Drug-Resistant TB Sequencing Globally: WHO Perspectives & Resources

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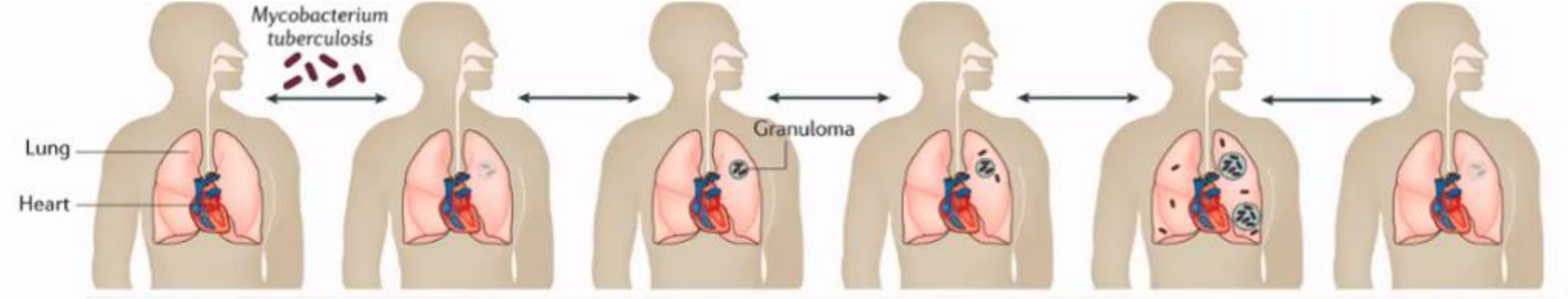
The Spectrum of TB: An Airborne Bacterial Disease



Symptoms	***Begin and Progress***			
Infectious	***Begins and Progresses***			
Tests	***Infection***	***Screening***	***Disease & Drug Resistance***	***Monitoring***
Treatment	***TB Preventive***	***TB & Drug-Resistant TB***		

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*Figure modified from Pai, M., Behr, M., Dowdy, D. et al. Tuberculosis. Nat Rev Dis Primers **2**, 16076 (2016).*

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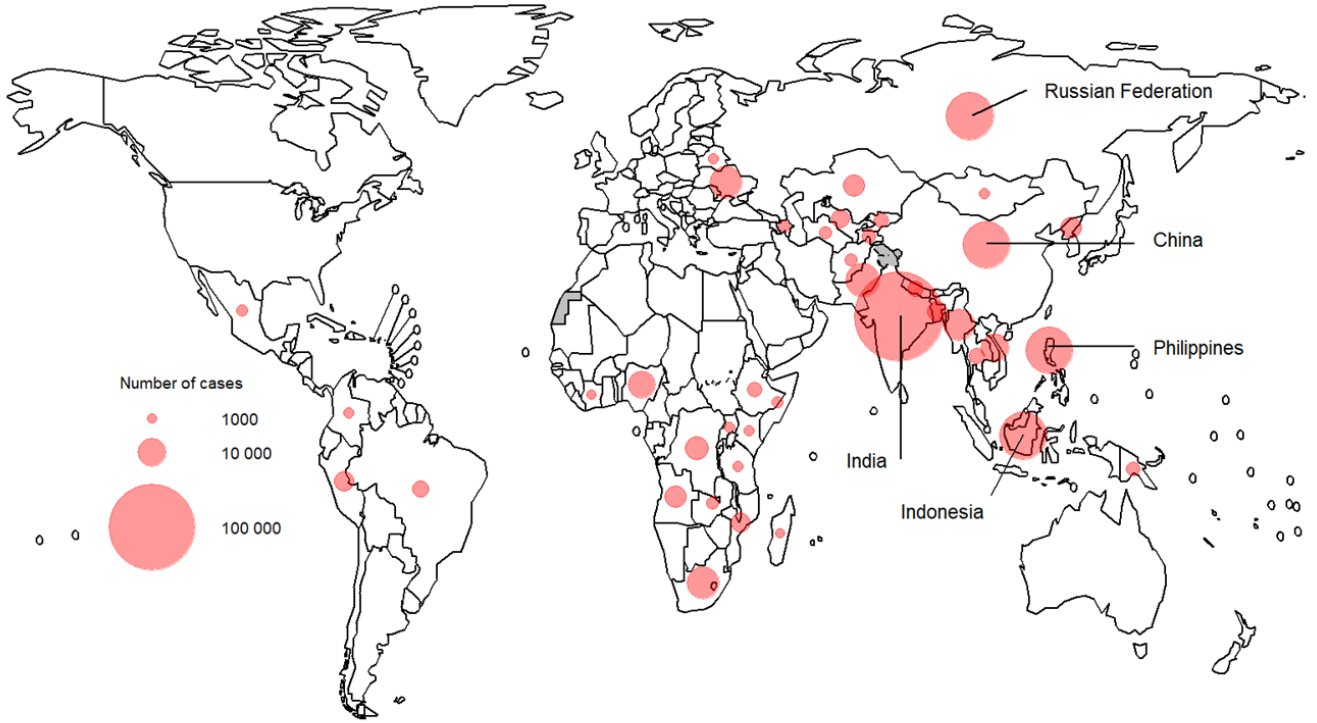
Tuberculosis: Leading Cause of Infectious Death Globally

