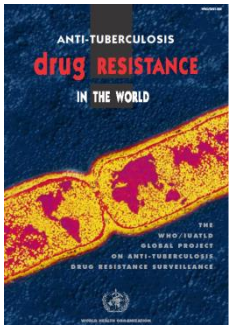
The Role of Genome Sequencing in Global Surveillance of Anti-tuberculosis Drug Resistance

Matteo Zignol
World Health Organization

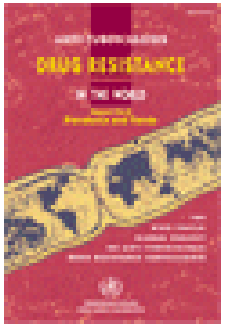
History of the Global DRS project

Global Project launched

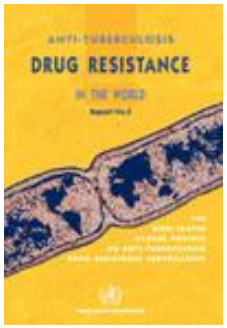
SRLN launched



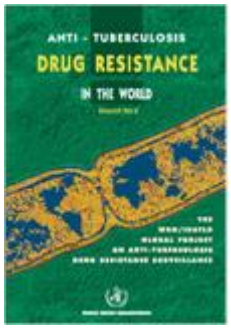
1st global DRS report



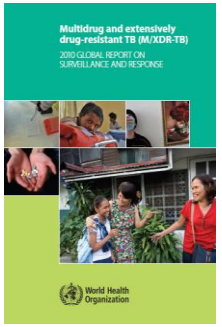
2nd global DRS report



3rd global DRS report



4th global DRS report



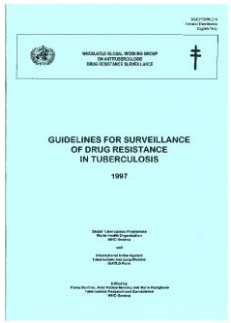
M/XDR-TB report

2016 TB report

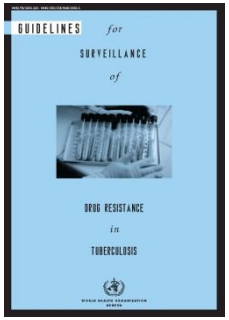
1994 1997 2000 2003 2004 2008 2009 2010 2016

