, e.g., through enrolling laboratories in EQA programme
- ■ Advise on engagement with and coordination of private providers towards meeting NTP goals

Suggested reading

International Standards for Tuberculosis Care. 3rd Edition. TB Care I. 2014.
http://www.who.int/tb/publications/ISTC_3rdEd.pdf?ua=1

Engaging All Health Care Providers in TB Control: Guidance on Implementing Public-Private Mix Approaches. Geneva, World Health Organization. 2006. (WHO/HTM/TB/2006.360).
http://apps.who.int/iris/bitstream/10665/69240/1/WHO_HTM_TB_2006.360_eng.pdf

2.10 Strategic planning for national TB laboratory networks

2.10.1 Laboratory strategic planning

It is important for national TB laboratory services to look at future needs for diagnosis and patient monitoring in order to develop goals and long-term plans to improve quality, build capacity, and expand services. Therefore, NTPs and MoHs should work together with NRLs to devise a long-term strategy with a supportive budget. As the need for diagnosing and managing drug resistance increases, the demand for services will climb. At present most networks have limited capacity to ensure quality DST and face challenges providing access to services for all those in need.

NRLs and networks are critical to ensuring that patients receive appropriate diagnosis, care, and treatment. They must also conduct routine surveillance activities to assess changes in the epidemic and measure the impact of the TB control programme on national public health. Therefore, it is important that these laboratories have a strategic plan to ensure the delivery of high quality services. A strategic plan describes an organization's direction and outlines the activities that need to be undertaken to successfully implement the plan during a fixed time period. In a dynamic environment where planning for the future is difficult, two- to three-year plans have been recommended. Traditionally, strategic plans are written for a 5-year period synchronized with current funding mechanisms. It is understood that needs may change depending on the fluctuations in the epidemic or with the implementation of new technologies that may become essential to TB control. The strategic plan considers current and future internal and external influences that may impact the laboratory's activities.

The importance of having strategic plans for laboratories was emphasized in the Maputo declaration on strengthening of laboratory systems (2008), which recommended that a strategic plan for national laboratories be part of national health plans. Specifically, the Maputo declaration "call[s] on national governments with support of their donors and partners in resource-limited settings to develop national strategic laboratory plans that integrate laboratory support for the major diseases of public health importance including HIV, tuberculosis, and malaria".

Additionally, the Global Fund to Fight AIDS, Tuberculosis and Malaria considers strategic planning to be an integral component of effective TB control. Developing a national strategic plan for the NTP is considered fundamental to the effective organization and management of TB care and control activities. Consequently, success in obtaining funding may depend on having a strategic plan for the NRL and its associated network. To assist countries in developing or improving their NSPs, WHO's Global TB Programme is developing a framework of key components that can be used to guide countries in creating or improving their strategic plans.

GLI partners have developed and endorsed *A Practical Handbook for National TB Laboratory Strategic Plan Development*, which provides important information and guidance on the steps necessary to write a complete and comprehensive

plan with a projected budget. Laboratory strategic plans allow the NTP to earmark funding for projected laboratory activities and developments in Global Fund funding proposals.

2.10.2 Laboratory Strategic Plan development

When creating or improving a strategic plan, it is advisable to first determine if there is already a laboratory strategic plan in place under either the NTP or the ministry's programme for national laboratory services. This is to ensure that all plans are integrated with one another and are complementary rather than overlapping.

A starting point for creating a strategic plan is to formulate a vision statement. This statement is used to define the role of the NRL and TB laboratory services. The vision statement is followed by a mission statement, which more specifically describes the roles and activities of the laboratory and its network, and identifies the customers.

Basic steps involved in laboratory strategic plan designs are:

- define a vision and mission
- perform a situational analysis
- identify desired outcomes
- prioritize strategy and activities
- identify indicators and targets
- establish a monitoring platform
- outline a work plan and budget

An initial step in creating a relevant strategic plan for a laboratory is to perform a gap analysis to compare the laboratory's current performance with the desired performance. A gap analysis can be conducted in steps to determine which resources are needed to develop a national network of TB laboratories that will provide diagnostic testing services.

Before performing a gap analysis, an assessment must be conducted using the national testing algorithm to determine which laboratory services are needed; additionally, this assessment should compare the national algorithm with the GLI model algorithms (see Section 1.3) and evaluate which elements of the national laboratory network should be improved or created. Once this has been completed, the steps required to undertake a gap analysis are:

- From the plan for the laboratory network, determine the number, location, and type (or level) of existing laboratories and whether additional laboratories are needed
- Determine the number and location of laboratory personnel in each job classification and whether and how many additional personnel are needed
- Learn which, if any, funds are available for additional employees (including salaries, benefits, and training), supplies, equipment, and designing and building new laboratories, if relevant

- Determine the feasibility of obtaining administrative authorization for adding new employees or contract workers if funding can be made available

A gap analysis is most often performed using a SWOT analysis. SWOT is an acronym for Strengths, Weaknesses, Opportunities, and Threats. A SWOT analysis is an analytical tool that helps identify internal factors (that is, strengths and weaknesses) and external factors (that is, opportunities and threats) relevant to the laboratory. Once factors that may affect a laboratory's performance have been identified by SWOT analysis, they can be used to outline goals and objectives for the strategic plan and activities for the operational plan.

