

## BRIEFING NOTE: TB DIAGNOSTICS AND LABORATORY STRENGTHENING

### Key documents

- The Global Laboratory Initiative (GLI), under WHO guidance, has developed a *Roadmap for TB Laboratory Strengthening* aimed at ensuring quality TB diagnostics in appropriately laboratory services within the context of national laboratory strategic plans.
- WHO has developed a *Policy Framework for Implementing TB Diagnostics* to facilitate implementation at country level.
- The GLI, under WHO guidance, has developed a *Laboratory Tool Set* to standardise laboratory methods, including standard operating procedures, equipment specifications, guidelines for procurement of laboratory equipment and supplies, training packages for microscopy and culture, and a costing/budgeting tool to facilitate supply chain management and stock control at country level.

These tools are available at <http://www.stoptb.org/wg/gli> and at <http://www.who.int/tb/laboratory/policy/en>.

### Key considerations: Selecting appropriate algorithms and technologies/methods

1. The prevalence of HIV and drug-resistant TB to a large extent dictates the use of laboratory policies and diagnostic algorithms at country level. Management of HIV-associated and drug-resistant TB also requires concurrent clinical laboratory capacity (e.g. biochemistry, haematology, general microbiology) to monitor treatment and associated co-morbid conditions.
2. In high HIV-burden settings a substantial investment in Xpert MTB/RIF diagnostic capacity or conventional culture capacity is required, given the need to diagnose smear-negative TB. In high MDR-TB burden settings, laboratory diagnostic algorithms based on groups at greatest risk of drug-resistant TB (including those with HIV infection) is the most cost-effective use of scarce laboratory and diagnostic resources.
3. As a minimum, countries embarking on drug-resistant TB programmes should establish laboratory capacity to diagnose MDR-TB and monitor culture conversion of patients on MDR-TB treatment. Rifampicin resistance is a good and reliable proxy for MDR. Risk categories for drug-resistant TB vary greatly among countries and careful assessment at country level is therefore essential. Algorithms for testing of patients suspected of having drug-resistant tuberculosis are dependent on several factors:

- Local epidemiology
- Local treatment policies
- Existing country laboratory capacity
- Specimen referral and transport mechanisms
- Availability of human and financial resources

4. Currently available technologies are not mutually exclusive. Molecular line probe assays and selected non-commercial culture and DST methods are suitable for direct application on smear-positive specimens only. Conventional culture capacity is still required for smear-negative specimens while conventional DST capacity is needed to detect XDR-TB;

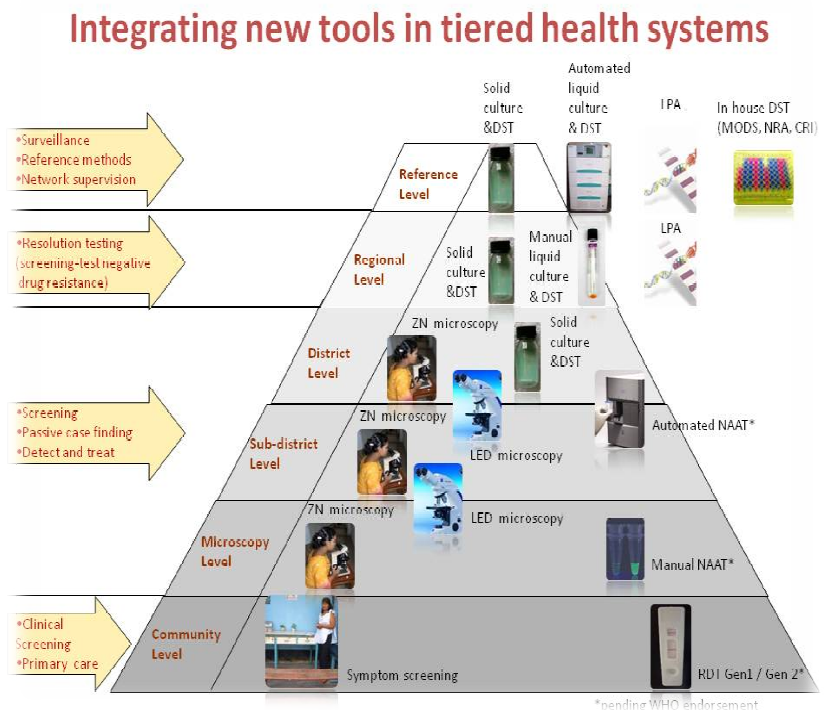
5. Liquid culture and molecular line probe assays are regarded as current international gold standards, to be phased in without loss of existing solid culture and DST capacity;

