

TB Diagnostics Update
AWACC 2026

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UNIVERSITY OF KWAZULU-NATAL

INYUVESI YAKWAZULU-NATALI

Outline

- Detection of *M. tuberculosis*
- Detection of Drug Resistance
- Interpretation of Results

Diagnostic tools available in the NHLS for initial diagnosis of TB: Molecular Assays (TB NAATs)

Low-volume laboratories	Medium-volume laboratories	High-volume laboratories
Cepheid	Becton Dickinson	Roche Diagnostics



Low Complexity NAAT





Moderate Complexity NAAT

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Diagnostic tools available in the NHLS for initial diagnosis of TB

- TB Nucleic acid amplification test (TB NAAT)
- Detect presence of ***M. tuberculosis* complex** DNA
  - **Specific for *M. tuberculosis* complex**
- Increased sensitivity: Multi copy target
- Cannot be used to monitor response to treatment
- Xpert MTB/RIF Ultra
  - Respiratory and extra-pulmonary
- MC NAAT:
  - Respiratory specimens only

TB Detection: Culture



- **Gold Standard**
- Most sensitive
- Viable bacteria
- All specimens
- Limitations: Long TAT, contamination, laborious, need skill, expensive, biosafety issues.
- Reserved for paucibacillary TB: TB NAAT negative or TB NAAT fails to detect resistance

Alternative (non-sputum) sample types

- Limitations of Sputum Specimens
  - Only pulmonary TB
  - Unable to produce sputum: Severely ill, altered mental status, children, asymptomatic

- Alternative sample types:
  - Urine
  - Stool
  - Tongue swabs

Urine-Xpert Ultra for the diagnosis of tuberculosis in people living with HIV: a prospective, multicentre, diagnostic accuracy study

Bianca Sossen, Rita Székely, Madalo Mukoka, Monde Muyoyeta, Elizabeth Nakabugo, Jerry Hella, Hung Van Nguyen, Sasiwimol Ubolyam, Berra Erkosar, Marcia Vermeulen, Chad M Centner, Sarah Nyangu, Nsala Sanjase, Mohamed Sasamalo, Huong Thi Dinh, The Anh Ngo, Weerawat Manosuthi, Supunnee Jirajariyavej, Nhung Viet Nguyen, Anchalee Avihingsanon, Andrew D Kerkhoff, Claudia M Denkinger, Klaus Reither, Lydia Nakiyingi, Peter MacPherson, Graeme Meintjes, Morten Ruhwald, FujiLAM Study Consortium

Summary

Background Diagnostic delays for tuberculosis are common, with high resultant mortality. Urine-Xpert Ultra (Cepheid) could improve time to diagnosis of tuberculosis disease and rifampicin resistance. We previously reported on lot-to-lot variation of the Fujifilm SILVAMP TB LAM. In this prespecified secondary analysis of the same cohort, we aimed to determine the diagnostic yield and accuracy of Urine Xpert Ultra for tuberculosis in people with HIV

Lancet Glob Health 2024; 12: e2024-34

See Comment page e1917

Clinical Infectious Diseases

MAJOR ARTICLE

Infectious Diseases Society of America

HIV Medicine Association

OXFORD

Comparative Performance of Urine Lipoarabinomannan and Urine Xpert MTB/RIF Ultra for Diagnosing Tuberculosis in Adult Inpatients With Human Immunodeficiency Virus in East London, South Africa

David Stead,[1,2] Sean Wasserman,[3,4] Ebrahim Steenkamp,[5] Andy Parrish,[1,2] David Barr,[6] and Graeme Meintjes[3,7,8]

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AOSIS

Page 1 of 10 Original Research

Urine-based assays for inpatients with HIV-associated tuberculosis in rural South Africa

Check for updates

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Nicola Wearne[5]

Background: Accurate non-sputum-based tuberculosis (TB) diagnostics are urgently needed to improve diagnostic yield and patient outcomes.

