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A Roadmap for Ensuring Quality Tuberculosis Diagnostics Services within National Laboratory Strategic Plans

Prepared by

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Advancing TB Diagnosis



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GLOSSARY

AFB	Acid fast bacilli
DOTS	Directly observed treatment short-course
DST	Drug susceptibility testing
FM	Fluorescence microscopy
GLI	Global Laboratory Initiative
HIV	Human immunodeficiency virus
IUATLD	International Union against Tuberculosis and Lung Disease
LED	Light emitting diode
LJ	Lowenstein-Jensen medium
LPA	Line probe assay
MDR-TB	Multi-drug resistant tuberculosis
MTB	<i>Mycobacterium tuberculosis</i>
NTM	Nontuberculous mycobacteria
NTP	National TB programme
PCR	Polymerase chain reaction
SRLN	Supra-national TB Laboratory Network
TB	Tuberculosis
WHO	World Health Organization
XDR-TB	Extensively-drug resistant tuberculosis
ZN	Ziehl Neelson

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EXECUTIVE SUMMARY

In order to reach universal access to quality-assured TB diagnostic services by 2015, a strategic plan and roadmap to guide the massive scale-up of laboratory services is an essential first step in effectively addressing the diagnostic challenges of TB, notably HIV-associated and drug-resistant TB.

In 2002, recognizing the pressing need for improved TB laboratory services, the DOTS Expansion Working Group (DEWG) of the Stop TB Partnership (STP) established a Subgroup on Laboratory Capacity Strengthening (SLCS), comprising mainly of the directors of the Supranational Reference Laboratory Network (SRLN), heads of National TB Reference Laboratories (NRLs) and STP representatives. To maximize the activities of the SLCS and the SRLN, and optimize the network of Stop TB partners involved in laboratory strengthening, a Global Laboratory Initiative (GLI) was proposed to and endorsed by the STP Coordinating Board in October 2007. The GLI provides a focus for TB within the framework of a multi-faceted yet integrated approach to laboratory capacity strengthening through a network of partners. The GLI Secretariat is hosted in the Stop TB Department at the World Health Organization (WHO) in Geneva, Switzerland.

The momentum for the Roadmap was created by the current unprecedented effort in TB laboratory strengthening spearhead by the Global Laboratory Initiative (GLI) and its multiple partners, supported by significant investment from several funding and technical agencies. In addition, rapidly evolving experience from key countries and partners such as the Foundation for Innovative New Diagnostics (FIND) and UNITAID in implementing TB laboratory services within the context of national laboratory strategies was instrumental in building momentum. Several technical agencies have also agreed to share their collective experiences with GLI, while in-country interviews have facilitated a much-needed understanding of the realities and constraints faced by Ministries of Health and NTPs in meeting the demand for scale-up of TB laboratory services.

The development of the Roadmap the GLI Core Group is one of the key GLI strategic objectives. Country visits and in-depth interviews were conducted with key stakeholders and common themes identified to guide the conceptual framework of the Roadmap.

This document aims to provide a structured framework for scaling-up TB laboratory services and is based on WHO-recommended norms and standards, documented country best-practices and growing lessons learnt from field experiences by many partners involved in the Global Laboratory Initiative (GLI). Of particular urgency is the integration of TB-specific laboratory networks into national strategic plans for development of comprehensive laboratory systems.

The Roadmap was developed by the GLI Core Group following a decision in May 2008 to pursue this activity as one of the key short-term GLI strategic objectives. Country visits and in-depth interviews were subsequently conducted with key stakeholders and common themes identified to guide the conceptual framework of the Roadmap.

This document aims to provide a structured framework for scaling-up TB laboratory services, based on WHO-recommended norms and standards, documented country best-practices and growing lessons learnt from field experiences by many partners involved in the Global Laboratory Initiative (GLI). Of particular need is the integration of TB-specific laboratory networks into national strategic plans for development of comprehensive laboratory systems.

A roadmap for ensuring quality tuberculosis laboratory services within national laboratory strategic plans

Introduction

Quality assured laboratory services in resource-poor countries are essential to meet the Millennium Development Goals for Health and those of major global health initiatives and financial mechanisms such as The Global Fund and PEPFAR. Member states are also now required to report to WHO any potential public health risk under the International Health Regulations, which necessitate the availability of accurate, reliable, and rapid laboratory results. Arguably the weakest component of health systems, laboratory services in developing countries have historically been grossly neglected and underfunded. Diagnostic and surveillance capacity is therefore a major bottleneck for scaling up management and control of the highest-burden infectious diseases, largely as a result of one or more of the following factors:

- Lack of recognition of laboratory services as an integral component of disease control;
- Inadequate and unsafe laboratory infrastructure;
- Insufficient and underfunded country-level strategic plans for laboratory strengthening;
- Vastly inadequate numbers of skilled technical staff;
- Slow diagnostic tool development and delayed, extremely slow, technology transfer;
- Insufficient and uncoordinated technical assistance at country level to strengthen laboratories.

Increasing funding for global health initiatives and in particular for health systems components, requires a focused approach to strengthening of key elements of laboratory services that cut across diseases. Increasing investment in research and development has resulted in the largest pipeline of new TB diagnostics ever. There is therefore an urgent need to develop a road map for ensuring quality TB diagnostics within National strategic plans to strengthen laboratory systems, as an integral part of strengthening overall health systems of developing countries.

How to use this Document

This document is intended to guide the development or updating of National Laboratory Strategic plans to incorporate the specific requirements for providing the laboratory services needed for TB diagnosis, treatment, and control. The document should also be used as one of the resources in a national process that involves the participation of all global and national partners and organizations involved in laboratory work to create a national public health laboratory strategic plan that addresses the needs of all diseases of public health importance. Shared technological platforms (eg. for molecular assays and advanced/modern microscopy) and increasing convergence in test platforms (eg. rapid tests for TB, HIV, malaria) present a unique and exciting opportunity for integrated or harmonized laboratory services, for combined use of diagnostic equipment and laboratory space, and for expanding diagnostic capacity to more remote health facilities. Because of the complexity of strategic planning and technical issues, countries may choose to use an expert laboratory consultant to guide the planning process.

The roadmap is a document that matures and evolves to respond to issues such as:

- Disease burden and epidemiology
- New diagnostic tools
- Costs and benefits of technology advancement
- Government and donor support levels
- Clinical indications for diagnosis and monitoring
- Human resource requirement

Who should use the Document?

This document has been developed as a reference for everyone involved in activities that strengthen laboratory systems and the diagnosis of tuberculosis, such as laboratory technicians, program managers, technical advisors, procurement officers, warehouse managers, service providers, government officials, implementing partners, donor agencies etc. The document will assist National TB Control Programme Managers and Laboratory Directors in coordination with external laboratory consultants, donors and other decision makers in TB control to help in setting priorities to address the specific requirements for TB laboratory scale-up. The document provides guidance for laboratory

strategic planning committees on how to address TB issues within a broader national laboratory strengthening plan. Anyone who may be responsible for program planning, budgeting, and mobilizing resources for diagnostic services will also benefit from using this document.

Purpose of the Document

This document aims to provide a structured framework for TB laboratory strengthening based on WHO-recommended norms and standards, documented country best-practices and growing lessons learnt from field experiences that can be used to develop a strategic plan for providing reliable TB laboratory services as part of the National TB Programme, or preferably, as part of a strategic plan for comprehensive laboratory services. It is expected that countries will adapt the generic Roadmap to suit country-specific needs, within the context of their own epidemiological situation and resource availability.

Due to the diversity of resources and needs in different countries and the geographical variation in the epidemiology of TB, HIV-associated TB and drug-resistant TB, no single Roadmap can address all issues in detail. This document is therefore aimed at providing a generic Roadmap or template for TB laboratory strengthening, encompassing the managerial, technical and operational processes required for developing and implementing a national TB laboratory strategy able to meet the needs of DOTS expansion, HIV-associated and drug-resistant TB, within national strategic plans for laboratory strengthening.

The Roadmap is not meant to prescribe how individual countries develop their own TB laboratory strategies and plans, nor is it a detailed technical document. More complete and comprehensive technical information can be found in various published documents, journals, laboratory manuals and policy publications. Selected references and tools available are listed throughout the Roadmap.

Rationale for the TB Diagnostics Roadmap

Care of patients with tuberculosis (TB) starts with a quality assured laboratory diagnosis; however; lack of appropriate diagnostics and vastly inadequate existing laboratory

capacity are key barriers to TB control. Many deaths could be avoided and patients cured if a correct diagnosis of TB was done in time. Unfortunately TB diagnosis is often not reliable, especially in resource-poor settings. The reasons are many: complexity of identification of persons suspected of having TB; lack of simple, accessible, sensitive and specific diagnostic tools; lack of trained laboratory professionals; and grossly inadequate diagnostic laboratory infrastructure and quality assurance. Additionally, the lack of access to laboratory services and insufficient links between the laboratory and treatment services can be major weaknesses of National TB Programmes (NTPs).

HIV-associated TB and drug-resistant TB pose particular diagnostic challenges, given that sputum smear microscopy (the cornerstone of TB diagnosis) lacks sensitivity to detect many TB patients with HIV co-infection, can only identify acid-fast bacilli as a group (ie. not individual mycobacterial species), and cannot distinguish drug-susceptible from drug-resistant TB. Given the slow growth rate of *Mycobacterium tuberculosis*, results from conventional culture and drug-susceptibility testing (DST) are invariably delayed and in high HIV-burden settings may result in patients dying even before a diagnosis of drug-resistant TB can be made. Multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) are particularly difficult to diagnose. As a direct consequence of critical gaps in laboratory capacity for culture and DST, less than 5% of the estimated global burden of MDR-TB cases and an even smaller fraction of XDR-TB cases are currently being detected, as illustrated in Figures 1 and 2:

Figure 1.
Global
TB
estimate
s, 2007

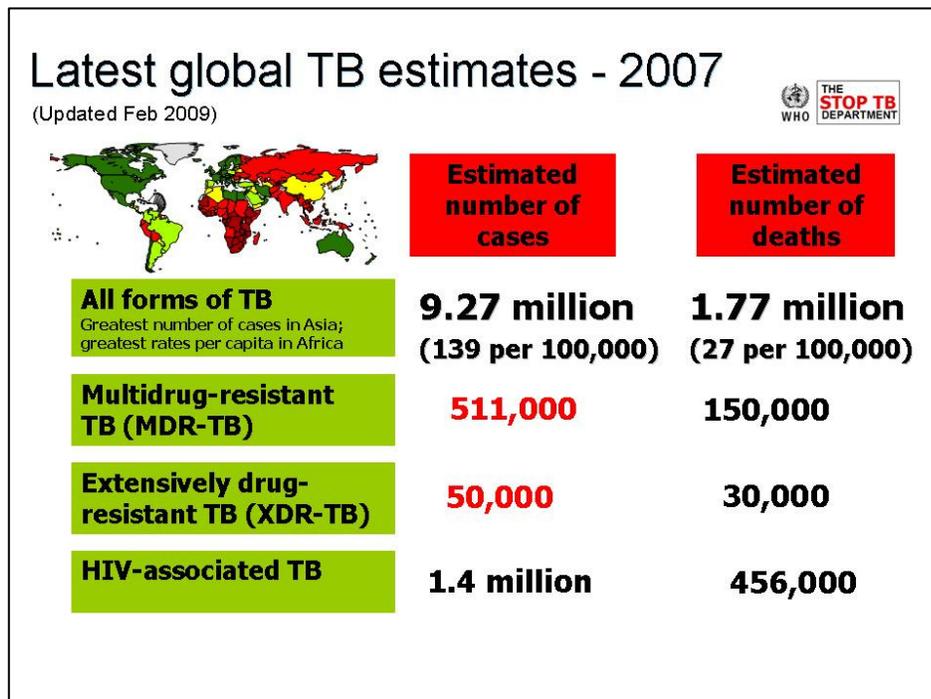
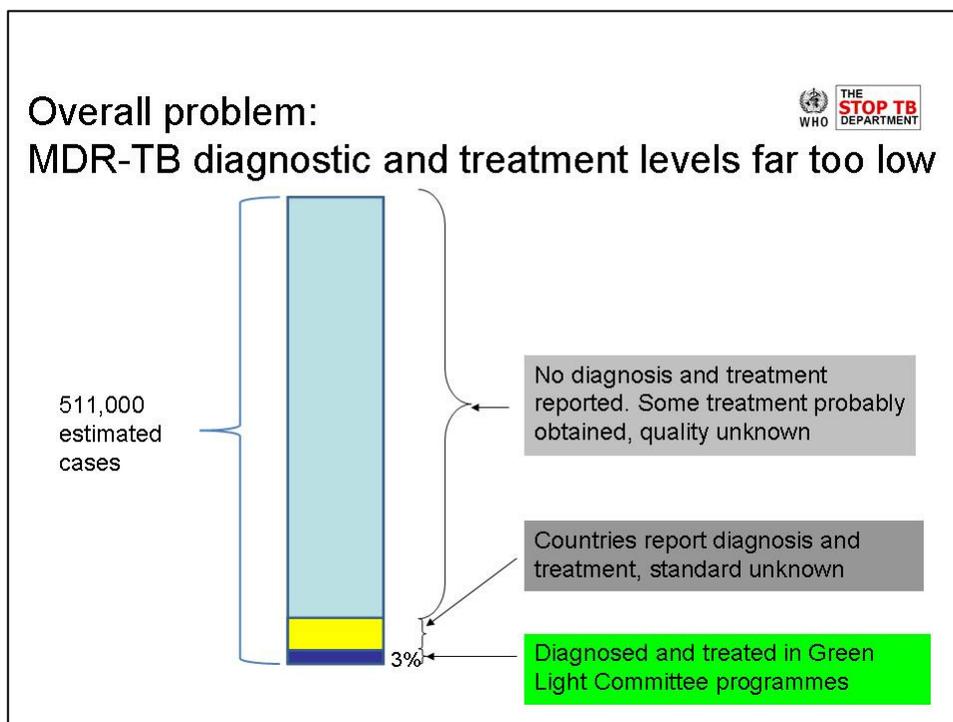


