global laboratory initiative
advancing TB diagnosis

Guide for providing technical support
to TB laboratories in low- and middle-income countries

Stop **TB** Partnership

Guide for providing technical support to TB laboratories in low- and middle-income countries

A publication of the Global Laboratory Initiative (GLI), a working group of the Stop TB Partnership

ACKNOWLEDGMENTS

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PREFACE

The Global Laboratory Initiative (GLI), established in 2007, is a working group of the Stop TB Partnership. The GLI Secretariat is hosted by the World Health Organization (WHO) Global TB Programme. More than 100 international partners have joined forces to accelerate and expand access to quality-assured TB diagnostic services within integrated laboratory systems.

The GLI works closely with national TB programmes (NTP), nongovernmental organizations, scientific and academic institutions, and WHO offices at country and regional levels to strengthen TB laboratory services. GLI activities include:

- Implementation of WHO policy guidance on appropriate laboratory technologies and best practices.

- Effective technology transfer and coordination of technical assistance.

- Laboratory advocacy and resource mobilization.

- Laboratory capacity development.

- Interfacing with other laboratory networks to ensure appropriate integration.

- Standardized laboratory quality assurance.

- Effective knowledge sharing.

GLI strategic priorities include:

- Implementation of WHO laboratory norms and standards.

- Acceleration of country laboratory network strengthening.

- Prioritization of human resource development and training.

- Laboratory accreditation.

- Laboratory biosafety guidance.

- Laboratory strategic plan development.

PURPOSE OF THE GUIDE

This guide is intended to familiarize those who are providing technical assistance to TB laboratories in low- and middle-income countries with WHO recommendations and international best practices. Since an important function of the GLI is harmonization of the technical assistance provided by its many partners to TB laboratories in high-burden countries, it is critical that the guidance provided by GLI partners be consistent with global policy and guidelines.

Historically, technical assistance was provided largely by external international consultants, often during short term missions to the country. While this continues to be an important form of technical support in many low- and middle-income countries, significant technical support is now provided by local and regional consultants and mentors and in-country consultants (international, regional or local). Different consultancies to support NTPs will invariably include different terms of reference, related to policy, technical, or programmatic issues. Consultants working with NTPs may be TB specialists, laboratory or non-laboratory specialists, involved in short term missions or longer term in-country engagements. This guide seeks to provide guidance and information for all of the above categories of technical consultants.

The guide may be used as a training resource for new TB laboratory consultants or as refresher training for established consultants prior to a technical assistance assignment. The manual is intended to provide a comprehensive overview of topics to be considered before and during an assignment. In addition, those providing technical assistance may also use the guide as a reference for resources and tools which may be used before or during an assignment, such as identifying where to find the latest guidance to training materials. Because many of these materials are 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.

This guide is not intended to be a comprehensive manual or to repeat information already provided by other guidance documents. Rather it is intended to orient those providing technical assistance, and to provide context and commentary on the provision of technical assistance in low- and middle-income countries.

This guide is also available at http://www.stoptb.org/wg/GLI/documents.asp. The online version includes links to cited resources.

The most up-to-date WHO policy guidance and resources can be found at http://www.who.int/tb/laboratory/en/

ABBREVIATIONS

AFB	Acid-fast bacilli
APHL	Association of Public Health Laboratories
ASLM	African Society for Laboratory Medicine
BSA	Broad spectrum antimicrobials
CLSI	Clinical & Laboratory Standards Institute
CXR	Chest X-ray
DRS	Drug resistance survey
DST	Drug-susceptibility testing
DSC	Dried spot culture
DR-TB	Drug-resistant tuberculosis
EQA	External quality assessment
EPTB	Extrapulmonary TB
FM	Fluorescence microscopy
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
GLI	Global Laboratory Initiative
HIV	Human Immunodeficiency Virus
IUALTD	International Union against Tuberculosis and Lung Disease
ISO	International Organization for Standardization
ISTC	International for TB
LAMP	Loop-mediated isothermal amplification
LED	Light-emitting diode
LIMS	Laboratory information management system
LSP	Laboratory strategic plan
L-J	Löwenstein-Jensen
LPA	Line probe assay
MDR-TB	Multidrug-resistant tuberculosis
MGIT™	Mycobacterial growth indicator tube
MODS	Microscopic observation for drug susceptibility
MoH	Ministry of Health
MTB	*Mycobacterium tuberculosis*
NAAT	Nucleic acid amplification test
NGO	Non-governmental organization

NRA	Nitrate reductase assay
NSP	National strategic plan
NTM	Nontuberculous mycobacteria
NTP	National Tuberculosis Programme
NTRL	National Tuberculosis Reference Laboratory
PCR	Polymerase chain reaction
PT	Proficiency testing
QA	Quality assurance
QC	Quality control
QI	Quality improvement
QSE	Quality system essential
QMS	Quality management system
SLIPTA	Stepwise Laboratory Improvement Process Towards Accreditation
SLMTA	Strengthening Laboratory Management Towards Accreditation
SOP	Standard operating procedure
SRL	WHO TB Supranational Reference Laboratory
SRLN	WHO TB Supranational Reference Laboratory Network
SWOT	Analysis of strengths, weaknesses, opportunities, and threats
TB	Tuberculosis
TWG	Technical Working Group
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis

1   BACKGROUND

1.1   WHO-recommended testing for diagnosing TB and detecting drug resistance

Since 2006, the World Health Organization's (WHO) Global TB Strategy has recommended bacteriological confirmation of TB using both microscopy and culture. However, due to infrastructure, financial and human resource constraints, acid-fast bacilli (AFB) smear microscopy has continued to be used as the primary diagnostic tool in many high-burden resource-limited settings. Using culture as a gold standard, direct AFB microscopy has a sensitivity of only about 50% and yields no information about susceptibility or resistance to anti-TB drugs. Resistance to anti-TB drugs can increase if patients are treated with inappropriate regimens because the clinician does not know whether the disease is susceptible to first-line agents. In 2013, there were an estimated 480 000 new cases of multidrug-resistant TB (MDR-TB) worldwide.

WHO recommends using 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 these techniques requires a large-scale effort coordinated by Ministries of Health and supported by local and international partner organisations.

WHO has issued recommendations on some newer tests since 2007, including commercial liquid culture and DST systems, LED fluorescence microscopy, commercial line-probe assays (LPA) for first-line anti-TB drugs, and rapid TB identification tests. All tests are to be used in accordance with established, standardized national algorithms for testing, and with quality assured laboratory services. Table 1 presents a summary of WHO-recommended methods for diagnosing TB in low- and middle-income settings.

Table 1: Summary of WHO-recommended methods and their turnaround times[a]

Test or procedure	Description	Laboratory Turnaround time[1]	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 lamp or high-pressure mercury vapour lamp. Microscopes are expensive. Requires a dark room.
	LED fluorescence microscopy		LED microscopy is at least 10% more sensitive than conventional light microscopy and the observation time is significantly shorter than for conventional microscopy. LED conversion kits for light microscopes are available. 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.
Solid culture	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%.
	Middlebrook agar-based medium (7H10 or 7H11)		Agar-based medium. Acceptable level of contamination 3-5%.
Automated liquid culture	Commercial test systems	8-10 days for smear-positive samples 2–6 weeks for smear-negative samples	BACTEC MGIT 960 TB System automated liquid TB culture reference method for bacteriological confirmation. Susceptible to contamination. Acceptable level of contamination 8-10%.
Phenotypic DST – 1st line	Solid medium - Löwenstein–Jensen or Middlebrook agar-based media (7H10 or 7H11)	4-6 weeks from positive culture (indirect DST)	Egg-based medium. Capacity to perform DST at least to RIF and INH is needed. Recommended critical concentrations are found in the critical concentration table[b].
	Liquid medium - Commercial test systems[c]	1-3 weeks from positive culture (indirect DST)	Capacity to perform DST at least to RIF and INH is needed. Recommended critical concentrations are found in the critical concentration table[b].
Phenotypic DST – 2nd line	Solid medium - Löwenstein–Jensen or Middlebrook agar-based media (7H10 or 7H11)	4-6 weeks from positive culture (indirect DST)	Capacity to perform DST at least to an injectable agent and a FQ is needed*. Recommended critical concentrations are found in the critical concentration table[b].
	Liquid medium - Commercial test systems	1-3 weeks from positive culture (indirect DST)	Capacity to perform DST at least to an injectable agent and a FQ is needed*. Recommended critical concentrations are found in the critical concentration table[b].

Test or procedure	Description	Laboratory Turnaround time[1]	Comments
Molecular testing	Line-probe assay detection of rifampicin resistance (alone or with isoniazid resistance) 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 (once batched)	LPA is suitable for use on AFB smear-positive specimens and culture isolates.
	Xpert MTB/RIF assay Detects M. tuberculosis and 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 should be used rather than conventional microscopy, culture, and DST as the initial diagnostic test for pulmonary and extrapulmonary TB in adults and children suspected of having MDR-TB or HIV-associated TB. The test may be used as a follow-on test to microscopy in adults and children for whom MDR-TB and HIV are of lesser concern, especially when further testing is required for smear-negative specimens (this recommendation is made recognizing that it has major implications for resources).
Rapid TB identification tests	Immunochromatographic assay to be performed on solid or liquid culture growth	15 min (testing time)	Rapid identification of M. tuberculosis isolated from conventional solid or liquid culture in central and regional level laboratories. Commercial examples of this test include the following: – Capilia TB-Neo® [Tauns Laboratories; Numazu, Japan]; – SD Bioline's TB Ag MPT64 Rapid Test© [Kyonggi-do, South Korea]; – Becton Dickinson's TBcID© [Sparks, Maryland, USA]

1 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.
a Tests not endorsed by WHO are not included in the table.
b Critical concentration table http://www.stoptb.org/wg/gli/assets/documents/Updated%20critical%20 concentration%20table_1st%20and%202nd%20line%20drugs.pdf
* WHO recommends second line DST for all second-line injectable agents and fluoroquinolones (FQ) available for use in each national TB programme.

WHO has conditionally recommended selected non-commercial tests for detecting rifampicin resistance as an interim solution pending the development of genotypic capacity for rifampicin resistance detection. 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 is not recommended.

WHO issued initial policy guidance on drug susceptibility testing to second-line drugs in 2008. 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 agents. Based on experience and limited evidence from several TB Supranational Reference Laboratories, the concentrations were revised as an interim measure. Updated interim critical concentrations for first-line and second-line DST (as of May 2012) are available at http://www.stoptb.org/wg/gli/assets/documents/Updated%20critical%20 concentration%20table_1st%20and%202nd%20line%20drugs.pdf.

WHO did not proceed with formal policy guidance recommending the revised concentrations because they were based on limited evidence. Emerging evidence suggests that the revised concentrations may require further revision. WHO plans to convene another Expert Group in 2016 to review the evidence for both phenotypic and genotypic DST and to make formal policy recommendations.

The use of LPA for the detection of second-line drug resistance is currently not recommended by WHO (http://apps.who.int/iris/bitstream/10665/78099/1/WHO_HTM_TB_2013.01.eng.pdf).