WHO Global TB Report

- *1/4 World has been infected*
- *~10.8 Million Incident cases*
- *1.25 Million Deaths*
- *>1.5 Million Drug-resistant cases*
  - *<50% diagnosed*
- *Drug Susceptibility Testing:*
  - *79% tested for rifampicin resistance*
  - *55% tested for fluoroquinolone resistance*
  - *Low rates resistance testing to new TB drugs*

*Estimated Number of People who Developed Rifampicin-Resistant/ Multidrug-Resistant TB in 2023**



**Map shows countries with at least 1000 incident cases*

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Global Tuberculosis Report 2024

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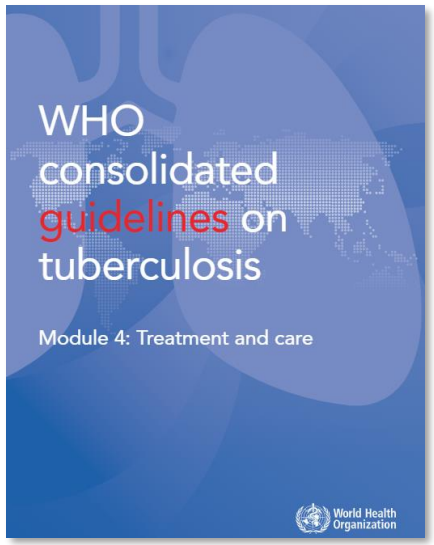
Advances in TB Treatment: New Drugs & Shorter Durations



Type of TB Disease	Regimen(s)*	Drugs	Duration
Drug-Susceptible (First-Line)	2HRZ(E)/ 4HR	RIF, INH, PZA, EMB	6 months
	2HRZ(E)/ 2HR	RIF, INH, PZA, EMB	4 months
	2HPMZ/ 2HPM	RPT, INH, PZA, MOX	4 months
INH-Resistant (RIF-S)	"Mono-INH"	RIF, LEV, PZA, EMB	6 months
MDR/RR & Pre-XDR	BPaL(M)	BDQ, PTD, LZD, MOX	6 months
MDR/RR (+/-) Pre-XDR	BDLLfxC	BDQ, DLM, LZD, LEV, CFZ	6 months
MDR/RR (-) Pre-XDR	"All Oral"	BDQ, LZD, PZA, MOX BDQ, LZD, PZA, LEV, CFZ BDQ, LZD, PZA, DLM, LEV	9 months
	"Longer"	BDQ, LZD, CS, MOX/LEV + CFZ	>9 months

** Regimen selection should always consider disease severity, patient/ family preference, and access and cost of drugs. Regimens and drug components may vary based on prevalence of resistance, age, and HIV status, among other factors.*

Expanding Landscape of WHO-Recommended DR-TB Diagnostics

Diagnostic Class	Resistance Detection													Time to Result
	RIF	INH	PZA	EMB	LEV	MXF	LZD	PTD*	DLM	CS	CFZ	AMK	SM	
Low-Complexity Automated Nucleic Acid Amplification Tests (NAATs)	✓	✓			✓	✓						✓		2h
Moderate-Complexity Automated NAATs	✓	✓												4-8h
Line Probe Assays/ HC-rNAAT	✓	✓	✓		✓	✓						✓		1-2d
Liquid & Solid Culture-based Drug Susceptibility Tests	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	3 - 12+wks
Whole Genome Sequencing	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	3+ wks
Targeted Next Generation Sequencing	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	1-2d

