The changing environment for diagnostics implementation

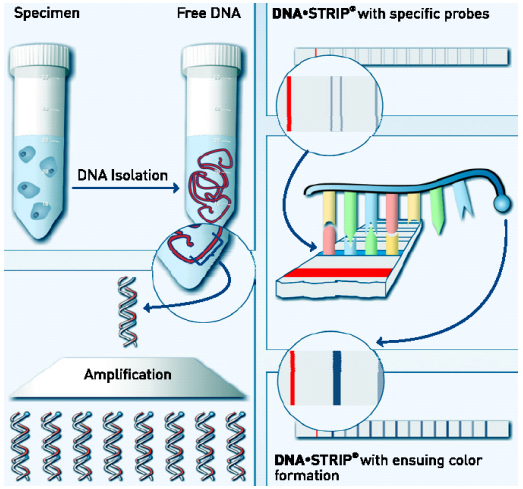
Karin Weyer

Laboratories, Diagnostics and Drug Resistance

THE STOP TB DEPARTMENT

Strengthening TB laboratories

‘From unimaginable…to indispensable’



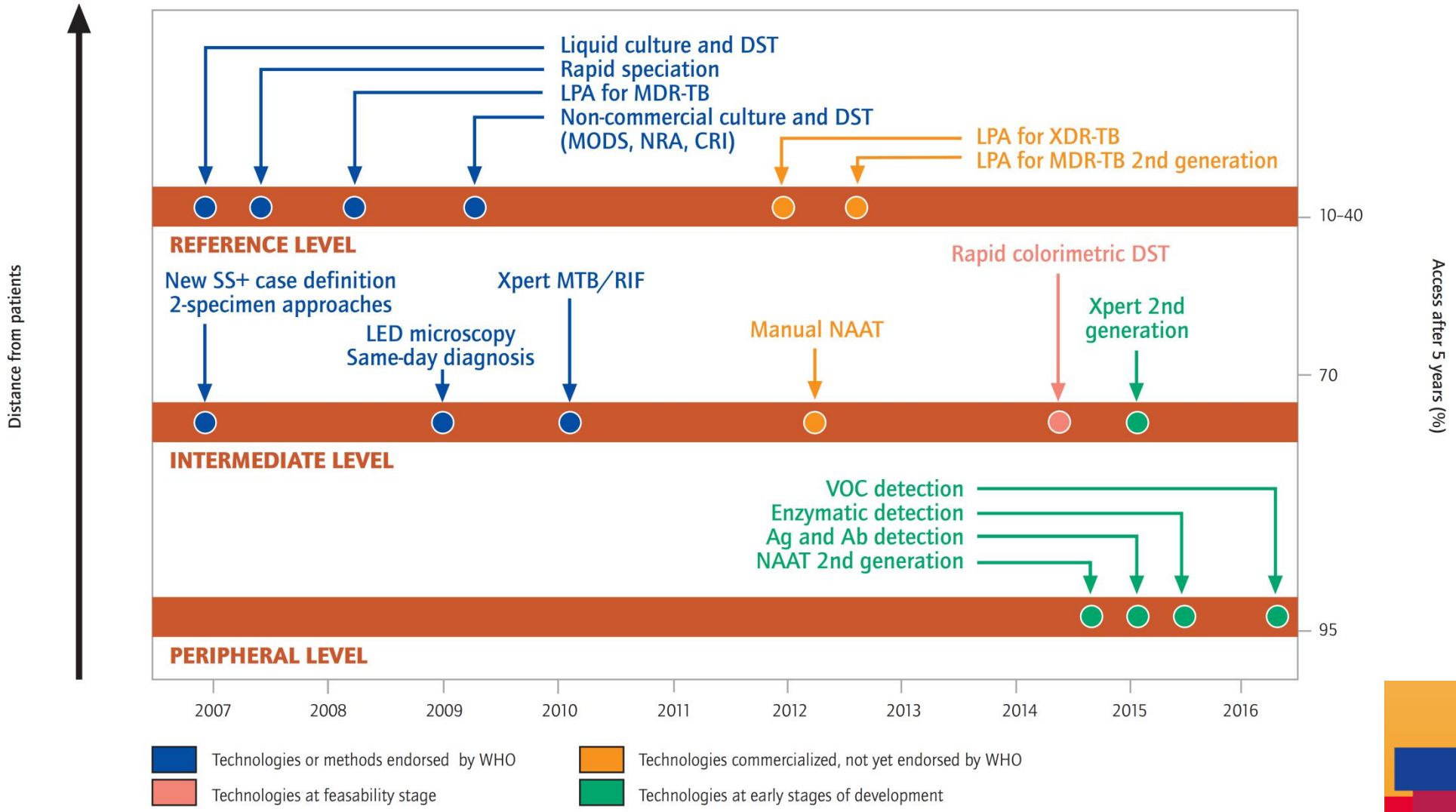
1st GLI Meeting, Annecy
April 2008

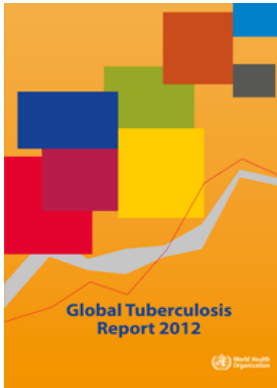
gli
global laboratory initiative
advancing TB diagnosis

Landscape rapidly changing

- Growing diagnostics pipeline
- Accelerated WHO policy formulation
- Policy transfer, uptake and innovation
- Policy impact
- Access to new diagnostics and laboratory services
- Need to align diagnosis, treatment and care delivery

The development pipeline for new TB diagnostics





Acceleration

- **Tools development**: At least 20 new technologies in various stages of development and evaluation in last 10 years
- **WHO policy formulation***
  - 2007 : New SS+ case definition, two-specimen approach, liquid culture, rapid speciation
  - 2008 : Line probe assay
  - 2009 : LED microscopy, 'same-day diagnosis', selected non-commercial culture and drug susceptibility testing methods