Figure 2. Estimated proportion of MDR-TB patients diagnosed and treated under WHO recommended strategies

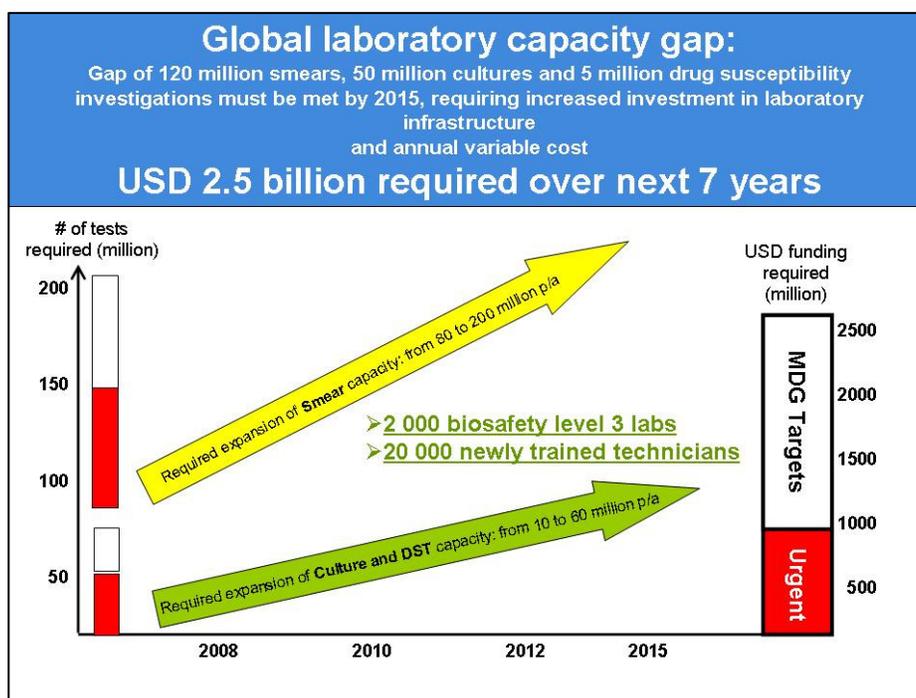


Effectively addressing HIV-associated and drug-resistant TB require, at its core, a robust network of TB laboratories with adequate biosafety, modern methods for diagnosis, standard operating procedures and adequate quality assurance. However, the situation in resource-constrained settings is particularly dire as a result of one or more of the following factors:

- Most resource-constrained countries have limited or no laboratory capacity for the tests, culture and DST, required to diagnose smear-negative (common in HIV/TB cases) TB disease and drug-resistant strains of *M. tuberculosis*;
- The functionality and reliability of existing national reference laboratories (NRLs) for performing culture and DST are questionable, due to major infrastructure constraints such as electricity and water supply, inappropriate design, suboptimal biosafety conditions, insufficient funding, and a lack of standardized laboratory procedures and quality standards;
- Human resource capacity in the NRLs is also far below the critical mass needed for providing reliable services as a result of inadequate financial resources, training programs and retention strategies, which are exacerbated by a lack of structured career paths, inadequate remuneration, and non-recognition of the importance of laboratory staff in TB control;
- Technology transfer is delayed and extremely slow, largely as a result of the lack of national strategic plans for laboratory services, compounded by inadequate funding, lack of appropriate systems for specimen referral, logistics and supply chain management, inadequate systems for information management and rapid, effective knowledge sharing, and a lack of regulatory frameworks to safeguard quality, safety, performance, accuracy and cost-effectiveness of new diagnostic tests;

Current estimates by the GLI are that at least 2 000 laboratories would need to be either newly built or renovated to meet required biosafety levels, and be equipped with at least 20 000 newly trained technologists. Figure 3 outlines the huge scale-up efforts required: TB laboratory needs are most pressing in the 22 high-burden countries (HBCs), 27 MDR-TB priority and 63 TB-HIV priority countries.

Figure 3: Efforts required for scaling up TB laboratory capacity in developing countries



The Roadmap was developed to facilitate and guide efforts to develop and implement a national laboratory strategic plan to provide reliable TB laboratory services.

General considerations for developing of the Roadmap

Establishing, equipping, financing, and ensuring sustainability of appropriate laboratory networks are challenging, complex and expensive. The establishment of well maintained TB laboratories with appropriate bio-safety measures and equipment for quality assured testing presents the greatest challenges for both initial financing and sustainability. Hence, innovative approaches to expanding to TB laboratory services are needed to address different tiers of laboratories with different levels of laboratory testing with good referral mechanisms to higher level laboratories while still addressing the epidemiological disease burden in each country setting.

Many international agencies and donors have expressed interest in investing resources in laboratory capacity development. Coordination of laboratory strengthening activities is essential to avoid wasting of scarce resources, unnecessary duplication, and confusion at country level due to conflicting technical advice and approaches. Also, TB laboratory constraints often centre on cross-cutting issues such as infrastructure and human resource

development which may be best addressed using a coordinated, integrated approach to laboratory capacity strengthening within the context of overall laboratory quality assurance systems and integrated disease control approaches. Thus, integration of TB laboratory strengthening efforts into routine laboratory services provided by country Ministries of Health is therefore imperative, as is a stable political environment to allow sustained integration of contemporary diagnostic and laboratory standards into respective National TB Programmes.

Strengthening TB laboratory services may offer one of the best avenues for financing overall laboratory improvement as an essential health systems component. Fundamental to this work is collaboration between TB control programmes and public health laboratory systems at country level, in the areas of: 1) infrastructure, biosafety and utilities, 2) human resource development (including training and retention), 3) specimen referral, supply chain management and logistics, 4) equipment and maintenance, 5) technical procedures (disease-specific), 6) quality assurance, and 7) data management

Sustained and prolonged technical assistance (TA) is considered integral to the success of scaled-up laboratory services. Conventional approaches to TA are, however, expensive and not realistically feasible given the scope of scale-up of TB laboratory services required. For example, Supranational reference laboratories (SRLs) are stretched beyond capacity supporting primarily current drug resistance surveillance and quality assurance of drug susceptibility testing activities and have not been resourced to assist countries with the expansion of routine diagnostic services, external laboratory quality assurance, or training.

Coordination of TA efforts and optimizing resource allocation through a partnerships approach is paramount. A globally agreed Roadmap for laboratory strengthening would be expected to ensure coordination, compliance with international norms and standards, ensure standardization and uniformity in funding applications, avoid duplication of efforts, and should lead to optimized use of resources.

There are common elements that must be addressed in TB laboratory strengthening efforts to ensure appropriateness and sustainability of laboratory services:

- Laboratory infrastructure and maintenance;
- Equipment validation and maintenance;
- Specimen transport and referral mechanisms;
- Management of laboratory commodities and supplies;
- Laboratory information and data management systems;
- Laboratory quality management systems; and
- Appropriate, adequate strategies and funding for laboratory human resource development.

Shared technological platforms, common health systems barriers to implementing laboratory services, and the shared disease burden of especially TB, HIV and malaria in many countries point to the need - and opportunity - to establish tiered yet integrated laboratory systems, at appropriate health service levels, to ensure universal access to diagnosis. In addition, the need for general clinical laboratory services (eg. biochemistry, serology) is often overlooked in disease-specific programmes, yet essential for adequate patient monitoring and care. Cross-cutting health systems components of laboratory services amenable to integration, areas that require close collaboration between disease-specific programmes, and areas requiring a technical disease-specific focus are summarized in Table 1:

Table 1. Conceptual framework for laboratory activities

<p>Normative (Technical, disease and/or technique-specific)</p>	<ul style="list-style-type: none"> • Evidence-based policy development • Norms and standards • Standard operating procedures • Training manuals and tools • Quality assurance and proficiency testing
<p>Collaborative</p>	<ul style="list-style-type: none"> • Country support and technical assistance • Stakeholder liaison

	<ul style="list-style-type: none"> • Donor coordination at global, regional and country level • Operational research • Advocacy and resource mobilization
Integrated (Health systems components)	<ul style="list-style-type: none"> • Regulatory framework to safeguard quality, safety, performance, accuracy and cost-effectiveness of diagnostic tests • Infrastructure development, upgrade and maintenance of laboratory networks at country level • National laboratory strategy development, country national laboratory plans, operational manuals (with adequate specificity for disease-specific needs) • Human resource development, including skills mapping, competency analyses, curriculum development, training and retention strategies, task-sharing and task-shifting • Training, eg. Good Laboratory Practice (GLP) • Logistics and supply chain management, including specimen referral systems, procurement strategies, equipment specifications and maintenance • Laboratory administration and management systems, quality management and supervision, laboratory information systems • Laboratory accreditation and certification

The rapidly changing landscape of TB diagnostics necessitates that country strategies and plans be dynamic and responsive to new policy developments and to the availability of new tools. Delayed and extremely slow transfer of technology to developing countries has been highlighted as a special concern in addressing the scale-up needs of drug-resistant- and HIV-associated TB. One reason has been the slow uptake of new global policies in country screening and diagnostic algorithms, which is relatively easy to address. New tools will, however, be impossible to implement if the required laboratory networks, infrastructure, training and deployment of skilled laboratory workers, quality assurance and information systems are not developed and maintained in tandem.

It is therefore vital that country-specific TB laboratory plans be developed under guidance of laboratory consultants and in-country laboratory experts well-versed and experienced in the complexities of TB laboratory services, including laboratory design (particularly biosafety), provision of appropriate equipment, tools and supplies, establishing of technical procedures, and implementation of quality management and improvement principles.

Essential Components Of A Laboratory Services System

National laboratory strategic plans should strive to create a laboratory system based on quality laboratory management principles. Essential components of quality laboratory systems and quality management systems have been addressed by several international organizations including the International Organization for Standardization (ISO), European Committee for Standardization (CEN), Clinical and Laboratory Standards Institute (CLSI), and WHO. The key elements to be addressed in a national laboratory plan are listed in Table 2.