Genomic sequencing for the detection of DR-TB is:

- More rapid and nearly as comprehensive as the phenotypic DST gold standard
- Adaptable, scalable, and can provide resistance results across various treatment regimens from a single primary sample

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**New WHO guidance is planned to support sequencing-based DST for pretomanid.*

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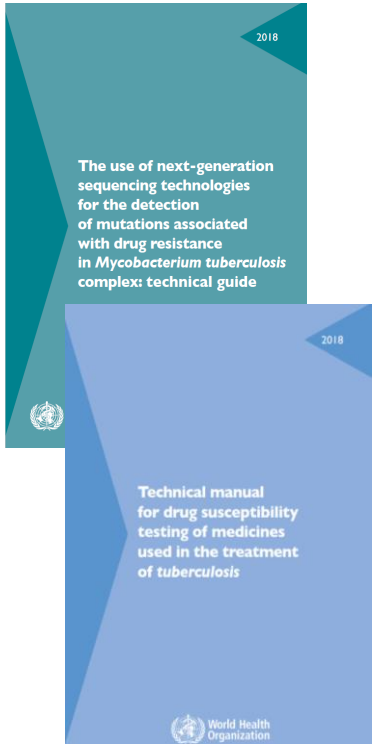
Timeline for WHO DR-TB Sequencing Guidance