Once the current situation has been assessed, specific outcomes or objective required to achieve the overall goals can be set. For example, objectives could include:

Objective 1: Increase access to Xpert MTB/RIF with effective EQA

Objective 2: Improve the diagnosis of TB for AFB-negative cases especially among PLHIV

Objective 3: Increase access to rapid laboratory diagnosis among TB patients considered at risk for MDR-TB or XDR-TB

Objective 4: Establish laboratory QMS

Under each these objectives, the strategic plan would list measurable targets. Activities required to achieve these targets would then be included in a multi-year work plan and budget. For a more thorough explanation, please refer to the *Practical Handbook for National TB Laboratory Strategic Plan Development*, in the suggested reading list.

All strategic plans should be follow by an operational plan that defines how the strategic plan will be implemented. Generally, operational plans are more detailed than strategic plans and cover a shorter timeframe: they are usually prepared annually.

KEY ACTIVITY AREAS FOR TECHNICAL SUPPORT

- **Participate as a member of the technical working group for planning**
- **Coordination or participation in sub-groups or task teams responsible for strategic planning**
- **Providing information to technical working groups or sub-groups on partner-specific activities and budgets for inclusion in strategic planning**
- **Leading or participating in strategic planning workshops**

Fig. 11 Laboratory Strategic Plan Framework (*Practical Handbook for National TB Laboratory Strategic Plan Development*)
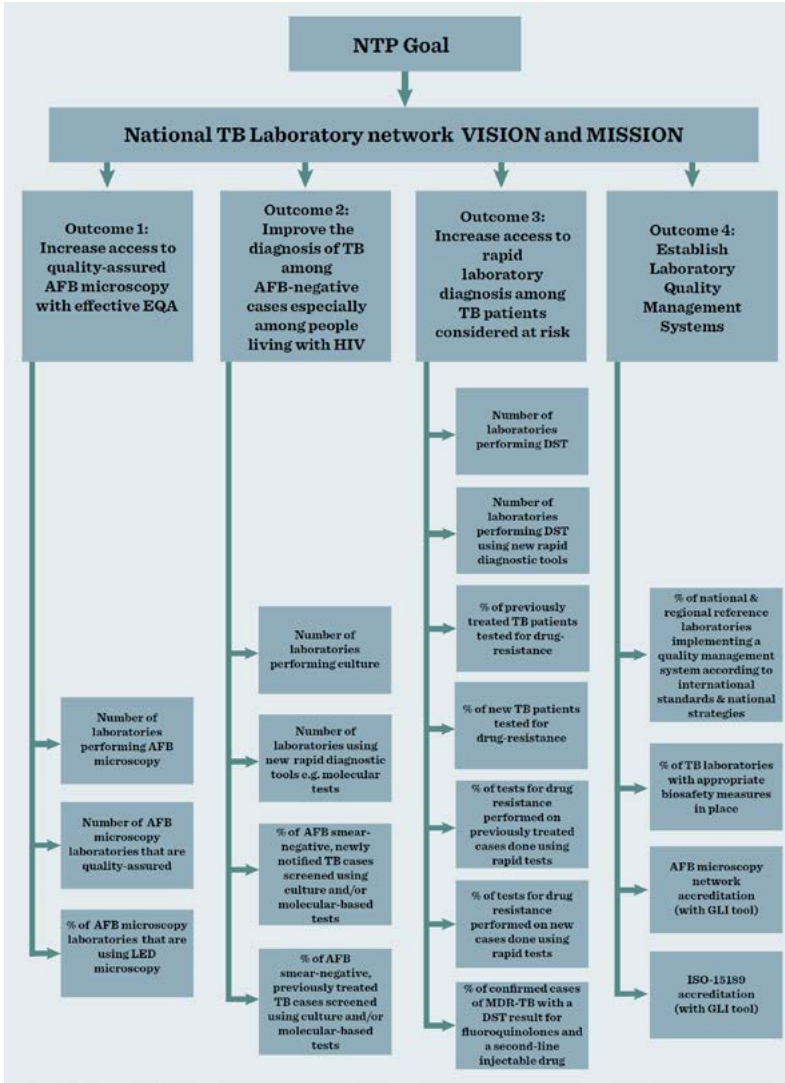
Suggested reading

A Practical Handbook for National TB Laboratory Strategic Plan Development. Global Laboratory Initiative. 2014.
http://stoptb.org/wg/gli/assets/documents/Lab_Strategic_Handbook.pdf

The Maputo declaration on strengthening of laboratory systems. Geneva, World Health Organization. 2008.
http://www.who.int/diagnostics_laboratory/Maputo-Declaration_2008.pdf

2.11   Funding TB laboratories and services

In many high burden TB countries, there is usually very little or no separate budget for TB laboratory services within the overall ministry of health budget. If a budget exists, it typically covers basic reagent costs and staff. Most of the other costs (and some basic reagent and staff costs) are covered by external funding. The primary source of external funding for TB laboratories in high burden TB countries is through the Global Fund to Fight AIDS, Tuberculosis and Malaria.[7] However, as countries move into higher income brackets, they are no longer eligible for Global Fund grants, and therefore they need to develop strategies to advocate for and receive appropriate funds for TB laboratories through domestic resources.

