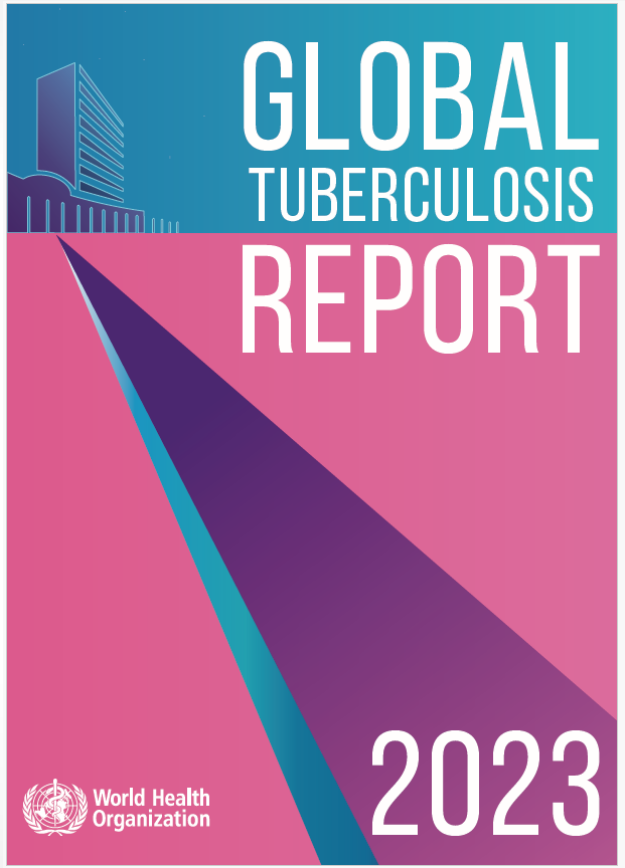
Closing the Gap: Improving Diagnostics for Drug-Resistant TB

Name: Dipti Lallubhai
Date: 4 July 2024

Current state

COVID-19 changed the world. The tuberculosis (TB) response must adapt to a new reality[2]



A mWRD* was used as the initial diagnostic test for only 47% of the 7.5 million people newly diagnosed with TB in 2022, up from 38% in 2021 and 33% in 2020. [1]

Decline in global funding available on essential TB services from U.S.$ 6.5 billion in 2019 to U.S.$ 5.8 billion in 2022.[1]

TB deaths reduced for the first time in over a decade: **1.3 million people** died from TB in **2022.**[1]

* mWRD - WHO recommended Molecular Diagnostic

1. Global tuberculosis report 2023. Geneva: World Health Organization (WHO); 2023. Accessed June 2024 Global tuberculosis report 2023 (who.int)

WHO Global Report 2023

Estimated number of people who developed MDR/RR-TB (incident cases) in 2022, for countries with at least 1000 incident cases[a]

[a] The eight countries ranked in descending order of the total number of RR-TB incident cases in 2022 are India, the Philippines, the Russian Federation, Indonesia, China, Pakistan, Myanmar and Nigeria.

Three countries accounted for 42% of the estimated global number of people who developed MDR/RR-TB in 2022:

- India (27%),
- Philippines (7.5%)
- Russian Federation (7.5%)

Global tuberculosis report 2023. Geneva: World Health Organization (WHO); 2023. Accessed June 2024 Global tuberculosis report 2023 (who.int)

Access to TB Diagnostics

1. **62%** of people have no access to rapid molecular tests for TB

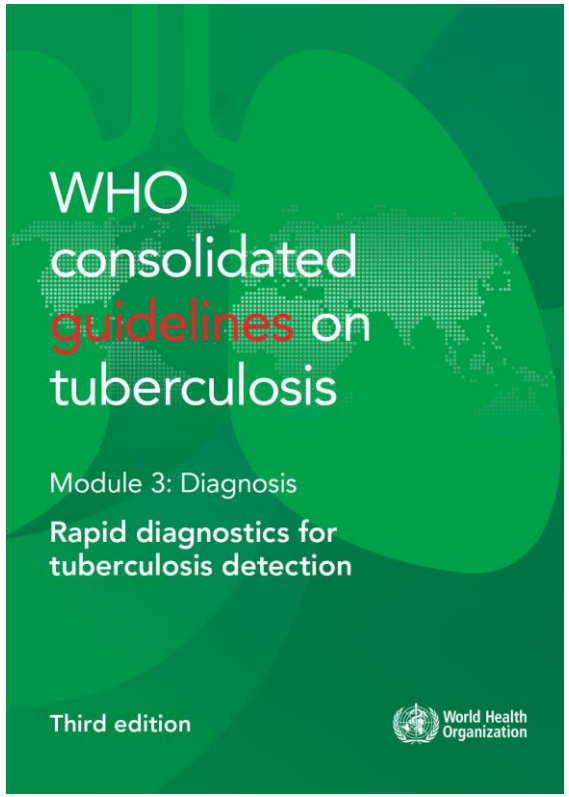
2. More than **4 Mn** people are undiagnosed, untreated, and potentially transmit the disease in the community