1st ed. DRS

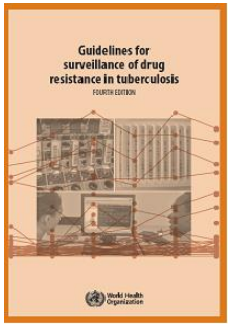
2nd ed. DRS guidelines



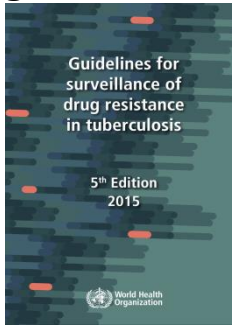
3rd ed. DRS guidelines



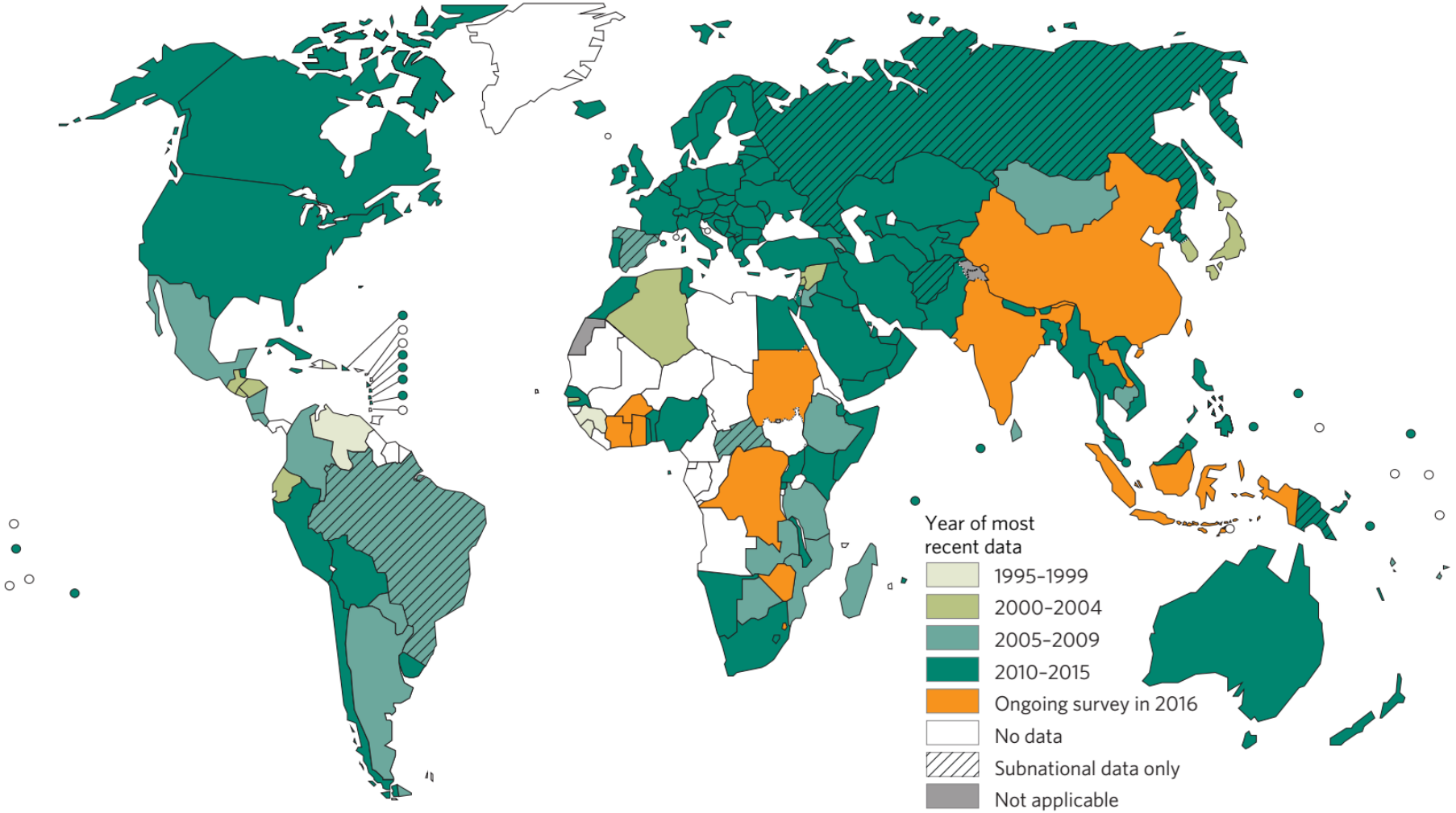
4th ed. DRS guidelines



5th ed. DRS guidelines

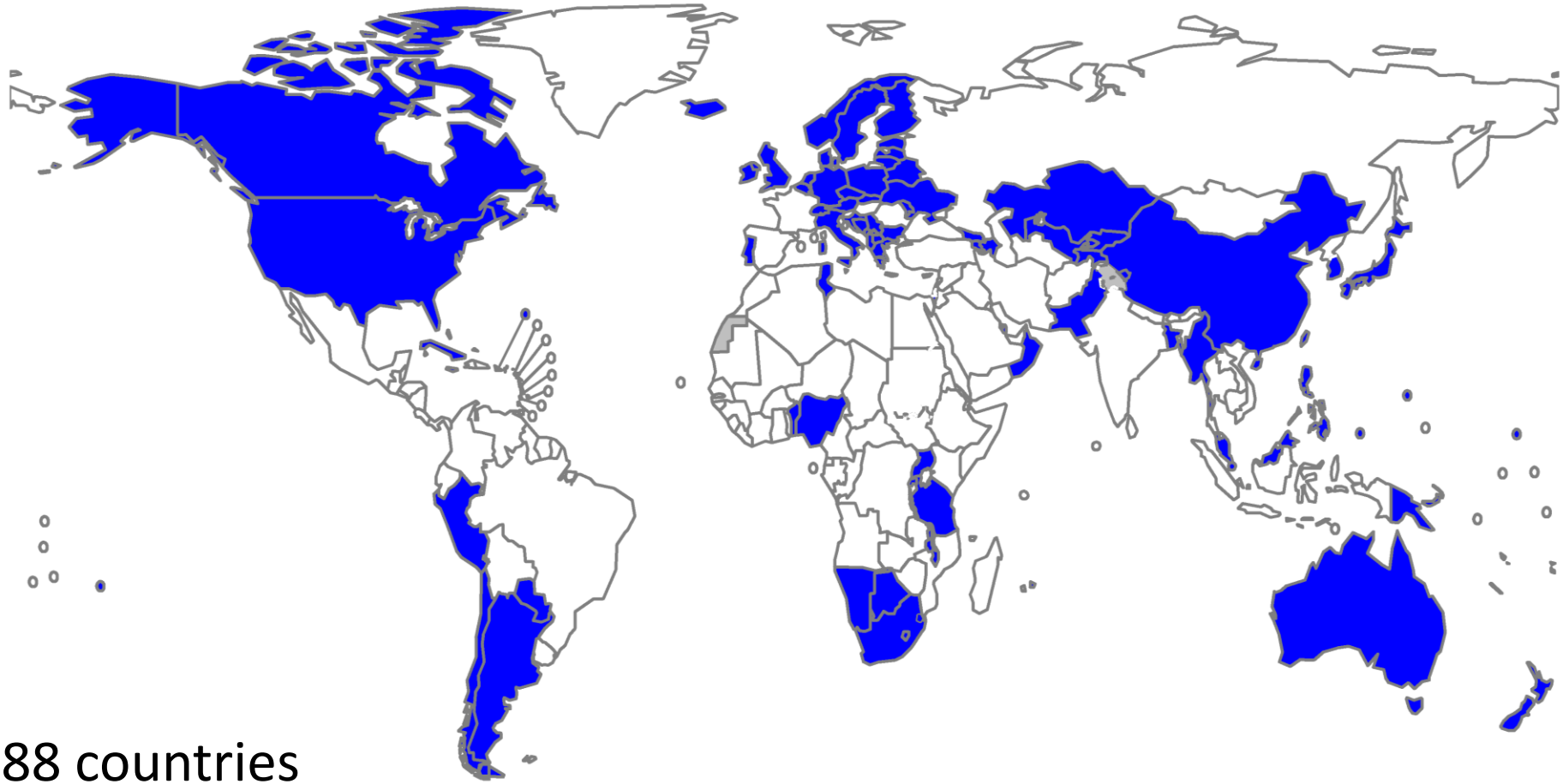


Global coverage of RIF and INH data, 1995-2016



N Engl J Med. 2016; 375:1081-9

Global coverage on data on second-line resistance among MDR-TB patients, 2006-2016



88 countries

Survey operations

- ~ 15 national surveys ongoing each year
- ~ 15 national surveys in preparation each year
- Xpert MTB/RIF used in most surveys (often after smear microscopy)
- challenges with sample transport (in-country and also international)
- high workload for laboratories performing phenotypic testing

Solution: to replace conventional DST with NGS

Use of sequencing technologies in DR surveillance

project funded by BMGF and USAID: ~ 7,000 patients

Country	Survey site	Survey status	No. of patients (new & retr)	Phenotypic DST method	Sequencing method
Azerbaijan	nationwide	survey completed in 2013	748	LJ: RIF, INH MGIT: OFX, MFX, PZA	Illumina (WGS)
Bangladesh	nationwide	survey completed in 2011	955	LJ: RIF, INH MGIT: OFX, MFX, PZA	Illumina (WGS)
Belarus	Minsk city	survey completed in 2011	201	MGIT: RIF, INH, OFX, MFX, PZA	Ion Torrent (WGS)
Pakistan	nationwide	survey completed in 2013	1,503	LJ: RIF, INH MGIT: OFX, MFX, PZA	Illumina (WGS) Sanger
Philippines	nationwide	survey completed in 2011	1,198	LJ: RIF, INH MGIT: OFX, MFX	Sanger
South Africa	Gauteng & Kwazulu-Natal provinces	survey completed in 2014	1,651	MGIT: RIF, INH, OFX, MFX, PZA	Illumina (WGS)
Ukraine	nationwide	survey completed in 2014	1,444	LJ: RIF, INH, OFX MGIT: MFX, PZA	Illumina (WGS)

Ongoing and planned surveys in 2017

Ongoing:

- **DR Congo**: NGS (Illumina) using the Deeplex-MycTB assay (Genoscreen) on 1,500 sputum samples for 18 main gene targets