  - 2010 : Xpert MTB-RIF
  - 2011 : IGRAs, commercial serodiagnostics
  - 2012 : TB laboratory biosafety
  - 2012 : Updated guidance on drug susceptibility testing
- **Access** to new diagnostics and laboratory strengthening (GLI and EXPAND-TB)

*Available at: http://www.who.int/tb/dots/laboratory/policy/en

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Tools/methods not recommended

- **Evidence base too weak, to be reassessed**
  - 2009: Sputum processing methods
  - 2009: TLA method for rapid DST
  - 2010: LPA for XDR-TB
  - 2012: TB-LAMP

- **'Negative' policy (do-not-use)**
  - 2011: Commercial serodiagnostics
  - 2011: IGRAs (high TB or HIV burden settings)

Policy pipeline 2013

- **Guidance on drug susceptibility testing**
  - Update on 2008 guidance
- **LPA update**
  - Update on 2008 guidance
  - New 2nd-line LPA (XDR)
- **Xpert MTB/RIF update**
  - Extra-pulmonary TB
  - Paediatric TB

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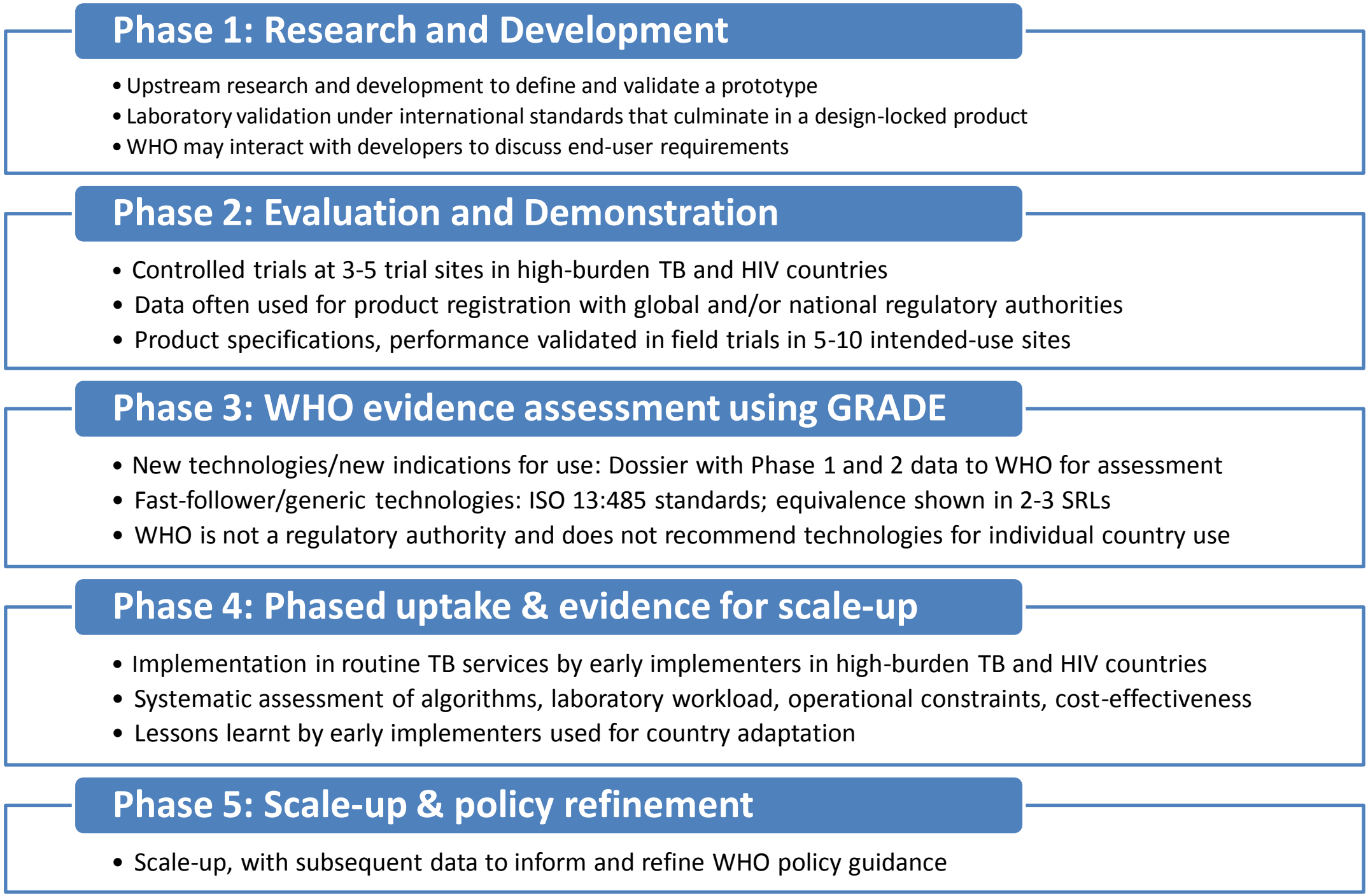
WHO TB diagnostics policy formulation process