As cross-resistance between the second-line injectables and fluoroquinolones is incomplete, the Genotype MTBDRsl cannot be used to identify individual drugs to be used for treatment.

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.

- LPA to detect resistance to second-line anti-TB drugs.

- Loop-mediated isothermal amplification (LAMP) test for TB.

- 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.

- Interferon γ release assays (IGRAs) for detecting active TB in all settings.

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. See suggested reading for more information.

1.1.1   Suggested reading

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

Training package on DST by phenotypic and molecular method. Global Laboratory Initiative 2012.
http://www.stoptb.org/wg/gli/assets/documents/Training%20Package%20DST_October%20 2012.zip

Training package on culture on solid and liquid medium. Global Laboratory Initiative 2012.
http://www.stoptb.org/wg/gli/assets/documents/Training%20Package%20Culture_October%20 2012.zip

Training package on lineprobe assays (LPAs). Global Laboratory Initiative 2012.
http://www.stoptb.org/wg/gli/assets/documents/Training%20Package%20LPA_%20
October%202012.zip

Critical concentrations table. World Health Organization 2012
http://www.stoptb.org/wg/gli/assets/documents/Updated%20critical%20concentration%20
table_1st%20and%202nd%20line%20drugs.pdf

Grade approach: www.gradeworkinggroup.org

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 national TB control programme (NTP). When a NRL is managed separately from the NTP, coordination between both entities is essential to ensure that programme priorities and strategies are reflected in the NRL activities and vice versa. Consultants need to fully understand where management of TB laboratory services fall within the MoH, and how activities are coordinated with the NTP.

Countries vary widely with how they set up and manage laboratory services under their Ministry of Health (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 ministry of health. 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. Early access to diagnostic testing and treatment monitoring is often at the community 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.

The Global Plan to Stop TB (2011-2015) stated that countries should have at least one laboratory per 100,000 population able to perform quality-assured AFB microscopy and at least one culture laboratory per 5 million population or equivalent capacity to diagnose smear-negative TB and perform drug resistance testing using conventional or molecular tests. Since these estimates were made in the pre-Xpert MTB/RIF era, they require review and revision based on modelling of the impact of Xpert MTB/RIF rollout.

1.2.2   Laboratory network structure

In many resource-limited or high-burden settings, the 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 patients and most individuals suspected of having TB; a moderate number of intermediate laboratories, known as Level 2 laboratories, usually located in mid-sized population centres and health facilities; and a single, central laboratory of Level 3 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. 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 laboratorians 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 and illustrates the recommended WHO diagnostic methods and activities under each tier. 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 AFB smear microscopy and in some cases Xpert MTB/RIF. Patients may self-refer to these facilities or may be referred from rural health posts for initial testing. Further testing may be acquired through referral of specimens to another institute or specialized laboratory (*e.g.* partner or NGO lab, regional reference laboratory or national reference laboratory).

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.
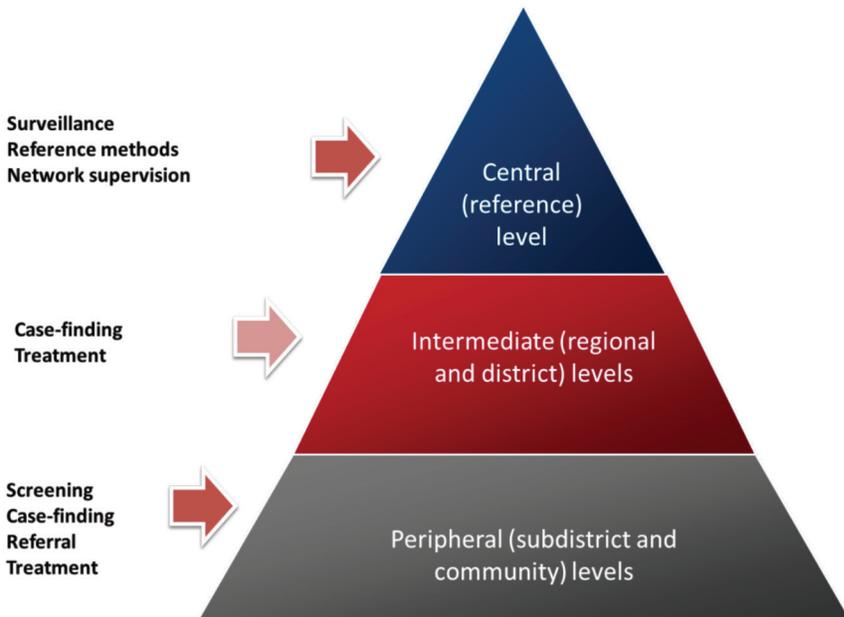

Figure 1: The three tiers of the network of TB laboratories (*Implementing tuberculosis diagnostics: A policy framework* by WHO, 2015)

Table 2: Functions and Responsibilities

Level 1. Peripheral (or community) laboratory – Microscopy and Xpert MTB/RIF

- Receives specimens
- Prepares, stains, and examines smears with Ziehl–Neelsen (ZN) or light emitting diode (LED) fluorescence microscopy (FM)
- May use the Xpert MTB/RIF assay as the initial diagnostic test 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 (bio) safety measures in place

Level 2. Intermediate (or regional) laboratory – Level 1 plus Culture and LPA

- Performs all of the functions of a Level I laboratory
- Uses line-probe assay (LPA) for direct detection of mutations for isoniazid and rifampicin resistance in positive AFB smears from processed sputum samples
- Performs digestion and decontamination of specimens, inoculates cultures
- Uses culture to isolate and identify Mycobacterium tuberculosis complex
- Refers positive cultures to appropriate reference laboratory for drug susceptibility testing (DST)
- Trains microscopists and supervises peripheral-level staff in microscopy and the use of the Xpert MTB/RIF assay*
- 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 I and Level II laboratories
- Collaborates closely with the central level of the national TB control 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)
- Identifies non-tuberculous mycobacteria (NTMs)
- 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
- Organizes surveillance of resistance to anti-TB agents
- Undertakes operational and applied research relating to the laboratory network and coordinates this with the requirements and needs of the national TB control programme
- Establishes a formal collaboration agreement with a TB supranational reference laboratory (SRL) for EQA, for support in implementing and validating new diagnostics, assistance with laboratory development and expansion strategies, and referral for challenging cases who need specialized testing

* Xpert MTB/RIF testing 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 national TB programme 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 quality assurance 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 currently being pursued to facilitate higher quality services and in order 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 which 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 time frame 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 under mentorship from a member of WHO TB SRLN (see section 1.4). Countries with larger populations should prioritize the development under national TB reference laboratory (NRL) or the leading Institute's guidance.

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 HR 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. Xpert MTB/RIF is being implemented at this level in facilities that are able to meet infrastructure requirements for the test (specifically, uninterrupted power and temperature-controlled storage and testing areas). Nevertheless, these technologies are also suitable for implementation at the intermediate and central levels provided that 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 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 develop and gain capacity, the need for local human resources becomes more acute. Each laboratory will have specific requirements for their staff, according to the tests they perform.

As networks are developed and capacity strengthened, it is essential to build human resources in situ. 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 drug susceptibility testing 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, quality assurance 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. Also, 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.

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

Procedure	No. of tests (maximum)	
AFB light microscopy	20-25	per technician
AFB fluorescence microscopy	40-50	per technician
Culture (liquid/solid media, including specimen processing)	20-40	per technician
DST (using liquid media)	10-20	per technician
DST (using solid media)	10-20	per technician
LPA (manual method)	12-24	per instrument
Xpert MTB/RIF assay (using four-module instrument)	12-16*	per instrument

AFB, acid-fast bacilli; DST, drug-susceptibility testing; LPA, line probe assay.

* 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 was available, a single technician may have time to perform other duties, such as reading smears. Number of specimens that can be processed 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.

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 give five minutes each and smears stained with Auramine O (fluorescence microscopy) for two minutes each; these specifications have been taken from the Handbook: Laboratory diagnosis of tuberculosis by sputum microscopy. Additional time will be required to engage in quality assurance (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.

Similarly, in order to maintain overall laboratory proficiency in culture, laboratories should process a minimum of 20 specimens per week with a minimum of five (5) cultures per person. The same minimum requirements hold for maintaining proficiency in culture-based DST.

Establishing and maintaining networks of laboratories is demanding, complex, and expensive. Therefore, it is essential that adequate resources, both human and financial, are allocated to ensure that sufficient, qualified, trained, and competent laboratory staff are available, that the laboratory infrastructure functions at the appropriate biosafety level, and that the laboratory has well maintained equipment and sufficient consumables. In most countries, the NRL has oversight over the network and is responsible for its developments and quality performance. The NRL along with NTP and supporting SRL provides guidance and policy regarding general testing and operations, management and distribution of laboratory supplies and consumables, regulations on biosafety, external quality assurance programmes, and supervision and monitoring activities.

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

1.2.5   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/assets/documents/TB%20MICROSCOPY%20HANDBOOK_FINAL.pdf

The global plan to stop TB 2011–2015. Geneva, World Health Organization, 2010
http://www.stoptb.org/assets/documents/global/plan/TB_GlobalPlanToStopTB2011-2015.pdf

Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Geneva, World Health Organization, 2011 (WHO/HTM/TB/2011.6)
http://apps.who.int/tb/challenges/mdr/programmematic_guidelines_for_mdrtb/en/index.html

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
http://www.who.int/tb/publications/implementing_TB_diagnostics/en/

1.3   Diagnostic algorithms

In resource-limited setting, national diagnostic algorithms are usually designed according to WHO policy recommendations, taking into account country specific circumstances and laboratory testing capacity.

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 the tests are recommended by WHO;
- • The limited sensitivity of AFB sputum-smear examinations, particularly in patients with HIV infection and children;
- • The capacity of the country's laboratories, the laboratory infrastructure, and the availability of competent personnel to conduct the tests;
- • The laboratory tests available, the workload of the laboratories, and the availability of supplies, such as reagents, as well as the need for regular maintenance of equipment;
- • The adequacy of systems for specimen collection and transport;
- • The capacity of clinical services to offer diagnosis and treatment;
- • The availability of anti-TB agents necessary for treatment;
- • 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, and the proportion of cases of child TB.

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 patients are suspected of having drug-resistant TB, HIV associated TB, when the patients are children, or when they have extrapulmonary disease.

The following figures suggest sample algorithms that show how WHO-recommended diagnostics could be implemented. These algorithms are illustrative and need to be adapted by countries to the local situation.

Those providing technical assistance to countries in designing their national diagnostic algorithms should promote the latest WHO recommendations for TB diagnosis. However, in some cases, countries may opt to not follow the latest guidelines, or there may be a delay in adoption of the latest recommendations. Countries should be supported to optimise the quality of services and access to TB diagnosis according the national algorithm, while maintaining the conversation with national policy makers on adoption of new recommended tools and approaches to improve TB diagnosis.