2.11.1 Preparing applications to the Global Fund

In order to develop the Concept Note that needs to be used when applying for grants under the Global Fund's new funding mechanism, countries should have a strategic plan for their national TB laboratories, either incorporated into a national strategic plan or as stand-alone document. It should describe:

- the capacity of different levels of the laboratory network

- gaps in capacity that the funds will be used to remedy

- a clear description of the burdens of TB, MDR-TB, and HIV-associated TB

Requests for funding from the Global Fund may include budgets for:

- building or renovating facilities

- purchasing equipment and supplies including maintenance contracts

- hiring, training, and supervising staff

- developing and implementing QA and QMS

- requesting external technical assistance

In preparing applications for support from the Global Fund, the following issues should be considered:

- epidemiological situation

- the diagnostic algorithms used for different risk groups

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[7] http://www.theglobalfund.org

- laboratories' infrastructure needs, including needs for implementing biosafety measures

- the need to purchase additional equipment, and the potential for maintaining the equipment

- whether the required referral mechanisms for specimens exist

- whether there are links to external partners who can provide technical assistance

The *WHO Planning and Budgeting for TB control activities* Excel-based tool is designed to help countries develop plans and budgets for TB control at national and sub-national level within the framework provided by the Global Plan to Stop TB and the End TB Strategy (http://www.who.int/tb/dots/planning_budgeting_tool/download/). These plans can be used as the basis for resource mobilization from national governments and donor agencies. Details of the Global Fund's funding process are available at http://www.theglobalfund.org/en/fundingmodel/process/.

Fig. 11 New funding model for the Global Fund
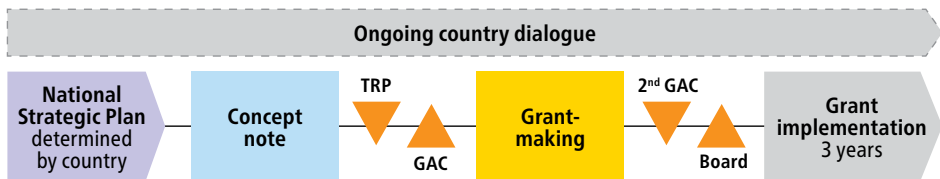
TRP – Technical review panel, GAC – Grant approvals committee

KEY ACTIVITY AREAS FOR TECHNICAL SUPPORT

- ■ **Participate in planning and budgeting for TB laboratory activities as part of the NTP strategic planning process**
- ■ **Participating in developing Joint Concept Notes for the Global Fund and applications for other funding**

Suggested reading

WHO TB planning and budgeting tool. Geneva, World Health Organization.
http://www.who.int/tb/areas-of-work/monitoring-evaluation/financing/planning-tool

The End TB Strategy – global strategy and targets for tuberculosis prevention, care and control after 2015. Geneva, World Health Organization.
http://www.who.int/tb/strategy/End_TB_Strategy.pdf

Global tuberculosis report 2016. Geneva, World Health Organization. 2016. (WHO/HTM/TB/2016.13).
http://www.who.int/tb/publications/global_report

3. Providing technical assistance

3.1   Types of technical assistance

Technical assistance (TA) can encompass a wide variety of activities, including:

- Capacity building through training and mentoring
- Specialized training programmes for new diagnostics
- Guidance on policy and programme development
- Writing of an operations manual for the NRL
- Developing SOPs
- Laboratory strategic planning
- Global Fund programme reviews
- Accreditation and laboratory QMS implementation
- Implementation of new technologies
- Developing routine surveillance practices
- Assisting with survey planning and capacity building
- LIMS implementation
- Diagnostics connectivity implementation
- Strengthening the diagnostic cascade and linkage to care
- Laboratory management mentoring
- Gap analysis and assessments
- Biosafety development
- Supply chain management
- Building specimen referral strategies
- Operational research activities

TA for these activities can come from a local country consultant, a leading institute or partner organization, or an international professional. The duration of the consultancy can depend on the tasks outlined in the national work plan, the extent of skill development or capacity building to be accomplished, and the current capacity of skilled in-country human resources. All three determine which activities require short-term TA and which will require longer-term assistance. Short-term assistance can vary from a one-time visit of one to three weeks to multiple visits over the course of a year. Requests for longer-term assistance may require that the consultant reside

in-country for several weeks, months, or in some instances for an entire year. SRLs may be able to recommend consultants.