Objectives: To compare the diagnostic accuracy and diagnostic yield of Urine Xpert Ultra (Urine-XPU) and Urine Determine™ TB Lipoarabinomannan (LAM) antigen test (AlereLAM) against both a microbiological and composite reference standard (MRS and CRS) in a rural, routine care setting in South Africa.

Xpert MTB/RIF Ultra on Urine

- Performed better in:
  - In combination with Urine LAM, sputum Xpert MTB/RIF Ultra
  - Inpatients
  - Low CD4 count
- Associated with inpatient death

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Package of care for adults with HIV who are hospitalised with possible Tuberculosis

PWH, inpatients:

- LAM and TB NAAT on sputum
- If sputum not possible: Urine TB NAAT

NHLS/DoH:

- **Not yet implemented**

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People living with HIV and children

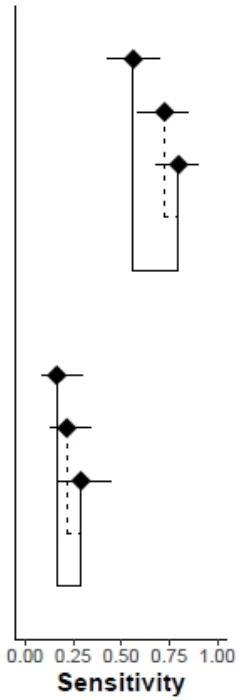
- **WHO 2025**: The following three scenarios of recommendations:
- **1. Adults and adolescents living with HIV**
  - LC-aNAAT on respiratory samples and urine LF-LAM
- **2. Children without HIV or with unknown HIV status**
  - LC-aNAAT on respiratory samples and stool in children
- **3. Children with HIV**
  - LC-aNAAT on respiratory samples and stool, as well as urinary LF-LAM

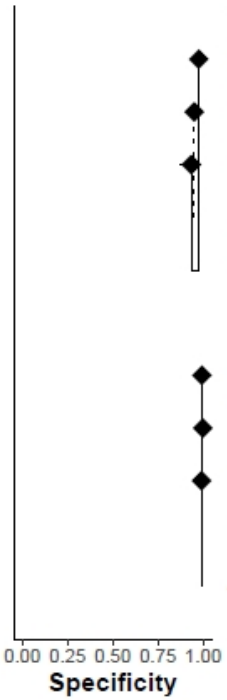
Incremental diagnostic accuracy of concurrent testing compared with single sample testing

What is the incremental diagnostic accuracy of concurrent use of LC-aNAATs on respiratory and stool samples for diagnosis of pulmonary TB disease in children who are HIV-negative or have an unknown HIV status, with signs and symptoms or who screened positive for pulmonary TB, compared with use of an LC-aNAAT on one sample type (either respiratory or stool)?

Fig. 2.3.2.1 Forest plot of pooled sensitivity and specificity for all studies, by each index test

Reference	Test	N	No. (%) with TB	Summary (95% CrI)	Summary (95% CrI)
MRS	LC-aNAAT stool	2145	173 (8.07%)	56.3% (42.9 to 69.9)	97.5% (94.8 to 99)
	LC-aNAAT resp	2145	173 (8.07%)	72.6% (59.0 to 84.6)	95% (90.6 to 97.7)
	Concurrent	2145	173 (8.07%)	79.9% (67.8 to 89.8)	93.4% (87.2 to 97)
	Δ Concurrent vs. resp			7.1% (3.2 to 13.4)	-1.7% (-3.8 to -0.6)
	Δ Concurrent vs. stool			22.1% (13.7 to 32.7)	-4.1% (-8.0 to -1.7)
CRS	LC-aNAAT stool	3579	1513 (42.3%)	16.4% (8.4 to 29.4)	99.3% (97.8 to 99.8)
	LC-aNAAT resp	3579	1513 (42.3%)	21.7% (12.9 to 34.4)	99.7% (97.9 to 1)
	Concurrent	3573	1507 (42.2%)	29.0% (17.3 to 44.7)	99.1% (96.1 to 99.8)
	Δ Concurrent vs. resp			4.7% (2.1 to 8.9)	-0.5% (-1.4 to -0.1)
	Δ Concurrent vs. stool			10.5% (6.9 to 15.0)	-0.1% (-0.7 to -0.005)





