

РЕГИОНАЛЬНЫЙ СЕМИНАР ПО ВОПРОСУ УСКОРЕННОГО ВНЕДРЕНИЯ РУКОВОДСТВА ВОЗ ПО ПРОФИЛАКТИКЕ И ДИАГНОСТИКЕ ТУБЕРКУЛЕЗА И ЛЕЧЕНИЮ ТУБЕРКУЛЕЗА С ЛЕКАРСТВЕННОЙ УСТОЙЧИВОСТЬЮ (ЛУ-ТБ)

REGIONAL WORKSHOP ON ACCELERATED IMPLEMENTATION OF WHO GUIDELINES ON TB PREVENTION, DIAGNOSIS, AND DRUG-RESISTANT TB (DR-TB) TREATMENT

WHO Policy Updates: Initial Molecular testing for TB and DR-TB

EURO workshop to plan the accelerated implementation of new WHO policies

Almaty 28-30 April, 2025

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2025 TB Diagnostic Policy Updates: 3 Categories

Structural Updates

Consolidated Content on TB Infection & Diagnosis Added Recommendation Lists & Summaries of Changes Added a Chapter on Diagnostic Class Determination & Prequalification Revised Diagnostic Algorithms & Annex Structure

New Testing Classes & Product Endorsements

2 New Classes of Low Complexity Nucleic Acid Amplification Tests (automated and manual)
 2 New Interferon Gamma Release Assays for Detection of TB Infection
 1 Updated Targeted NGS Solution for Detection of Drug-Resistant TB Updated

Testing Strategy Updates

Recommendations for Concurrent Testing of Multiple Sample Types for Children and People Living with HIV





WHO Now Recommends Classes of TB Diagnostic Technologies

- The WHO assessment process for TB diagnostics has evolved to focus on evaluating 'classes' of TB diagnostic technologies rather than specific products
- Class include diagnostic testing technologies that share the following characteristics:
 - purpose of use (i.e., detection of TB or drug-specific resistance)
 - principle of action
 - infrastructure and human resource requirements
 - complexity of the testing procedure and associated instrumentation
 - reporting method (automated versus manual)
 - setting of use (e.g., reference or peripheral low-complexity, near point-of-care, point-of-care)





Initial tests for detection of TB with drug resistance

Initial tests for detection of TB *without* drug resistance

Follow-on tests for detection of drug resistance

Tests for detection of TB infection





Recommendation Pathways for TB Diagnostics

TB Diagnostic Class Determination

Pathway A: First-In-Class Technologies

Evidence synthesis, review and development of recommendations will be conducted through the guideline development process following the GRADE methodology



WHO Prequalification Assessment

Introduction of the table and description for the WHO GTB recommended diagnostic classes