Readers are referred to the WHO Policy framework for Implementing Tuberculosis Diagnostics for a detailed discussion of key features of each of the algorithms.
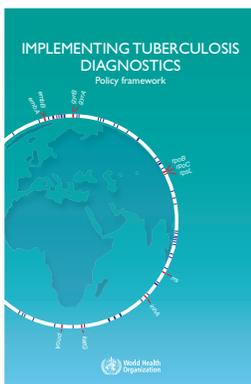
http://www.who.int/tb/publications/implementing_TB_diagnostics/en/

Algorithm 1. Using microscopy, solid or liquid culture, species identification and drug-susceptibility testing to diagnose TB
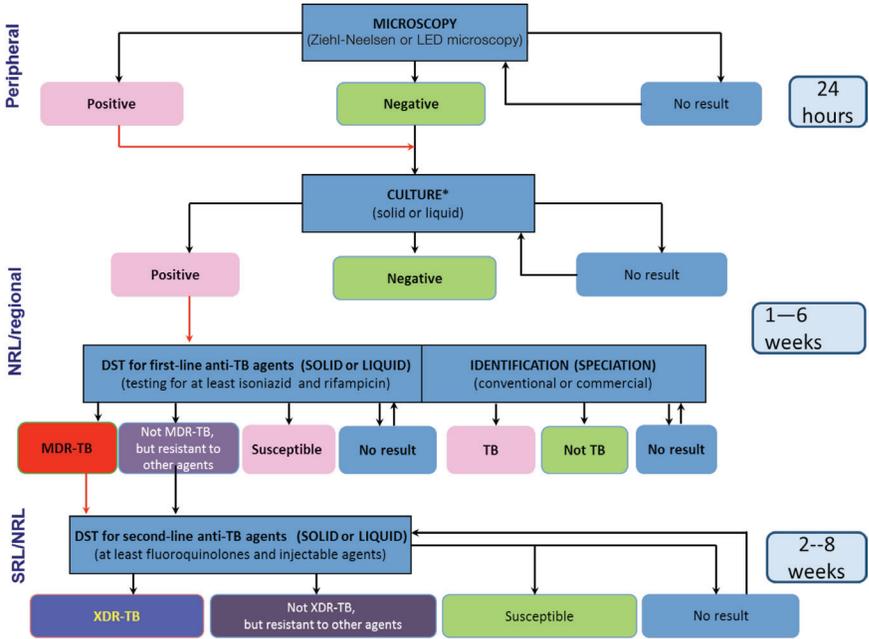
* Implementing this algorithm (culture for diagnosis of all persons suspected to have TB) is highly resource dependant. Efficiency can be improved if culture is performed only for selected smear negative persons with strong clinical suspicion of TB.

Algorithm 2. Using microscopy and line-probe assays in conjunction with drug-susceptibility testing (with solid or liquid media) to diagnose TB
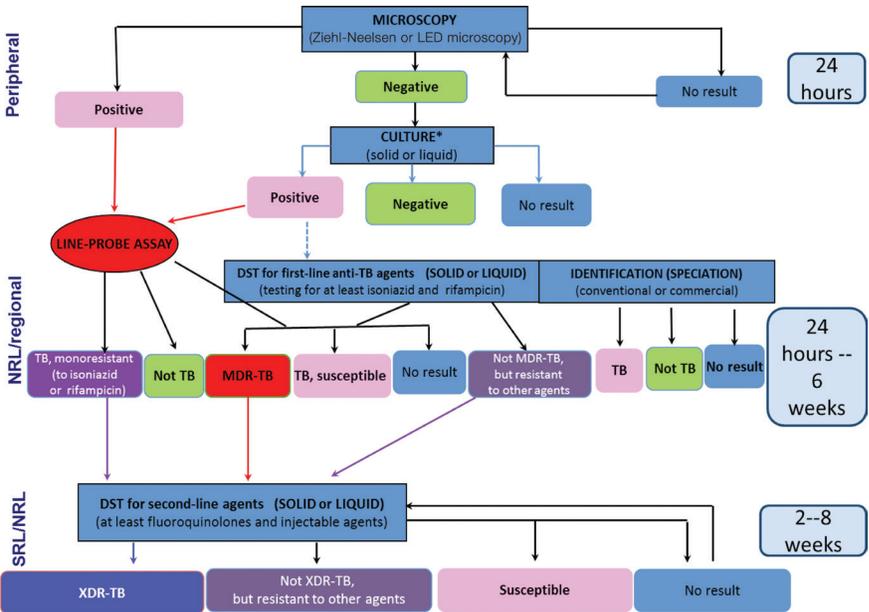
* Implementing this algorithm (culture for diagnosis of all persons suspected to have TB) is highly resource dependant. Efficiency can be improved if culture is performed only for selected smear negative persons with strong clinical suspicion of TB.

Algorithm 3. Using the Xpert MTB/RIF assay as an initial diagnostic test for TB followed by drug-susceptibility testing for second-line anti-TB agents when necessary
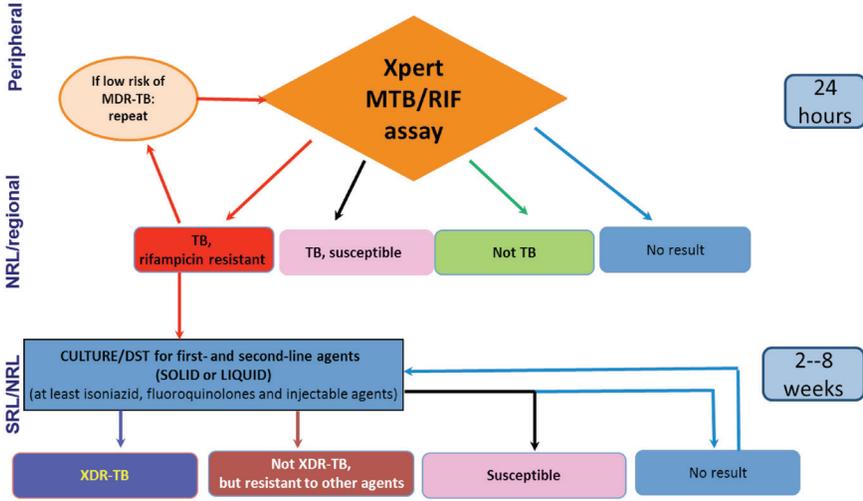
Algorithm 4. Using LPA and the Xpert MTB/RIF assay as follow-up diagnostic tests to microscopy for TB with drug-susceptibility testing for second-line anti-TB agents when necessary
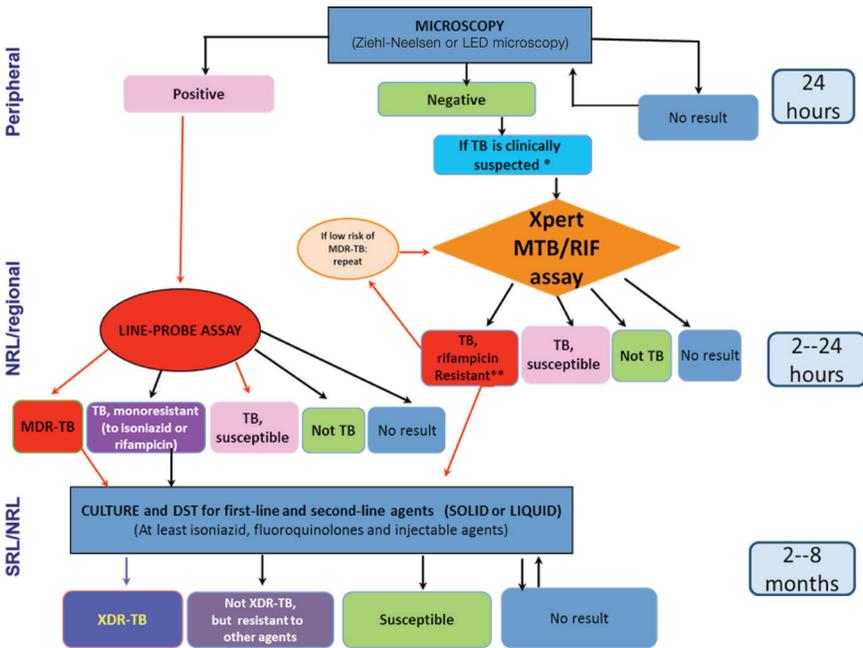
* In this scenario the use of Chest X-ray (CXR) in smear negative persons in whom TB is clinically suspected may significantly reduce Xpert MTB/RIF tests needed.

** In patients who are not at risk for drug resistance but who initially test positive for rifampicin resistance by Xpert MTB/RIF, a second Xpert MTB/RIF test should be performed to control for preanalytical and postanalytical errors, and to improve the clinician's confidence in the diagnosis.

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Algorithm 5. Diagnosis and treatment of LTBI among high risk individuals

Individuals, or their guardians (in the case of small children) should be asked about symptoms of TB before being tested for LTBI. Chest radiography should be done in all individuals with a positive LTBI test, and LTBI treatment should be limited to those who do not have radiological abnormalities. Individuals with TB symptoms or any radiological abnormality should be investigated further for active TB and other conditions.
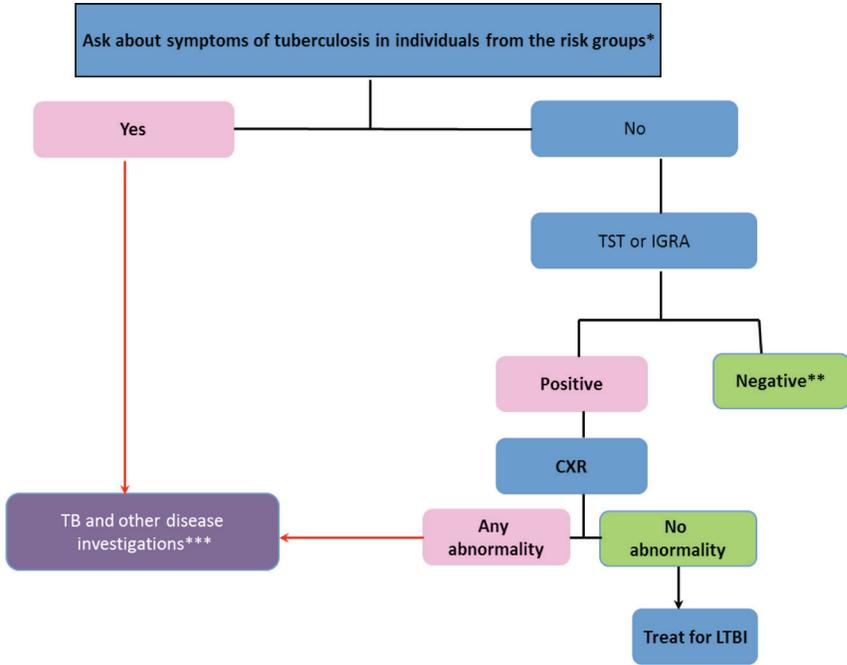
(*) Any symptoms of TB include any one of: cough, haemoptysis, fever, night sweats, weight loss, chest pain, shortness of breath, fatigue. HIV test could be offered based on national or local guidelines or clinical judgment. Similarly chest radiographs can be done if efforts are intended also for active TB case finding

(**) Patients for whom LTBI treatment is not indicated should be provided information about TB including on the importance of seeking care if symptoms of TB developed.

(***) National TB guidelines should be followed while investigating for TB. In addition, those individuals in whom TB is excluded after investigations (including individuals with fibrotic radiologic lesions) can be considered for LTBI treatment.