Specimen	Technology	Population	Sensitivity (95% CI)	Specificity (95% CI)
NAAT platforms				
LC-aNAAT platforms—Sputum				
Sputum	Xpert Ultra	Presumtive TB	91% (88–93)	95% (93–96)
Sputum	Xpert Ultra	PLHIV	88% (82–92)	95% (92–97)
Sputum	Xpert Ultra	HIV-negative	90% (85–94)	96% (91–98)
Sputum	Xpert Ultra	Children (sputum), age 1–4 years	75% (63–83)	95% (92–97)
Sputum	Xpert Ultra	Children (sputum), age 5–9 years	82% (65–92)	95% (92–98)
Sputum	Truenat MTB Plus	Presumptive TB	91% (84–95)	96% (95–97)
Sputum	Truenat Ultima	Presumptive TB	90% (85–93)	85% (80–88)
Sputum	Truenat Ultima	Presumptive TB/ACF	84% (76–89)	97% (96–88)
Near-point-of-care NAAT—Sputum				
Sputum	MiniDock	Presumptive TB	85% (82–88)	98% (97–98)
Sputum	MiniDock	PLHIV	79% (69–87)	97% (95–98)
Sputum	EasyNAT MTC	Presumptive TB	93% (88–99)	95% (90–100)
LC-aNAAT platforms—Tongue swab				
Tongue swab	Xpert Ultra	Presumptive TB	66% (61–70)	99% (98–99)
Tongue swab	Truenat Ultima	Presumptive TB/ACF	74% (64–82)	98% (96–99)
Near-point-of-care NAAT—Tongue swab				
Tongue swab	MiniDock	Presumptive TB	76% (71–81)	99% (99–100)
Tongue swab	MiniDock	PLHIV	69% (58–79)	99% (98–100)
LC-aNAAT platforms—Urine				
Urine	Xpert Ultra	PLHIV	33% (27–39)	98% (97–99)
LC-aNAAT platforms—Stool				
Stool	Xpert Ultra	Children <15 years (vs MRS)	73% (53–81)	–
Stool	Xpert Ultra	Children <15 years (vs TB clinical case definition)	38% (22–56)	–
Stool	Xpert Ultra	PLHIV adults	24% (16–32)	94% (92–96)
Stool	Xpert Ultra	PLHIV adults, CD4 ≤200 cells/μL	46% (24–68)	–
Stool	Xpert Ultra	PLHIV adults, CD4 >200 cells/μL	22% (13–32)	–

Tongue swabs

The new guidelines on TB diagnosis recommend:

A new class of near-point-of-care nucleic acid amplification tests (NPOC-NAATs) for the initial detection of TB without rifampicin resistance at peripheral levels of the health system (i.e., peripheral laboratories, primary healthcare centers and communities) and at lower unit costs than other molecular test and instrument types;

Tongue swabs as new, readily available and easy-to-collect specimens for use with NPOC-NAATs and low-complexity automated NAATs (LC-aNAATs) for the initial detection of TB with and without rifampicin resistance among adults and adolescents that are unable to produce sputum; and

New near point-of-care (NPOC) assays

- MiniDock (PlusLife, China)
- WHO recommended in 2026
- Swab-based assay: performed using sputum or tongue swab specimens.
- Sputum sensitivity 85%, tongue swab sensitivity 76%
- Compact, portable, battery-operable, simple to use and less expensive
- Initial detection of TB **without rifampicin resistance** at peripheral levels of the health system
- SA: Demonstration study ongoing

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Detection of Drug Resistance