3. More than **400k** people are infected with drug-resistant TB (MDR, RR-TB).
   63% treatment success rate for people who started on 2nd line treatment

Global tuberculosis report 2023. Geneva: World Health Organization (WHO); 2023. Accessed Nov 2023 Global tuberculosis report 2023 (who.int)

World Health Organization (WHO) 2024

Consolidated Guidelines and Operational Handbook^*



- In adults with bacteriologically confirmed pulmonary TB, Xpert MTB/XDR^ may be used on sputum for the **initial detection of resistance to isoniazid and fluoroquinolones rather than culture-based phenotypic DST.**
- In adults with bacteriologically confirmed pulmonary TB and resistance to rifampicin, Xpert MTB/XDR may be used on sputum for the initial detection of resistance to ethionamide **rather than DNA sequencing of the *inhA* promoter.**
- In adults with bacteriologically confirmed pulmonary TB and resistance to rifampicin, Xpert MTB/XDR may be used on sputum for the **initial detection of resistance to amikacin, rather than culture-based phenotypic DST.**

WHO recommends Xpert MTB/XDR as a low-complexity automated NAAT for the detection of resistance to isoniazid and second-line anti-TB drugs

*WHO operational handbook on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection, third edition. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO.

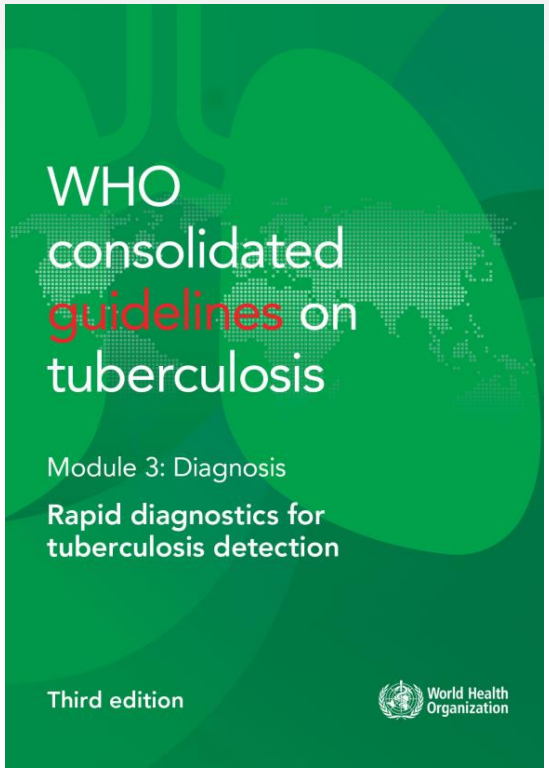
^The WHO Operational Handbook contains information about unapproved uses of Xpert® MTB/XDR. Consult the instructions for use for the approved intended use.

^ CE-IVD. *In Vitro* Diagnostic Medical Device. May not be available in all countries. Not available in the United States. Xpert MTB-XDR ENG PI 302-3514 Rev F

World Health Organization (WHO)

Operational Handbook on Tuberculosis

Module 3: Diagnosis - Rapid diagnostics for tuberculosis detection, 2021 update.*



Classes of technology and associated products evaluated ^1

Technology Class	
Low complexity automated Nucleic Acid Amplification Test (NAATs) for detection and resistance to isoniazid and second–line anti-TB agents	• **Xpert® MTB/XDR*^ (Cepheid)**
Moderate complexity automated NAATs for detection of resistance to rifampicin and isoniazid	• 7 products recommended
High complexity hybridization-based NAATs for detection of resistance to pyrazinamide	• 1 product recommended

Source

*WHO **operational handbook** on **tuberculosis**. Module 3: **diagnosis – rapid** diagnostics for tuberculosis detection, **third edition. Geneva: World Health Organization; 2024**. **Licence**: **CC BY-NC-SA 3.0 IGO**.