6. Rapid phenotypic DST methods offer an interim solution, especially in resource-constrained settings, while capacity for genotypic testing is being developed;

7. Xpert MTB/RIF should be used as the initial diagnostic test for individuals suspected of having MDR-TB or HIV-associated TB. Xpert MTB/RIF can be used at lower levels of the health service (eg. district/sub-district), and should be supported by conventional microscopy, culture and DST (liquid or LPA) for monitoring of treatment, diagnosis of resistance other than rifampicin, for prevalence surveys and for drug resistance surveillance;

8. Implementation of new technologies/methods for TB should be decided by Ministries of Health within the context of national strategic plans for laboratory strengthening and with input from laboratory experts;

9. TB diagnostic capacity should be linked to drug access and programmatic capacity to ensure treatment of patients under appropriate international standards of care.



<p><b>Microscopy</b></p> <ul style="list-style-type: none"> <li>• LED fluorescence microscopy should be phased-in and eventually replace conventional bright field microscopy and ZN staining in all settings;</li> <li>• Microscopy is suitable for peripheral and higher level laboratories;</li> <li>• Microscopy can be done safely under minimum bio-safety conditions;</li> <li>• Microscopy has limited sensitivity, which is further reduced in HIV-positive individuals;</li> <li>• Microscopy identifies AFB and not <i>Mycobacterium tuberculosis</i>;</li> <li>• Microscopy cannot distinguish between viable and non-viable organisms, or between drug-susceptible and drug-resistant organisms;</li> <li>• Microscopy is used to monitor response to anti-TB therapy.</li> </ul> <p><u>Recommended coverage:</u> One microscopy centre per 100,000 population is usually sufficient; however, expansion should also take into account the location and utilisation of existing services, urban/rural population distribution, and specimen transport mechanisms.</p>	<p><b>Culture</b></p> <ul style="list-style-type: none"> <li>• Culture is suitable for national or regional level laboratories;</li> <li>• Both solid and liquid culture are recommended by WHO, with liquid culture regarded as the gold standard;</li> <li>• Liquid culture results are available more rapidly;</li> <li>• All positive cultures must be speciated to confirm <i>M. tuberculosis</i>;</li> <li>• Manipulation of both solid and liquid cultures requires maximum bio-safety measures in the laboratory, and results are inevitably delayed due to slow growth of mycobacteria;</li> <li>• Conventional culture (solid or liquid) is required to monitor response to treatment in MDR-TB patients.</li> </ul> <p><u>Recommended coverage:</u> At least one culture laboratory to cover 500,000 - 1 million population.</p>
<p><b>Molecular line probe assay (LPA)</b></p> <ul style="list-style-type: none"> <li>• LPA is suitable for national or regional level laboratories;</li> <li>• LPA is recommended for use on smear-positive sputum specimens and <i>M. tuberculosis</i> isolates only;</li> <li>• LPA requires at least three separate rooms to avoid DNA cross-contamination;</li> <li>• LPA detects MDR-TB; conventional second-line DST is required to detect XDR-TB;</li> <li>• LPA can be used as a stand-alone diagnostic test for MDR-TB;</li> <li>• Conventional culture (solid or liquid) is required to monitor treatment response (culture conversion) of MDR-TB patients.</li> </ul> <p><u>Recommended coverage:</u> At least one LPA laboratory to cover 500,000 - 1 million population.</p>	<p><b>Phenotypic drug susceptibility testing (DST)</b></p> <ul style="list-style-type: none"> <li>• Phenotypic DST is suitable for national or regional level laboratories;</li> <li>• Rifampicin resistance is a good and reliable proxy for MDR-TB;</li> <li>• Phenotypic DST requires maximum bio-safety measures in the TB laboratory;</li> <li>• Second-line DST should be done on all MDR isolates of <i>M. tuberculosis</i>.</li> <li>• Phenotypic second-line DST is required to confirm/exclude XDR-TB;</li> </ul> <p><u>Recommended coverage:</u> At least one DST laboratory to cover 500,000 - 1 million population.</p>

**Molecular Xpert MTB/RIF assay**

- Xpert MTB/RIF detects both TB and rifampicin resistance in a single test.
- Xpert MTB/RIF is suitable for all levels of laboratories but capacity of one device is limited to 20 specimens per day. Higher-volume settings may require more than one device;
- Xpert MTB/RIF can be used as a stand-alone diagnostic test;
- Xpert MTB/RIF requires uninterrupted and stable electrical power supply and yearly calibration of the cartridge modules;
- Conventional culture (solid or liquid) is required to monitor treatment response (culture conversion) of MDR-TB patients.

Recommended coverage: Dependent on local prevalence of TB, MDR-TB and HIV.