- WHO Universal DST

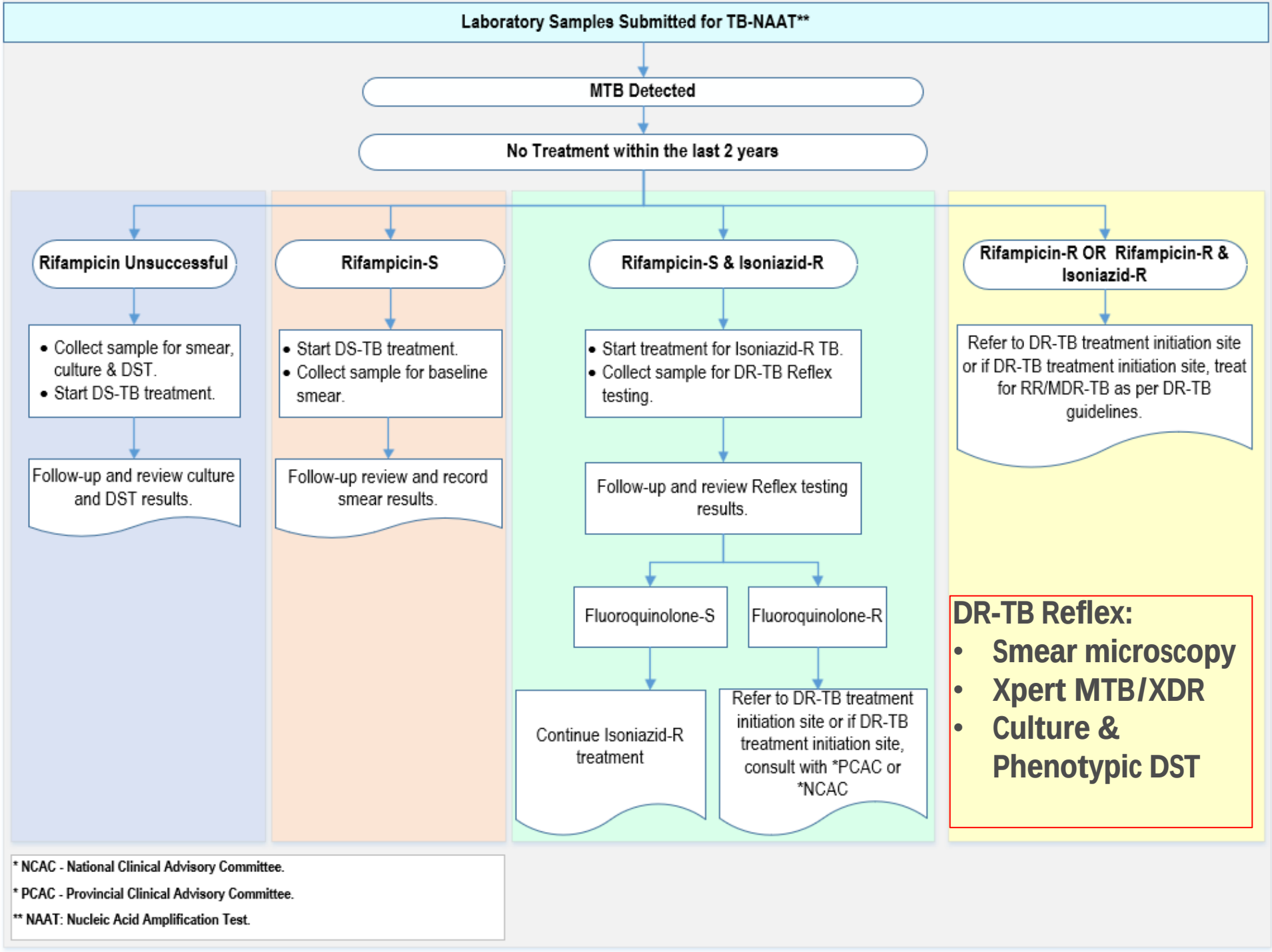
Test at least RIF Resistance in All Bacterio-logically confirmed TB