Technology class	Included products
Initial tests for TB diagnosis with drug-resistance detection	
NEW: Low-complexity automated nucleic acid amplification tests (NAATs) for	Xpert [®] MTB/RIF and Xpert MTB/RIF Ultra (Cepheid)
detection of TB and resistance to rifampicin	Truenat [®] MTB Plus and Truenat MTB-RIF Dx (Molbio)
Moderate-complexity automated NAATs for detection of TB and resistance to	Abbott RealTime® MTB and Abbott RealTime MTB RIF/INH (Abbott)
rifampicin and isoniazid	BD MAX TM MDR-TB (Becton Dickinson)
	cobas® MTB and cobas MTB-RIF/INH (Roche)
	FluoroType® MTB and FluoroType MTBDR (Hain Lifescience/Bruker)
Initial tests for TB diagnosis without drug-resistance detection	
NEW: Low-complexity manual NAATs for detection of TB	LoopampTM MTBC Detection Kit (TB LAMP) (Eiken Chemical)
Antigen detection in a lateral flow format (biomarker-based detection) (LF-LAM) for detection of TB	Determine TM TB LAM Ag (Alere/Abbott)
Follow-on tests for detection of TB drug resistance	
Low-complexity automated NAATs for detection of resistance to isoniazid and	Xpert® MTB/XDR (Cepheid)
second-line anti-TB agents	
Line probe assays (LPAs) for detection of TB drug resistance	GenoType® MTBDRplus v1 and v2; and GenoType MTBDRsl (Hain Lifescience/Bruker)
	Genoscholar [™] NTM+MDRTB II and Genoscholar PZA-TB II (Nipro)
Targeted next-generation sequencing (NGS) tests for detection of TB drug resistance	Deeplex® Myc-TB (GenoScreen/Illumina)
	AmPORE-TB® (Oxford Nanopore Technologies)
	TBseq® (Shengting Medical Technology Company)
Tests for TB infection	
Mycobacterium tuberculosis antigen-based skin tests (TBSTs)	Diaskintest® (Generium)
	Cy-Tb [™] (Serum Institute of India)
	C-TST (Anhui Zhifei Longcom)
Interferon-gamma release assays (IGRAs)	QuantiFERON TB Gold Plus ELISA (Qiagen, Hilden, Germany)
	T-SPOT®.TB (Oxford Immunotec, Oxford, UK)
	Wantai IB-IGRA ELISA (Wantai BioPharm Enterprise Co, Bejing, China)
World Health	STANDARD E TB-Feron ELISA (SD BIOSENSOR, Gyeonggi-do, Republic of Korea)
- Groanization	LIAISON QF1-Flus CLIA (Diasorin, Saluggia, Italy)
I COCHCIMII SKILDICSIS	rubercum purmed protein derivative (PPD) products



New TB Testing Classes

Class of LC-aNAATs includes:

- Xpert[®] MTB/RIF Ultra (Cepheid)
- Truenat[®] MTB Plus with MTB-RIF Dx (Molbio)
- Instrument-based, require a well-established laboratory network, laboratory infrastructure and trained testing staff





Cepheid GeneXpert

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Purpose		Detection of TB and Rifampicin Resistance			
Principle of Action		Nucleic acid amplification testing			
Complexity	Reagents	Most reagents are enclosed in a disposable sealed container to which a clinical specimen is added. The disposable sealed container does not have special storage requirements.			
	Skills	Basic technical skills (e.g., basic pipetting, precision not critical)			
	Pipetting	Either no, or only one, pipetting step in the process			
	Testing procedure	 May require an initial manual specimen treatment step before transferring the specimen into the disposable sealed container for automated processing Automated DNA extraction Automated real-time PCR Results generation 			
Type of Result Reporting		Automated			
Setting of Use		Basic laboratory (no special infrastructure needed)			



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Population	Assessed Technology	Sample(s)	Purpose and Performance [^]	Strength of Evidence	Quality of Evidence
Adults and adolescents with signs or symptoms or who screen positive for PTB	Xpert MTB/RIF Ultra Truenat MTB Plus + MTB-RIF Dx	Respiratory samples	Detection of TB	Strong	High
People with bacteriologically confirmed TB	Xpert MTB/RIF Ultra Truenat MTB Plus + MTB-RIF Dx	Respiratory samples	Detection of resistance to rifampicin	Strong	High
People with signs or symptoms of TB meningitis	Xpert MTB/RIF Ultra	Cerebral spinal fluid	Detection of TB	Strong	Moderate
People with signs or symptoms of EP TB	Xpert MTB/RIF Ultra	Lymph node tissue/ aspirate, pleural tissue/fluid, synovial/ peritoneal/ pericardial fluid	Detection of TB	Strong	Low to Very Low

<u>Acronyms</u>: PTB = Pulmonary TB, EP TB = Extrapulmonary TB, RR TB = rifampicin-resistant TB.