2018



2021

2022

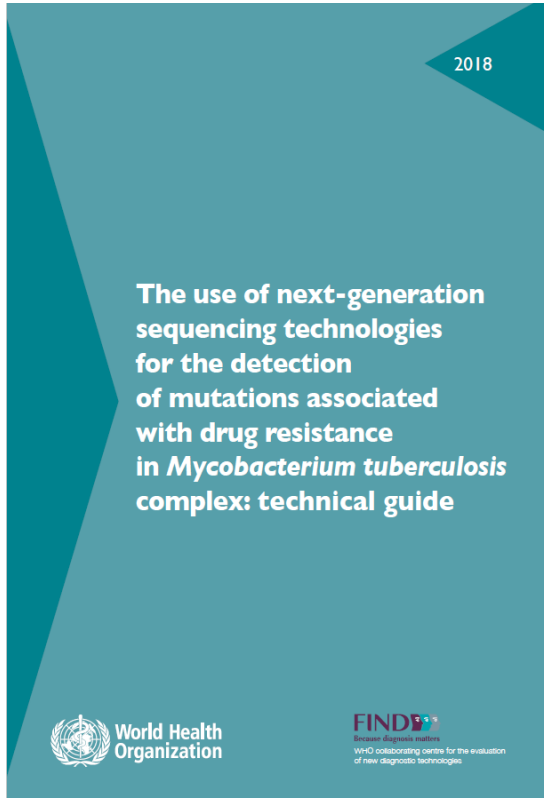
2023

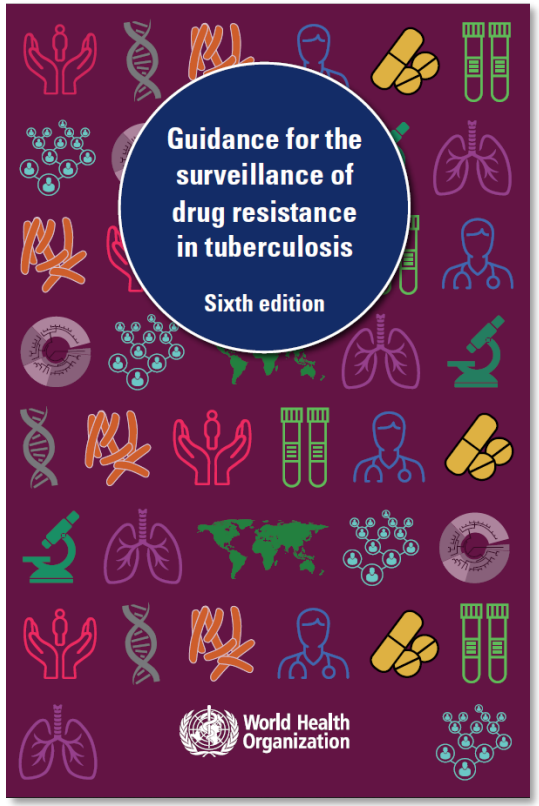
2024

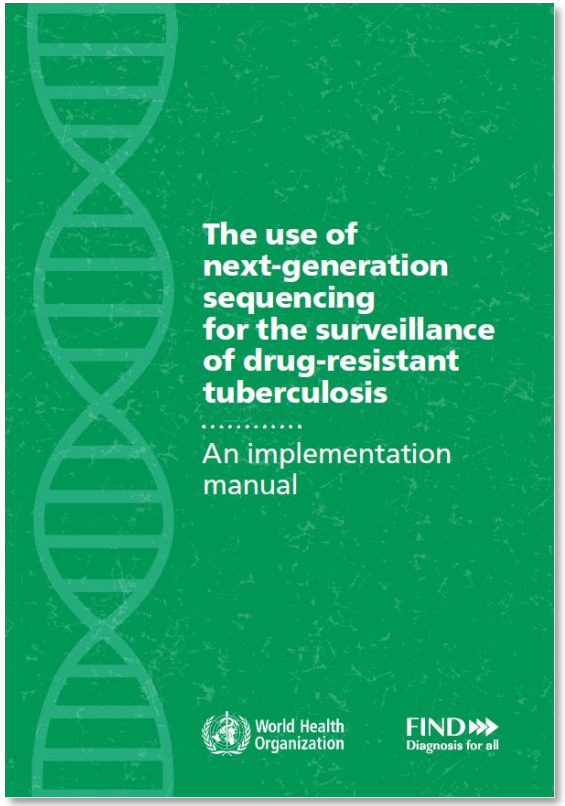
2025

Initial Guidance: NGS for DR-TB Surveillance

Shaheed Vally Omar







Resulted in NGS capacity for detection of DR-TB that could benefit disease control programs in advance of result use for clinical care

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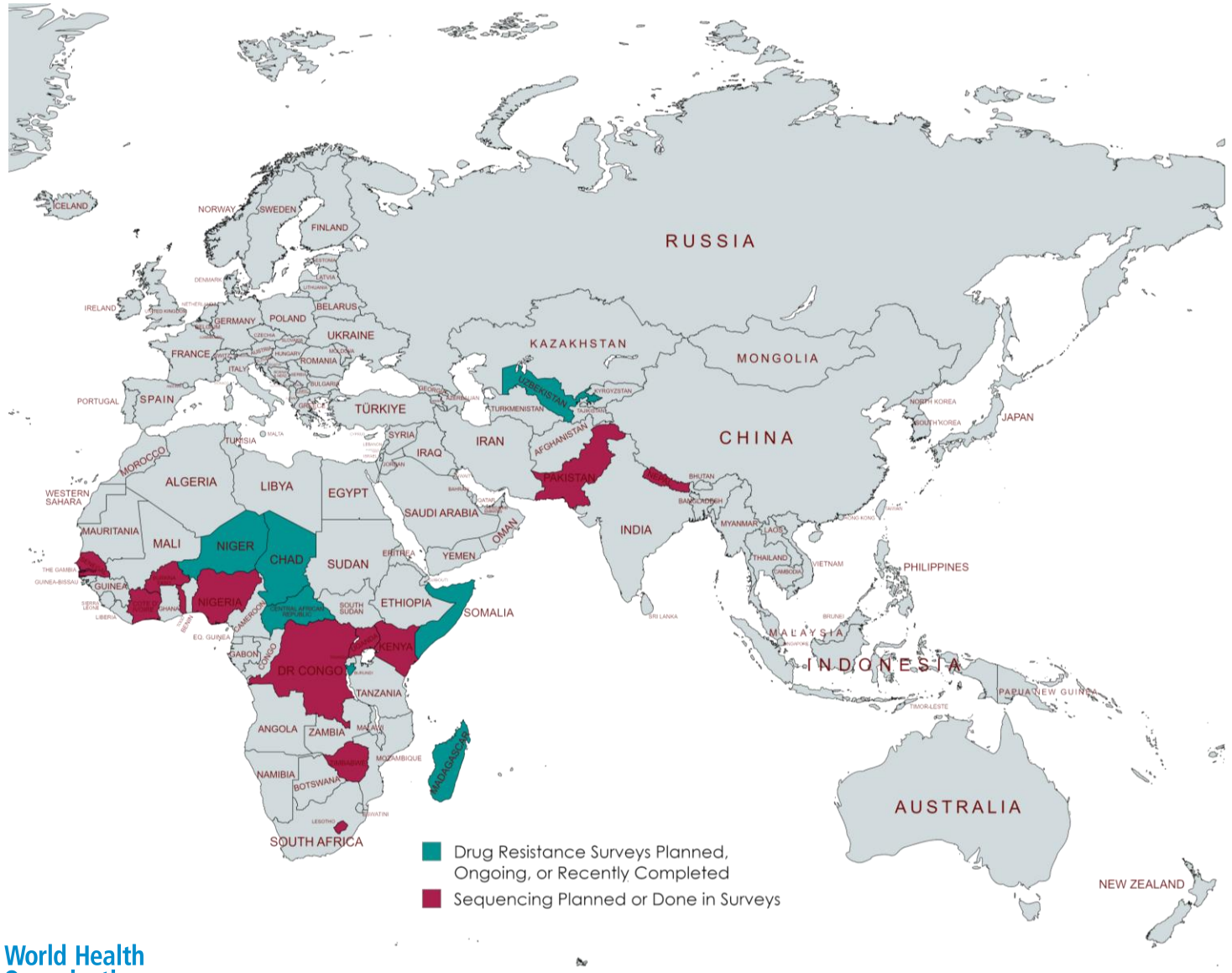
Map of Sequencing Use for TB Drug Resistance Surveys