Test for FLQ Resistance in ALL RIF-Resistant TB

Test for BDQ and LZD Resistance in ALL Resistance to both RIF and FLQ

Detection of Resistance: TB NAAT

- Detect changes (mutations) in the DNA that may be associated with drug resistance.
- Single target: less sensitive compared to *M. tuberculosis* detection
- Resistance to rifampicin: 81bp region of ***rpoB*** (hot spot): codon **426-452**; rifampicin resistance determining region
- Resistance to isoniazid (*katG* gene and *inhA*)
- Xpert MTB/RIF Ultra: Resistance to rifampicin only
- MC NAAT: Resistance to rifampicin and isoniazid


Laboratory Samples Submitted for TB-NAAT**
MTB Detected
No Treatment within the last 2 years
Rifampicin Unsuccessful
• Collect sample for smear, culture & DST.
• Start DS-TB treatment.
Follow-up and review culture and DST results.
Rifampicin-S
• Start DS-TB treatment.
• Collect sample for baseline smear.
Follow-up review and record smear results.
Rifampicin-S & Isoniazid-R
• Start treatment for Isoniazid-R TB.
• Collect sample for DR-TB Reflex testing.
Follow-up and review Reflex testing results.
Fluoroquinolone-S
Fluoroquinolone-R
Continue Isoniazid-R treatment
Refer to DR-TB treatment initiation site or if DR-TB treatment initiation site, consult with *PCAC or *NCAC
Rifampicin-R OR Rifampicin-R & Isoniazid-R
Refer to DR-TB treatment initiation site or if DR-TB treatment initiation site, treat for RR/MDR-TB as per DR-TB guidelines.
DR-TB Reflex:
• Smear microscopy
• Xpert MTB/XDR
• Culture & Phenotypic DST
* NCAC - National Clinical Advisory Committee.
* PCAC - Provincial Clinical Advisory Committee.
** NAAT: Nucleic Acid Amplification Test.

DR-TB Reflex Algorithm

Version 2

January 2025



*Unsuccessful = Indeterminate on instrument report and only for a specific drug (INH or FLQ) that has an indeterminate result. Please note that BDQ, LZD and Pa should be done in parallel.

**Pa - all FLQ-R isolates should be referred to the National TB Reference Laboratory (CTB/NICD/NHLS, Johannesburg) for Pretomanid testing