Table 2. Framework for national laboratory strategic plans

(Adapted from WHO-AFRO, CDC-Atlanta. *Guidance for Development of National Laboratory Strategic Plans, 2009*. For detail please refer to original document)

Component	Elements
Objectives, Vision, Mission	
Structure of laboratory services	<ul style="list-style-type: none"> • Governance • Levels of tiered services
Infrastructure and equipment	<ul style="list-style-type: none"> • Buildings • Capital equipment • Reagents and consumables • Specimen transport and referral • Data management

Legal and policy framework	<ul style="list-style-type: none"> • Laws, statutes, government policies
Human resources	<ul style="list-style-type: none"> • Capacity • Development and retention strategies • Salary structures • Training curricula and institutions
Financial resources	<ul style="list-style-type: none"> • Funding sources • Financial systems • Fiscal oversight
Technology	<ul style="list-style-type: none"> • Screening and diagnostic algorithms • Tests available at tiered laboratory levels
Quality management	<ul style="list-style-type: none"> • Quality control • Quality assurance • Proficiency testing • Laboratory accreditation
Systems	<ul style="list-style-type: none"> • Supply chain management • Laboratory information systems • Communications systems • Monitoring and evaluation

ESSENTIAL COMPONENTS OF A ROADMAP FOR TB LABORATORY SERVICES

Setting Objectives

Defining country strategic objectives is a critical first step in the process for laboratory strengthening in countries. The objectives will vary between countries, as they will be in part influenced by disease prevalence, the current in-country laboratory capacity, infrastructure, human and financial resources and existing quality systems.

Based on the individual epidemiological setting in each country the strategic objectives may use a stepwise approach to laboratory scale-up for TB diagnosis depending on needs.

An example could be to:

1. Ensure country wide access to quality assured AFB microscopy services
2. Detect MDR-TB among treatment failures or other at risk groups
3. Detect TB among persons co-infected with HIV.
4. Detect TB in children and extrapulmonary TB

Achieving different objectives will require different levels of services, infrastructure and equipment, human and financial resources in addition to implementing appropriate algorithms using available diagnostic technologies. It is essential that each objective is linked to an associated work plan which is realistic and achievable.

Legal and Policy Framework

It is important to investigate laws, statutes, government policies to enact country legislation to control the use of TB diagnostics and facilitate implementation of internationally recommended technologies. In accordance with the strategic objectives for implementing quality assured TB diagnostic services other considerations are as follows:

- Establishing one or more regulatory oversight bodies that will provide approval for TB diagnostic tests and determine the cost of TB tests applied in public and private settings.
- Engage professional bodies and those which regulate standards for training to ensure that changes with govern laboratory staff are instituted by the professional bodies.
- Establish a National Bio-safety Committee which will ensure compliance of laboratory services with TB bio-safety requirements.

Structure of the Laboratory System within Country

Implementing TB laboratory scale-up should address the issue of how well-structured the laboratory system is currently, and what is required to improve service delivery. This requires an analysis of user needs in the hospitals and clinics, and an assessment of what the TB burden is within the country. The analysis should also include other diseases such as malaria and HIV which are important to diagnose and monitor. Results of the assessments will be used to determine an optimal tiered laboratory system that reflects

varying levels of service sophistication according to a predetermined schedule and to provide the MOH with sufficient information to implement, monitor and evaluate public health programs.

The roadmap intends to describe a well-structured laboratory system with multiple tiers of laboratory service. Depending on the size of the country, the population and their geographical distribution, peripheral and regional laboratories supporting local clinics and hospitals, will perform simple and more regularly requested sample analyses, while referral centers will have a higher level in the laboratory structure and perform more specialized tests, or those tests which are performed less frequently. The central level laboratory should be resourced to perform all levels of TB testing including microscopy, culture and DST, as well as rapid molecular methods for diagnosis and detection of drug resistant form of TB. At the regional level, decentralisation of testing may take the form of laboratory performing specimen processing for microscopy and rapid resistance detection with or without the capacity to perform culture inoculation. Attention must be given to the transport of samples, tracking of samples referred in the system and return of test results to the correct site for appropriate patient management.

The considerable variation of complexity, difficulty and requirements of different TB laboratory tests make it impossible to provide all services at any type of health institution disposing of a laboratory. Three levels are generally recognised, each with its particular responsibilities, although these can vary to some extent, depending on the level of development besides country-specific needs and diagnostic strategies. These include the peripheral, intermediate and central level. Very small or very large countries may function better with one level less respectively more within this pyramid. Additionally, one may consider a still more peripheral level with only specimen collection and possibly preliminary processing; also private laboratories may take a particular position attached to this structure; and there is the network of Supra-National Tuberculosis Reference Laboratories providing certain services to the national level. While the peripheral and most intermediate level labs are integrated and perform the whole range of tests needed at

their level of the health service, the National Reference Laboratory is often dedicated to TB only, although it may be part of a comprehensive National Public Health Laboratory.

Typical requirements and tasks specific to the main three levels:

Peripheral Level

- Very basic laboratory requirements but with the pre-requisite of a good microscope and regular supply of reagents and multi-purpose staff, which may also include community health care workers
- Performs only AFB smear-microscopy, ZN or FM
- Provides referral of samples or patients in need of further tests such as rapid molecular testing culture and or DST to a higher testing, coordinating and/or screening level

Intermediate Level

- Requirements vary with tests that will be done. May be only microscopy or also more demanding tests such as rapid molecular, culture or even DST. The latter require reliable supply of power and water, facilities for safely manipulating pathogenic mycobacteria and professional, on-the-job trained lab staff
- Performs at least AFB smear-microscopy, ZN or FM, and possibly also culture for mycobacteria with forwarding of possible TB isolates to a higher level laboratory performing culture identification and DST
- May screen patients referred for DST, i.e. performing special tests such lineprobe assays for the rapid detection of resistance and coordinates referral of specimens and/or patients for DST at a higher level, and feedback of the results
- May prepare AFB staining solutions for the peripheral AFB-smear labs belonging to its administrative division and ensures uninterrupted laboratories supplies in collaboration with the NTP coordinator at the same level
- Performs AFB-microscopy network training, supervision and EQA for its jurisdiction, in collaboration with the local NTP coordinator

Central or National level

- High requirements targeting all types of tests, as above. In addition, highly qualified staff are indispensable for management of the laboratory itself as well as the network, data management and possibly research
- Microscopy will be performed, ZN as well as FM, but its volume needs to be limited by ensuring routine services are provided at other laboratories in nearby institutions. Culture and DST volume may also need to be limited and where possible decentralise some testing to regional centers.
- Appropriate testing algorithms need to be developed to ensure best use of resources. Molecular tests for TB diagnosis and drug resistance detection can be performed as well, but referral to a specialised molecular laboratory (i.e. at a nearby university, or even commercial services) or a regional laboratory is a valid alternative.
- Decides on laboratory equipment and supply specifications, and ensures availability of adequate funding mechanisms and regular procurement in collaboration with the NTP and the procurement section at the Ministry of Health
- Organises and coordinates AFB-microscopy network training, supervision, EQA and recording/reporting for the country; this includes responsibility for manuals, SOPs, training curricula and materials, and formats for recording and reporting
- Compiles reports from various levels and on various tests into a national report, including analysis and appropriate recommendations to the NTP and the Ministry of Health's laboratory services
- Identifies suitable operational research projects together with the NTP and collaborates in and executes laboratory tests for research projects initiated by the NTP and partners, in as far as these can be reconciled with its capacity at service provision to the NTP
- Regularly takes part in external quality assurance organised by the SRLN

Infrastructure and Equipment

Laboratory design, layout and renovation to meet adequate biosafety standards for TB are complex and expensive. Laboratory workers manipulating TB cultures for identification and DST are at a particularly high risk of becoming infected with *M. tuberculosis*, and thus at high risk for developing TB. Most laboratories in developing countries anticipating performing TB culture, DST and/or molecular line probe assays are in need of extensive renovation and/or redesign, which, due to its cost and complexity, should be conducted by engineering experts and based on contemporary biosafety standards. To avoid duplication and unnecessary expenditure, effective laboratory strengthening requires strong collaboration and coordination between departments responsible for laboratory services at country level, between disease-specific programmes, and between those responsible for human resource development and training. TB, HIV and malaria have attracted significant donor funding, albeit through different funding streams. Using these different funding sources to effect much need improvement to overall laboratory infrastructure and service may be one of the most cost-effective interventions to improve diagnosis and care of patients suffering from one or more of these conditions. In particular, addressing the infrastructure and biosafety needs of TB is bound to create a laboratory environment that can easily incorporate HIV and malaria testing.

Buildings

Ensure consultation with and input from specialist architects and engineers for laboratory design, layout and renovation to ensure appropriate biosafety depending on the risk associated with different TB technical procedures. WHO guidance on TB laboratory design is currently under development and should be available by early 2010.

Capital equipment

Establish appropriate systems for validation and maintenance of essential biosafety equipment to ensure a quality diagnosis and adequate protection of TB laboratory staff. *M. tuberculosis* is classified as a Risk Group 3 pathogen, requiring the use of appropriate negative pressure systems, biological safety cabinets, safety centrifuges, and a whole range of related laboratory equipment and supplies. A regular schedule for validation and

maintenance of equipment is therefore imperative, in return requiring adequate resources and the necessary expertise, both of which are currently in critical short supply

Reagents and consumables

Continuous availability of adequate amounts of good quality supplies for diagnosis is as essential for the national TB programme as availability of drugs, and one of the pillars of the DOTS strategy. This pertains equally to the network of microscopy laboratories all over the country as to the usually fewer culture and DST laboratories. Responsibility for free supplies may even be extended to private laboratories, thus assuring their cooperation and ideally free services for TB patients.

Dedicated budget lines are an essential prerequisite, and often forgotten particularly with integrated laboratory services which may not fall directly or solely under the responsibility of the NTP. The Head of the NTP and the Head of the NRL will have to collaborate and coordinate with other programmes and branches within the Ministry of Health to assure adequate budgets, and to ensure uniformity and continuous quality for some commonly needed items such as microscopy slides, staining solutions or immersion oil. Further requirements are the overall responsibility of the Head of the TB laboratory services, and apply to the microscopy network as well as culture / DST and molecular laboratories alike:

- It is necessary to define the specifications of reagents and consumables needed, based on global recommendations and standard operating procedures (SOPs) specific to the country. Additionally, decide on the level at which they should be available (for instance some microscope spare parts).
- Appropriate stock keeping with regular inventories at all levels, providing the necessary formats and instructions; for the peripheral microscopy units this only requires using simple stock cards, but culture / DST laboratories and molecular laboratories will need a more sophisticated tool.
- Establish a system of reagent preparation and distribution, particularly for the AFB-smear staining solutions. This will include deciding on the level of decentralisation of solution preparation with SOPs and quality control of each lot, unless these solutions are procured ready for use.

Specimen transport and referral

Establish appropriate specimen transport mechanisms for TB bacteriology, including cold-chain systems and delivery of specimens to laboratories with the shortest possible delay. The referral of samples for molecular testing using lineprobes do not require organisms to be viable, hence are less vulnerable to sample deterioration than samples referred for culture. Packaging and transport of specimens suspected of containing infectious disease should be done according to international standards, including those of the aviation industry when such specimens are sent by air.

Data Management

At a minimum, proper recording of laboratory tests performed is required for patient diagnosis and treatment follow-up. However, ideally a data management system also aims to achieve the following:

- Internal and external monitoring and quality assurance of laboratory performance, which is particularly important for mycobacterial culture laboratories, but also an indispensable tool during supervision at any level.
- Evaluation of the NTP services for their continuous improvement. In its simplest form this includes operational parameters such as numbers of tests and positivity rates. More elaborate recording and reporting will also allow monitoring of the epidemiological impact of the NTP, for instance case detection rates or trends of important drug resistance in the population

While NTPs are generally well organised and highly efficient for management of data regarding treatment of patients, very often the diagnostic part is underdeveloped because of long-standing neglect starting at global level. Essential requirements for development of an efficient data management system include:

- Decide which data need to be collected, keeping in mind the aims described above. The main challenge will often be to restrict recording and especially reporting to what is essential and likely to be used routinely. This has to be decided in discussion between the NTP and the Head of the TB laboratory services, taking

into account also the needs and existing formats from related branches in the Ministry of Health, particularly the Laboratory and Information Divisions.

- Decide on formats to be used, i.e. paper registers and reporting forms versus electronic databases and report generating tools. These will generally vary according to the type and level of the laboratory (i.e. peripheral microscopy versus central DST laboratory; intermediate level microscopy EQA laboratory).
- Decide on who is responsible for data keeping and reporting, and define appropriate qualifications and training curricula. This will be applicable to all levels to assure transparency and uniform application of definitions for data parameters and their entry. Designated data staff is not required for the peripheral microscopy units, and handouts and training at this level will be limited and part of their general NTP lab training. Requirements will be higher at intermediate level (i.e. use of simple computer databases and analysis tools for the EQA data generated), while at the highest levels ideally professional data management staff should be available.
- Establish a monitoring, compilation, analysis, feedback and transmission system for the incoming data, for instance incorporating the large mass of intermediate level EQA data into a national database, with regular comments on completeness and results to the lower levels, as well as generation of a national comprehensive report. Ideally this will include presentation and discussion of specific data at forums bringing together the laboratory and NTP staff of a particular level.

