CHECKLIST OF KEY ACTIONS FOR THE USE OF

LIQUID MEDIA FOR CULTURE AND DRUG SUSCEPTIBILITY TESTING (DST)

Rationale for liquid culture systems

Laboratory diagnosis of tuberculosis (TB) relies on the direct microscopic examination of sputum specimens. Although sputum smear microscopy is specific, it has low and variable sensitivity and cannot identify drug-resistant strains. Mycobacterial culture is more sensitive, but growth of TB bacilli on traditional solid medium requires four to eight weeks, which delays appropriate treatment in the absence of a confirmed diagnosis. Laboratories also need to use a rapid and affordable method of species identification to differentiate isolates between *M. tuberculosis* complex and nontuberculous mycobacteria.

Expanding culture capacity is urgently needed to address challenges due to the epidemics of HIV-associated TB and drug-resistant TB, especially in resource-limited settings. Liquid culture systems are the standard of care for TB diagnosis and patient management in industrialized countries. Liquid systems are more sensitive for detecting mycobacteria and may increase the case yield by 10% over solid media, and also reduce the delays in results to days rather than weeks. For drug susceptibility testing (DST), the delay may be reduced to as little as 10 days, compared to 28–42 days with conventional solid media. With increased sensitivity and reduced delays, liquid systems may contribute significantly to improve patient management.

Liquid systems, however, are more prone to contamination by other micro-organisms. In experienced laboratories, approximately 5–10% of specimens cannot yield results because of contamination. Laboratories must strictly follow procedures to prevent cross-contamination (due to carryover of bacilli from positive to negative specimens), especially in high-incidence countries where laboratories process many positive specimens. In addition, laboratory staff should process specimens and perform culture inoculation in biological safety cabinets that have an uninterrupted power supply system to minimize their risk of exposure to possibly harmful aerosols.

WHO recommendation on the use of liquid culture and DST systems

The Stop TB Partnership Laboratory Strengthening Subgroup, partner organizations, laboratory experts, and the World Health Organization (WHO) Strategic and Technical Advisory Group for Tuberculosis have endorsed the WHO recommendation to use liquid culture and rapid species identification to address the needs for culture and DST. This should be based on a country-specific comprehensive plan for laboratory capacity strengthening, and implemented as a step-wise approach[1].

[1] World Health Organization. New WHO Policies: Use of Liquid TB culture and drug susceptibility testing (DST) in low- and medium-income settings. [http://www.who.int/tb/dots/laboratory/policy/en/print.html]

Preparing for country adoption, introduction, and implementation of liquid culture systems

Timely and effective adoption, introduction, and implementation of liquid culture systems by national TB programs require significant stakeholder engagement, preparation, and communication[2]

At country level, the adoption of liquid culture systems is a multi-sector process leading to an explicit policy decision to access and use this technology. The policy decision follows an analysis of its benefits, risks, and costs and the health system's capacity to finance, manage, and ensure its sustainable access and appropriate use. Ministries of health should decide on the adoption of liquid culture systems in the context of a comprehensive and detailed country plan for strengthening TB laboratory capacity; moreover, they must communicate the policy decision before introducing and implementing the technology.

Introducing liquid culture and DST systems requires countries to carry out *coordinated activities* to prepare for effective and sustainable access to this diagnostic technology. Such global and/or country activities include ensuring appropriate regulation and registration; preparing phase-in plans for equipment and supplies procurement and logistics management; revising guidelines, tools, and training materials; mobilizing financial resources; initiating staff training; and carrying out advocacy, communication, and social mobilization strategies. Country plans for expanding TB culture and DST should be based on a strong network of quality-assured microscopy, which is the cornerstone for TB diagnosis. Laboratories should have demonstrated experience in cultures and DST using conventional methods. Countries should implement liquid systems in a phased manner, starting with the national reference laboratory, and integrate them into a country-specific comprehensive plan for laboratory capacity strengthening that addresses the following key issues, at minimum:

1. Appropriate biosafety level
2. Detailed customer plan describing guarantees and commitments of the manufacturer
3. Appropriate training of staff
4. Maintenance of infrastructure and equipment in laboratories
5. Quick transportation of samples from the peripheral to the culture laboratory
6. Rapid communication of results

The implementation process encompasses the steps needed to operationalize the liquid culture and DST policy, including a system to monitor and evaluate the progress of these activities and their impact on tuberculosis control.

The checklist

The Stop TB Partnership Task Force on Retooling has prepared the following checklist of key actions to facilitate global and country stakeholder planning for timely assessment, adoption, introduction, and implementation of the WHO recommendation, as appropriate. The guide illustrates actions that may be adapted to each country's situation.

To download the electronic version of this document: www.stoptb.org/retooling

[2] New Technologies for TB Control: A Framework for their Adoption, Introduction and Implementation. Geneva, World Health Organization 2006 (WHO/HTM/STB/2007.40).