Population	Assessed technology	Sample(s)	Purpose	Performance^
Adults and adolescents with signs or symptoms or who screen positive for PTB	Xpert MTB/RIF Ultra Truenat MTB Plus + MTB-RIF Dx	Respiratory samples	Detection of TB	Sensitivity 90.4% (95% CI: 88.0–92.4) Specificity 94.9% (95% CI: 93.0–96.3)
People with bacteriologically confirmed TB	Xpert MTB/RIF Ultra Truenat MTB Plus + MTB-RIF Dx	Respiratory samples	Detection of resistance to rifampicin	Sensitivity 95.1% (95% CI: 83.1–98.7) Specificity 98.1% (95% CI: 97.0–98.7)
People with signs or symptoms of TB meningitis	Xpert MTB/RIF Ultra	Cerebral spinal fluid	Detection of TB	Sensitivity 88.2% (95% CI: 83.7–91.6) Specificity 96.0% (95% CI: 86.8–98.9)
People with signs or symptoms of EP TB	Xpert MTB/RIF Ultra	Lymph node tissue/ aspirate, pleural tissue/fluid, synovial/ peritoneal/ pericardial fluid	Detection of TB	Sensitivity range 33% - 99% Specificity range 74% - 99% (sample dependent)

<u>Acronyms</u>: PTB = Pulmonary TB, EP TB = Extrapulmonary TB, RR TB = rifampicin-resistant TB. ^Performance values represent summary sensitivity and specificity systematic review data.





Class of LC-<u>m</u>NAATs includes:

- Loopamp[™] MTBC Detection Kit (TB LAMP) (Eiken Chemical)
- Basic equipment and UV lamp required for testing and reading; can be implemented at the lowest levels of the laboratory network by trained testing staff.

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Eiken Chemical TB-LAMP

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Purpose		Detection of TB			
Principle of Actior	า	Nucleic acid amplification testing			
Complexity	Reagents	Most reagents are enclosed in multiple disposable sealed containers not requiring special storage requirements.			
	Skills	Basic technical skills (e.g., basic pipetting, precision not critical)			
	Pipetting	Multiple pipetting steps (maximum of 10) from processed sample to result generation			
	Testing procedure	 At least four distinct steps: Specimen treatment step before transferring the specimen into the disposable sealed container DNA extraction PCR amplification Results visualization 			
Type of Result Reporting		Automated or manual			
Setting of Use		Basic laboratory (no special infrastructure needed)			



Population	Assessed	Sample	Purpose	Performance^
	technology			
Adults and adolescents	Loopamp MTBC	Respiratory	Detection of TB	Sensitivity 84.1% (95% CI: 78.3–88.6)
with signs and symptoms	Detection Kit (TB LAMP)	samples		Specificity 96.1% (95% CI: 94.2–97.4)
or who screen positive	(Eiken Chemical)		(Strong recommendation,	
for pulmonary TB			High quality of evidence)	

^Performance values represent summary sensitivity and specificity systematic review data.

Remark Highlights:

- Applies to all people living with HIV and extrapolated to children for use with respiratory samples (induced sputum and gastric aspirate), with the caveat of low to moderate certainty of evidence and noting concurrent testing with LC-aNAAT and LF-LAM for PLHIV are recommended where available.
- Data on the use of paediatric stool samples were very limited, and there were no data on the use of nasopharyngeal aspirates. The recommendation was, therefore, not extrapolated to these sample types.
- As LC-mNAATs do not provide rifampicin-resistance results, all positive diagnostic tests for TB require follow-up and referral for DST for, at a minimum, rifampicin.







Concurrent Testing for Children and PLHIV

What is It?

- ✓ Multiple samples are taken simultaneously (whenever possible) and tested using one or more test.
- \checkmark A positive result on any test is a positive result for the combination.
- ✓ However, the inability to collect one or more specimens at the initial visit, or lack of one of the test types should not delay testing of available specimens and tests but instead trigger specimen collection and testing as soon as possible.

Why Do It?