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 Ministry of Health and the national TB programme. 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.

1.3.1   Suggested reading

Implementing Tuberculosis Diagnostics. Policy Framework. World Health Organisation, 2015. http://www.who.int/tb/publications/implementing_TB_diagnostics/en/

Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Geneva, World Health Organization, 2011. (WHO/HTM/TB/2011.6) http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf?ua=1

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/en/

1.4   The TB Supranational Reference Laboratory Network

The TB Supranational Reference Laboratory Network (SRLN) is a WHO network coordinated through the Global TB Programme. Created in 1994 to support the WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance, the SRLN has expanded from 14 initial laboratories to 36 laboratories including two candidate SRLs and four national Centres of Excellence. It strives to respond to the urgent need to scale-up quality-assured TB laboratory services to meet the diagnostic challenges of TB, HIV-associated TB, and drug-resistant TB (Figure 2).

The network identifies synergies and coordinates activities among individual SRLs to serve as a platform to:

- Provide standardized external quality assessment panels for microscopy, culture, DST of *M. tuberculosis*, and molecular methods as needed.

- Disseminate WHO guidance on biosafety requirements and a QMS to national reference laboratories and laboratory networks.

- Assist national TB reference laboratories and national TB-control programmes in implementing WHO policies on TB diagnostics and diagnostic algorithms, complying with laboratory norms and standards using recording and reporting systems, and implementing other laboratory tools endorsed by the GLI.

- Collaborate with national TB programmes to help ensure that capacities for the diagnosis and treatment of TB and drug-resistant TB are aligned.

- Facilitate the sharing of standardized technical reports from technical assistance missions to countries with in-country partners and among the SRLs.

- Coordinate the comparison of evaluations of diagnostic tests among individual SRLs and define priorities for evaluating different tests as needed.

- Coordinate the pathway for developing and implementing standardized protocols to test the susceptibility of M. tuberculosis to new and existing anti-TB agents.

Figure 2: WHO TB Supranational Reference Laboratory Network, August 2015

In 2010, the SRLN Terms of Reference (TORs) were revised http://www.who.int/tb/laboratory/tor_srln.pdf?ua=1
and new eligibility and inclusion criteria were developed http://www.who.int/tb/laboratory/eligib_incl_criteria.pdf?ua=1.

Under these revised TORs, each SRL is required to provide both programmatic and technical support to NRLs in at least two countries.

Formal collaboration agreements must be established between the SRL and the appropriate national health authority or Ministry of Health on behalf of the NRL. The agreement establishes a collaborative framework that includes a minimum set of activities to be undertaken to assist in the programmatic and technical development of TB laboratory services, research, and technical assistance.

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 Ministry of Health-led national (TB) laboratory strategic plan to leverage complementary skill sets and mandates to meet a county's needs for technical assistance and capacity building. To facilitate this communication and coordination, individuals and organisations providing technical support to TB laboratories should request information from the NTRL 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/laboratory/srln_list1.pdf?ua=1

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

Improving collaboration between technical support provided by SRLs and other partners is a priority. A repository of technical reports from technical assistance missions provided by the SRL network are available at http://apps.who.int/tb/srl/report_repository/map/atlas.html.

1.4.1 Suggested reading

WHO TB Supranational Reference Laboratory Network. http://www.who.int/tb/laboratory/srln_factsheet.pdf?ua=1

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

Global tuberculosis report 2014. Geneva, World Health Organization, 2014. (WHO/HTM/TB/2014.08 http://www.who.int/tb/publications/global_report/en/

2. KEY TECHNICAL AREAS FOR GUIDANCE

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 which 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 quality assurance 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*.

Figure 3: 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.
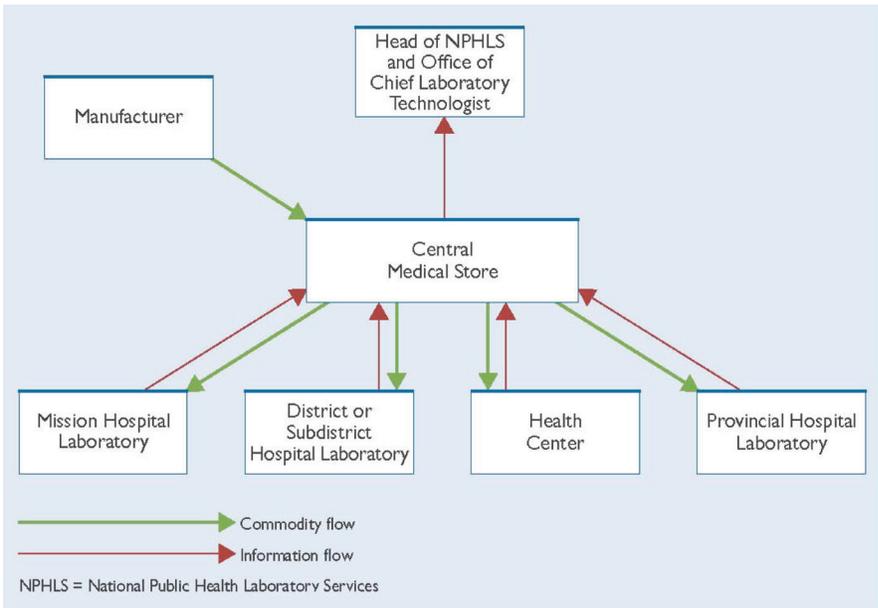
WHO has developed guidelines and specifications which provide standard guidance on procuring TB laboratory equipment, consumables and supplies for TB microscopy, culture, and DST equipment and supplies.

http://whqlibdoc.who.int/publications/2011/9789241503068_eng.pdf

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 has resulted 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.

Each country will have its own process and distribution system. It is essential to understand the existing system before implementing new technologies or adapting current testing capacity. Furthermore, individuals providing technical support should ensure they work with MoH to strengthen existing processes rather than introducing parallel systems.

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 LIMS systems 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

2.1.1   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 equipment and supplies. World Health Organisation. Geneva, Switzerland. 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, transportation, and reception*

Specimen referral mechanisms are essential to improve access to diagnostic testing. Lower level laboratories must be linked to higher level laboratories for follow-up testing to be able to provide efficient patient management, ensure optimal use of different technologies at different levels of the tiered network, and maintain staff competence in these techniques. Optimization of the specimen referral network requires careful consideration to balance access, costs, and turnaround time.

The initial steps in the process are to collect, label, transport, and register the clinical specimens. These steps must be done in a timely manner in order to expedite treatment initiation and/or regimen changes.

Regardless of the location of the laboratory, 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 to the nearest laboratory for testing. Transporting sputa must be done according to recommended protocols, taking into account the distance and transit time, in order to ensure integrity.

The NTP/NRL should determine the information to be included on the specimen container and requisition form, drawing on WHO recommendations (http://www.who.int/ihr/publications/who_hse_ihr_2015.2/en/). It is critical that the NTP/NTRL 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 which includes information relating to collection, labelling, and transporting of specimens, with target turnaround times and specimen rejection criteria, which 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 drug susceptibility testing (http://www.stoptb.org/wg/gli/documents.asp?xpand=2). Target turnaround times should be set locally and monitored for adherence. For more information, see *General Quality Indicators* in section 2.3.2.

2.2.1   Collection

Good quality specimens are necessary to ensure proper laboratory diagnosis of TB. Non-salivary sputa 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*.

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.

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 4) 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*.

http://apps.who.int/iris/bitstream/10665/78075/1/WHO_HSE_GCR_2012.12_eng.pdf

Figure 4: Example of triple packaging for Category B infectious substances (IATA) from *Guidance on regulations for the transport of infectious substances* 2015. World Health Organization.
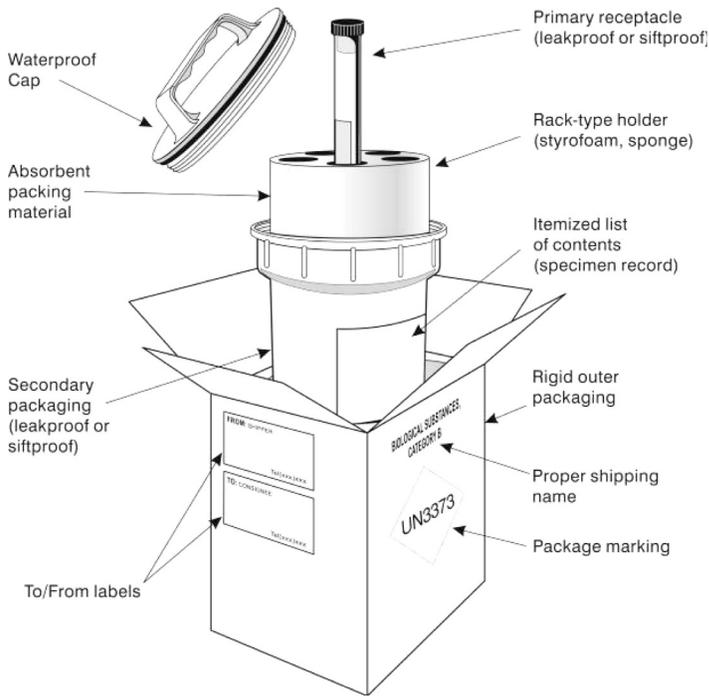
If delays in transport are anticipated, specimens should be transported to the laboratory in a cool box. This is especially relevant for specimens for TB culture. Sample contamination due to inappropriate storage and long transport times is less of a concern with smear or rapid molecular tests than with conventional culture-based approaches.

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 Documentation and specimen transport

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 sputa 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 form is provided in Figure 5.

Figure 5: Specimen transport log

Specimen registers are required for all laboratories. The register contains the information from the test 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 is provided in Figure 6.

Figure 6: Sample register for a peripheral laboratory

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

Test 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 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 from a peripheral level laboratory is shown in Figure 7.

Figure 7: Sample test request form for a peripheral laboratory

Request for examination of biological specimen for TB Microscopy and Xpert MTB/RIF

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:...

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:..

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 AFB smear microscopy, culture, Xpert MTB/RIF testing, or DST (including LPA).

http://www.who.int/tb/publications/definitions/en/
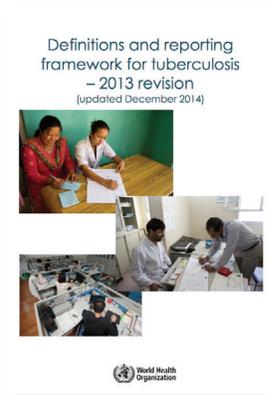
Key activity areas for technical support

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

2.2.4   Suggested reading

Laboratory diagnosis of tuberculosis by sputum microscopy. The handbook: global edition. Global Laboratory Initiative. 2013. http://www.stoptb.org/wg/gli/assets/documents/TBLabDiagnosis Sputum%20Microscopy_Handbook.pdf

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

Definitions and reporting framework for tuberculosis – 2013 revision. Geneva, World Health Organization, 2013 (WHO/HTM/TB/2013.2) http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf

TB diagnostics and laboratory strengthening: WHO policy. Definition of a new sputum smear-positive TB case, 2007. Geneva, World Health Organization, 2014 http://www.who.int/tb/laboratory/policy_sputum_smearpositive_tb_case/en/index.html

Guidance on regulations for the transport of infectious substances: 2013–2014. Geneva, World Health Organization, 2012 (WHO/HSE/GCR/2012.12). http://apps.who.int/iris/bitstream/10665/78075/1/WHO_HSE_GCR_2012.12_eng.pdf

2.3   Quality assurance

2.3.1   Introduction to quality assurance

A comprehensive and systematic quality assurance (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.