3.2 The role of the TB Supranational Reference Laboratory Network

As a key partner in strengthening the capacity and quality of TB diagnostic testing in many countries, the WHO TB Supranational Reference Laboratory (SRL) Network comprises 36 laboratories that provide a benchmark for proficiency testing, and can also provide long-term TA under the framework of collaborative agreements.

Improved coordination of technical assistance provided by the SRLs remains a key priority for the network. As individual SRLs vary in terms of capacity, competencies, and available funding, it is important that SRLs, donors, and technical partners collaborate closely in the context of a MoH-led national (TB) laboratory strategic plan to leverage complementary skill sets and mandates to meet a county's needs for TA and capacity building. To facilitate this communication and coordination, individuals and organisations providing TA to TB laboratories should request information from the NRL on the SRL providing support to the country and contact this SRL to discuss ways to harmonise approaches and support provided. For a complete listing of current SRLs and candidate SRLs, including contact information, see: http://www.who.int/tb/areas-of-work/laboratory/srl-network/en/

The network has also adopted a reporting system that uses standardized forms to assess laboratories and laboratory networks, and a standardized form for reporting on visits to countries made by SRLs.[1]

The WHO TB Supranational Reference Laboratory Network

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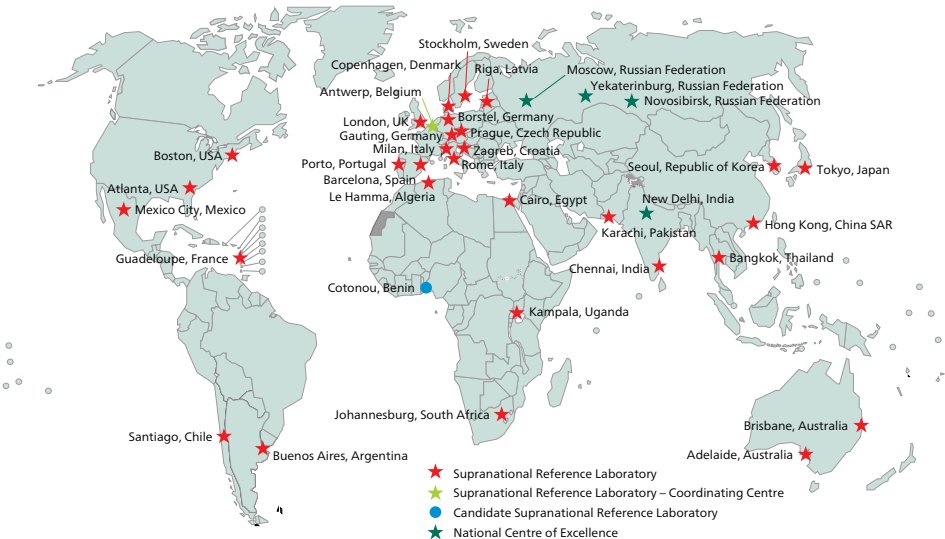
[1] http://www.who.int/tb/laboratory/srln_mission_report_blank_template.pdf?ua=1

A repository of technical reports from TA missions provided by the SRL network is online[2] and should be consulted as a source of information on laboratory issues in a country. However, it must be noted that the reports of TA missions belong to the host country and must not be shared without their permission.

3.3 Processes for technical assistance

The processes involved in TA provided by internationally based consultants are outlined in Figure 13. TA provided from consultants based in country (i.e., local TAs) follow a similar process with the exception of the various activities concerning preparation and travel. Country-based consultants from partner organizations are
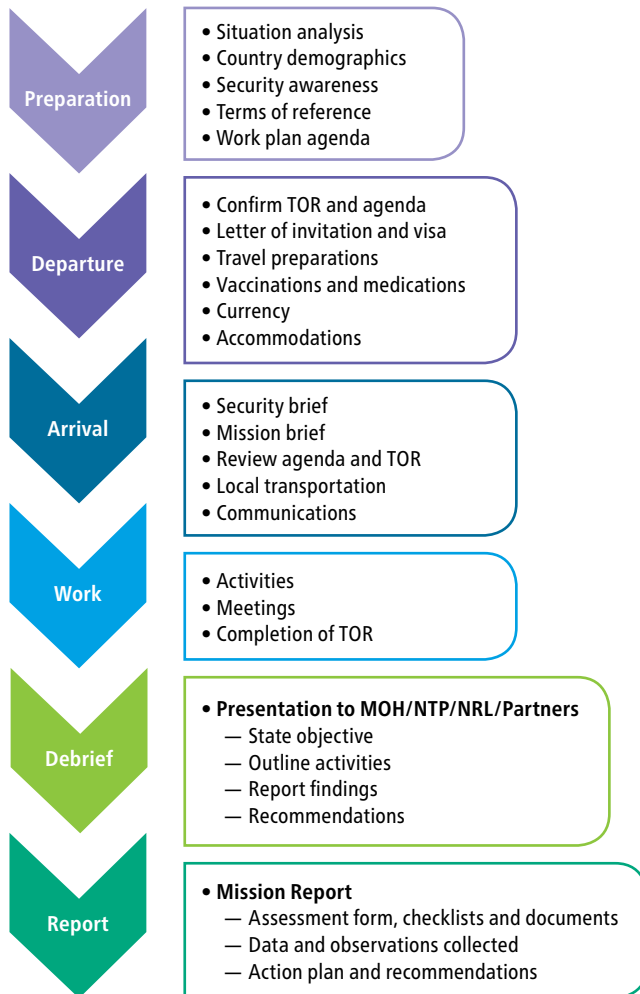
Preparation
- Situation analysis
- Country demographics
- Security awareness
- Terms of reference
- Work plan agenda