Figure 4. Body of evidence required by WHO for policy development



GRADE evolution for TB Diagnostics

- Refined quality assessment tools (eg. QUADAS-2)
- Refined statistical methodology for meta-analyses
- Standardised proxies for patient- and public health impact
- Cost-effectiveness modeling
- **But**: **Test-specific recommendations necessary**
  - Different technologies, targets, performance characteristics

Table 1: Pooled values (95% CI) of sensitivity and specificity of five commercial NAATs for pulmonary TB in 60 published studies (Greco, Girardi et al. 2006)

Test	AFB+		AFB-	
	Sensitivity	Specificity	Sensitivity	Specificity
Amplicor (PCR)	96 (94-97)	83 (80-86)	61 (57-65)	97 (96.8-97.4)
Cobas Amplicor (PCR)	96 (95-97)	74 (68-8)	64 (59-69)	99 (99.2-99.4)
BDP (SDA)	98 (96-99)	89 (84-93)	71 (66-76)	97 (96.4-97.4)
E-MTD (TMA)	97 (95-98)	96 (93-97)	76 (70-80)	97 (96.6-97.4)
LCx (LCR)	96 (94-98)	71 (64-78)	57 (50-64)	98 (97.8-98.5)

PCR: polymerase chain reaction; SDA: strand displacement amplification; TM: transcription mediated amplification; LCR: ligase chain reaction.

Policy uptake at country level (1)

- **Rapid uptake**
  - SS+ case definition
  - Xpert MTB/RIF
- **Limited or no uptake**
  - Two-specimen strategy
  - Same-day-diagnosis
  - Non-commercial culture and DST methods
- **Gradual uptake**
  - LED microscopy
  - Liquid culture and DST
  - Rapid speciation
  - Line probe assay