Quality assurance 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 quality assurance 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 quality assurance 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 quality assurance programme can significantly improve TB laboratory services. Individuals providing technical assistance to countries can play an important role in this area.

Figure 8 illustrates the essential elements of a quality assurance programme applied to any technology. Some requirements are general to all technologies and others have test-specific requirements or definitions.

Figure 8: Essential elements of a comprehensive quality assurance programme

| Environment
Safe and functional

Temperature control | Personnel
Trained and competent staff

Test user is documented

Current SOPs readily available | Equipment
Maintained and serviced | Supplies
Uninterrupted supplies

Appropriate transport and storage conditions | Specimens
Good quality

Labelled with unique ID

Completed request form | Internal quality monitoring
Test working properly | External Quality Assessment (EQA)
Lab's work checked by another lab | Accurate and timely reporting
Turnaround time

Results review |

Accurate, reliable and timely results

Quality assurance activities should be seen as an integral part of the routine workload and not as a separate activity. All quality assurance activities must be documented. Feedback to testing sites and implementing corrective and preventive measures are the most critical aspects of any quality assurance programme, and also those aspects which are often poorly implemented.

Quality assurance is, however, just one part of a Laboratory Quality Management System, which is required to ensure the quality of all a laboratory's processes.

2.3.2   Key quality assurance activities

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

Key quality assurance 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

a. Training and competence assessment

Training materials have been developed and are freely available for WHO-approved TB diagnostics (http://www.stoptb.org/wg/gli/documents.asp?xpand=2), including smear microscopy (light and fluorescence), solid and liquid culture, drug susceptibility testing, line probe assay, and Xpert MTB/RIF. They may be downloaded from the *Resources* section of the GLI website http://www.stoptb.org/wg/gli/documents.asp. Quality assurance 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 quality assurance in more detail, for example *External quality assessment for AFB smear microscopy* (WHO, 2002).

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 a NRL/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.

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 drug susceptibility testing, 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 competency assessment of the participants. Competency is defined as a *demonstrated ability to apply knowledge and skills*, and clear criteria for competency should be set in advance. Staff competency 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/or 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, 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 *M. tuberculosis* complex or non-tuberculous mycobacteria, 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 quality controls, or their use only with certain tests. One of the commonly cited reasons for the absence of quality controls is a lack of funding. However, local solutions can be found to fulfil quality control 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.

Quality controls in a TB laboratory can for example include monitoring the following activities (see Table 4 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

Quality control 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.

All laboratories should ensure that all tests are part of an EQA programme. However, 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.

• 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 quality assurance 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) 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, proficiency testing 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.

• Proficiency testing

Proficiency testing 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 proficiency testing (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.

• 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, which is available online.
http://www.aphl.org/AboutAPHL/publications/Documents/External_Quality_Assessment_for_AFB_Smear_Microscopy.pdf

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 quality assurance 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. 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. A standard set of quality indicators should be used for all sites conducting a particular test to allow for comparison. A system should be in place for centralized reporting of monthly quality indicators to the NTRL or NTP. Documentation of corrective actions and subsequent improvement and normalization of laboratory indicators following the corrective actions are critical.

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.

• General quality indicators

The following set of quality indicators (apply to all technologies) 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 4: 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 *
Customer satisfaction	>80% surveyed customers are satisfied
Technician productivity	Report average number of tests performed per month per technician

* 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.

• Test-specific quality indicators

This section provides recommended quality indicators for each WHO-approved methodology, which are in addition to the general quality indicators listed in Table 4. 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 5 lists quality indicators recommended for AFB smear microscopy should be collected, analysed on a monthly basis, and disaggregated by type of microscopy (light, FM) where more than one method is employed.

Table 5: Quality indicators for smear microscopy

Indicator	Description	Target#	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 turn around time (TAT)	Time between receipt of specimens for smear at the laboratory and result reporting (mean, range and 90th centile)	24-48 hours	

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

Culture

Table 6 lists quality indicators recommended for culture 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 TB culture further disaggregation is recommended.

Table 6: Quality indicators for culture

Indicator	Description	Target	Reference
Number and proportion of diagnostic specimens (new and relapse) that were culture positive (MTBC and NTM combined)	Number of diagnostic specimens (new and relapse) that were culture positive for MTBC 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 MTBC positive	Number of diagnostic specimens culture positive for MTBC / 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 MTBC	Number of AFB smear positive specimens culture positive for MTBC / 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 MTBC	Number of AFB smear negative specimens culture positive for MTBC / Number of smear negative diagnostic specimens processed for culture	20-30%	
Number and proportion of contaminated cultures leading to uninterpretable results*	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 turn around time	Time between receipt of specimens for culture at the laboratory and result reporting (mean, range and 90th centile)	*Solid culture:* 3 weeks on average for smear-positive samples and 4-8 weeks on average for smear-negative samples *Liquid culture:* 8-10 days for smear-positive samples and 2-6 weeks for smear-negative samples	

* 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 7 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 7. Quality indicators for DST

Indicator	Description	Target	Reference
Number and proportion of mono-resistance and multidrug resistance to all combinations of drugs tested (*e.g.* INH monoresistance, RIF monoresistance, 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 TAT	Time between inoculation of DST and result reporting (mean, range and 90th centile). For total DST TAT, add this value to culture TAT.	*Solid media:* 8-16 weeks# *Liquid media:* 4-6 weeks	

Total turnaround time, including time for primary culture to produce inoculum for phenotypic DST.

Line probe assay

Table 8 lists indicators recommended for use with line probe assays for the detection of TB and rifampicin resistance. They should be collected and analysed on a monthly basis in addition to the general quality indicators.

Quality control indicators for LPA are listed in Table 8. 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).

Table 8: Quality indicators for LPA

Indicator	Description	Target	Reference
Number and proportion of mono-resistance and multidrug resistance (i.e. INH monoresistance, RIF monoresistance, MDR)	Number of isolates with mono- or multidrug resistance / Total number of isolates 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/documents. asp?xpand=2
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 TAT	Time between receipt of specimens for LPA at the laboratory and result reporting (mean, range and 90th centile). For indirect LPA, add the culture TAT for total TAT	1-2 days (longer if batching of tests)	

GeneXpert MTB/RIF

Table 9 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 risk, extra-pulmonary 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.

Table 9: Quality indicators for Xpert MTB/RIF

Indicator	Description	Target	Reference
Number and proportion of MTB detected, RIF resistance not detected	Number of MTB detected RIF resistance not detected / Total number tested	Dependent on population tested and country drug resistance prevalence and patterns	*Xpert MTB/RIF training package.* Global Laboratory Initiative. http://www.stoptb. org/wg/gli/ TrainingPackage_ XPERT_MTB_RIF.asp
Number and proportion of MTB detected, RIF resistance detected	Number of MTB detected RIF resistance detected / Total number tested	Dependent on population tested and country drug resistance prevalence and patterns	
Number and proportion of MTB detected RIF indeterminate	Number of MTB detected RIF indeterminate / Total number tested	Dependent on population tested and country drug resistance prevalence and patterns	*Xpert MTB/RIF implementation manual* http://www.who.int/ tb/laboratory/xpert_ launchupdate/en/
Number and proportion of MTB not detected	Number of MTB not detected / Total number tested	Dependent on population tested and country drug resistance prevalence and patterns	
Number and proportion of errors	Number of errors/ Total number tested	<3%	
Number and proportion of invalid results	Number of invalid results / Total number tested	<1%	
Number and proportion of no results	Number of no results / Total number tested	<1%	
Laboratory TAT	Time between receipt of specimen for Xpert MTB/RIF at the laboratory and result reporting.	2-24 hrs	

• 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 proficiency testing (PT), reviewing quality indicators, reporting of issues identified by staff members, and audits.

The quality improvement cycle in figure 9 involves four steps: Plan, Do, Check, and Action. Non-conformities identified during routine testing and quality assurance activities should be analysed, corrective actions implemented, and the results monitored over time. These four steps should 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.

Figure 9: Continuous quality improvement cycle from WHO LQMS Handbook
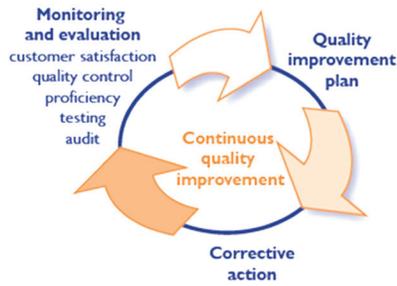
Procedures for identifying non-conformities, determining responsibility, recalling the results associated with the non-conformities, and resuming routine testing following corrective actions must be clearly defined. Follow up actions to prevent the same non-conformity from occurring in the future must also be put in place.

Table 9: Quality assurance components for TB diagnostics

Test	Quality indicator monitoring	Quality control	Proficiency testing	On-site supervision	Blinded re-checking	Source of Training / 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. Restaining of slides may be considered.	*External Quality Assessment for AFB Smear Microscopy.* Geneva, APHL, CDC, IUATLD, KNCV, RIT, WHO, 2002. http://www.stoptb.org/wg/gli/assets/documents/External%20Quality%20Assessment%20for%20AFB%20Smear%20Microscopy.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. Restaining of slides may be considered.	*External Quality Assessment for AFB Smear Microscopy.* Geneva, APHL, CDC, IUATLD, KNCV, RIT, WHO, 2002. http://www.stoptb.org/wg/gli/assets/documents/External%20Quality%20Assessment%20for%20AFB%20Smear%20Microscopy.pdf
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 (*M.tuberculosis* complex, drug susceptible isolate) 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 TB and non-TB isolates. This is 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/documents.asp?xpand=2

Test	Quality indicator monitoring	Quality control	Proficiency testing	On-site supervision	Blinded re-checking	Source of Training / Reference
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 (*M.tuberculosis* complex, drug susceptible isolate) and one negative (decontamination solution, water or other bacteria e.g. *E.coli*) with each batch of specimens processed for culture. *Internal QC:* Crosscheck 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. This is 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/documents.asp?xpand=2 *MGIT Manual.* http://www.finddiagnostics.org/resource-centre/reports_brochures/071130_mgit_manual.html
Species identification tests, MPT64 antigen	Monthly. Refer to list of indicators (general and test specific) in section 2.3.2.h above.	Incoming QC of new batches. Process positive culture controls included in batch, and add positive (MTB complex) and negative (non-tuberculous mycobacteria – *M.avium, M.intracellulare,* or *M.kansasii*) to batch of MPT 64 antigen tests. 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/documents.asp?xpand=2

Guide for providing technical support to TB laboratories in low- and middle-income countries