Human Resources

Need to set up a national mechanism to ensure coordination at all levels among government departments responsible for laboratory services, disease-specific programmes, human resource development, and training. Adequate human and financial resources are essential health systems components of TB control, yet often under-budgeted and poorly planned. Human resource capacity in laboratory services constitutes a particular crisis, with almost 80% of countries reporting critical shortages in skilled laboratory staff

Capacity

Attaining health objectives in a population depends to a large extent on effective, efficient, accessible, viable and high quality services provided by all personnel, in sufficient numbers and appropriately allocated across different occupations. The lack of clear policies for human resource development in many countries has produced an imbalance that threatens the capacity of health care systems. Next to laboratory infrastructure, the critical shortage of appropriately skilled and compensated laboratory workers constitutes the biggest challenge in scaling up access to TB diagnostics. Defining and developing the required expertise to perform TB procedures at each level of the laboratory service is essential.

- Prepare a national inventory of the current TB laboratory workforce involved in providing laboratory diagnostic, monitoring and support services in the country, including numbers, qualifications and levels of training, in-service training courses attended, years of service, and staff placement needs;
- Quantify the number and types of laboratories providing TB diagnostic services and the distribution of laboratory workers by numbers, categories and workload at the different levels of the laboratory service;
- Analyze the causes of existing shortages of TB laboratory workers and assess the factors that contribute to the availability of workers to perform productively and effectively;

Development and retention strategies

Need to identify and remove barriers to laboratory staff career development, remuneration, staff retention, and sustainability of technical competency. Human resource development is an activity requiring input from human resource experts. In addition to mapping out current human resources for TB laboratory services at different levels of service delivery, human resource strategies need to include the following:

- Creating relevant posts, appropriate remuneration packages and career paths for all levels and types of laboratory staff required;
- Developing capacity retention strategies, including incentive schemes for staff working outside of countries and wishing to return;
- Review career and governance structures that may impact on TB laboratory human resource performance and development, addressing reasons for lack of interest in the profession.
- Consider incentives for laboratory staff working in remote and rural settings, including remuneration, training, and benefits such as housing, home travel, and children's education, to attract and retain staff to these areas for a period of time;

Training curricula and institutions

Laboratory health workers provide a pivotal service in healthcare delivery, especially in those diseases that depend on diagnostic testing for decision-making, such as TB. However, laboratory workers often remain invisible to patients, policy makers, and funders, being overlooked or unrecognized as an essential part of the health care team. Opportunities for further training and career advancement of laboratory staff are often limited and pre-service and in-service curricula may not be aligned to the needs of the health services. In many countries, laboratory workers lack formal and legal representation through associations and governing bodies. Staff training needs to address both pre- and in-service training strategies. The technical and managerial challenges of new TB diagnostics call for training of new laboratory workers skilled in both the technical aspects of individual procedures but also in overall laboratory administration and management, quality improvement, information technology, and financial management. At an international level, there is a need to create an expert cadre of new professional laboratory experts who can be trained and embedded back into host institutions where they can create robust, efficient and effective laboratory systems.

- Prepare a national inventory of in-service TB laboratory training courses developed by different governmental departments and external stakeholders and the institutions capable of delivering such courses;
- Assess the pre-service and in-service training curricula for TB laboratory workers at different levels, developed by both governmental departments and external stakeholders, including the institutional capacity to deliver such courses;

Financial Resources

It is essential to recognize and acknowledge the importance of laboratory systems in TB control and commit adequate human and financial resources. Ensure that health sector plans include adequately conceptualized and budgeted components for comprehensive laboratory capacity development.

The WHO Budgeting and Finance tool (ADD URL) provides a solid framework for appropriate budgeting and costing of TB laboratory services. Of note when using this tool is that the prices provided are so-called 'free on board', i.e. these exclude costs related to shipping, insurance, import tax, local distribution, service and support, installation and maintenance. All of these are highly variable depending on country context and may result in cost of equipment, reagents, supplies etc. being significantly increased when these components are included.

- Identify the individuals responsible for TB policy development and funding for TB laboratory services, ensuring adequate input from laboratory experts;
- Ensure that TB laboratory services are integrated into comprehensive national laboratory services;
- Ensure that TB laboratory budgets include the seven essential components of:
 - Infrastructure, biosafety and utilities;
 - Human resource development (including training and retention);
 - Specimen referral, supply chain management and logistics;
 - Equipment and appropriate maintenance;
 - Technical procedures at appropriate levels of the laboratory service
 - Internal quality control, external quality assurance, proficiency testing;
 - Data and information management.

Funding Sources

It is necessary to prepare a national inventory of donor and technical partner efforts in laboratory strengthening and identify synergies and opportunities for optimization of resources. It is necessary to delineate the nature of laboratory technical assistance and funding required, the process of engaging with all in-country stakeholders, and how to align donor efforts with national structures, policies and systems. It is furthermore important to develop a plan to effectively engage international agencies to support TB laboratory services within the context of broader laboratory strengthening, allowing for coordination of multiple sources of funding for laboratory services.

Technical Support

To optimize technical support to countries it is necessary to engage private and nongovernmental organization laboratories, professional bodies, research groups, and regulatory oversight bodies to improve access to TB diagnostic capacity, ensuring adequate support, training and quality assurance. In many developing countries, private sector laboratories are well-funded and resourced, frequently having skills and human resources which are absent from public sector laboratories. In addition, laboratory services in several countries are supported by nongovernmental organizations, often with critical links to rural and under-serviced communities. Research organizations, as well as clinical and contract research laboratories may offer infrastructure and technical assistance and diagnostic services to routine laboratory services. It is therefore important to include these stakeholders in planning and capacity building for TB laboratory services, ensuring that their activities and services add value to country needs.

An often neglected component of national laboratory strategies is a regulatory framework to ensure quality, safety, effectiveness and appropriateness of diagnostic tools. In the absence of such a framework, aggressive marketing strategies and unscrupulous sales efforts may result in inappropriate and poor quality diagnostics being used for TB control, jeopardizing patient care. Developing countries currently have significant and multiple opportunities to engage with global stakeholders interested in laboratory capacity development and support. There are several multilateral and unilateral donors that have

laboratory strengthening as a key component and the ultimate aim should be to align funding with national priorities and systems. It is of utmost importance that establishment of parallel structures is avoided and that potential synergies between different funding sources be explored. An important step in this regard is to prepare a national inventory of stakeholders and funders involved in laboratory strengthening activities at country level. The SRL network has until now been resourced to provide technical assistance to countries and mainly for the provision of quality assurance for DST. The SRLN remains the strongest technical resource for laboratory capacity strengthening and in the provision of technical advice. The SRL network should provide technical assistance to countries in establishing national policy on culture and DST; to build a cadre of skilled laboratory personnel; implementing quality assurance mechanisms for smear microscopy, culture and Drug Sensitivity Testing (DST); ensure regular Drug Resistance Surveys (DRS); and provide laboratory support for MDR-TB treatment.

It is envisioned that the SRLN will receive additional funding to provide a more active role in assisting countries to scale-up implementation of quality assured diagnostics for TB.

Available Technologies Endorsed by WHO

Sputum smear microscopy – Light Microscopy

Despite recent advances in mycobacteriology, early laboratory diagnosis of TB still relies heavily on the examination of stained smears of sputum specimens. Microscopy of sputum smears is a simple and inexpensive technique, quickly detecting those cases of pulmonary TB who are infectious; however, direct smear microscopy using acid-fast stains is a relatively insensitive technique, with the reported sensitivity ranging widely from 25% to 80% when compared with mycobacteriological culture. Between 5,000 and 10,000 per milliliter of sputum are required for direct microscopy to be positive. Sputum specimens from patients with pulmonary TB - notably those with cavitory disease - often contain sufficiently large numbers of acid-fast bacilli to be readily detected by direct microscopy. Smear sensitivity is, however, poor in patients with extra-pulmonary TB,

those with HIV-co-infection, and those with disease due to nontuberculous mycobacteria (NTM).

Microscopy for acid-fast bacilli (AFB) cannot distinguish *M. tuberculosis* from NTMs, viable from non-viable organisms, or drug-susceptible from drug-resistant strains. The main use of microscopy for drug-resistant TB management are therefore limited to assessing initial infectiousness of patients, triaging specimens to different algorithms for culture, DST or molecular line probe assays, and confirming that organisms growing on (or in) culture media are mycobacteria rather than contaminants.

Conventional, direct Ziehl-Neelsen (ZN) microscopy conducted on sputum specimens from persons suspected of having TB is suitable for peripheral laboratories based at primary health care centres or districts hospitals. The maximum number of ZN smears examined per microscopist per day should not exceed 25 as visual fatigue will lead to a deterioration of reading quality. On the other hand, proficiency in reading ZN smears can only be maintained by examining at least 10-15 ZN smears per week. Usually, one ZN microscopy centre per 100 000 population is sufficient to attain these targets; nevertheless, the number of microscopy centres should be planned against the following:

- Location and utilization of existing services
- Population distribution
- Transport facilities

Sputum smear Microscopy - Fluorescent Microscopy

Fluorescence microscopy, typically using quartz-halogen lamps or high-pressure mercury vapour lamps, is suitable for use in regional laboratories with large workloads. One advantage of fluorescence microscopy is that a lower magnification objective can be used, allowing a much larger area of the smear to be seen and therefore more rapid smear examination. However, the capital cost and running expenditure are considerably higher than for ZN microscopy, and more expertise and experience are required for reliable reading. Usually, one fluorescence microscopy centre can serve 500,000 to one million population .

However, light-emitting diode (LED) technology allows fluorescence microscopy to be done at a much lower cost, largely due to the long life expectancy of the light source (10,000 hours if powered correctly versus 200 hours for a conventional mercury lamp). Unlike the light emitted by mercury vapour lamps, LEDs do not produce ultra-violet (UV) light (a cause of concern to many users). LEDs also significantly decrease the instrument's power consumption, allowing long-lasting battery operation. Problems reported from evaluation studies include instability of reagents under field conditions and instability of stained smears upon prolonged storage. Performance characteristics, operational constraints, and applicability of LED microscopy as a replacement for fluorescence microscopy are currently under evaluation by WHO, aimed at developing policy guidance before the end of 2009.

Mycobacterial Culture

Examination by mycobacteriological culture and identification of *M. tuberculosis* provide the definitive diagnosis of TB, significantly increases the number of cases found (often by 30-50%), and can detect cases earlier (often before they become infectious). Culture also provides the necessary strains for drug susceptibility testing. Culture of specimens is, however, much more costly than microscopy and requires sophisticated laboratory infrastructure and adequate biosafety.

Both solid and liquid culture methods are suitable for central/national reference laboratories (or regional laboratories in large countries). Usually, one culture laboratory is adequate to cover 500,000 - 1 million population.

Solid culture methods are less expensive than liquid culture systems, but results are invariably delayed (up to six or eight weeks) due to the slow growth of mycobacteria. Liquid culture increases the case yield by 10% over solid media, and also reduces the delays in results to days rather than weeks. Liquid systems are, however, more prone to contamination and manipulation of large volumes of infectious material mandates appropriate and adequate biosafety measures.

As recommended by WHO, the adoption of liquid culture systems should take place in the context of a comprehensive and detailed country plan for strengthening TB laboratory capacity, in a phased manner, starting with the national reference laboratory.

Identification of Mycobacteria

In countries with a high burden of TB, the vast majority of mycobacterial isolates will be *M. tuberculosis*. The prevalence of non-tuberculous mycobacteria (NTM) varies from country to country and can be more common in patients infected with the human immunodeficiency virus (HIV). Unless the species is confirmed as *M. tuberculosis*, mycobacterial isolates appearing phenotypically resistant to first-line drugs may represent infection with NTM and not drug-resistant TB. Treatment of NTM is entirely different from treatment of drug-resistant TB. As a minimum, laboratories supporting drug resistant TB programmes should be able to conduct conventional biochemical identification tests or another method that follow international guidelines. Immunochromatographic assays (so-called strip speciation tests) allow rapid discrimination of *M. tuberculosis* complex and NTMs. Both conventional biochemical tests and strip speciation assays are suitable for central/national reference laboratories where culture is performed.