Departure
- Confirm TOR and agenda
- Letter of invitation and visa
- Travel preparations
- Vaccinations and medications
- Currency
- Accommodations

Arrival
- Security brief
- Mission brief
- Review agenda and TOR
- Local transportation
- Communications

Work
- Activities
- Meetings
- Completion of TOR

Debrief
- **Presentation to MOH/NTP/NRL/Partners**
  — State objective
  — Outline activities
  — Report findings
  — Recommendations

Report
- **Mission Report**
  — Assessment form, checklists and documents
  — Data and observations collected
  — Action plan and recommendations

Fig. 13 Processes involved in providing TA

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2   https://sites.google.com/site/srtblaboratories

already familiar with the various aspects of the country and its national programme, which includes the directions for implementation and programme developments involved in laboratories. Local consultants also often have well-formed relationships with the MoH, NTP, and NRL and often can provide more efficient and cost effective support. However, the use of a local consultant should not mean that the work should be overly informal. Local consultants still require formal terms of reference (TOR), work plans, or agendas for their activities in order to offer the necessary assistance. Consultants should prepare debriefings, final reports, and recommendations, since they are important for the advancement of laboratory development. The next sections describe critical aspects of the TA process for both international and local technical support.

3.3.1 Preparation

Preparing for a TA visit is a complex process: technical, professional, and practical issues must be considered. This applies both to short-term assistance and to longer-term work in the country. In order to plan technical activities effectively, it is important to prepare for the visit by becoming familiar with background information on the organization and the functioning of the laboratory network as well as on the epidemiological profile of TB in the country. Close collaboration with local authorities is essential to acquire relevant information and data. It is important to review various reports and previous assessments to gain a comprehensive understanding of the current laboratory situation.

a. Situational analysis – desk review

Prior to going to a country, a consultant should acquire the necessary information regarding the current status of the TB laboratory network and diagnostic services presently in use. This information can be provided by the supporting SRL, by reviewing documents from previous programme reviews or missions, or by reviewing the NTP guidelines and other national documents. However, the most accurate information is often through direct communications with the NTP, the NRL, or the lead affiliation for the national laboratory services, depending on the organizational scheme established for the individual country.

As part of the desk review, it is important to consider that level of laboratory development and diagnostic services can vary tremendously depending on country context and the local situation. For example, not all countries have an NRL or a functional network for systematic TB diagnosis. Many national programme services typically offer microscopy examination as the initial test for diagnosis; however, some countries or regions within countries still rely on basic clinical examination and chest X-ray as the primary case finding strategies. On the other hand, countries with highly evolved laboratory networks may have implemented rapid molecular testing methods for TB case detection, which also provides information on drug resistance. More advanced services will be found at the provincial, regional, or central level laboratories that have the required infrastructure. More traditional modes of TB screening are generally used at levels closer to the patient, but effective systems of specimen transport can allow rural clinics access to advanced testing. These links

are necessary to expand coverage and increase case finding, and therefore play a significant role in national TB control.

The process of performing a situational review of a country's TB diagnostic services requires an understanding of the current TB situation. Questions that may help guide this review include:

QUESTIONS?	INFORMATION
What is the country population?	Country population with demographics data from recent census
What is the current TB situation or epidemiology?	Notification, incidence, and prevalence data for TB, MDR-TB, XDR-TB, TB/HIV, extrapulmonary TB, and pediatric TB
What is the country landscape?	Geographic information. National structure or how the country is divided, current socio-economic situation. Regions or states with hot spots for TB, HIV, drug-resistant TB, or other pertinent health issues (diabetes, under-nutrition, or other chronic illnesses)
What are the primary risk groups for TB in this population?	PLHIV, children, immigrants, cross-border workers, prisoners, diabetics, contacts, other vulnerable peoples, etc.
How is the TB programme organized in the MoH?	Within Public Health, Infectious Diseases, or independent
What are the existing treatment guidelines?	Drug-susceptible TB and drug-resistant TB, TB/HIV, pediatric TB, extrapulmonary TB, and TB-diabetes
Who are the existing donors and partners of the NTP?	e.g., CDC, USAID, UNITAID, CIDA, MSF, WHO, Union, KNCV, MSH
How are laboratory services organized?	Public and private services
	As an arm of the national laboratory, or TB services stand-alone
How is the current TB laboratory network structured?	Hierarchy under NRL or under another institute
	Minimal structure
What are the existing laboratory services for TB?	Microscopy, culture, culture and DST, molecular diagnostics (Xpert MTB/RIF, LPA, TB-LAMP), other
What is the current diagnostic coverage?	No. of Microscopy centres
	No. of Culture and DST laboratories
	No. of LPA laboratories in country (first- and second-line)
	No. of TB-LAMP laboratories
	No. of GeneXpert laboratories in country and their capacity
What is the current testing algorithm?	Priority risk groups and flow of testing with recommended line of treatment
What is the annual workload for testing?	Total test performed and average throughput per diagnostic per facility for microscopy, culture, Xpert MTB/RIF, TB-LAMP, LPA, phenotypic DST, or other
Is there a National Laboratory Strategic Plan in place?	Design for laboratory expansion and capacity building over the next 3–5 years
Are there National TB Laboratory Guidelines established?	Outlines the national TB laboratory network structure, diagnostic services provided, biosafety guidelines, waste management practices, quality assurance measures, etc.

Resources for this information are:

- WHO Global TB Report
- Global Fund or WHO programme reviews
- Regional Green Light Committee mission reports
- National TB guidelines
- National epidemiological assessments
- Surveillance reports
- National TB laboratory guidelines or quality manual
- National strategic plans
- Laboratory strategic plans
- SRL reports
- Annual NRL or NTP reports

The extent of the review will vary depending on the scope of work outlined in the TOR for the consultancy. Some consultancies are based purely on bench work activities such as technical training or mentoring during the implementation of new diagnostics, while others could include assisting with policy development, strategic planning activities, or performing a programme review. The focus of the TA may be on developments for a single laboratory or cover the entire network. Information that it may be essential to have prior to beginning a consultancy could include the following:

- Recent TB epidemiology
- Structure of the organization (MoH, NTP, NRL). Consultants must aim to fully understand where management of TB laboratory services fall within the MoH and how activities are coordinated with the NTP.
- Existing network capacity and services
- Annual workload data
- National algorithms and guidelines
- Any formal laboratory manuals or strategic plans
- Current capacity building activities
- A list of partners involved in laboratory development
- Information on referral mechanisms
- Information on data management practices
- Methods of routine surveillance activities
- Available funding mechanisms to support laboratory strengthening and capacity building
- Current laboratory training or human resource development programmes

- Procurement and supply chain management practices

- Biosafety regulations and health surveillance measures already in place

- Facilities and equipment management programmes available

- QA practices

A complete desk review will provide the necessary background and understanding prior to travel, but may also be requested as a deliverable as part of the mission. Once all the relevant information has been collected from the desk review, the consultant will be able to provide the necessary technical assistance contracted under the official TOR.

b. Terms of reference

Different consultancy activities to support the NTP and NRL will invariably include different TOR covering policy, technical, or programmatic issues. It is important to be realistic about what can be achieved during the chosen timeframe. Clear TOR should be established prior to each technical visit. These terms should be tailored to the type of work required and the objectives of the mission, and all TOR should include the goal of establishing links with local and international partners participating in TB laboratory strengthening efforts. The TOR should be specific, well-defined, and in line with the national programmes strategy for TB control. The desk review will help ensure that the terms of reference are aligned with a broader vision of the health system context and development trends in order to provide sustainable interventions.

Defining the TOR may include the following steps:

- Communicating with officials from the NTP, NRL, MoH, other appropriate government bodies, and the WHO office or partner office in country facilitating the hire

- Communicating with the donors and partners working to implement TB-related laboratory interventions within the country

- Defining the mission objectives and outlining specific tasks with a daily schedule of activities to achieve these objectives

- Determining the appropriate duration required to perform all activities and establishing a start date and completion date. If multiple visits are required to fulfil the stated goals, then defined dates for consecutive interventions with specific milestones or outcomes should be outlined

- Determining dates for intermediate and final deliverables

- Establishing distribution lists for deliverables (e.g., final reports or assessments)