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Cepheid

The Cepheid Solution

The Continued Evolution of TB Diagnostics

Xpert® MTB/RIF*

The original test

Results in
110 minutes[1]

Xpert MTB/RIF Ultra^

The better test

Results in
<80 minutes[2]

Xpert MTB/XDR^

Product to aid diagnosis of multidrug-resistant MTB

Results in
<90 minutes[3]

Complex technology made easy

Exceptional clinical performance

Expanded diagnostic scope

1. Xpert MTB/RIF Package Insert, 301-0191,
2. Xpert MTB/RIF Ultra Package Insert, 301-5987
3. Xpert MTB-XDR ENG PI 302-3514

* CE-IVD. *In Vitro* Diagnostic Medical Device. May not be available in all countries. ^ CE-IVD. *In Vitro* Diagnostic Medical Device. May not be available in all countries. Not available in the United States.

Cepheid

Intended Use of the Xpert® MTB/XDR*

- The Xpert MTB/XDR test, performed on the GeneXpert Instrument Systems, is a qualitative, nested real-time polymerase chain rection (PCR) in vitro diagnostic test for the detection of extensively drug resistant (XDR) Mycobacterium tuberculosis (MTB) complex. DNA in unprocessed sputum samples, concentrated sediments prepared from
- In specimens where MTB is detected, the Xpert MTB/XDR test can also detect **isoniazid** (INH) resistance associated mutations in the ***katG*** and ***fabG1*** genes, ***oxyR-ahpC*** **intergenic region** and ***inhA*** promoter; **ethionamide** (ETH) resistance associated with ***inhA*** promoter mutations only; **fluoroquinolone** (FLQ) resistance associated mutations in the ***gyrA*** and ***gyrB*** quinolone resistance determining regions (QRDR); and **second line injectable drug** (SLID) associated mutations in the ***rrs*** gene and the ***eis*** promoter region.

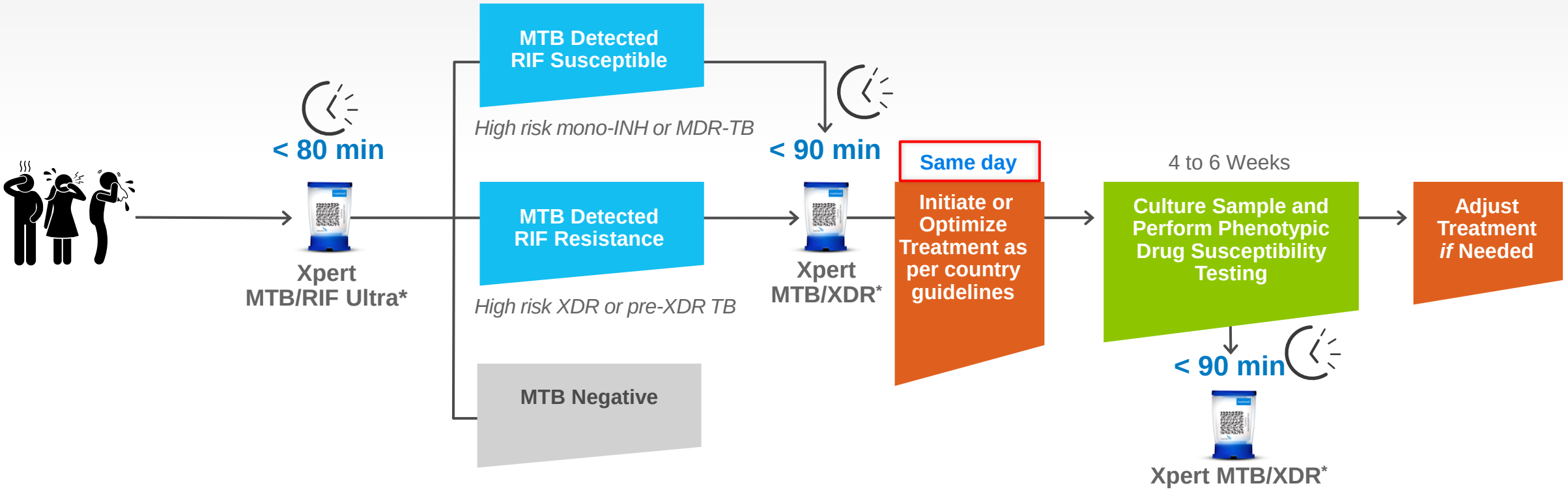
- The Xpert MTB/XDR test is intended for use as a **reflex test for a specimen (unprocessed sputum, concentrated sputum sediments, or MGIT culture) that is determined to be MTB positive.** This test is intended as an aid in the diagnosis of XDR tuberculosis (TB) when used in conjunction with clinical and other laboratory findings.