First-line drug susceptibility testing

A number of different techniques are available for DST. Classic phenotypic methods involve culturing of *M. tuberculosis* in the presence of anti-TB drugs to detect inhibition of growth. Phenotypic methods allow the detection of drug resistance regardless of mechanism or molecular basis. Phenotypic DST methods can be performed as direct or indirect tests on solid media. In the direct test, a set of drug-containing and drug-free media is inoculated directly with a concentrated specimen. An indirect test involves inoculation with a pure culture grown from the specimen. Indirect phenotypic tests have been extensively validated and are currently regarded as the gold standard. Three methods are commonly used: proportion, absolute concentration, and resistance ratio.

Several rounds of proficiency testing in the SRL network have shown that DST results do not differ between the three methods for first-line anti-TB drugs.

The accuracy of DST (performed under optimal circumstances) varies with the drug tested. For first-line anti-TB drugs, DST is most accurate for rifampicin and isoniazid and less reliable and reproducible for streptomycin, ethambutol and pyrazinamide (ref). Current WHO policy guidance on first-line DST (ref) is summarized as follows:

- Laboratory capacity to reliably detect MDR-TB through quality-assured DST of isoniazid and rifampicin resistance is a minimum prerequisite for drug-resistant TB programmes;
- Formal links with one of the laboratories in the Supranational Reference Laboratory (SRL) network is preferable to ensure adequate expert input on laboratory design, specimen and process flow, biosafety, maintenance of equipment and external quality assurance of DST results;
- Strategies for laboratory services in support of drug-resistant TB programmes should follow a systematic approach. DST should be focused on those drugs for which reliable and reproducible methodology is available and limited to those drugs available in individual country treatment strategies;

Second-line drug-susceptibility testing

For second-line DST, broth or liquid methods and the proportion method on solid medium have been studied; methods for the absolute concentration or resistance ratio on solid medium have not been validated (ref). Current WHO policy guidance on second-line DST is summarized as follows:

- Routine DST for second-line drugs is not recommended unless the required laboratory infrastructure and capacity has been established, rigorous quality assurance is in place, and sustainable proficiency has been demonstrated. In order to retain proficiency and expertise, it is recommended that second-line DST only

be performed if at least 200 specimens from high-risk patients are expected per year.

- Aminoglycosides, polypeptides, and fluoroquinolones have been tested in different laboratory environments and shown to have relatively good reliability and reproducibility (ref);
- Routine DST for other second-line drugs (ethionamide, prothionamide, cycloserine, terizidone, *P*-aminosalicylic acid, clofazimine, amoxicillin-clavulanate, clarithromycin, linezolid) is not recommended as reliability and reproducibility of laboratory testing cannot be guaranteed.

DST of second-line anti-tuberculosis drugs is still problematic. No studies have systematically evaluated all available DST methods for all available SLDs, established critical concentrations for all available SLDs or evaluated a large number of clinical isolates for microbiological and clinical end-points. Most importantly, the correlation of *in vitro* DST results with clinical outcome has not been established and the prognostic value of *in vitro* resistance to second-line anti-TB drugs is therefore not known. Recent consensus has, nevertheless been reached that DST for the injectable drugs (kanamycin, amikacin, capreomycin) and the fluoroquinolones (ciprofloxacin, ofloxacin) is reliable and reproducible, allowing a quality-assured diagnosis of XDR-TB.

Molecular testing

Conventional methods for mycobacteriological culture and DST require sequential procedures for isolation of mycobacteria from clinical specimens, identification of *Mycobacterium tuberculosis* complex, and *in vitro* testing of strain susceptibility to anti-TB drugs. During this time patients may be inappropriately treated, drug resistant strains may continue to spread, and amplification of resistance may occur. Novel technologies for rapid detection of anti-TB drug resistance have therefore become a priority in TB research and development. Molecular line probe assays (LPAs) focused on rapid detection of rifampicin resistance (alone or in combination with isoniazid) have been endorsed by WHO in 2008, with detailed policy guidance on its introduction at country level.

The adoption of LPAs for rapid detection of MDR-TB does not eliminate the need for conventional culture and DST capability, as currently available LPAs are registered for use only on sputum smear-positive specimens and on *M. tuberculosis* isolates grown from smear-negative specimens by conventional culture methods. Second-generation LPAs to detect XDR-TB is currently under development.

Expanding access to diagnosis of HIV-associated and drug-resistant tuberculosis inevitably require facilities for mycobacterial culture, drug susceptibility testing, and rapid technologies such as molecular line probe assays. Table 4 provides a summary of current WHO diagnostic policies:

WHO laboratory policies

- Automated liquid culture and DST (2007): Use of liquid culture systems in the context of a comprehensive country plan for strengthening TB laboratory capacity; in a phased manner starting at national/central reference laboratory.
- Rapid speciation (2007): Strip speciation for rapid *Mycobacterium tuberculosis* from non-tuberculous mycobacteria; established at regional or central level in combination with liquid culture.
- Line probe assays (2008): Use of line probe assays for rapid detection of R resistance within the context of country plans for MDR-TB management, including development of country-specific screening algorithms and timely access to quality-assured second-line anti-tuberculosis drugs; do not eliminate the need for conventional culture and DST capability; should be phased in, starting at national/central reference laboratory or those with proven molecular capability.
- Second-line drug susceptibility testing (2008): Reliable and reproducible for injectables and fluoroquinolones; to be conducted in national/central reference laboratories using standardised methodology and drug concentrations; routine DST not recommended for ethionamide, prothionamide, cycloserine, terizidone, PAS, thioacetazone, clofazimine, amoxicillin/clavulanat, clarithromycin, linezolid

Available at: <http://www.who.int/tb/dots/laboratory/policy/en/print.html>

The role of non-commercial methods for rapid detection of drug resistant TB

Although commercially available liquid culture systems and molecular line probe assays for rapid detection of MDR-TB have been endorsed by WHO, their complexity and cost, as well as the need for sophisticated laboratory infrastructure, has limited the implementation of these technologies in many resource-constrained settings. Several non-

commercial culture and DST methods have been developed at the same time, aimed for use in laboratories that lack access to more sophisticated infrastructure and techniques. Among these methods, microscopic observation of drug susceptibility (MODS), thin layer agar (TLA), colorimetric redox indicator (CRI) methods, the nitrate reductase assay (NRA) and mycobacteriophage-based assays are most advanced and have shown initial promise as rapid, inexpensive methods. In November 2009, WHO convened an expert group meeting to evaluate the strength of the evidence for implementing these non-commercial technologies based on systemic reviews and meta-analyses of available data.

The recommendations from the expert group were that there was sufficient evidence that in resource-constrained settings and under clearly defined programmatic and operational conditions including appropriate bio-safety that:-

1. MODS and NRA are recommended by WHO as an interim solution for screening of patients suspected of MDR-TB.
2. The use of indirect CRI methods are recommended by WHO as an interim solution for screening of *M. tuberculosis* isolates from patients suspected of having MDR-TB, acknowledging that time to detection of MDR-TB would not be faster with indirect methods (but less expensive) than conventional DST methods using commercial liquid culture.

The expert panel agreed that as yet there insufficient evidence to recommend the use of TLA or phage based assays as rapid tests for screening of patients suspected of having MDR-TB.

As these non-commercial methods currently only detect resistance to rifampicin and/or isoniazid, countries with documented or suspected cases of XDR-TB should establish or expand conventional culture and DST capacity for quality-assured susceptibility testing with second-line drugs, based on current WHO policy guidance.

Testing Algorithms

Depending on the prevalence of TB and HIV in different settings it is necessary to formulate/modify policies and laboratory diagnostic algorithms to facilitate scale-up of TB diagnostics to enable a diagnosis of TB among HIV infected persons and the early detection of MDR- and XDR-TB. The development of appropriate laboratory diagnostic algorithms based on groups at greatest risk of drug-resistant TB makes the most cost-effective use of scarce laboratory and diagnostic resources and reduces the diagnostic delay. Risk categories for drug-resistant TB vary greatly among countries and careful assessment at country level is essential. WHO-endorsed technologies should be used in an algorithm-based diagnostic approach to allow the most reliable and cost-effective use of scarce resources. As mentioned above, algorithms for testing of patients suspected of having drug-resistant tuberculosis are dependent on several factors, most notably the local epidemiological situation, existing country laboratory capacity, the availability of human and financial resources and local treatment policies.

Ideally, all countries should establish laboratory capacity to identify drug-susceptible- and drug-resistant TB, HIV-associated- and extrapulmonary TB. In addition, the concurrent establishment of adequate clinical laboratory capacity (eg. biochemistry, haematology, general microbiology) to monitor treatment and associated co-morbid conditions is highly desirable. In high HIV-burden settings this will require a huge investment in culture capacity, given the absence of current tools to diagnose smear-negative TB. As a minimum, countries embarking on drug-resistant TB programmes should establish laboratory capacity to diagnose MDR-TB and co-morbidities, and monitor bacteriological conversion patients on MDR-TB treatment.

Figures 5a 5b present an algorithm-based approach using WHO-endorsed technologies within the current WHO diagnostic policy framework, taking the limitations of currently available diagnostic modalities into account. These limitations include the need for appropriate bio-safety measures for liquid culture and DST, the need for appropriate identification methods for positive cultures, and the need for adequate molecular testing facilities with good physical separation of different laboratory areas to ensure appropriate contamination control.

Figure 5a. Algorithm for use of conventional culture (solid or liquid) and drug-susceptibility testing