❒ NEW POLICY DEVELOPMENT AND GLOBAL ADOPTION

ISSUES	KEY ACTIONS	TECHNICAL/ OPERATIONAL LEAD	ESTIMATED TIMELINE
Global policy development	Promote policy on the use of Liquid Culture media for TB diagnosis	WHO	
	Develop initial global forecasts for Liquid Culture and DST systems	WHO	
	Develop, endorse and communicate the new recommendations and guidelines/standards, covering: • Laboratory Assessment tools • Staffing and training levels • Infrastructure and equipment • Biosafety and contamination aspects • Generic SOPs manual • Supervisory guidelines and checklists • Information storage and recording • QA guidelines (both external and internal programmes) covering o Proficiency testing o Rechecking o Supervision o Internal QC and quality improvement	WHO	
Manufacturing and supply	Initiate large scale production of equipment and consumables	Manufacturer	
	Ensure that manufacturers build capacity of suppliers and local distributors for after sales services at the country or regional level	Sponsoring Agency, Manufacturer	
	Assist countries to review manufacturer service contract including customer support plan and equipment maintenance plan	Sponsoring Agency, WHO	
	Negotiate preferential pricing of equipment and consumables with manufacturer	NTP/NRL, Sponsoring Agency	
Financing	Assist countries to identify potential sources of funding; provide technical assistance to capacitate countries to develop proposals	WHO, Partner Organizations	
	Compute illustrative introduction costs for Liquid Culture and DST systems at various levels of health system (national, district laboratories)	NTP/NRL, Sponsoring Agency	
Monitoring and Evaluation	Develop well defined performance indicators to measure success of Liquid Culture and DST systems implementation, validation and maintenance. Determine approaches to assist countries to review Liquid Culture and DST systems performance monitoring and impact on TB programming.	WHO, NTP/NRL, Partner Organizations	

❒ COUNTRY POLICY DEVELOPMENT

ISSUES	KEY ACTIONS	TECHNICAL/ OPERATIONAL LEAD	ESTIMATED TIMELINE
Country policy development	Establish National Laboratory Committee consisting of NRL, NTP manager, NTP lab focal points and technical partners	NRL, NTP	
	Develop general strategy for TB case detection and identify how liquid-culture-DST fits (eg. Indications, culture/DST, level of health system) and ensure that the laboratory improvement plans are in conjunction with NTP strategic plan	NTP, NRL	
	Determine the full costs of adopting and introducing the Liquid Culture and DST systems (automated and manual)	NRL, NTP	
	Inform policy makers and key stakeholders of ongoing discussions at global level and progress regarding plans to introduce and implement Liquid Culture and DST systems	NTP, NRL	
	Assemble and analyze available information on the risks and benefits of Liquid Culture and DST systems; determine the relevance to the country, and appraise the options (e.g. automated versus manual system), including the benefits/risks of maintaining the status quo.	NRL, NTP	
	Review national regulations and policies to identify potential barriers to implementation and need for reinforcement of regulatory framework and oversight	NRL, NTP	
	Analyze the capacity of health care system to appropriately manage and use the Liquid Culture and DST systems; key considerations may include: • Alignment with national laboratory strengthening and expansion plan • Laboratory infrastructure requirements, including those associated with biosafety criteria (addressing those appropriate for the different levels of the laboratory system, i.e. reference/district level) • Accreditation of laboratory based on standards such as quality assurance/proficiency testing as an important precondition before laboratory provides services to patients • Role of private laboratories and mechanism of collaboration • Quality Assurance requirements, including those for internal and external QA, and supervision • Human resource and training requirements • After-market support needs, including consumables, equipment maintenance • Requirements for recording and communicating information • Ensuring good management of equipment and supplies and minimizing inappropriate use	NRL, NTP	
	Identify opportunities to leverage funding for the liquid culture-DST system and to introduce other TB programme or health system strengthening activities to minimize transition costs, including the possible advantages of cross-platform technology which could improve diagnostic capacity for other diseases	NRL, NTP	

❒ COUNTRY IMPLEMENTATION

ISSUES	KEY ACTIONS	TECHNICAL/ OPERATIONAL LEAD	ESTIMATED TIMELINE
Registration	Register the Liquid media system for Culture and DST	NTP, NRL, MANUFACTURER	
Planning	Make key decisions on: • The level of the health care system (e.g. reference/district lab) and/or sector (e.g. public and private) where the Liquid Culture and DST system will be available • Category of patients that will benefit from the rapid culture and DST method • Determine laboratory technician's acceptability of Liquid Culture and DST system through pilot phase • Method of introduction of the Liquid Culture and DST system – phasing in or introduction through a multiple site rollout • How to complement use of existing solid media technique • Criteria for a facility to start using the Liquid Culture and DST system (automated versus manual)	NTP, NRL	
	Determine the first possible arrival date for the Liquid Culture and DST system; develop roll out or phase in plan	NRL	
	Determine specimen collection, contamination aspects, storage, and transportation	NRL	
Financing	Develop multi-year budget for: • Laboratory infrastructure (e.g. physical space, biosafety, UPS, air-conditioning, etc) • Equipment purchase • Equipment maintenance and operating costs • Consumable(specimen containers/slides, culture media, reagents, etc.) supply and re-supply, including buffer stocks and stock to fill the pipeline; including costs for transport, insurance, QA testing and clearing • Recruitment and training of new personnel • Supervision and monitoring costs • Quality Assurance related costs (both internal and external QA) • Recurrent training costs to maintain proficiency in performance		
	Map out potential resources at national level; evaluate current spending and redirect funds if necessary; determine funding gap	NRL	
	Map out potential international resources e.g. GFATM, GDF, multilateral and bilateral donors, foundations, and develop a funding strategy	NRL, NTP	
	Secure commitments from MoH departments and from donors	NRL, NTP	