- ✓ In 2024, 21 surveys were planned, ongoing, undergoing analysis, or recently completed
- ✓ 14 of 21 (74%) of drug resistance surveys were planning to use, using, or used NGS locally or remotely by a WHO Supranational Reference Laboratory (SRL)

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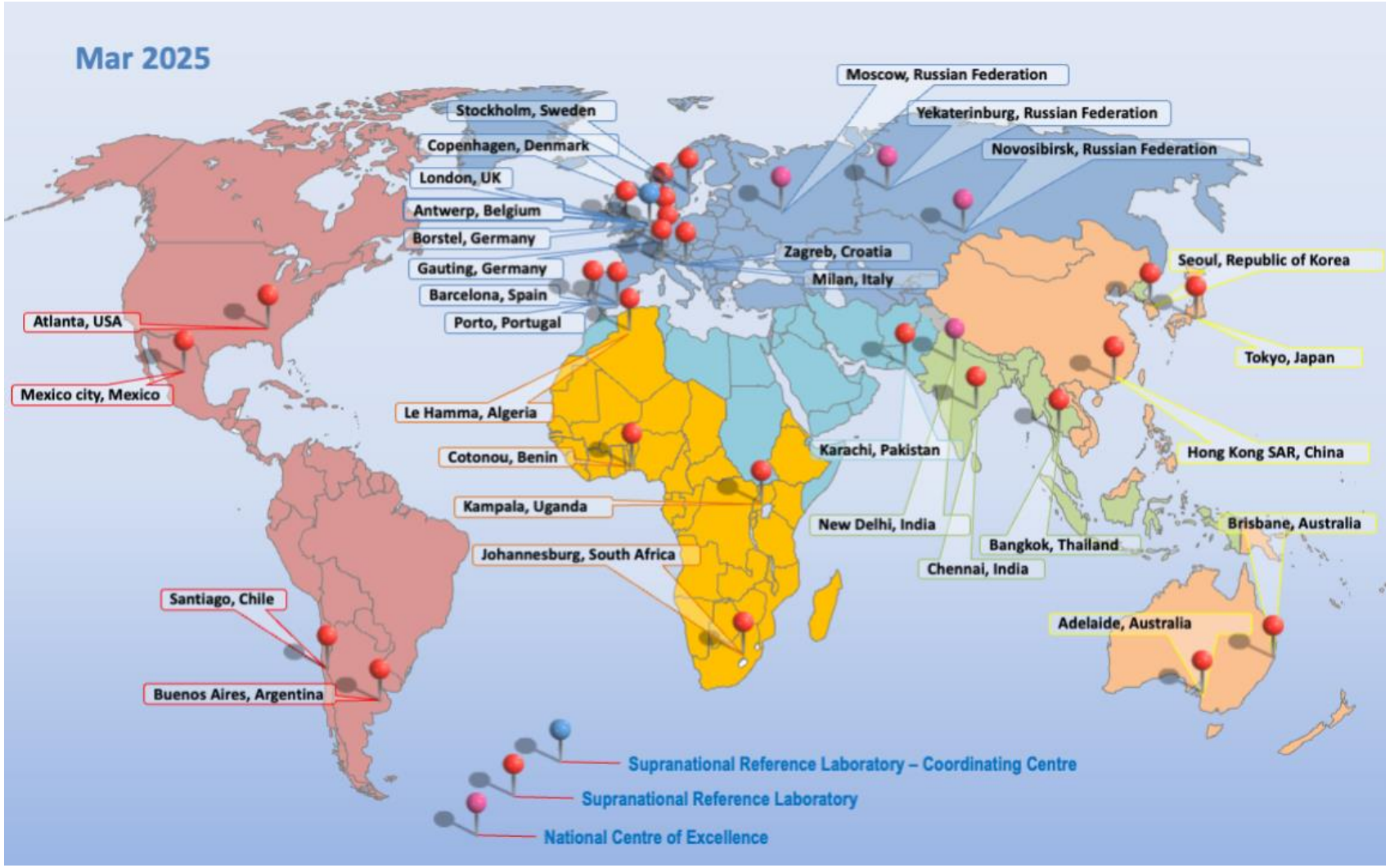
NGS Capacity in the WHO TB SRL Network