- **Djibouti**: NGS (Illumina) using the Deeplex-MycTB assay (Genoscreen) on 250 sputum samples for 18 main gene targets
- **Indonesia**: WGS (Illumina) on 1,400 isolates
- **Uganda**: WGS (Illumina) on 200 survey isolates

Planned to start in 2017:

- **Eritrea**: NGS (Illumina) using the Deeplex-MycTB assay (Genoscreen) on 550 sputum samples for 18 main gene targets
- **Ethiopia**: WGS (Illumina) on 1200 survey isolates
- **Swaziland**: WGS (Illumina) on 900 survey isolates

Use of sequencing data for surveillance

1. Assessment of test accuracy for RIF, INH, PZA, OFX, MXF, KAN, AMK in population-based surveys:

- Very high specificity for all drugs (RIF, INH, PZA, OFX, MXF, KAN, AMK)
- INH: suboptimal sensitivity vs. phenotypic test
- FQL: suboptimal sensitivity vs. phenotypic test
- AGL: suboptimal sensitivity vs. phenotypic test
- New drugs (BQL, DLM): to be studied

Adjustment for test misclassification

2. Development of simple model for estimation of drug resistance proportions using genotypic data

Model for estimation of drug resistance using genotypic data

- NGS useful for measurement at the population level (DR surveillance)
- Apparent prevalence adjusted for test misclassification (bias-corrected prevalence)
- Propagate uncertainty using a simple Bayesian approach

Global DR surveillance: vision for the future (near future)

- Xpert MTB/RIF as entry test in surveys
- Targeted NGS from leftover of Xpert MTB/RIF cartridge (or from a new sputum sample)
- Estimation of resistance to multiple drugs based on NGS data

Acknowledgments

Implementing group:

- Anna Dean, Andrea Cabibbe, Philippe Glaziou
- NRLs and NTPs of Azerbaijan, Bangladesh, Belarus, Pakistan, South Africa
- SRLs of Antwerp, Borstel, Johannesburg, Karachi, Milan, Stockholm
- WHO (CO, RO, HQ)

Donor Agencies:

- BMGF
- USAID
- TB Alliance