Source
1. Xpert MTB-XDR Package Insert, 302-3514
2. * CE-IVD. In Vitro Diagnostic Medical Device. May not be available in all countries. Not available in the United States

Cepheid

Xpert® MTB/XDR*

Diagnostic Pathway for Accurate Results



Fast molecular DST allows more people to start appropriate treatment on the same day

Source
1. Xpert MTB-XDR Package Insert, 302-3514
2. Xpert MTB/RIF Ultra Package Insert, 301-5987

*CE-IVD. *In Vitro* Diagnostic Medical Device. May not be available in all countries. Not available in the United States.
^US-IVD and CE-IVD. In Vitro Diagnostic Medical Device. May not be available in all countries

Xpert® MTB/XDR*
Clinical Performance

	Vs. phenotypic DST		Vs. sequencing	
	Sensitivity	**Specificity**	**Sensitivity**	**Specificity**
isoniazid	91.4%	99.1%	98.8%	98.7%
fluoroquinolones	93.1%	98.5%	93.3%	100%
amikacin	91.9%	99.4%	96.4%	100%
kanamycin	87.9%	99.6%	96.7%	100%
capreomycin	84.0%	100%	96.3%	100%
ethionamide	64.7*	98.3%	97.2%	100%

Sequencing as reference standard used the same gene targets

- For ethionamide, Xpert MTB/XDR* and sequencing only target the inhA promoter region, therefore have a higher discrepancy vs. phenotypic DST

Source: Xpert MTB-XDR 302-3514

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Xpert® MTB/XDR*

Clinical Performance (Prospective Specimens)

	Vs. phenotypic DST		Vs. sequencing	
	Sensitivity	**Specificity**	**Sensitivity**	**Specificity**
isoniazid	95.0%	95.5%	96.0%	97.7%
fluoroquinolones	94.0%	94.6%	97.1%	99.0%
amikacin	85.7%	98.4%	73.5%	99.3%
kanamycin	91.7%	92.1%	89.5%	98.4%
capreomycin	74.6%	99.4%	66.2%	99.8%
ethionamide	53.3%^	95.2%	96.4%	98.9%

Clinical performance in sputum samples is comparable across different geographies in retrospective and prospective data sets.

Source

1. Xpert MTB-XDR Package Insert, 302-3514

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^ Several specimens with A90V/S91P/D94A mutations in the *gyrA* gene were detected as susceptible by pDST and resistant by the test, resulting in lower specificity. Several specimens with *eis* promoter mutations and *rrs* wild type gene were detected as susceptible by pDST and resistant by the test, resulting in lower specificity. Reporting of ETH resistance is based only on the detection of inhA promoter mutations, resulting in a lower sensitivity

Cepheid

Analytical Performance of the Xpert® MTB/XDR* Assay

Georghio et al. Diagnostic Microbiology & Infectious Disease Journal, 2021

Highlights

- The Xpert MTB/XDR assay demonstrated equivalent limit of detection to Xpert MTB/RIF.
- The Xpert MTB/XDR assay detected 100% of tested resistance mutations and showed some utility for resistance detection in strain mixtures.
- For the hetero-resistance assessment, there was 100% detection of resistance when resistant populations comprised 10% of the mixture for INH resistance, 25% for FQ resistance, 50% for ETH, AMK and KAN resistance, and 60% for CAP resistance.
- The Xpert MTB/XDR assay reliably detects a wide range of globally relevant isoniazid, ethionamide, fluoroquinolone and second-line injectable resistance mutations.
- The Xpert MTB/XDR assay is a reliable, sensitive assay for tuberculosis and expanded resistance detection.

1. Georghiou S. B, et al, Analytical performance of the Xpert MTB/XDRR assay for tuberculosis and expanded resistance detection, Diagnostic Microbiology & Infectious Disease, 2021. https://doi.org/10.1016/j.diagmicrobio.2021.115397

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Q&A

Thank You

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