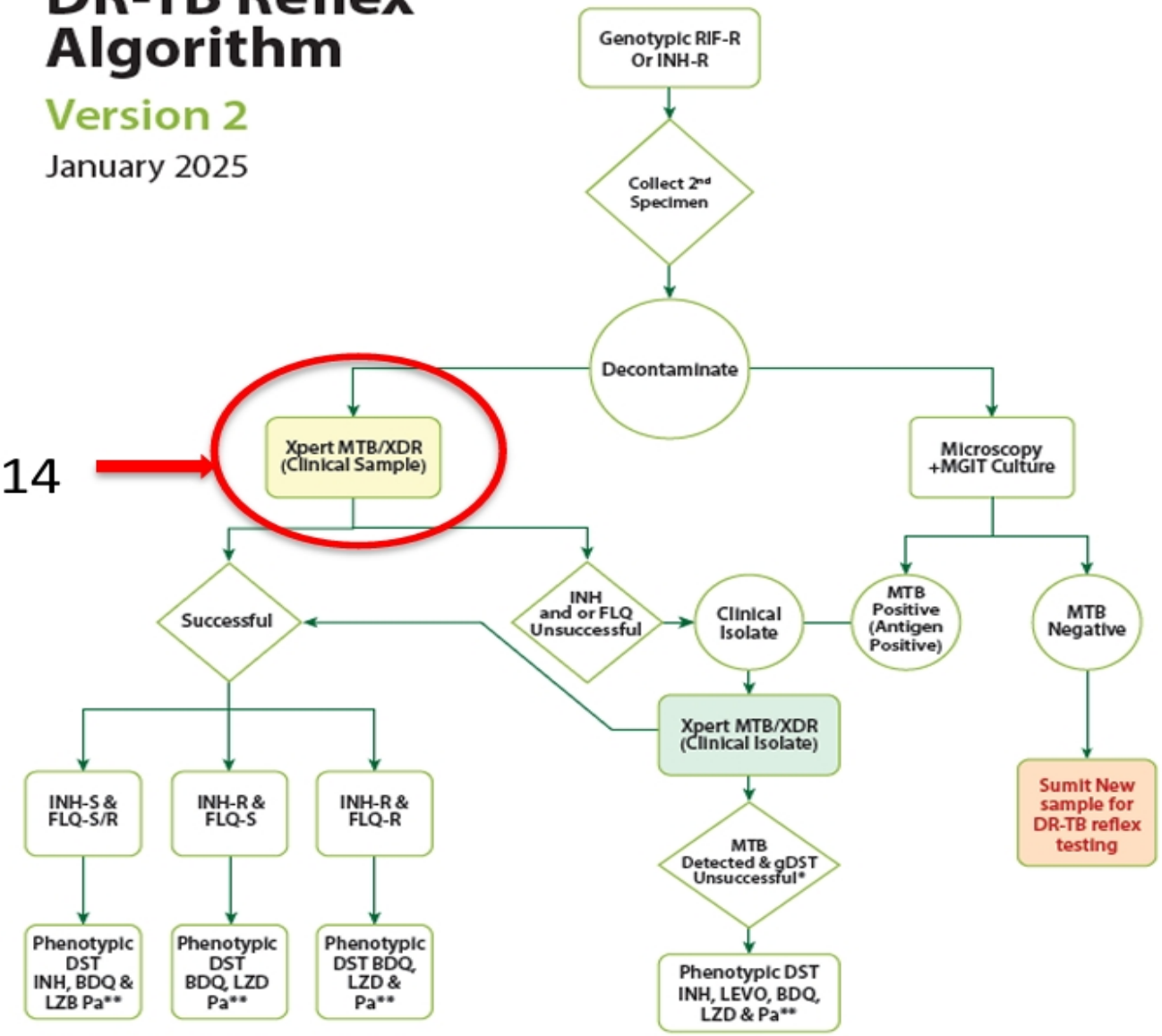
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tNGS
Expected TAT ~14 days

DR-TB Reflex Algorithm

Version 2

January 2025

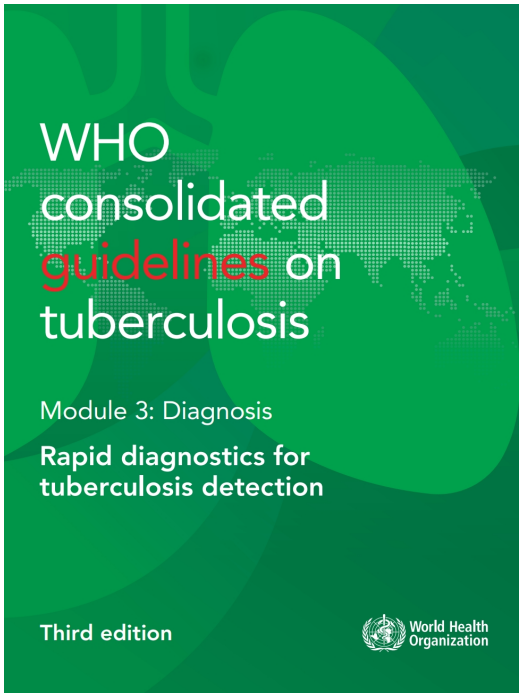


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Targeted next generation sequencing (tNGS)

- Deeplex® Myc-TB assay (Genoscreen, Lille, France)
- Ten drugs: Rifampicin, isoniazid, pyrazinamide, ethambutol fluoroquinolones, **bedaquiline, linezolid**, clofazimine, amikacin.
- **No Pa or DLM**