- > There are significant burdens of TB in PLHIV and children, particularly in low- and middle-income countries
- > Diagnostic testing for TB in persons living with HIV and children is challenging, because of:
 - Non-specific clinical presentations, including disseminated TB
 - Often low and varying numbers of mycobacteria in samples
 - Inability to provide sputum samples
- Implementing concurrent sample testing could:
 - Simplify diagnostic processes using easy-to-collect sample types
 - Shorten the patient journey
 - Improve TB detection rates and health outcomes for these at-risk populations





Population	Intervention	Performance	95% Confidence Interval	Strength of Evidence	Quality of Evidence
Adults and adolescents with signs or symptoms of	LC-aNAAT respiratory sample + LF-LAM on urine	Δ Se: 6.7% (I:77.5%; C: 68%)	3.8% to 10.7%	Strong	High
TB, screen positive for TB, are seriously ill or have advanced HIV disease		<mark>Δ Sp: - 6.8% (I:89.4%; C: 97%)</mark>	-9.5% to -4.7%		
Children	LC-aNAAT respiratory sample + LC-aNAAT on stool	Δ Se: 7.1% (I:79.9%; C: 72.5%)	3.2% to 13.4%	Strong	Low
		Δ Sp: - 1.7% (I:93.4%; C: 95.0%)	-3.8% to -0.6%		
Children living with HIV	LC-aNAAT respiratory sample + LC-aNAAT on stool	Δ Se: 6.9% (I:77.8%; C: 69.3%)	1.5% to 20.1%	Conditional	Low
	+ LF-LAM on urine	Δ Sp: - 10.2% (I:83.9%; C: 95.4%)	-19.6% to -4.9%		

Technology Assessed: Xpert MTB/RIF Ultra. No or limited data for Truenat MTB Plus. **Remark Highlight**: Supersedes prior guidance on use of LF-LAM for TB detection among PLHIV.





	Mycobacterium Tuberculosis complex and resistance to first and/or second line anti-TB drugs Tests						
TSS 17 - In vitro diagnostic	Product name	Product code(s)	Manufacturer name	Dossier review	Quality Management System review	Product performance evaluation	Labelling review
gualitative detection of	BD MAX MDR-TB	443878	Becton, Dickinson and Company, BD Biosciences (USA)	•	٠	Ŋ	þ
Mycobacterium tuberculosis	Truenat MTB Plus	601130020, 601130005, 601130025, 601130050, 6011301100, and 601130200	Molbio Diagnostics Private Limited	R	•		
associated with drug-	Truenat MTB-RIF Dx	601210200, 601210005, 601210020, 601210100, 601210025, and 601210050	Molbio Diagnostics Private Limited	R	•		
resistant tuberculosis	cobas MTB-RIF/INH	09040617190, 09040625190, 09051953190, 08185476001	Roche Diagnostics GmbH	þ	s	Alternative laboratory evaluation pathway	
TSS 23 - Rapid diagnostic	cobas MTB	09040579190, 09040587190, 09051953190, 08185476001	Roche Diagnostics GmbH	R	S	Alternative laboratory evaluation pathway	
tests to detect mycobacterial	Loopamp MTBC Detection Kit	972000, 970000, 971000	Eiken Chemical Co., Ltd.	R			
lipoarabinomannan (LAM)	Xpert MTB/XDR	GXMTB/XDR-10	Cepheid AB	R	Ŋ	Alternative laboratory evaluation pathway	•
antigen in urine	In Vitro Diggnostics Under Assessmen	t WHO - Pregualification of Medical F	Products (IVDs. Medicines. V	accines and	Immunizati	on Devices. Vec	tor Control)

- WHO PQ evaluates each specific diagnostic product brand for quality, safety and performance within the product intended use
- Prequalification Technical Specification Series and Performance Evaluation protocols available for NAATs
- Xpert MTB/RIF Ultra prequalified as the first TB diagnostic
- Prequalification Technical Specification Series available for LF-LAM + Performance Evaluation protocol publication in 2025
- At least 7 additional low and moderate complexity products undergoing evaluation





Summary and Next Steps

- Two new classes of Low Complexity Nucleic Acid Amplification testing are now recommended for detection of TB (with and without rifampicin resistance detection)
- Concurrent testing of multiple samples is now recommended for persons living with HIV and children
- WHO Consolidated Guidelines and Operational Handbook on TB Diagnosis (Module 3) are planned for publication in Q2 2025
- Dissemination activities will include workshops, webinars, and ad hoc engagements
- Planning for 2025 Guideline Development Group and Technical Advisory Group meetings underway



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https://extranet.who.int/tbknowledge
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THANK YOU! СПАСИБО!







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