- Scheduling arrival and departure briefings with all relevant parties

c. Country demographics

Before traveling to a country it is important to understand the country's demographics. The consultant should do some background reading on the culture, history, socio-economics, population dynamics, and the current political situation of the host

country. By having some understanding of the local landscape, the consultant will be prepared for various situations and discussions that may arise with clients or local colleagues, as well as having a clear understanding of the current local challenges or the issues of the day. Understanding political and social realities allows the consultant to develop work plans, which take into account national holidays, as well as political activities, or social events that might pose a risk. Knowing the economic status and population dynamics will prepare the consultant for observing severe poverty, wide social disparity or caste systems, infrastructure limitations (limited or unavailable power, water, or sanitation facilities), or systems rendered dysfunctional due to rapid economic development or growth (e.g., transportation). Understanding specifics about the culture, traditions, and religion(s) of a country helps to prevent inappropriate behaviours or actions. It is also important that the consultant consider internal travel locations outside of the capitol city in their work agenda to assess security or health risks in those areas. Prior to leaving the consultant should be sure to review travel warnings posted on government or embassy websites as well as WHO alerts for recent outbreaks or residual pockets of emerging diseases that could be a health risk (e.g., dengue, Ebola, Marburg viruses). Areas where there is unrest, violence, or war should be avoided and not included in the scope of work. Vaccinations or prophylaxis for endemic diseases are also recommended; further information can be found on the CDC and other travel websites. Climate, seasonal changes, and terrain in the regions where travel is planned need to be understood in order to be fully prepared with appropriate clothing, shoes, or other personal items.

3.3.2 Departure for an international TA mission

The following steps should be taken before departing for an international assignment:

- Finalize the TOR

- Draw up a working agenda with the MoH, NTP, and NRL including dates, places, and people traveling

- Outline travel routes if traveling outside of the capitol to assess personal risk

- Inform the WHO's country office of the visit (if necessary)

- Acquire a letter of invitation from the MoH

- Acquire a visa

- Obtain appropriate vaccinations and other medications needed for travel

- Exchange currency to pay for transportation if needed upon arrival. Money can typically be exchanged at hotels, banks, or via ATMs where they exist.

- Ensure arrangements for transportation and accommodations:

   — Flight

   — Transfer from and to the airport or point of arrival

   — Safe local transportation for work travel

   — Hotel reservations. Note that it is wise to ask what the best form of payment

is for the hotel prior to arrival, since some rural hotels do not take credit cards.

— Internet access, which should be available at the hotel or work office

— Local telephone or SIM card, which should be provided

• Confirm language requirements and arrange for translation to be provided if needed

3.3.3 Arrival for an international TA mission

After arriving, the consultant should:

• Receive a security and country briefing from WHO or host

• Be briefed by the NTP and other parties involved

• Review and confirm the TOR with the NTP and other relevant parties

• Review the proposed activities and expected outcomes, and revise if needed

• Clarify whether the NTP has any specific concerns about the mission

• If the duration of the technical visit is longer than a few weeks, schedule meetings to report on progress with targeted outcomes or milestones

• Establish proper lines of communication with host, NTP, and other interested parties

3.3.4 Work

During the TA visit, it is critical to involve NTP and NRL representatives in the work of the mission as much as possible, ideally conducting joint site visits and activities. If this is not possible, at a minimum the NTP and NRL must be briefed before and after all activities. In most settings, formal written approval must be obtained prior to site visits. Certain sites may require that the consultant brief local health directors or hospital or laboratory administrators on the objectives and proposed outcomes of the interventions before and after accomplishing the work. Again, during these official meetings, lines of communication must be kept open and local protocols observed. When working on site, it is important to involve key staff as well as some junior staff in order to build internal capacity. This is an opportunity for exchange and sharing of knowledge; engaging with local staff helps ensure that the work will continue after the consultant has left. The primary goal for a TA visit is obviously to complete the TOR; however, the consultant must provide quality work and strive to build local capacity along the way.

When a consultant is developing TB laboratory services, managers of NTPs and national laboratory services should be actively involved throughout the process. It is particularly important to get support from individuals who have direct knowledge of and experience within the current system. Such individuals may include staff working in public and private TB laboratories; consultants from WHO's regional office or SRL network; and personnel from the NRL, local research institutes, and academic institutions specializing in infectious diseases or surveillance epidemiology. It is also

important to engage all country partners and consultants from non-governmental organizations that are actively involved in supporting programme development.

3.3.5 Debrief

At the end of the TA mission, consultants should:

- Summarize their findings and prepare a list of important recommendations in collaboration with the MoH and NTP; these should be shared at a debriefing meeting with the relevant stakeholders before departing

- Ensure that the recommendations are consistent with the TOR for the mission; if they are not, then the report should explain why they varied

- Ensure that there is evidence for the recommendations being made

- Seek clarification of any issues that are unclear before departing

- Ensure that they have correct contact information for providing follow-up

- Secure the list of parties who are to receive the final report and relevant data or documents acquired during the mission

3.3.6 Final Report

It is essential that consultants be able to write a mission report. The aim of the report is to clearly and concisely present information and facts, not opinions, using a consistent and appropriate format. The author(s) must ensure that the report presents information clearly to all readers. It is best to use short paragraphs, supported by appropriate illustrations where necessary (such as tables or graphs), and to include numbered headings and subheadings. This section offers some general guidance on writing a mission report, but it is most important that the consultant follow the terms of reference agreed to before the visit.