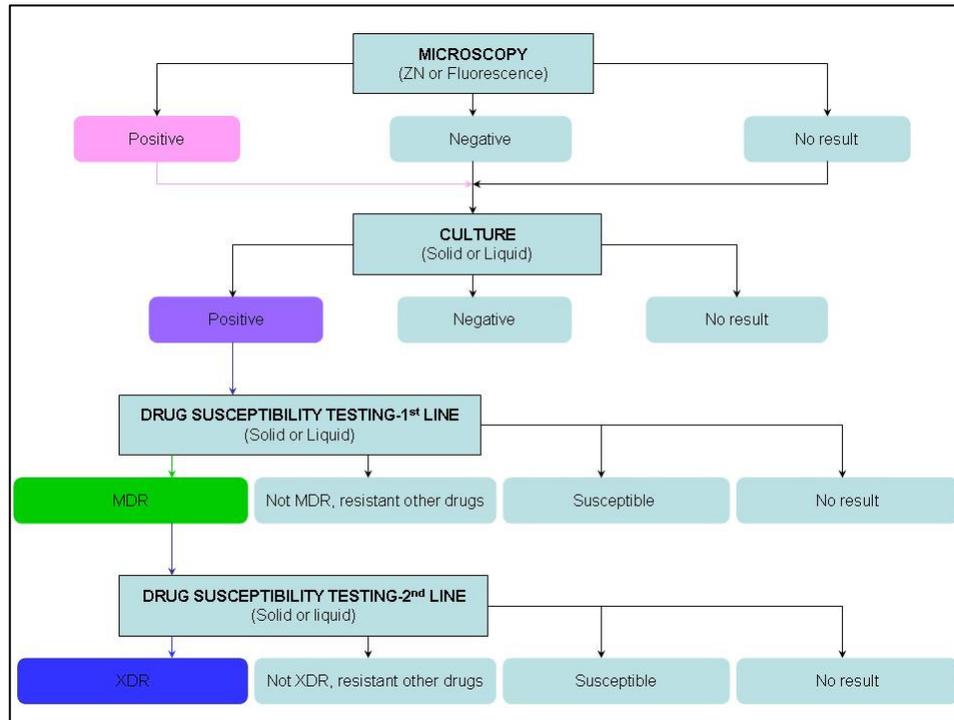
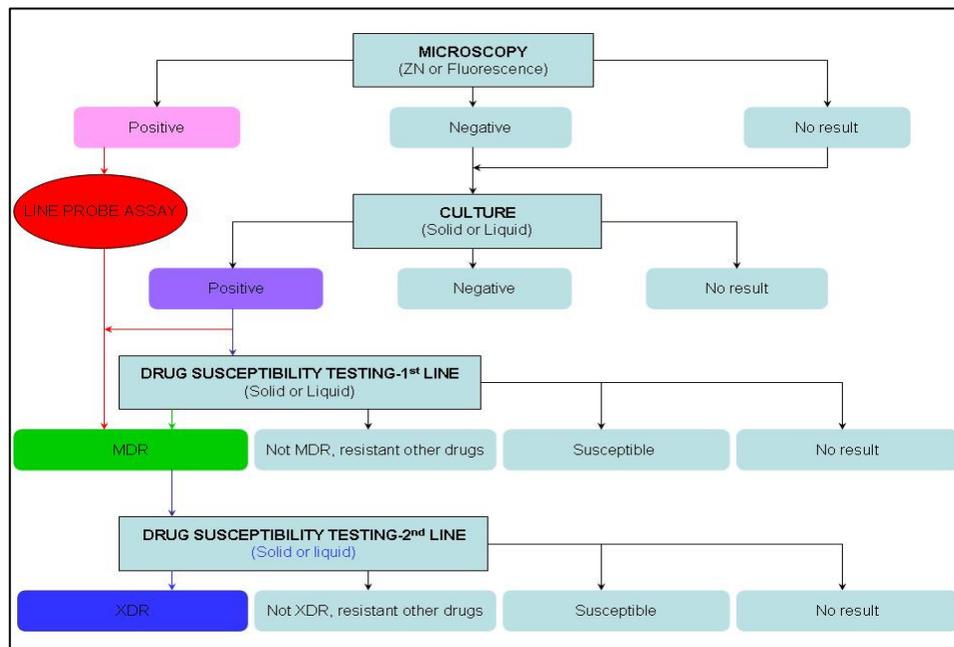
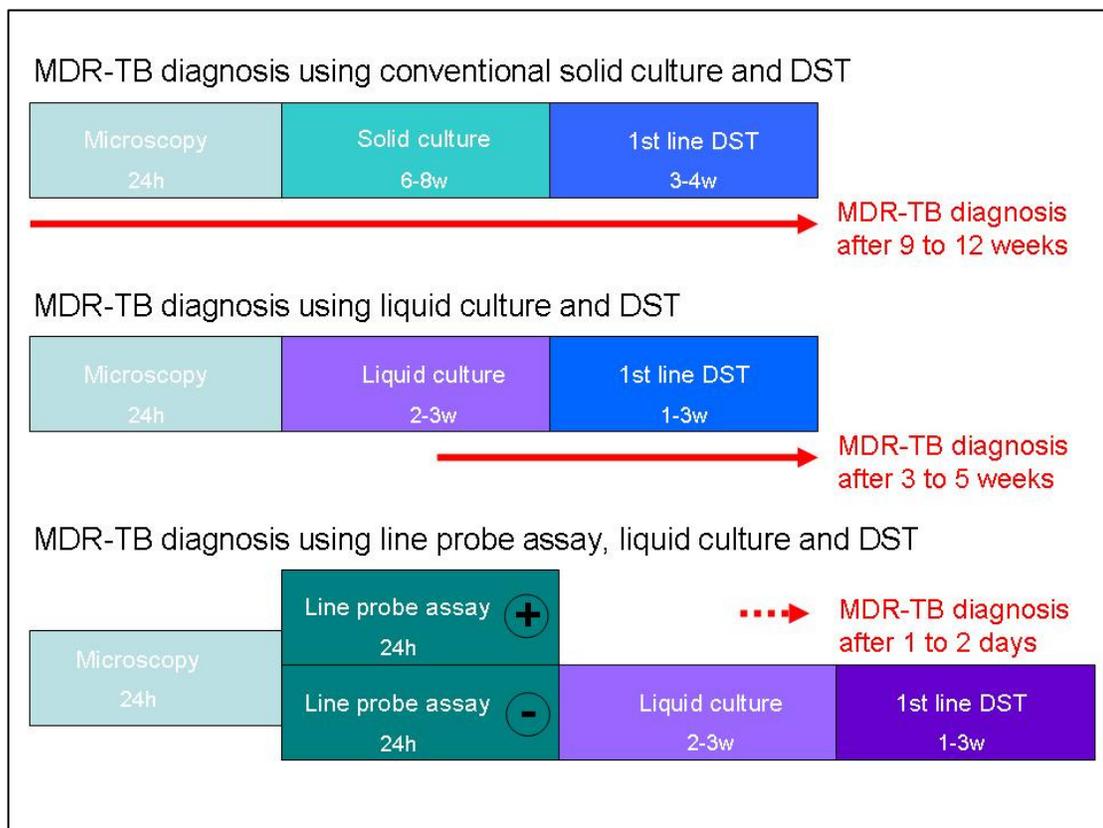


Figure 5b: Algorithm for use of line probe assays in conjunction with conventional culture (solid or liquid) and drug susceptibility testing



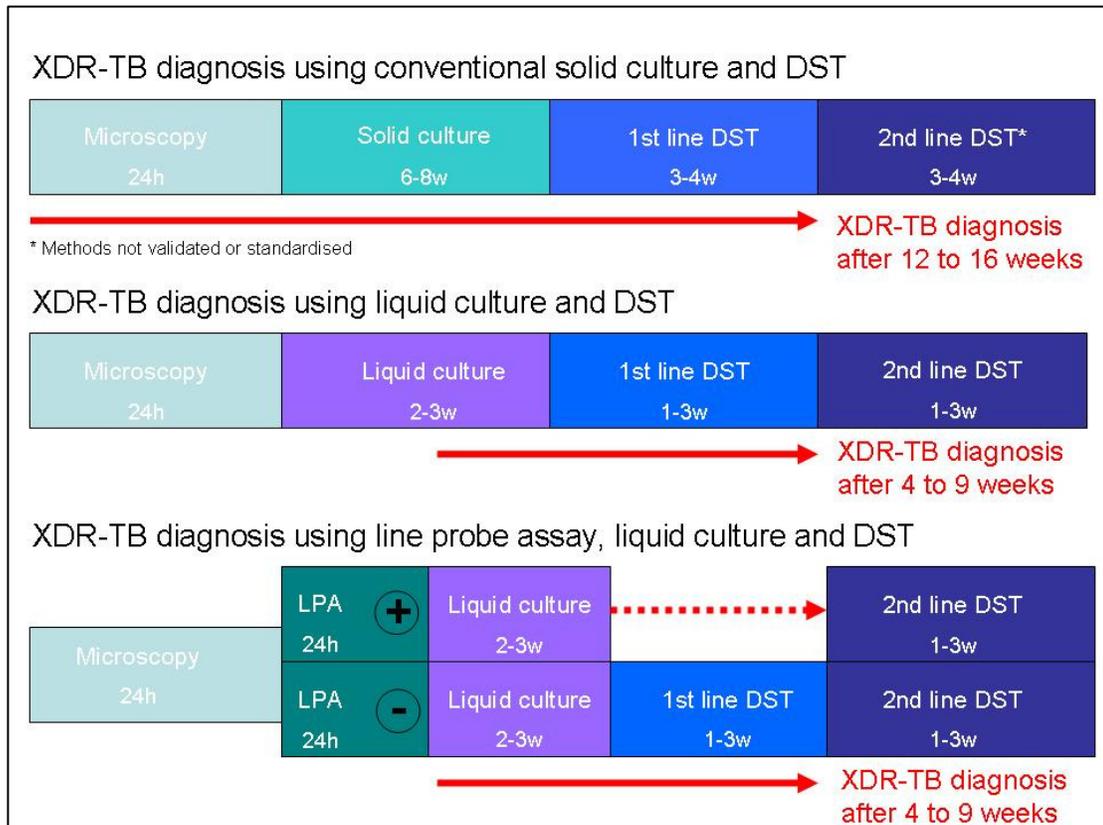
Various permutations of the algorithms are possible depending on the local situation, eg. using microscopy and line probe assays together in high MDR-TB burden, low HIV-prevalence, resource-constrained settings. Decisions regarding appropriate algorithms are highly country-specific and need to be taken by the NTP in close consultation with laboratory experts, taking existing infrastructure and available resources into account. Of particular importance is the need to link diagnostic capacity for drug-resistant TB very closely to treatment access, taking into account the complexities and cost of MDR- and XDR-TB management and the fact that new diagnostics enable a definitive diagnosis of MDR-TB in a few days, as summarized in Figure 6a:

Figure 6a. Expected time to MDR-TB diagnosis using different diagnostic modalities



The diagnosis of XDR-TB is currently dependent on conventional DST as second-generation LPAs are still under evaluation. The expected time to diagnosis of XDR-TB is summarized in Figure 6b:

Figure 6b. Expected time to XDR-TB diagnosis using different diagnostic modalities



Quality Management

Quality management is a systematic process to ensure specific international standards for technical procedures are adhered to and that laboratory services meet specific performance requirements to enable accurate diagnoses. There are specific requirements for TB diagnosis in terms of quality control, quality assurance and proficiency testing which need to be incorporated in national laboratory strategic plans. Procedures for TB microscopy, culture and DST of first-line anti-tuberculosis drugs have been standardized

globally and are well described in the literature, with consensus on methodologies, critical drug concentrations to be tested, and reliability and reproducibility of testing. Implementing a quality management system requires the allocation of adequate resources to the quality assurance processes and oversight and usually requires developing a team of skilled technicians to address quality issues. The quality management issues faced by developing countries are substantial, but there are many groups including the Supranational TB Laboratory Network and expert consultants who are skilled in this area who need to be engaged to analyse existing situations and recommend options for improvement. Laboratory accreditation for laboratory services is mandatory for many developed countries but should become an important goal for developing countries to achieve for all laboratory testing.

Systems Management

Fully functioning laboratory services providing reliable, valid and timely results are required to support the NTP in care and treatment, including the diagnosis of TB infections and monitoring of treatment at each level of care. Uninterrupted availability of laboratory commodities (functioning equipment, stains, reagents and consumables) are mandatory to realize a fully functional TB diagnostic and monitoring service support to the NTP program. Unlike pharmaceutical commodity management, little attention has been given to particular needs of laboratories for a commodity management system. In most cases, the lack of overall laboratory management has resulted in particular problems at facility level. Therefore, it is proposed that NTPs should concentrate on those aspects of equipment and supply chain management that are required to realize a fully functional TB diagnostic and monitoring service. It is important at all times that there is collaboration between laboratory staff and decision makers in the TB commodity management systems.

The role of the national TB laboratory is to set standards, provide quality assurance, reporting mechanisms and evaluate the quality, accuracy and performance of the equipment and supplies.

More specifically the national TB laboratory, in collaboration with the NTP should be responsible for:

- Selection, specification and quantification of equipment and supplies
- Participation in the budgeting and planning process, including taking part in the verification of tender bids and awards of contracts for TB laboratory equipment and supplies.
- Working with local and national procurement committees for purchasing equipment and supplies
- Arranging for training of laboratory managers and staff in equipment and commodity management

ANNEXES

Expanding laboratory capacity - Country examples

The 2009 World Health Assembly Resolution calling for universal access to quality-assured TB diagnostic services highlights the public health function and responsibility for providing diagnostic and curative services for persons suspected of having both drug-susceptible and drug-resistant TB. As a result, significant attention has been drawn to the precarious state of laboratory services in resource-limited settings and the dramatic capacity gap necessary to meet the anticipated targets. Growing experience from the flagship GLI-FIND-GDF EXPAND-TB project with financial support by UNITAID and multiple other donors is illustrating how accelerated laboratory capacity development can be achieved in a best-practice partnership model.

Case Study 1. Achieving national coverage of laboratory services in Peru

Adapted from:

Shin S, Yagui M, Ascencios L, Yale G, Suarez C, Quispe N, Bonilla C, Blaya J, Taylor A, Contreras C, and Cegielski P. Scale-up of Multidrug-Resistant Tuberculosis Laboratory Services, Peru. *Emerg Infect Dis.* 2008; 14: 701-708

SETTING

Over the past 10 years, the Peruvian National Tuberculosis (TB) Program, the National Reference Laboratory (NRL), Socios en Salud, and US partners have worked to strengthen the national TB laboratory network to support treatment of multidrug-resistant TB. The preparation phase involved establishing criteria for drug susceptibility testing (DST), selecting appropriate DST methods, projecting the quantity of DST and culture to ensure adequate supplies, creating biosafe laboratory facilities for DST, training

laboratory personnel on methods, and validating DST methods at the NRL. Implementation involved training providers on DST indications, validating conventional and rapid first-line DST methods at district laboratories, and eliminating additional delays in specimen transport and result reporting. Monitoring included ongoing quality control and quality assurance procedures. Hurdles included logistics, coordinating with policy, competing interests, changing personnel, communications, and evaluation. Operational research guided laboratory scale-up and identified barriers to effective capacity building.