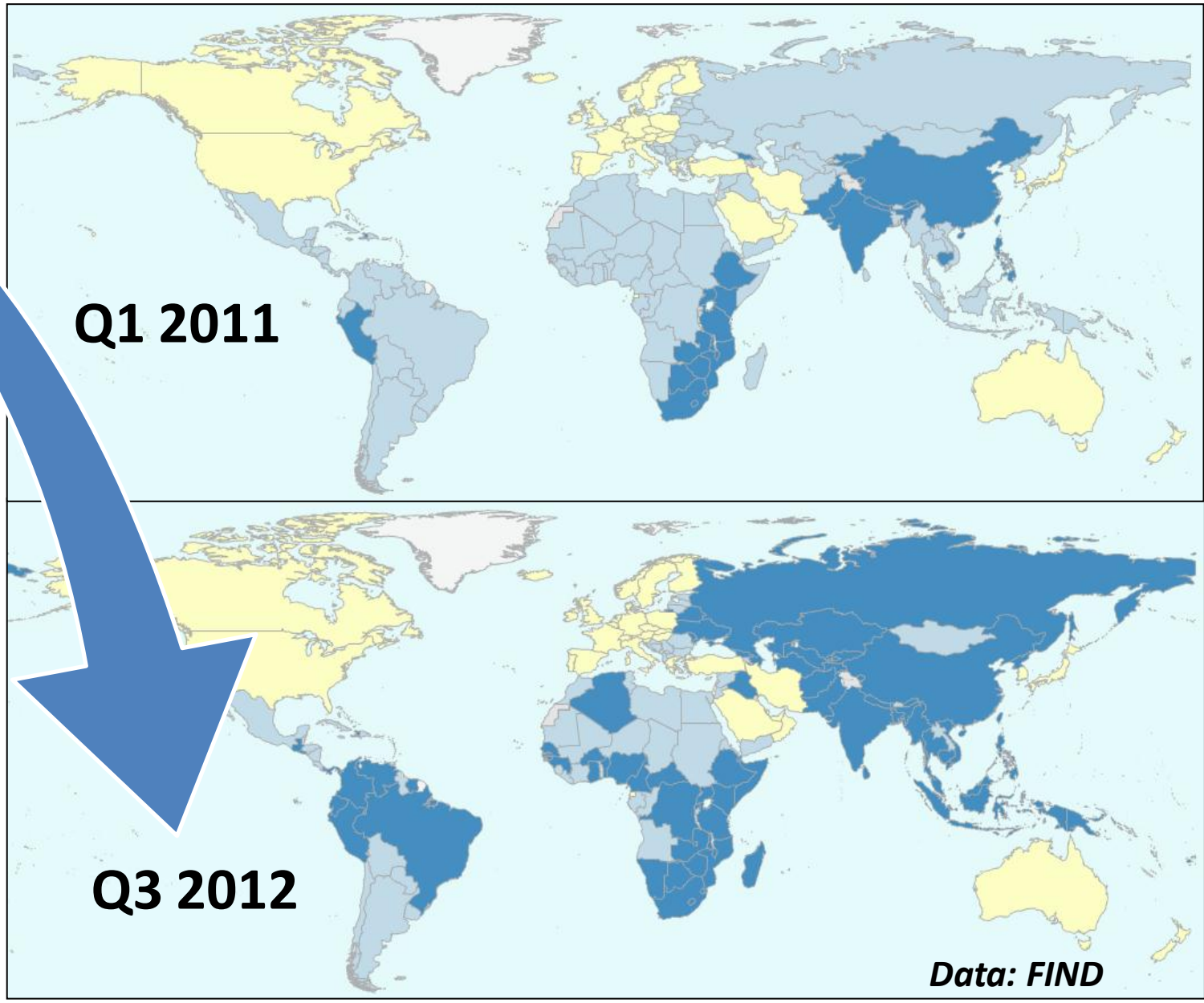
Policy uptake at country level (2)

Incorporation of WHO policy guidance for diagnosis of TB, 2011	High-burden countries	High MDR-TB burden countries	Global
Conventional drug susceptibility testing (DST)	95%	100%	85%
Liquid culture and rapid speciation test	73%	75%	67%
Line probe assay for detecting resistance to rifampicin	64%	74%	44%
Algorithm for the diagnosis of TB in people living with HIV	86%	87%	74%
Xpert MTB/RIF assay	64%	50%	33%