WHO 2024

Drug	Reference standard	Accuracy % (95% CI)	Studies (persons)	Certainty in evidence
Isoniazid	Phenotypic DST	Se: 96.5 (93.8–99.2)	12 (1440)	High
	Phenotypic DST	Sp: 95.8 (91.8–99.8)	12 (517)	High
Levofloxacin	Phenotypic DST	Se: 95.8 (90.4–100)	6 (654)	Moderate
	Phenotypic DST	Sp: 96.0 (93.1–98.9)	7 (913)	High
Moxifloxacin	Phenotypic DST	Se: 96.5 (93.6–99.5)	6 (652)	High
	Phenotypic DST	Sp: 95.2 (91.0–99.4)	8 (921)	High
Pyrazinamide	Phenotypic DST+WGS	Se: 90.0 (86.8–93.2)	3 (346)	High
	Phenotypic DST+WGS	Sp: 98.6 (96.8–100)	3 (269)	High
Bedaquiline	Phenotypic DST	Se: 67.9 (42.6–93.2)	3 (31)	Low
	Phenotypic DST	Sp: 97.0 (94.3–99.7)	4 (519)	High
Linezolid	Phenotypic DST	Se: 68.9 (38.7–99.1)	4 (31)	Low
	Phenotypic DST	Sp: 99.8 (99.6–100)	6 (1093)	High
Clofazimine	Phenotypic DST	Se: 70.4 (34.6–100)	4 (36)	Low
	Phenotypic DST	Sp: 96.3 (93.2–99.3)	6 (789)	High
Amikacin	Phenotypic DST	Se: 87.4 (74.5–100)	5 (115)	Very low
	Phenotypic DST	Sp: 99.0 (98.4–99.6)	8 (1003)	Moderate
Ethambutol	Phenotypic DST+WGS	Se: 96.7 (95.0–98.4)	4 (431)	Moderate
	Phenotypic DST+WGS	Sp: 98.4 (96.1–100)	4 (123)	Moderate
Streptomycin	Phenotypic DST	Se: 98.1 (96.1–100)	5 (493)	High
	Phenotypic DST	Sp: 75.0 (59.5–90.5)	5 (250)	Low

Phenotypic Drug Susceptibility Testing (pDST)

- **pDST: Gold Standard**
- Culture based, viable organism: can be used to monitor treatment response
- No need to know the resistance mechanism
- Test drugs used in the treatment regimen
- Extended pDST: Contact NICD
- Long TAT, risk of contamination

INTERPRETATION OF RESULTS

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Case 1: TB NAAT Rifampicin unsuccessful

- 52 year old female
- Seen at a clinic

Specimen received: Sputum
Tests requested: BD Max MTB/RIF/INH (direct)

TB-NAAT: BD MAX MTB/RIF/INH (Direct)

MTB PCR result	Mycobacterium tuberculosis complex detected
Rifampicin (molecular)	Unsuccessful

TB has been detected. The rifampicin testing was unsuccessful. Submit another sample for smear, culture and DST. Please start first line TB treatment and monitor response to treatment.

Case 1: TB NAAT Rifampicin unsuccessful

- Culture positive after 38 days

TB-NAAT: GeneXpert MTB/Rif Ultra (Cultured Isolate)

PCR M.tuberculosis result	Mycobacterium tuberculosis complex detected
Rifampicin (molecular)	Resistant

Rifampicin resistant TB has been detected. Please refer the patient to the DR-TB treatment initiation site for further management. If the health facility is a DR-TB treatment initiation site, submit a sample for DR-TB reflex testing, if this has not been done already and initiate appropriate treatment. INH results will be reported as part of the DR-TB reflex testing results. Refer to the current Rifampicin Resistant TB Clinical Management Guidelines.

TB-NAAT DR-TB: GeneXpert MTB/XDR (Cultured Isolate)

PCR M.tuberculosis result	Mycobacterium tuberculosis complex detected
Isoniazid, INH (molecular)	Resistant
Fluoroquinolones, FLQ (molecular)	Low resistance
Amikacin, AMK (molecular)	Resistant
Ethionamide, ETH (molecular)	Resistant

Antimycobacterial Drug Sensitivity Testing:

Second Line Drugs - MGIT Culture Based:

Bedaquiline	Resistant
Linezolid	Sensitive

This is a case of extensive (also known as extreme) multi-drug resistant tuberculosis (XDRTB). The patient should be referred for specialist opinion.