From 1996 through 2005 in Peru, a consortium of institutions implemented one of the most comprehensive national MDR TB treatment programs in the world. One component of this effort was the Laboratory Improvement Project, which was charged with scaling-up laboratory services to support MDR TB treatment. Many lessons were learned in expanding laboratory access to quality TB culture and drug susceptibility testing (DST).

BACKGROUND

TB incidence in Peru is among the highest in Latin America, at 108.2/100,000 persons in 2005. In the densely populated periphery of Lima, where half of all national cases are detected, the risk for infection with *Mycobacterium tuberculosis* may be among the highest recently documented. Rates of MDR TB are also high, with a national prevalence of 3% among patients never treated for TB and 12.3% among previously treated patients. During 1990–2000, Peru implemented a model program based on the World Health Organization (WHO)–endorsed strategy of directly observed treatment, short course (DOTS). Despite massive use of sputum smear microscopy and standardized first-line treatment resulted in effective case detection and cure, there was overall decrease in TB incidence by the end of the decade. During that period, however, the rates of MDR TB increased.

Because DOTS alone was insufficient to control ongoing transmission of drug-resistant strains, Partners in Health (PIH), Harvard University, Massachusetts State Laboratory

Institute (MSLI), Socios en Salud, the Peruvian National Tuberculosis Control Program (NTP), and the Peruvian National Institute of Health (INS) initiated a collaborative MDR TB treatment effort in 1996. Principles included individualized MDR TB treatment and monthly culture to monitor treatment response. Community health promoters provided direct observation of all doses given outside health clinic hours. In 1997, the NTP implemented a standardized MDR TB treatment regimen, which achieved cure rates <50%. Although protocols changed over time, treatment failures, defaulters, and relapses after first-line treatment were generally referred for standardized MDR TB therapy. Those patients whose standardized treatments failed were, in turn, referred for individualized treatment.

When this project began only one level III laboratory, the National TB Reference Laboratory, performed DST on first-line drugs; 57 level II laboratories performed mycobacterial culture, and \approx 1,000 level I laboratories had smear microscopy capacity. Because DST on second-line drugs was not available in Peru, isolates were initially sent to the MSLI until local capacity could be established.

As the MDR TB treatment program expanded in absolute numbers and geographic coverage, so too did demand for laboratory services. From 1996 through 2000, the number of mycobacterial cultures and DSTs performed yearly more than doubled. The process of program scale-up posed additional challenges in patient management, information systems, drug procurement, and regional implementation. Responding to these needs, the Bill & Melinda Gates Foundation awarded a grant for \$45 million in 2000 to establish a consortium called PARTNERS, whose principal task was to achieve national coverage of MDR TB treatment in Peru and replicate this project elsewhere. Several key institutions were added to the initial group of collaborators: WHO, the Centers for Diseases Control and Prevention (CDC), and the Task Force for Child Survival and Development. Within the PARTNERS consortium, the Laboratory Improvement Project was established with specialists from MSLI, CDC, Harvard University, PIH, and INS.

STRATEGY TO SCALE-UP LABORATORY SERVICES

NTP norms for DST indications have evolved over the past 10 years. This heterogeneous and dynamic process provided lessons on matching the choice of DST to programmatic strategies. Salient aspects guiding laboratory strategies include the choice of standardized versus individualized treatment, criteria for performing DST, rates of HIV and resistance to second-line drugs, and empiric management while awaiting results.

On the basis of projected numbers, DST needs would not be met unless DST on first-line drugs was decentralized to regional laboratories in areas with high rates of TB and MDR TB. In choosing methods for decentralized DST, the INS matched method features with available resources in regional laboratories. The need for a rapid DST method was clear. Given that it took an average of almost 5 months to obtain results from a conventional DST performed in Peru, physicians often had to make treatment decisions empirically. Once results did arrive, they were no longer accurate because patients had been exposed to additional drugs in the interim, to which amplified resistance could have occurred. Rapid DST implemented at the decentralized level would be the most effective way of providing timely results and decompressing the central bottleneck of DST demand.

The INS decided that rapid DST should serve as an initial screening test. By quickly identifying resistance to isoniazid and rifampin, isolates with drug resistance could be sent to INS for full DST while standardized MDR TB treatment was started. With input from MSLI, the INS chose the Griess method. This method is a rapid colorimetric method that uses Lowenstein-Jensen (LJ) medium prepared with antimicrobial drugs. Attributes of the Griess method are accuracy, fast turnaround time (21 days), minimal additional equipment needs, inexpensive materials and reagents, and reproducibility in laboratories proficient in mycobacterial culture.

On the basis of this rationale, the following plan was developed. Second-line DST (agar plate proportions method) would be implemented in the INS. Conventional first-line DST (proportions method, indirect variation by LJ medium) would be performed at regional laboratories. Direct Griess method would be performed at regional laboratories; and the indirect BACTEC-460 system (Becton Dickinson, Franklin Lakes, NJ, USA) for first-line

drugs would be implemented at INS for high-risk patients, including healthcare workers, HIV-positive patients, and pediatric patients.

Another priority was reducing the overall turnaround time of laboratory data, defined as the time when the patient is first identified at risk for MDR TB to the time that this determination has an effect on patient care. These delays included specimen transport, specimen processing, dissemination of results to the health center, and scheduling of clinical evaluation once results were obtained. The overall strategy for laboratory scale-up comprised the following activities:

1. Establish clear criteria for performing DST.
2. Select DST methods for use within the TB program and indications for each method.
3. Decentralize first-line DST to regional laboratories.
4. Project the quantity of DST and cultures and ensure adequate supplies.
5. Create biosafe laboratory facilities for DST.
6. Train laboratory personnel on new methods.
7. Train healthcare providers and level I laboratory personnel on DST indications.
8. Validate DST methods, first in the central level and then at each implementing site.
9. Establish and enact quality control and quality assurance protocols.
10. Eliminate additional delays in specimen transport and result reporting.

These strategies were used and modified in 3 phases of scale-up: preparation, implementation, and monitoring.

Preparation Phase

Key elements of the preparation phase were mobilizing political commitment (i.e., agreeing upon the strategic plan, obtaining adequate financial and human resources, and formalizing collaborations and the respective roles of different, competing and cooperating, institutions); establishing adequate laboratory infrastructure; and forming a

skilled workforce. A needs assessment performed early in the project identified the need for documented biologic safety cabinet (BSC) certification and maintenance and repair of BSCs throughout the TB laboratory network. Because Peru had no trained personnel who could certify BSCs, a training program was developed and delivered with the help of MSLI and the Eagleson Institute in Sanford, Maine. The trained certifiers then certified and repaired BSCs for the TB laboratory network.

To proceed with decentralization efforts, INS contacted directors of regional laboratories. Experts were identified with interest and competence in designing TB health facilities and encouraged collaboration by team, with technical assistance from an engineer experienced in TB infection control at CDC. Once elaborated, the proposals then required approval by the governmental institution responsible for approving renovations and construction of public health facilities. Construction for both projects was delayed by an average of 6 months because of these administrative requirements. District and laboratory leaders played an important role by making frequent inquiries into the status of the approval process. In the meantime, necessary equipment, materials, and supplies were purchased.

Another step to expand DST capacity was the training and validation process for each DST method. MSLI trained INS in DST to second-line drugs by the agar plate proportion method; validation was completed in 2005. Concomitantly, INS trained regional laboratory personnel in DST of first-line line drugs, by the LJ medium proportions method. To initiate rapid DST, the Griess method was validated first at INS; then personnel from each implementing laboratory were trained in the method. Both conventional DST and rapid DST were validated at the regional laboratories. Samples were collected under program conditions. DST was performed by trained personnel in the regional laboratories. These same strains were then sent to INS for validation. Finally, INS leaders developed standard operating procedures, including protocols for all laboratory methods, biosafety and equipment standards, and quality assurance and quality control procedures.

Other activities during the preparation stage were aimed at reducing turnaround time. An electronic laboratory information system connecting INS, regional laboratories, and health centers to provide health personnel (physicians, nurses, and laboratory technicians) with real-time access to culture and DST results was developed and piloted. Two automobiles were purchased to aid in specimen transport. At the administrative level, NTP increased the frequency of MDR TB treatment–approval meetings to reduce the bottleneck of cases pending approval for initiation of MDR TB treatment.

Implementation Phase

After successful completion of validation procedures in regional laboratories, DST was incorporated into programmatic services. Aggregate data on DST results were reviewed by each laboratory on a monthly basis to monitor rates of contamination, culture growth, and drug resistance. INS supervisors made frequent visits to these laboratories to monitor performance and troubleshoot any challenges. For instance, when low rates of culture growth were observed among acid-fast bacilli smear-positive samples, smear microscopy slides from these samples were reviewed by a biologist and decontamination protocols were reviewed. During this period, healthcare personnel were simultaneously trained in workshops and one-on-one interactions. Laboratory and TB program directors led workshops to review programmatic norms for soliciting each DST method and to explain the performance and characteristics of each method. Health workers were also trained to use the laboratory information system. Regional administrators trained providers in patient confidentiality and established a plan for sustained Internet access and computer maintenance after the pilot phase of the information system.

Monitoring Phase

Sustainable laboratory infrastructure depends on administrative commitment and monitoring laboratory performance quality. Throughout the entire planning and implementation stages, MSLI provided training to INS and regional laboratories in basic and method-specific quality control/quality assurance.

TB management protocols, such as DST indications and optimal DST methods, are dynamic; they must respond to changes in regional epidemiology as well as the availability of resources. For example, decentralization of DST resulted in an increased demand for DST because of increased awareness of MDR TB and availability of testing. Additionally, health professionals and patients perceived the benefit of rapid, real-time laboratory data. This increase in demand is an example of how our ongoing monitoring and evaluation could be applied to reassess the use and capacity of laboratory services. Preliminary data of adherence to NTP indications for DST and rates of MDR TB among risk groups have helped inform modifications of NTP policy. The experience thus far in matching the appropriate DST methods to NTP norms should enable a rational application and operational assessment of promising new DST methods. Without adequately quantifying and responding to an increase in DST demand, laboratory operations may become bottlenecked, and excessive demand on limited personnel could result in deviations from laboratory protocols and a decrease in laboratory performance.

LESSONS LEARNED

TB programs faced with incorporating MDR TB treatment must often expand laboratory infrastructure far beyond existing capacity. Although laboratory improvement efforts in Peru have taken a decade to accomplish and are still evolving, several key lessons can be distilled from our experience.

Responding in Time and Stepwise, Overlapping Efforts to Prevent Delays

The introduction and decentralization of DST and culture capacity can involve a wide range of activities, ranging from obtaining permits from national authorities to purchasing automobiles to streamline specimen transport. Attention to detail, the dedication of human resources to push these activities along, and parallel planning and coordination of activities can receive inadequate priority among program planners.

Coordination of National Reference Laboratory and National TB Programs

Political commitment must include stable leadership; a strong central, coordinating unit; and a working relationship between TB laboratories and a TB program. The importance of coordinating laboratory and programmatic efforts may seem obvious but cannot be overstated. Within the DOTS model, smear microscopy can be performed at health centers with local coordination with TB services. In contrast, MDR TB treatment requires more complex methods (culture, DST) and is usually performed and overseen at a central site. Strategies must be informed by NTP policy and vice versa. Coordination must persist because the needs of a TB program will likely change over time.

Importance of Operational Research

The experience in Peru was informed by operational research. The profile of a DST method and its characteristics, when first validated in a local laboratory, may be different from its performance, strengths, and weakness when it is operating under actual program conditions. Operational assessment of a laboratory method or strategy is the sole means of understanding its effectiveness when considered within the larger context of how the method is used, associated complexities or challenges in its implementation, the mitigation of its effect caused by other system delays, and other factors. If tools to monitor laboratory performance are incorporated into information and reporting systems at the outset, effective operational research can be conducted with minimal additional resources, coupled with ongoing feedback, to create a sustainable laboratory system.