By 2024, 22/24 SRLs reported having NGS testing capacity for research, surveillance, and/ or clinical care

WHO TB SRLN Network

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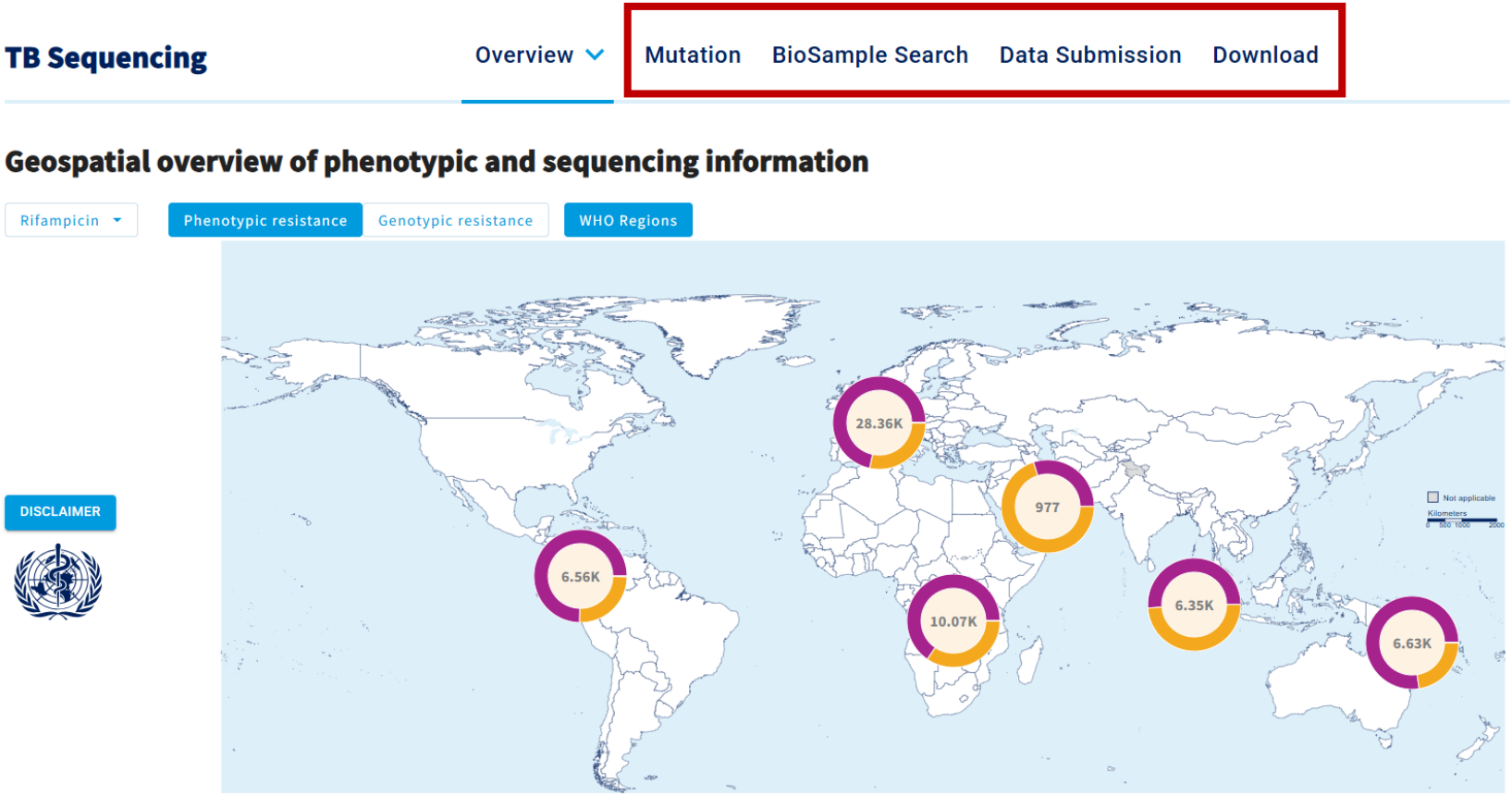
WHO Catalogue: Guides R&D and Standardizes Interpretation