Test	Quality indicator monitoring	Quality control	Proficiency testing	On-site supervision	Blinded re-checking	Source of Training / Reference
Culture-based drug susceptibility testing, 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 (*M.tuberculosis* complex, drug susceptible isolate) 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 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 level of agreement for RIF and INH is >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/documents.asp?xpand=2 *MGIT Manual.* http://www.finddiagnostics.org/resource-centre/reports_brochures/071130_mgit_manual.html
Culture-based drug susceptibility testing, 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 positive (*M.tuberculosis* complex, drug susceptible, and resistant isolate. 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 SL 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/documents.asp?xpand=2

Test	Quality indicator monitoring	Quality control	Proficiency testing	On-site supervision	Blinded re-checking	Source of Training / Reference
Line probe assay, rifampicin, and isoniazid resistance	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 MTB complex drug susceptible 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 complex. Crosscheck 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.		*Training package on LPA* (MTBDRplus v2) – October 2012 http://www.stoptb.org/wg/gli/documents.asp?xpand=2
Xpert MTB/RIF	Monthly. Refer to list of indicators (general and test specific) in section 2.3.2.h above.	Incoming QC of new batches. 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

> **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 external quality assurance 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

2.3.3   Quality assurance tools

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

GLI laboratory toolbox. Global Laboratory Initiative, 2014.
http://www.stoptb.org/wg/gli/documents.asp?xpand=2

TB Laboratory Standard Operating Procedures. FIND.
http://www.finddiagnostics.org/programmes/scaling_up/lab-strength/resources/

Quality assurance planning tool. FIND.
http://www.finddiagnostics.org/programmes/scaling_up/lab-strength/slmta/tb-slmta/
(Tool for planning human and financial resources when rolling out an on-site supervision programme. An automated calculation feature allows simple budgeting in local or donor currencies.)

2.3.4   Suggested reading

External quality assessment for AFB smear microscopy. Geneva, APHL, CDC, IUATLD, KNCV, RIT, WHO, 2002.
http://www.stoptb.org/wg/gli/assets/documents/External%20Quality%20Assessment%20
for%20AFB%20Smear%20Microscopy.pdf

MGIT procedure manual. Siddiqi SH, Rüsch-Gerdes S. Geneva, FIND, 2006.
http://www.finddiagnostics.org/resource-center/reports_brochures/071130_mgit_manual.html

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: microscop. 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

Guidelines for surveillance of drug resistance in tuberculosis, 4th ed. Geneva, World Health Organization, 2009 (WHO/HTM/TB/2009.422).
http://whqlibdoc.who.int/publications/2009/9789241598675_eng.pdf

Xpert MTB/RIF implementation manual. Technical and operational 'how to': practical considerations. Geneva, World Health Organization, 2014.
http://apps.who.int/iris/bitstream/10665/112469/1/9789241506700_eng.pdf

WHO policy statement: molecular line probe assays for rapid screening of patients at risk of multidrug-resistant tuberculosis (MDR-TB). Geneva, World Health Organization, 2008.
http://www.who.int/tb/laboratory/line_probe_assays/en

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

Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: 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://apps.who.int/iris/bitstream/10665/112472/1/9789241506335_eng.pdf

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.

2.4   Implementing quality management systems

2.4.1   Introduction to QMS

A quality management system 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 quality management system, 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 quality management system handbook and associated training toolkit, go to http://www.who.int/ihr/training/laboratory_quality/en/. This training toolkit can be customised to fit local needs.
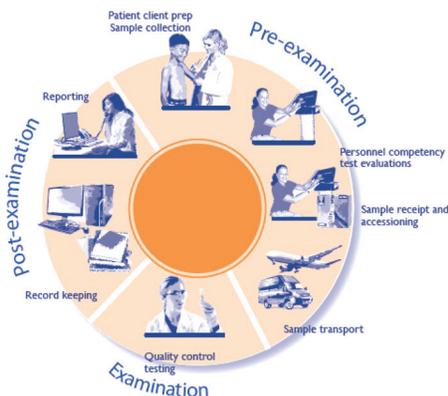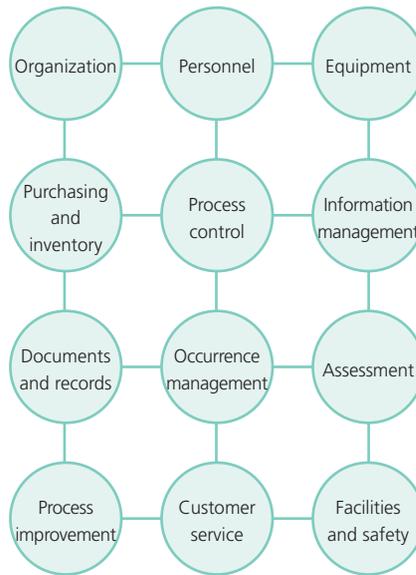

Figure 10: A Quality Management System incorporates pre-examination, examination, and post-examination phases of testing. (*WHO LQMS Handbook*)

```
Organization      Personnel       Equipment

Purchasing        Process         Information
and               control         management
inventory

Documents         Occurrence      Assessment
and records       management

Process           Customer        Facilities
improvement       service         and safety
```

Quality system essentials 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.

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.

The accreditation of clinical or medical laboratories is achieved by measuring performance against ISO (International Organization for Standardization) 15189, which addresses the 12 quality systems essentials. These quality system essentials are described in *Application of a quality management system model for laboratory services*, published by the Clinical and Laboratory Standards Institute.

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 quality management system 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 quality management systems within the TB laboratories.

Every NTRL should be engaged in implementing quality management systems 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 drug susceptibility testing 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* which 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 *Global Plan to Stop TB* (2010 – 2015) noted that less than 5% of national TB reference laboratories worldwide were accredited to international standards, and it identified a target of 50% NTRLs meeting international accreditation standards by 2015. This ambitious target has yet to be met. Nonetheless, progress is already being made in a number of resource-limited countries. For example, in the African region, NRLs in Uganda, Mozambique, Botswana, and South Africa have achieved international accreditation, and several other laboratories are approaching this status. Nonetheless, in many countries there is limited awareness or implementation of QMS.

Implementing a quality management system (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 Quality Management System

Consultants offering laboratories technical support should ensure that the purpose of the technical assistance is clearly articulated and agreed to in advance, to ensure the consultant's scope of work is aligned with the laboratory's goals and that the expectations and responsibilities of each party are clearly understood. The goal may be formal national or international accreditation, or it may simply be implementing or strengthening the QMS to improve the quality of results without intending to become formally accredited.

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 which may outlive any individual person or organization providing support. The consultant's or organisation's experience and familiarity with different approaches will of course play a role, as will their specific terms of reference for support.

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. A recently published guidance document, *ISO 15189 Quality Management System Implementation: Look Before You Leap- Best practice guidance document*, (http://www.tbcare1.org/publications/toolbox/lab/) describes the deployment of QMS in three NTRLs 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 quality management systems 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 U.S. Centers for Disease Control and Prevention (CDC) – Division of Laboratory Systems, and the Clinical and Laboratory Standards Institute (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.
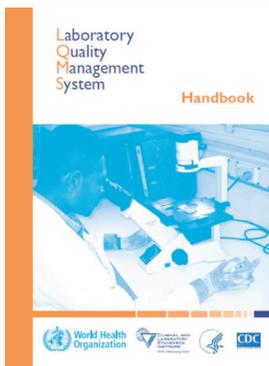
http://www.who.int/ihr/training/laboratory_quality/doc/en/

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 quality system elements 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, quality control and quality assurance.

- 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.

Figure 11: Sample roadmap for the implementation of elements of a QMS.

Phase 1: *To ensure that the primary process operates correctly and safely*
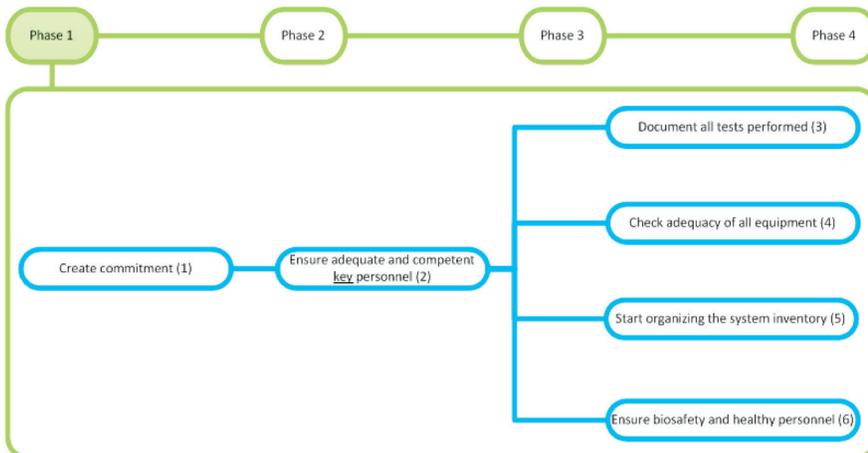
Since the GLI tool does not incorporate a training programme for country-wide implementation, it may be used in conjunction with other approaches, *e.g.* SLMTA, below, or used as a technical resource for mentoring by experienced laboratory mentors supporting individual laboratories.

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 quality system essentials identified by the Clinical and Laboratory Standards Institutes (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 (English, French and Portuguese) at http://www.afro.who.int/en/clusters-a-programmes/hss/blood-safety-laboratories-a-health-technology/blt-highlights/3859-who-guide-for-the-stepwise-laboratory-improvement-process-towards-accreditation-in-the-african-region-with-checklist.html.
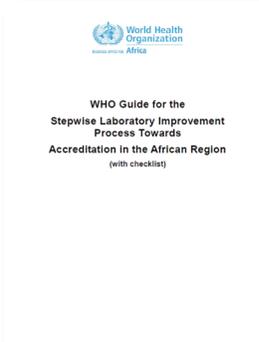
SLMTA: Strengthening Laboratory Quality Management Toward Accreditation

Developed by the US Centers for Disease Control and Prevention (CDC), in collaboration with the American Society for Clinical Pathology (ASCP), the Clinton Health Access Initiative (CHAI), and WHO AFRO, SLMTA is a task-based training and mentoring tool kit provided to laboratory personnel in a multi-workshop implementation model http://slmta.org/

A description of the programme is available at http://ajcp.ascpjournals.org/content/134/3/401.long

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 recently developed a TB specific programme, TB SLMTA, incorporating the GLI tool into the SLMTA programme, including a TB Laboratory Quality Management Systems Towards Accreditation Harmonized checklist, (http://www.finddiagnostics.org/programmes/scaling_up/lab-strength/slmta/tb-slmta/), specific training modules and tools that meet the differing requirements of TB laboratories, for example with regard to quality assurance and biosafety. The 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 Harmonised 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 laboratories' 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 WHO Laboratory Assessment Tool, 2012, or the GLI TB Microscopy Network Accreditation Assessment Tool, 2013. 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 quality management systems
>
> Prepare plans and budget for implementing QMS in TB laboratories and assist in liaising with partners for funding and technical support
>
> Conduct laboratory quality management 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 harmonised approach
>
> Provide support for country customisation of checklists used for laboratory assessments
>
> Review local checklists for conformance to international standards

2.4.6   Suggested reading

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

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

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

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

SLMTA: African laboratories working toward accreditation. Kampala, African Field Epidemiology Network, 2014.
http://www.afenet-lab.net/newstwo.php?id=20

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

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http://dx.doi.org/10.4102/ajlm.v1i1.6

ISO 15189 Quality Management System Implementation: Look Before You Leap. TB CARE I.
http://www.tbcare1.org/publications/toolbox/lab/

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

2.5 Safety in TB laboratories

2.5.1 Introduction to biosafety

The level of biosafety in NTRLs and other TB laboratories varies widely in low- and middle-income countries. Where significant investment has been made in infrastructure upgrades, particularly at the reference laboratory level, laboratories with international standard biosafety infrastructure and practises do now exist. However, 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, 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.

