World Health Organization

www.who.int/tb

TUBERCULOSIS DIAGNOSTICS

KEY MESSAGES

- Diagnostic algorithms should start with appropriate screening policies to identify persons at risk.
- New, rapid WHO-recommended tests should be prioritised in persons with risk factors for drug resistance and/or persons with HIV co-infection.
- One size does not fit all: Recommended diagnostics are not mutually exclusive and should be combined based on country epidemiology, the existing laboratory network (see Figure 1), and available resources.
- Implementation of any recommended diagnostic requires all core laboratory components to be in place (see Box).
- Drug susceptibility testing (DST) is accurate and reproducible for detection of multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR) TB. For other drugs, DST is problematic and the clinical relevance of results are unclear.
- Even with new, rapid diagnostics, conventional laboratory capacity (microscopy, culture and DST) must be maintained for monitoring patient response to treatment and detecting resistance to drugs other than rifampicin.
- Scale-up of diagnostic capacity must be matched with access to appropriate treatment and care.

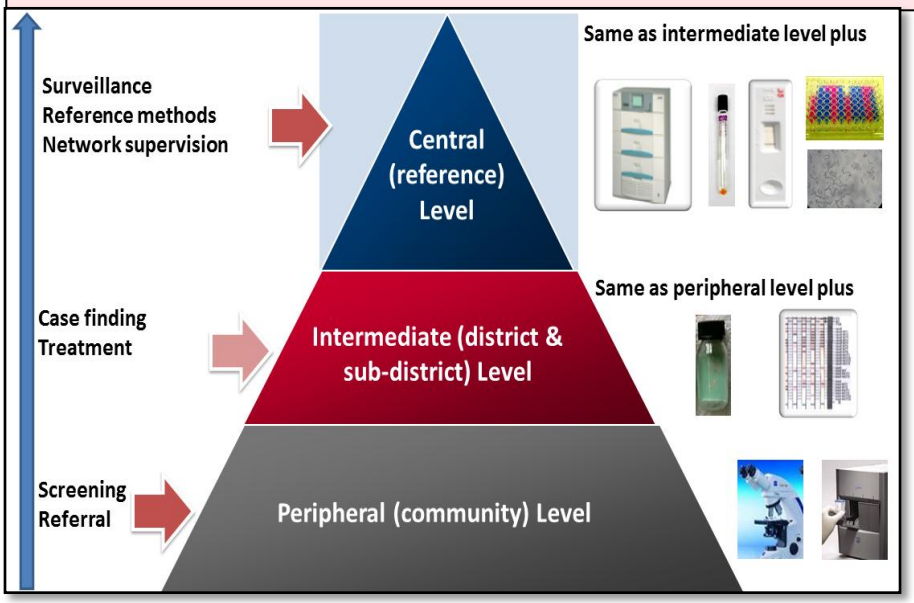

Figure 1: Currently recommended TB diagnostics require different levels of laboratory sophistication due to technical complexity and biosafety concerns

CORE LABORATORY COMPONENTS FOR UPTAKE OF DIAGNOSTICS

- Sufficient funding.
- Adequate human resources and training.
- Country-specific diagnostic algorithms.
- Appropriate infrastructure and biosafety.
- Specimen transport and referral mechanisms.
- Equipment validation and maintenance.
- Management of laboratory commodities.
- Laboratory information management systems.
- Laboratory quality management systems.

TARGET PRODUCT PROFILES

Consensus on the minimal and optimal specifications of four different types of TB diagnostic tests has been reached. Full report is available at http://www.who.int/tb/laboratory/resource/en/

WHO-RECOMMENDED DIAGNOSTIC TOOLS

RECOMMENDED FOR USE (detailed policy guidance: http://www.who.int/tb/laboratory/en/)

- **LED microscopy:** For use at all laboratory levels as replacement of conventional fluorochrome and light microscopy.
- **Commercial liquid culture and DST systems**: For use at central/regional reference laboratory level, as current reference standard.
- **Rapid speciation strip technology**: For use with conventional culture and DST at central/regional reference laboratory level, to identify *Mycobacterium tuberculosis.*
- **Commercial molecular line probe assays for 1st-line anti-TB drugs**: For use at central/regional reference laboratory level for rapid detection of rifampicin (alone or with isoniazid) resistance. Suitable for use on smear-positive specimens or culture isolates.
- **Selected non-commercial DST methods: MODS*, NRA**, CRI*****: For conditional use at central/reference laboratory level for detection of rifampicin resistance only. MODS and NRA suitable for use on smear-positive specimens or culture isolates, CRI suitable for use on culture isolates only.
- **Automated real-time nucleic acid amplification - Xpert MTB/RIF system**: For rapid detection of pulmonary and extrapulmonary TB and rifampicin resistance in both adults and children at decentralised laboratory and health care centres.

NOT RECOMMENDED DUE TO CURRENT INSUFFICIENT EVIDENCE

- Sputum concentration and decontamination methods.
- Phage-plaque technology for rapid rifampicin resistance.
- Thin-layer agar methods for rapid culture and DST.
- Interferon-gamma release assays as replacement for the tuberculin skin test for detection of latent TB in low- and middle-income (typically high TB and/or HIV) settings.
- Molecular line probe assays for 2nd-line anti-TB drugs.
- Loop-mediated isothermal amplification test kit for TB.

RECOMMENDED NOT TO USE (detailed policy guidance: http://www.who.int/tb/laboratory/en/).

- Commercial TB serodiagnostic tests.
- Interferon-gamma release assays for detection of active TB (all settings).

***MODS**: microscopic observation of drug susceptibility; ****NRA**: nitrate reductase assay; *****CRI**: colorimetric redox indicator

EVIDENCE REQUIRED FOR WHO REVIEW OF DIAGNOSTICS

Phase 1: Research and Development

•Typically consists of upstream research and development to define and validate a prototype, followed by laboratory validation under international standards that culminate in a design-locked product. WHO interacts with developers if requested to discuss end-user requirements such as biosafety, assay robustness, intended settings of use.

Phase 2: Evaluation and Demonstration

•The performance of the new diagnostic product should be evaluated in controlled trials at 3-5 trial sites in high-burden TB and HIV countries, ideally using pre-specified end-user product specifications. These data are often used for product registration with global and/or national regulatory authorities such as FDA and/or CE marking.

•Product specifications and performance should subsequently be validated in uncontrolled trials under field conditions in 5-10 trial sites in high-burden TB and HIV countries, and include cost-effectiveness studies.

Phase 3: WHO evidence assessment using GRADE

•For new technologies or new indications for use of technologies already approved by WHO: Submission of dossier with Phase 1 and 2 data to WHO. Structured evidence assessment process using GRADE.

•For fast-follower or generic versions of technologies already approved by WHO: Manufacture of the technology under ISO 13:485 standards; equivalent performance demonstrated, in 2-3 independent TB Supranational Reference Laboratories, to the reference technology already approved by WHO.

•WHO is not a regulatory authority and does not recommend technologies for individual country use.

Phase 4: Phased uptake and collection of evidence for scale-up

•New diagnostic successfully implemented in routine diagnostic services by early implementers in high/burden TB and HIV countries; systematic assessment of proposed algorithms, laboratory workload, operational constraints, country cost-effectiveness. Lessons learnt by early implementers used for country adaptation.

Phase 5: Scale-up and policy refinement

•Scale-up of the new diagnostic, with subsequent data used to inform and refine WHO policy guidance in a dynamic and on-going process.