Case Study 2. Experience establishing TB Laboratory Capacity in a Developing Country Setting - Lesotho

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Setting

Lesotho, a small, landlocked, country with limited natural resources and a population of approximately 2 million people, is affected by both the HIV and TB epidemics, with an estimated HIV prevalence of 25% among adults aged 15-49 and a case notification rate of 605 TB cases per 100,000 population^{i,ii}. As of 2006, however, TB diagnostic capacity within the National TB Programme (NTP) was limited to smear microscopy, which was performed in 17 microscopy centers without an adequate QA program. All clinical specimens from MDR TB suspects requiring culture and DST had to be sent out of the country, at high cost, to laboratories in either South Africa or the U.S. In October 2006, the Ministry of Health (MoH) of Lesotho requested assistance, through the WHO, for strengthening TB diagnostic services.

Establishment of TB culture and DST capacity and EQA for smear microscopy

In response a team from FIND made a laboratory assessment visit of the National TB Reference Laboratory (NTRL) located at Queen Elizabeth II Hospital in Maseru, the capital of Lesotho, in November 2006. The team found that significant renovation of the laboratory was needed, essential equipment for DST was missing, and that a QA program for smear microscopy was only partially implemented. It was evident that resolving these issues could best be accomplished in partnership with other agencies in order to upgrade

laboratory capacity at minimal cost. Several partners were rapidly identified, principally Partners In Health, which was in the process of establishing a treatment program for MDR-TB in Lesotho and the WHO. FIND provided a full-time, on-site consultant and procurement of an instrument for automated TB liquid culture and DST, in addition to a continuous supply of reagents. A multi-phase work-plan was drawn up for correcting the deficiencies.

In the first phase, which covered the period May to August 2007, the NTP, Lesotho, and other stakeholders collaborated to develop training modules and accompanying manuals to bring the performance of sputum microscopy up to quality standards. Laboratory personnel were given refresher training in smear microscopy. A QA program was put in place for smear microscopy, consisting of onsite evaluation and supervision and random blinded rechecking of slides following standard guidelines.ⁱⁱⁱ At first, this consisted of re-examination of 15% of all slides. Based on the data from this exercise and follow-up trainings as needed, Lot Quality Assurance Sampling (LQAS) was put in place for external (E) QA of smear microscopy across all centers starting September 2008. The EQA included on-site evaluation and random blinded rechecking every month to all sites except two sites where it was done less frequently for logistical reasons. Panel testing is being carried out periodically with slides obtained from the Supranational TB Reference Laboratory (SNRL) in Pretoria, South Africa.

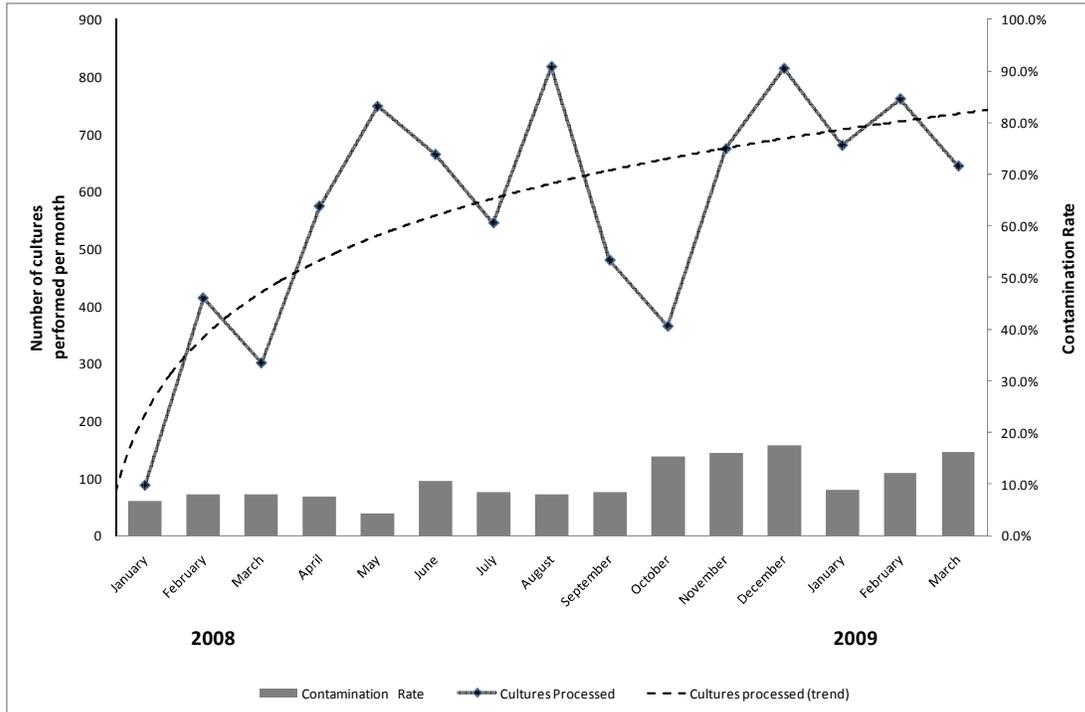
In parallel, the NTRL was renovated; with the creation of a BSL3 facility that would meet the WHO recommended requirements for handling liquid TB culture^{iv}. TB solid culture and DST were implemented, with EQA provided by the SNRL, South Africa.

With this basis for the activities in the first phase, TB liquid culture and DST, along with rapid immunoassay-based species identification, were introduced in the second phase. Isolation and contamination rates for solid culture on Lowenstein Jensen media and TB liquid culture using the BACTEC™ MGIT 960™ TB System were available by December 2007.

In the third phase, activities to prepare for the introduction of the LPA for detection of MDR-TB began with the construction of a clean-room facility during July and August 2008. The introduction of the assay and training of laboratory staff took place in October 2008.

Between January 2008 and March 2009, 8,569 specimens were processed for culture including the use of both LJ and MGIT, with an overall contamination rate of 10.8%. Considering all smear-positive cases, 87% of the samples were culture-positive. The smear-positive, culture-negative rate calculated as smear-positive/culture-negative divided by total number of cultures was low 104 (1.6%), and most of these samples were from follow-up cases. However, the rate of smear-negative, culture-positive results calculated as smear-negative/culture positive divided by total culture-positives was high: 538 (49.9%) which is not surprising considering the alarmingly high rate of HIV positivity among TB patients.

Fig: Number of cultures processed and contamination rates



After validation and retraining, line probe assay has started to be used on a routine basis in addition to liquid culture for MDR-TB suspects

The investment required to achieve this dramatic turnaround of the TB diagnostic services in Lesotho was less than US\$550,000 including: Laboratory infrastructure upgrade - US\$93,000; TB diagnostic instruments excluding the ones which were available but unused – US\$65,000; Reagents and consumables for one year – US\$280,000; human resources during the project - \$90,000.

Although the whole process of upgrading TB laboratory diagnostic services in Lesotho as described above was accomplished within a relatively short time period, there were challenges along the way which resulted in lessons learned.

First, it was necessary to secure political will and commitment, with full buy-in to the process at the highest levels of the Ministry of Health as well as by the National TB Programme, WHO, and other partners already working in the country. Secondly, ensuring the reliable supply of reagents and consumables was at times challenging, and required constant vigilance to ensure timely customs clearance and sufficient lead time in ordering. The very success of the lab quickly led to high expectations and increased demand on the lab for diagnostic testing, stretching the limits of the original facility and lab personnel. The high profile of the project also resulted in frequent partner visits, and requests for hand-on, on-site training for technicians from other African countries, which at times was stressful for the staff who were busy with trying to keep up with the workload, and who missed out on some training opportunities. This made it challenging to maintain contamination rates within acceptable limits.

To conclude, through strong political commitment and collaboration, it is possible to rapidly establish quality assured TB diagnostic capacity, including current methods, in a resource-limited setting. Case detection and management for TB and MDR TB has been greatly enhanced. From a low baseline, TB culture throughput in the lab increased by 10-fold and has been sustained. This experience has served as a catalyst to translate policy into practice with new diagnostic technologies. It supports global policy setting to enhance and modernize laboratory work in developing countries.

Resource List

Biosafety

World Health Organization. Laboratory. Biosafety Manual Third Edition. Geneva, WHO 2004. Available at:
<http://www.who.int/csr/resources/publications/biosafety/en/Biosafety7.pdf>

Financial resources

World Health Organization. Laboratory services in tuberculosis control, Part 1: Organization and management. WHO 1998. Available at:
[http://whqlibdoc.who.int/hq/1998/WHO_TB_98.258_\(part1\).pdf](http://whqlibdoc.who.int/hq/1998/WHO_TB_98.258_(part1).pdf)

World Health Organization. Planning and budgeting for TB control activities. Version 3, Available at:
http://www.who.int/tb/dots/planning_budgeting_tool/download/en/index.html

World Health Organization Global Tuberculosis Control: Surveillance, Planning, Financing: WHO Report 2009. (World Health Organization: Geneva, Switzerland,). Available at: http://www.who.int/tb/publications/global_report/2009/pdf/full_report.pdf

Available technologies endorsed by WHO

World Health Organization. Molecular Line Probe Assay for rapid screening of patients at risk of MDR-TB. Policy Statement. Geneva, WHO, 2008, available at
http://www.who.int/tb/features_archive/policy_statement.pdf

World Health Organization. The use of liquid medium for culture and drug susceptibility testing (DST). Policy Statement. Geneva, WHO, 2007. available at
<http://www.who.int/tb/dots/laboratory/policy/en/index3.html>

Stop TB Partnership Retooling Task Force 2008. New laboratory diagnostic tools for tuberculosis control. Available at: <http://apps.who.int/tdr/svc/publications/non-tdr-publications/diagnostic-tool-tb>

Quality management

WHO Regional Office for Africa and United States Centers for Disease Control and Prevention, Atlanta. *Guidance for Development of National Laboratory Strategic Plans*. WHO-AFRO and CDC-US, 2009. Available at:
http://www.who.int/hiv/amds/amds_guide_dev_nat_lab_strat.pdf

Association of Public Health Laboratories. External Quality Assessment for AFB smear microscopy. Washington; 2002. Available at http://wwwn.cdc.gov/dls/ILA/documents/eqa_afb.pdf

Reagents and consumables

Tools available from GLI (<http://www.who.int/tb/dots/laboratory/gli/en/>) include:

- a recommended format for reporting of performance and stock situation at a microscopy laboratory (intended for a push supply system)
- databases of items that may be needed by various types of laboratories, with their specifications and rough indication of cost; these need to be customised for the country
- an EXCEL workbook for automated calculation of the needs for AFB-microscopy (for one or any number of laboratories, any level), based on few basic input data (including the numbers of smears examined over a recent period; can be replaced by an estimate based on detection of smear-positive cases). It can be used both for ordering supplies as well as estimating the needs at the lower level to be supplied. For procurement, a cost estimate can be obtained also, provided data on current prices are part of the basic input at set-up.
- a second EXCEL workbook for use by culture, DST and molecular laboratories. This has the same initial input requirements and functions as the one above for the microscopy network, but it also includes a more extensive part for correct stock keeping. The latter is even more essential for this type of laboratory, in view of the large variety of items needed and the greater difficulty to estimate needs correctly, except based on past consumption.
- Other tools, such as a microscopy supplies request and calculation form can be found in standard texts, i.e. the IUATLD microscopy guide.

Data management

Tools available from GLI (<http://www.who.int/tb/dots/laboratory/gli/en/>) include:

- recommended request forms: AFB-microscopy; culture and DST (paper formats)
- recommended formats for manual recording in TB labs (smear microscopy, bench culture and DST registers)
- only for culture and DST: an electronic database meant to receive the essential data from the request form on one hand and the bench registers on the other hand, in Epidata software which is easily country customised by users familiar with this software or with Epi Info
- recommended paper formats for reporting of various tests and by various levels: AFB-microscopy (for one lab, including stock situation, or for an administrative division, without stock situation); culture and DST

- electronic tools for internal monitoring and reporting, only regarding culture and DST. These are largely automated and combine EXCEL workbooks and report formats with the previously mentioned electronic database
 - paper formats for recording and reporting of microscopy EQA rechecking, besides an electronic EXCEL workbook for entry and automatic analysis of EQA data, simple enough to be used at intermediate level, with transmission of the complete electronic data to national level.
-