ISSUES	KEY ACTIONS	TECHNICAL/ OPERATIONAL LEAD	ESTIMATED TIMELINE
Implementation	Update and disseminate guidelines and materials; coordinate process with training plan	NRL	
	Revise recording and reporting forms; field test, print and disseminate	NRL	
	Develop SOPs, Essential Laboratory Supplies List and reporting and recording forms	NRL, NTP	
Training of laboratory technicians	Develop training strategy, budget and plan; coordinate with dissemination of new SOPs and delivery of supplies	NRL	
	Coordinate off-site and on-site training plan with manufacturer; if necessary test training materials; adapt tools for supportive supervision to incorporate the new guidelines: • Test performance (microscopy, culture, DST) • Equipment operation and maintenance • Quality Assurance (internal and external) Laboratory management, including planning and budgeting	NRL, NTP	
	Train core team of trainers; Implement training plan; monitor quality of training	NRL	
	Plan for an external laboratory expert to visit site to address any contamination and performance issues 1-2 months after training	NRL, NTP	
Forecasting and quantification	Calculate needs for a phased or nationwide implementation; determine size of buffer stocks for the different levels and requirements to fill the pipeline. Determine availability and limitations of consumption and/or morbidity data; select quantification method(s) that will be used to develop an initial forecast	NRL, NTP	
	Determine procurement mechanisms available for procurement of laboratory equipment and supplies; review donor and/or government requirements and restrictions for the procurement. Utilize data from phased implementation to adjust estimates of the potential demand and uptake; refine forecasts and set schedule for quantifying ongoing needs. Calculate needs for a phased or nationwide implementation; determine size of buffer stocks for the different levels and requirements to fill the pipeline	NRL, NTP	
Procurement	Obtain service and maintenance contracts Assure financing for goods, transport, insurance, QA testing and clearing. Determine procurement method and develop a procurement plan; set procurement calendar	NRL	
	Ensure that contract includes detailed customer plan addressing training of staff, maintenance and repair issues and claim procedures. Monitor the procurement process and supplier performance. Communicate information on potential delays to the committee/working group managing the transition. Implement procurement; pay invoices and claim damages if any. Obtain service and maintenance contracts	NRL, NTP	
Distribution	Integrate the distribution of the new tool and ancillary supplies into the overall distribution plan. Develop a distribution strategy that synchronizes distribution of the new equipment and consumables (including specimen containers, reagents, etc.) with phased or nationwide implementation; identify resource needs for the transition e.g. for additional deliveries Ensure that contract includes detailed customer plan addressing training of staff, maintenance and repair issues and claim procedures. Monitor the procurement process and supplier performance. Communicate information on potential delays to the committee/working group managing the transition	NRL, NTP	

ISSUES	KEY ACTIONS	TECHNICAL/ OPERATIONAL LEAD	ESTIMATED TIMELINE
Quality and safety	Develop a plan for supervision at all levels of the laboratory system that are included in the NTP strategy. Set quality assurance standards and verification methods for procurement; identify and secure funding to implement testing (e.g. shipping of reagents). Adhere to registration requirements to assure safety, efficacy and quality of the new TB tool. Ensure capacity for equipment maintenance and upgrading is in place. Integrate capacity building activities to support the availability and appropriate use of the improved/new diagnostic with other initiatives to strengthen health systems. Identify resources and develop a plan for strengthening laboratory systems to meet criteria for a site to start using the Liquid Culture and DST system. Design and develop internal QA programmes. Develop a plan for supervision at all levels of the laboratory system that are included in the NTP strategy. Set quality assurance standards and verification methods for procurement; identify and secure funding to implement testing (e.g. shipping of reagents). Adhere to registration requirements to assure safety, efficacy and quality of the new TB tool. Synchronize timing of capacity building activities with the phased or nationwide implementation plan to ensure sites meet criteria for start up Integrate capacity building activities to support the availability and appropriate use of the improved/new diagnostic with other initiatives to strengthen health systems.	NRL, NTP	
Monitoring and evaluation	Develop a monitoring and evaluation plan to collect, analyze and report data on success of implementation; solicit feedback from health care staff, patients and other stakeholders. Take timely corrective action as needed. Set up a system to monitor for new tools and technologies that may impact NTP programming and evaluate use of the recently introduced Liquid Culture and DST system	NRL, NTP	