Report Outline:

- Cover page

- List of abbreviations

- Executive summary

- Purpose of the mission with primary objectives

- Background epidemiological information, context in which the NTP operates, and background supporting the particular mission

- A summary of each laboratory activity conducted with observations and data

- Specific recommendation to support current developments and progress for the NRL and network related to the mission

- Conclusions

- Acknowledgement of the work of those who contributed to the mission

- Annexes, which may include:

  — materials prepared prior to the mission

  — relevant data, checklists, or documents acquired during the mission

  — the itinerary of the mission and the final TOR, with an explanation for deviations

a. Executive summary

The executive summary should be an approximately one page long summary of the purpose, objectives, TOR, deliverables, activities, findings, conclusions, and recommendations of the mission. The executive summary should not contain any technical details.

b. Background information

As background information, the report should include a description of:

- The local epidemiology (TB, HIV, and MDR-TB)
- Country specific priorities for case detection
- A brief summary of local treatment policies and guidelines
- A description of the local TB laboratory organization, network, and capacity
- The situational overview of human resources for laboratories
- The financial resources available for laboratory support
- A list of partners involved supporting laboratory activities

c. Mission purpose and objectives

The purpose of the mission should be clear and concise. Objectives should be focused, with direct outcomes that support desired deliverables. The activities planned should link back to the primary objectives and complete the tasks outlined in the TOR. The TOR should be provided as an annex.

d. Summary of activities

The activities undertaken should be described in a logical sequence to demonstrate the systematic approach used during the visit. The itinerary or agenda for the activities should be placed in an annex. The report should include the sites visited, the type of work performed at each site, and a brief summary of observations and data.

e. Findings

The findings are the core of the report. Findings will include all data, complied results from checklists, graphs or tables, detail descriptions of observed practices, and specific challenges or deficiencies. When writing, try to be concise and accurate, particularly when describing challenges or deficiencies. Include positive aspects or outcomes first, then work toward difficult or sensitive findings. Simplify findings into tables, charts, or graphs. Photographs can also be helpful to illustrate a problem or demonstrate

a successful programme or intervention; permission must always be sought. Select only relevant information related entirely to the objectives and the mission TOR. Of course, if there is a serious observation outside the scope of the work, then it must be addressed.

Structure this section simply to make it easier to read and absorb important findings. Use subtitles for different categories to allow readers to quickly find specific information.

f. Recommendations

The findings should be summarized at the end of the visit and a list of the most important recommendations should be shared at a debriefing meeting with the relevant stakeholders before the consultant departs. These recommendations should be reiterated in the final report. Recommendations should clearly indicate to whom the recommendations are addressed.

The consultant's visit may include working at several sites, in which case it is important to clarify to whom the action or recommendation is addressed. Most of the recommendations will be addressed to the MoH, NTP, or NRL, unless the network system is divided according to regional or state governance, in which case recommendations may be directed accordingly. If the assistance is part of the implementation of a project, the recommendations could also be directed to the project director. If a partner organization is involved and is the focal point for the project, then they should also be included.

Recommendations should be consistent with and appropriate to the TOR, based on evidence, and derive clearly from the report's findings. Recommendations are often presented as concise bulleted points.

g. Conclusions

The conclusions should provide a clear interpretation of the author's evidence and findings. It should be brief and prioritized, with only relevant information included. Next steps or ways forward should be added to provide direction for future interventions.

h. Annexes

The annexes are the place to add bulk data or supplementary documentation to help understand the report. These may include:

- The final TOR

- Itinerary and meeting schedule

- Bulk data and results

- Checklists or tools used during the mission

- Added documents, photos, work plans, protocols, etc.

Suggested reading

Framework for conducting reviews of tuberculosis programmes. Geneva, World Health Organization. 2014.
http://www.who.int/tb/publications/jmm_2014/en/

Laboratory tools. United States Agency for International Development, TB CARE I and Challenge TB. Washington, DC.
http://www.challengetb.org/library/lab

Laboratory assessment tool. Geneva, World Health Organization. 2012. (WHO/HSE/GCR/LYO/2012.2).
http://www.who.int/ihr/publications/laboratory_tool/en/index.html

WHO TB Supranational Reference Laboratory Network: TA mission report template.
http://www.who.int/tb/laboratory/srln_mission_report_blank_template.pdf

Repository of technical reports from technical assistance missions provided by the SRL network.
https://sites.google.com/site/srtblaboratories

Resources of the Global Laboratory Initiative:
http://www.stoptb.org/wg/gli/gat.asp and
http://www.stoptb.org/wg/gli/trainingpackages.asp

Tuberculosis Laboratory Network Assessment. United States Agency for International Development, TB CARE I. Washington, DC.
http://www.challengetb.org/library/lab

Global tuberculosis report 2016. Geneva, World Health Organization. 2016. (WHO/HTM/TB/2016.132).
http://www.who.int/tb/publications/global_report

www.stoptb.org/wg/gli