WHO published a *Tuberculosis Laboratory Biosafety Manual* in 2012, which should be consulted for the latest detailed recommendations for biosafety.
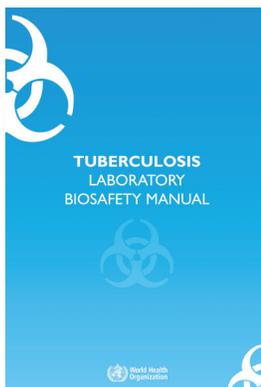
http://www.who.int/tb/publications/2012/tb_

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 10.

Table 10: Risk precaution levels associated laboratory activities and risk assessment for tuberculosis (TB) laboratories. (*WHO Tuberculosis Laboratory Biosafety Manual*, 2012)

Risk level of TB laboratory[a]	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

DST, drug-susceptibility testing.
[a] 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.
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 http://www.aphl.org/aphlprograms/global/Documents/GH_2011July_VentilatedWorkstationGuidance.pdf 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 *M. tuberculosis* 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 manual.

2.5.3   Infrastructure

Countries often require infrastructure development or upgrades in order to reach minimum standards of safety for conducting culture and drug susceptibility testing. With the support of donors and partners, many NTRLs are undergoing such upgrades. Consultants may be asked to

provide guidance 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, the consultant should clearly articulate the safety concerns and proposed solutions 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 (http://www.cdc.gov/niosh/npptl/respusers.html). 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 PPE 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-up with available diagnostic tests (X-ray, TST) 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; PPE 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 discouraged and the consultant should assist with training on proper methods of decontamination and sterilization. At lower level facilities in rural areas, access to equipment or disinfectants essential for proper disposal may be limited and thus these methods may be the

only options. However, in these instances, it is important to assist national programmes with designing waste segregation and pick-up strategies, to encourage programmes to provide proper decontaminating agents, or to have the programmes construct small incinerators to facilitate proper waste management practices.

In extreme situations, consultants may find programmes recycling materials. Some materials such as glassware, instruments, and laboratory clothing can be reused or recycled after proper sterilization. However, sometimes there are attempts at recycling other items by boiling and washing them, such as microscope slides and sputum cups (among others). These items should never be reused and it is the responsibility of the consultant to address these situations and educate both laboratory and programme officials regarding the problems associated with reusing these materials.

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. Continued encouragement by consultants and laboratory managers for improved waste management should persist.

As previously stated, it is important for programmes to establish policies, guidelines and protocols at the national level for laboratory waste disposal. In countries where these are not in place, it is recommended that the consultant assist and help direct these developments by working side-by-side with national officials, providing the necessary resources on internationally recommended guidelines and devising education and training programmes. Implementing waste management programmes for TB laboratories is an essential step in providing quality management systems which are essential for accreditation. Thus, proper guidance on appropriate methods, writing guidelines, and waste management documentation is often the responsibility of the consultant and is essential for laboratories and networks seeking to acquire official ISO15189 accreditation.

Specifics on waste management in TB laboratories can also be found in the *WHO Tuberculosis Biosafety Manual* listed in the reference section.

Local and international partners may provide biosafety training courses. 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 SOP development

Assist with development of occupational health programme

Assist with laboratory design and workflow for safe operations

Assist with developing an emergency preparedness plan

2.5.8   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

GLI stepwise process towards TB laboratory accreditation. Global Laboratory Initiative, 2014.
http://gliquality.org

Laboratory biosafety manual, 3rd ed. Geneva, World Health Organization, 2004 (WHO/CDS/CSR/LYO/2004.1).
http://www.who.int/csr/resources/publications/biosafety/WHO_CDS_CSR_LYO_2004_11/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

Ventilated Workstation Manual for AFB Smear Microscopy: manufacturing, validation and user guide. DHHS, CDC, GLI, IUATLD, APHL.
http://www.aphl.org/aphlprogrammes/global/Documents/GH_2011July_VentilatedWorkstation Guidance.pdf

TB Laboratory Biosafety Online Training. FIND.
http://www.finddiagnostics.org/programmes/scaling_up/online_training/

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

- quality control and external quality assessment 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 which 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 IT 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*.
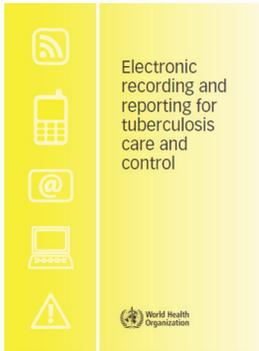
http://who.int/tb/publications/electronic_recording_reporting/en/

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.

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 national TB control programme.

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 (2005).

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

Advise on integration of LIMS data into national data management systems, including electronic databases, e.g. electronic TB registers

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2.6.1   Suggested reading:

Electronic recording and reporting for tuberculosis care and control. World Health Organisation. 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

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, staff 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 lab, 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. Consultants involved in strategic plan development should encourage programmes to improve human resource capacity and implement strategies to retain technically qualified staff. 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   HR 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 HR 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.

Consultants may be involved in performing an assessment of human resources. In light of a proper assessment of the situation, actions to improve human resources and build capacity can be suggested to the national laboratory programme. Areas of weakness can be addressed, such as the absence of consistent routine training programmes or the need for systems to manage human resources. The consultant can provide information and suggestions which can assist in future planning and budgeting processes to resolve gaps, improve the quality of staff, ensure appropriate working conditions, and improve the retention of experienced staff.

2.7.2   Training programmes

For many countries the human resources crisis is limiting 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.

As a consultant, 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. Consultants may be required to assist with building effective and routine mechanisms for training to ensure continuity of testing and maintain a high level of performance.

When offering training, it is important for a consultant to assist the laboratory or programme to incorporate the training into their current system in order to encourage knowledge transfer and internal capacity building. Often this is performed by Training-of-Trainers (TOT) 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 staff 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 SNRL, 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 which 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

2.7.5   Suggested reading

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

Roles of laboratories and laboratory systems in effective tuberculosis programmes. Bull World Health Organ. 2007 May; 85(5): 354–359.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2636656/

Assessing human resources development
www.who.int/tb/publications/tb_framework_checklist17.doc

2.8   Linking laboratory services to TB care and treatment

Timely and accurate diagnosis of TB is the key first step in the management of persons with TB, but diagnosis must 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 diagnosis and treatment include:

- Reporting the results back to the client and provider. Since 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, drug susceptibility testing, 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.

Some countries use electronic methods to capture and report laboratory results to treatment providers. There are also remote monitoring tools and software (such as GXAlert) that will connect GeneXpert instruments within a country to a national "cloud" dashboard, and push text messages to providers in real-time as results become available.

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

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2.8.1 Suggested Reading

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

2.9   Strengthening the role of private laboratories in national TB-control 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 national TB programme and the national reference laboratory at several points in the diagnostic and treatment path. 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 national TB programme.

- **Training and supervision:** private sector laboratories should be included in national training workshops and provided with national TB laboratory 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/NRL-recommended equipment validation and maintenance agreements for TB diagnostic instruments.

- **Quality assurance and management:** private laboratories should be required to participate in an EQA programme, which may include site visits, panel proficiency testing, 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.

2.9.1 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. WHO/HTM/TB/2006.360
http://whqlibdoc.who.int/hq/2006/WHo_HTm_Tb_2006.360_eng.pdf

A roadmap for ensuring quality tuberculosis diagnostics services within national laboratory strategic plans.
http://www.tbcare1.org/publications/toolbox/roadmap/

A Practical Handbook for National TB Laboratory Strategic Plan Development.
http://www.stoptb.org/wg/gli/assets/documents/Lab_Strategic_Handbook.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, national TB programmes and ministries of health should work together with national reference laboratories 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 drug-susceptibility testing and face challenges providing access to services for all those in need.

National TB reference laboratories 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". Subsequent to the Maputo declaration, WHO, the United States Centers for Disease Control and Prevention, and the APHL published *Guidance for Development of National Laboratory Strategic Plans*.

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 (NSP) for the national TB programme 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 national reference laboratory 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.

With funding from the United States Agency for International Development through TB CARE I, 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 (LSP) allow the national TB programme to earmark funding for projected laboratory activities and developments in Global Fund funding proposals.

http://www.stoptb.org/wg/gli/assets/documents/Lab_Strategic_Handbook.pdf

2.10.2   Laboratory Strategic Plan development

When assisting a NRL in creating or improving its strategic plan, it is advisable to first determine if there is already a strategic plan in place under either the national TB programme 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 LSP 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 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 quality-assured AFB microscopy with effective EQA

Objective 2
Improve the diagnosis of TB for AFB-negative cases especially among people living with HIV

Objective 3
Increase access to rapid laboratory diagnosis among TB patients considered at risk for M/XDR-TB

Objective 4
Establish laboratory quality management systems (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. A TB laboratory consultant's terms of reference may include assisting with strategic plan development, writing a LSP, conducting a gap analysis, or assisting with elements of LSP implementation.