Case 2: INH Monoresistant TB (Hr-TB)

- 25 year old male
- Previous Hr-TB in 2022 (LPA)
- HIV Negative
- Pulmonary TB

- 12/08/2024
- BD Max done at clinic
- Rifampicin: No resistance detected
- Isoniazid: Resistance detected (*katG* & *inhA* mutation)

Case 2: INH Monoresistant TB

Date	BD Max	Auramine	TB Culture	Xpert U/Xpert XDR
08/2024	INH MR	Pos 2+	Pos	Rif S
09/2024	-	Pos 2+	Pos (15 days)	Refer to Prev
10/2024	-	Scanty	Pos (21 days)	INH R/**FQ S**/Eth R
11/2024	-	Neg	Pos (11 days)	Refer to Prev
12/2024	-	Scanty	Pos (11 days)	Rif S
01/2025	-	Scanty	Pos (12 days)	Refer to Prev
02/2025		Pos 3+	Pos	Refer to Prev
03/2025 X 2	Pos (DST USF)	Pos 3+	Pos (7 days)	Rif S
03/2025 (Reflex)		Pos 3+	Pos (6 days)	Rif S/INH R/**FQ R**/Eth R
04/2025 (Reflex)		Pos 2+	Pos (13 days)	Rif S/INH R/**FQ R**/Eth R
04/2025		Pos 1+	Pos (14 days)	Rif S

Case 2: INH Monoresistant TB

- Xpert MTB/XDR: Resistant to INH/FQ/ETH
- Transferred to KDH: 10/05/2025 On BPaL

- Phenotypic DST (Taken in March before BPaL regimen): **Resistant to Bedaquiline**
- Change to individualized treatment regimen
- Culture converted 01/07/2025

- Sent to NICD for EDST and tNGS: ***rpoB* I491F** mutation **(XDR-TB)**

Case 3: DR-TB Reflex: Auramine, Xpert MTB/XDR & Culture

Auramine O Stain:

Result (concentrated) - IUALTD	Positive 2+ (7-60 AFB in one field)

TB-NAAT DR-TB: GeneXpert MTB/XDR (Clinical Sample)

PCR M.tuberculosis result	Mycobacterium tuberculosis complex detected
Isoniazid, INH (molecular)	Resistant
Fluoroquinolones, FLQ (molecular)	Sensitive
Amikacin, AMK (molecular)	Sensitive
Ethionamide, ETH (molecular)	Sensitive

1. Mutations associated with high-level Isoniazid resistance were detected.

2. No mutations conferring resistance to the Fluoroquinolones (FLQ) were detected. This assay is able to detect 94% of FLQ resistance.

3. No mutations conferring resistance to amikacin were detected.

4. No mutations conferring resistance to ethionamide were detected. Resistance to ethionamide cannot be excluded.

Case 3: tNGS

Targeted Next-Generation Sequencing Mycobacterium tuberculosis complex

MTB complex	Detected
Drug:	**gDST interpretation:**
Rifampicin	Resistant
Isoniazid	Resistant
Fluoroquinolone	Sensitive
Linezolid	Sensitive
Bedaquiline	Uncertain significance

Mutations associated with high-level Isoniazid resistance were detected.

Mutations associated with resistance to linezolid (LZD) have NOT been detected. Phenotypic DST for LZD will be performed on the cultured isolate.

Any mutations graded as uncertain significance according to the WHO catalogue of mutations currently do not have sufficient data correlating them with either susceptibility or resistance.

Case 3: Phenotypic DST

Antimycobacterial Drug Sensitivity Testing:

Second Line Drugs - MGIT Culture Based:

Bedaquiline	Resistant
Linezolid	Sensitive

Summary

- **Detection of TB**
- Value of non-sputum samples: combination testing

- **Detection of drug resistance**
- DST for drugs used in the treatment regimen
- pDST: Gold standard, follow up pDST results for final call

- **Discordant laboratory results or unexpected clinical response**: reassess, investigate further and consult.