Anita Suresh



https://tbsequencing.who.int/overview

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2023 WHO Recommendations for Clinical Use of tNGS

Anita Suresh

New TB Diagnostic Class: Targeted Next Generation Sequencing

Uses massively parallel sequencing to detect resistance to TB drugs, starting from a processed clinical sample and ending with an end-user report that relates detected *Mycobacterium tuberculosis* mutations to the presence (or absence) of drug resistance, based on the interpretation of a standard catalogue of mutations.

The products and drugs for which eligible data met the class-based performance criteria are listed below:

Deeplex® Myc-TB (Genoscreen, France): rifampicin, isoniazid, pyrazinamide, ethambutol, fluoroquinolones, bedaquiline, linezolid, clofazimine, amikacin and streptomycin

AmPORE-TB® (Oxford Nanopore Diagnostics, United Kingdom): rifampicin, isoniazid, fluoroquinolones, linezolid, amikacin and streptomycin

TBseq® (Hangzhou ShengTing Medical Technology Co., China): ethambutol

Cost-effective depending on setting and context

Acceptable and implementable, despite inherent complexity

Among people with bacteriologically confirmed pulmonary TB

Accurate for drugs used to treat drug-susceptible TB.

Pooled sensitivities of ≥ 95% for rifampicin, isoniazid, moxifloxacin and ethambutol, 94% for levofloxacin and 88% for pyrazinamide.

Specificity ≥ 96% for all drugs.

Among people with bacteriologically confirmed rifampicin-resistant pulmonary TB

Accurate or acceptable for drugs used to treat DR-TB.

Accurate for isoniazid, levofloxacin, moxifloxacin, pyrazinamide and ethambutol (pooled sensitivities ≥ 95%).

Acceptable for bedaquiline (68%), linezolid (69%), clofazimine (70%), amikacin (87%) and pyrazinamide (90%).

Specificity ≥ 95% for all drugs except streptomycin (75%).

The Future for Genomic Sequencing of DR-TB

- ❑ New WHO Guidance & Recommendations for Expanded Resistance Testing
  - ✓ Harnessing Advances: Mutations Catalogue 3rd Edition + Updated TB Sequencing Portal
  - ✓ Supporting Practical Use: Manual for Clinical Use (validation/ verification, clinical reporting)
  - ✓ Increasing Knowledge: WHO Academy eCourse on TB Drug Susceptibility Testing, including tNGS
  - ✓ Ensuring Evidence-Based Testing: Assessing New/ Updated Solutions for WHO Recommendation & Prequalification
- ❑ Increased Sequencing Use to Guide Clinical Management of DR-TB
  - ✓ Cross-sharing of enablers and barriers from high income and early implementer countries
  - ✓ Review of service delivery models that address TB-specific biosafety considerations
- ❑ Reduced Cost of Required Equipment and Reagents
  - ✓ Negotiation of DR-TB reagent and commodity pricing
  - ✓ Coordinated approaches to instrument procurement, maintenance, and use

Thank You

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