Figure 12: Laboratory Strategic Plan Framework. (Practical Handbook for National TB Laboratory Strategic Plan Development)
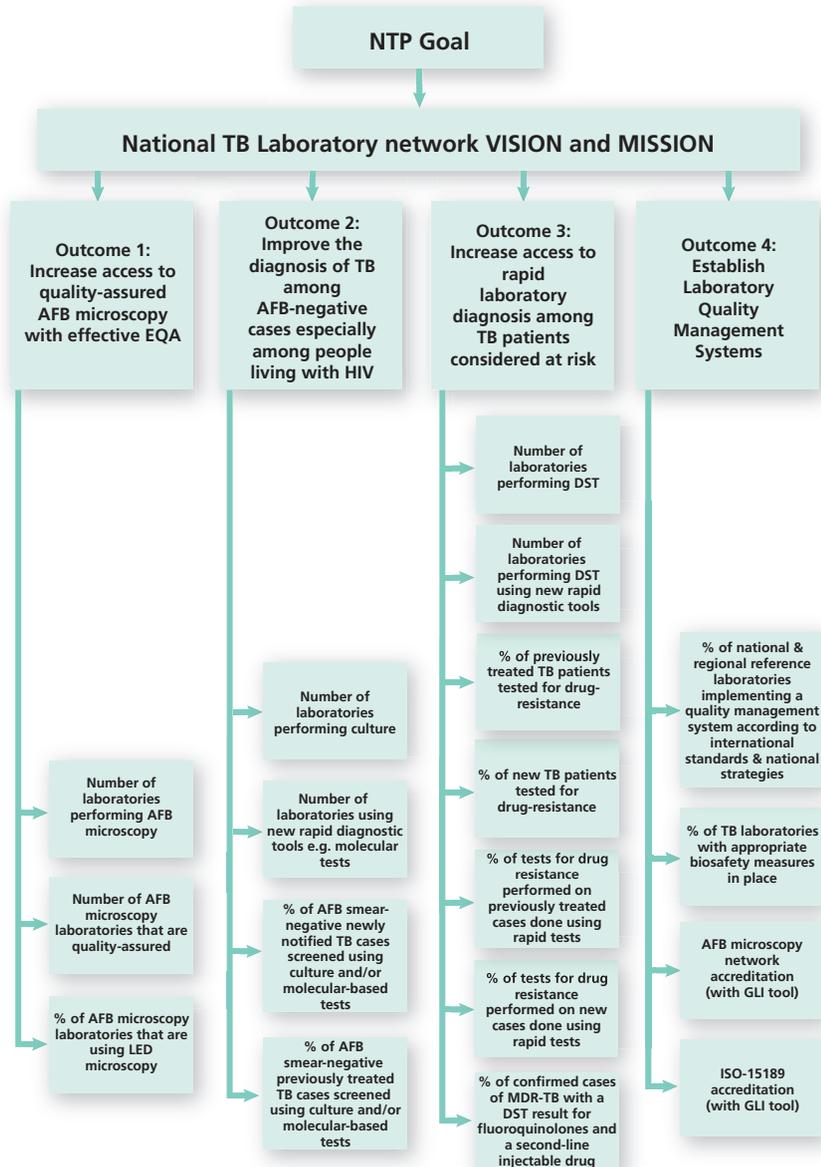
> **Key activity areas for technical support**
>
> Participate as a member of the technical working group for planning.
>
> Coordination and/or participation in sub-groups or task teams responsible for strategic planning.
>
> Providing information to TWG/sub-groups on partner-specific activities and budgets for inclusion in strategic planning.
>
> Leading or participating in strategic planning workshops.

2.10.3 Suggested reading

Practical Handbook for National TB Laboratory Strategic Plan Development. Global Laboratory Initiative, 2013.
http://www.stoptb.org/wg/gli/assets/documents/Lab_Strategic_Handbook.pdf

New funding model. Geneva, The Global Fund to Fight AIDS, Tuberculosis and Malaria, 2014.
http://www.theglobalfund.org/en/fundingmodel/

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

Guidance for development of national laboratory strategic plans: helping to expand sustainable quality testing to improve the care and treatment of people infected with and affected by HIV/ AIDS, TB and malaria. Geneva, World Health Organization, Regional Office for Africa, United States Centers for Disease Control and Prevention, Association of Public Health Laboratories, 2010.
http://www.aphl.org/aphlprogrammes/global/Documents/GH_2010Aug13_GuidanceNLStrategic Plans.pdf

TB Technical support and Coordination. Geneva, World Health Organization, 2014.
http://www.who.int/tb/tbteam/en/index.html

How to develop and cost a comprehensive technical assistance (TA) plan for implementing a national TB strategic plan (including the Global Fund TB grant). Geneva, World Health Organization, 2011.
http://www.who.int/tb/tbteam/TAPlanFINAL2011.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 (http://www.theglobalfund.org). 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 quality assurance and quality management systems;

- 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;

- 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 Stop TB Strategy. These plans can be used as the basis for resource mobilization from national governments and donor agencies. http://www.who.int/tb/dots/planning_budgeting_tool/download/en

Details of the Global Fund's new funding process are available at:
http://www.theglobalfund.org/en/fundingmodel/process/

Figure 13: New funding model for the Global Fund
TRP –Technical review panel, GAC – Grant approvals committee
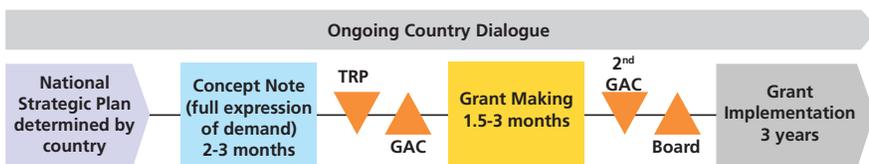
Key activity areas for technical support

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

2.11.2 Suggested reading

Planning and budgeting for TB Control activities.
http://www.who.int/tb/dots/planning_budgeting_tool/benefits/en/

New funding model. Geneva, The Global Fund to Fight AIDS, Tuberculosis and Malaria, 2014.
http://www.theglobalfund.org/en/fundingmodel/

The Global Plan to stop TB 2011–2015. Geneva, World Health Organization, 2010.
http://www.stoptb.org/assets/documents/global/plan/TB_GlobalPlanToStopTB2011-2015.pdf

Global tuberculosis report 2014. Geneva, World Health Organization, 2014 (WHO/HTM/TB/2014.08).
http://www.who.int/tb/publications/global_report/en/

3 PROVIDING TECHNICAL ASSISTANCE

3.1 Types of assistance

Technical assistance 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 a national TB laboratory operations manual;
- Developing standard operating procedures;
- Laboratory strategic planning;
- Global Fund programme reviews;
- Accreditation and laboratory QMS implementation;
- Implementation of new technologies;
- Developing routine surveillance practices;
- Assisting with survey planning (NPS or DRS) and capacity building;
- LIMS implementation;
- Laboratory management mentoring;
- Gap analysis and assessments;
- Biosafety development;
- Supply chain management;
- Building specimen referral strategies;
- Operational research activities.

Technical assistance (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. For example, SRLs may be able to recommend consultants and GLI has a list of TB laboratory consultants(available at:
http://www.stoptb.org/wg/gli/assets/documents/Lab%20consultants_June%202013.pdf).

3.2 Process for Technical assistance

The processes involved in technical assistance for International TAs are outlined in Figure 14. Local TAs follow a similar process with the exception of the various activities concerning preparation and travel. Internal country technical assistants from partner organizations are 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 TAs also have well-formed relationships with MoH/NTP/NRL and often can be more efficient and cost effective support. However, the use of a local consultant should not mean that the work should be overly informal. Local technical assistants still require formal TORs, 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.

Figure 14: Processes involved in providing technical assistance.
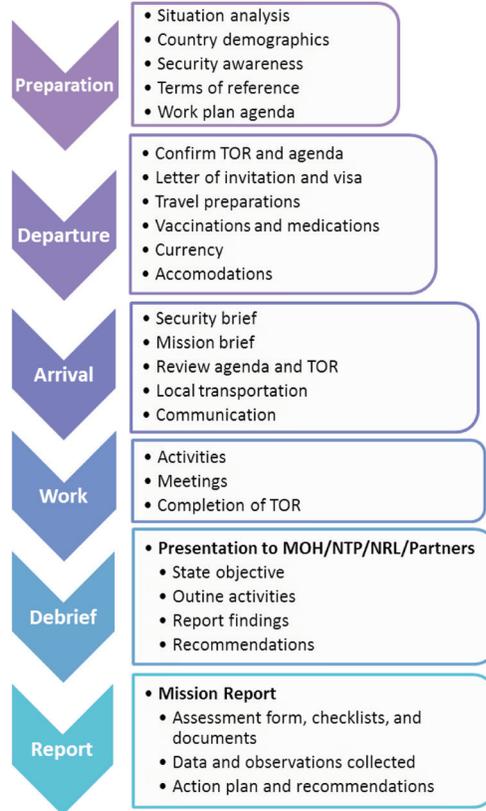
3.2.1   Preparation

Preparing for a technical assistance 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 effectively plan technical activities, 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 previous documents from programme reviews or missions, or by reviewing the national TB programme guidelines and other national documents. However, the most accurate information is often through direct communications with the national TB programme, the national TB reference laboratory, 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 a national reference laboratory 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 which 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, HIV/TB, EPTB, and child 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, DRTB, 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...
How is the TB programme organized in the MoH?	Within Public Health, Infectious Diseases, or independent
What are the existing treatment guidelines?	TB DOTS, TB/HIV, PMDT, child TB, EPTB, and TB-DM
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, Under another institute, Minimal structure
What are the existing laboratory services for TB?	Microscopy, culture, culture and DST, molecular diagnostics (Xpert/LPA), other
What is the current diagnostic coverage?	• Microscopy centres per 100,000 population • Culture and DST laboratories per 5 million population • LPA laboratories in country • GeneXperts in country
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 for microscopy, culture, Xpert, LPA, cDST, 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 national laboratory or TB programme reports

The extent of the review will vary depending on the scope of work outlined in the terms of reference (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 technical assistance 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)

- 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 HR development programmes

- Procurement and supply chain management practices

- Biosafety regulations and health surveillance measures already in place

- Facilities and equipment management programmes available

- Quality assurance 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/NRL will invariably include different terms of reference (TOR) covering policy, technical, or programmatic issues. It is important to be realistic about what can be achieved during the chosen timeframe. Clear terms of reference 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 terms of reference (TOR) may include the following steps:

- Communicating with officials from the national TB programme, the national reference laboratory, the Ministry of Health or 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.

3.2.2 Departure for an international technical assistance 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/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 ministry of health.

- 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. Euros or dollars are often the preferred currency for exchange.

- 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.

3.2.3 Arrival for an international technical assistance 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.

3.2.4 Work

During the TA visit it is critical to involve NTP/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/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 technical assistance 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 national TB programmes 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 national TB reference laboratory (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 nongovernmental organizations (NGOs) that are actively involved in supporting programme development.

3.2.5   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/NTP; these should be shared at a debriefing meeting with the relevant stakeholders before departing.

- Ensure that the recommendations are consistent with the terms of reference 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.

3.2.6   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 national TB-control programme 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 or to preparing the strategic plan.

- 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, terms of reference, 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. Photos can also be helpful to illustrate a

problem or demonstrate a successful programme or intervention. 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 ministry of health, 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 terms of reference, 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.

3.2.7 Suggested reading

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

Laboratory tools. United States Agency for International Development, TB CARE I. Washington, DC, 2014.
http://www.tbcare1.org/publications/toolbox/lab/

Resources. Global Laboratory Initiative. 2014.
http://www.stoptb.org/wg/gli/documents.asp

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

Repository of technical reports from technical assistance missions provided by the SRL network are available at
http://apps.who.int/tb/srl/report_repository/map/atlas.html.

WHO TB Supranational Reference Laboratory Network.
http://www.who.int/tb/laboratory/srln_factsheet.pdf?ua=1

WHO TB Supranational Reference Laboratory Network: Technical assistance mission report template.
http://www.who.int/tb/laboratory/srln_mission_report_blank_template.pdf?ua=1

Tuberculosis Laboratory Network Assessment. United States Agency for International Development, TB CARE I. Washington, DC.
http://www.tbcare1.org/publications/toolbox/tools/assess/Laboratory_Assessment_Form.pdf

Global tuberculosis report 2014. World Health Organization. Geneva, 2014 (WHO/HTM/TB/2014.08).
http://www.who.int/tb/publications/global_report/en/