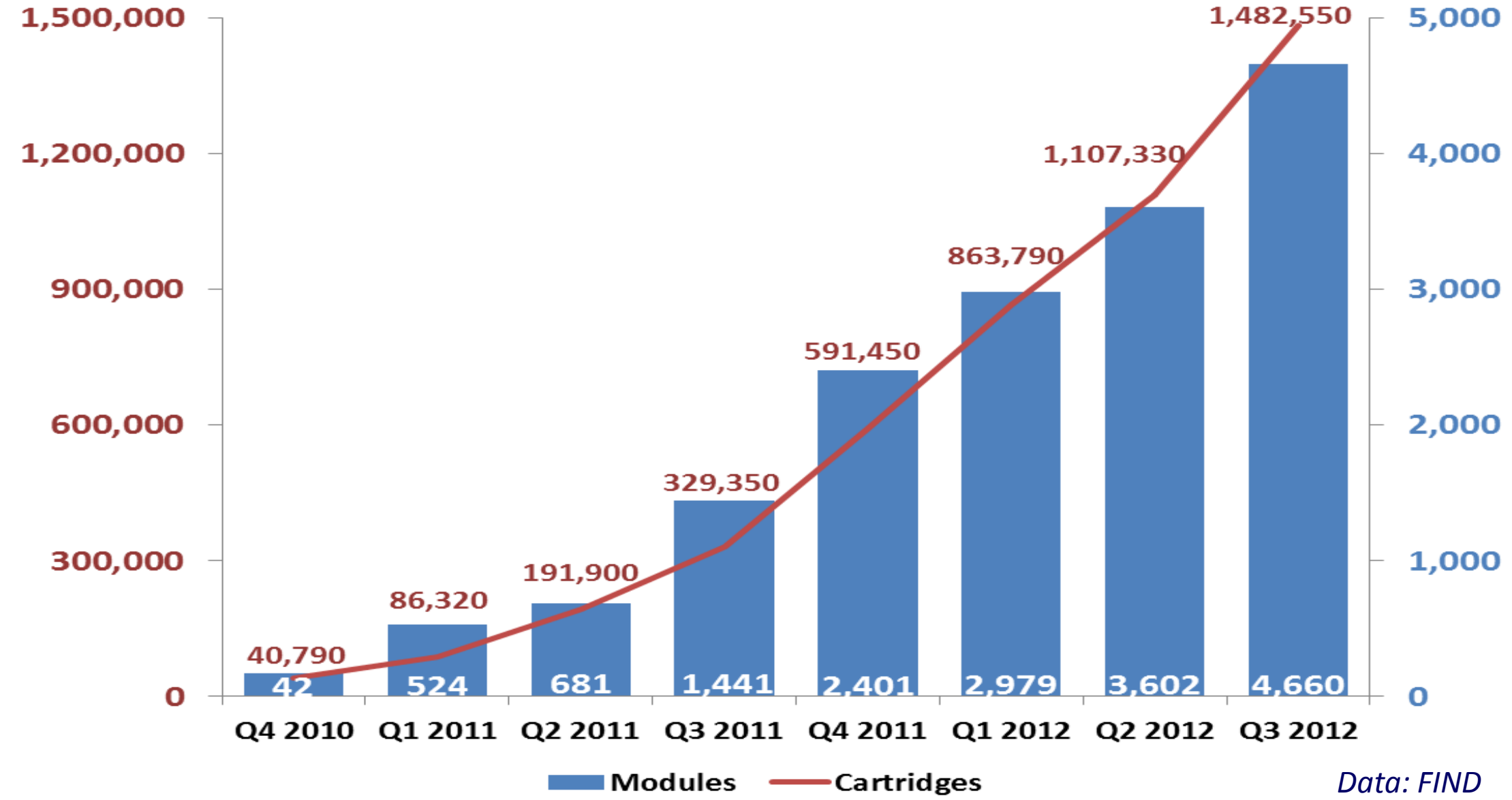
Policy impact (1)

99 GeneXperts
(524 modules)
in the public sector
in **23** countries

898 GeneXperts
(4,660 modules)
in the public sector
in **73** countries



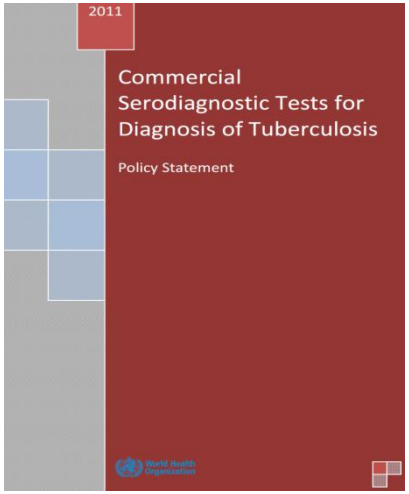
Cumulative number of GeneXpert modules and Xpert MTB/RIF cartridges procured under concessional pricing



Data: FIND

World Health Organization

Policy impact (2)



First 'negative' policy guidance by WHO

Unprecedented political commitment by India

Health Ministry set to ban commonly used TB test

Abantika Ghosh : New Delhi, Tue Mar 20 2012, 00:34 hrs

The Health Ministry has decided to ban serological diagnostic test for tuberculosis, in line with a World Health Organisation recommendation. India is going to become the first country to execute the ban on the test, which is highly inaccurate but commonly used.

It is estimated that 1.5 million patients are subjected to the test every year in India for diagnosis of Mycobacterium tuberculosis and many of them are started on anti-TB treatment on the basis of the results. In many cases, all it does is result in antibiotic resistance.

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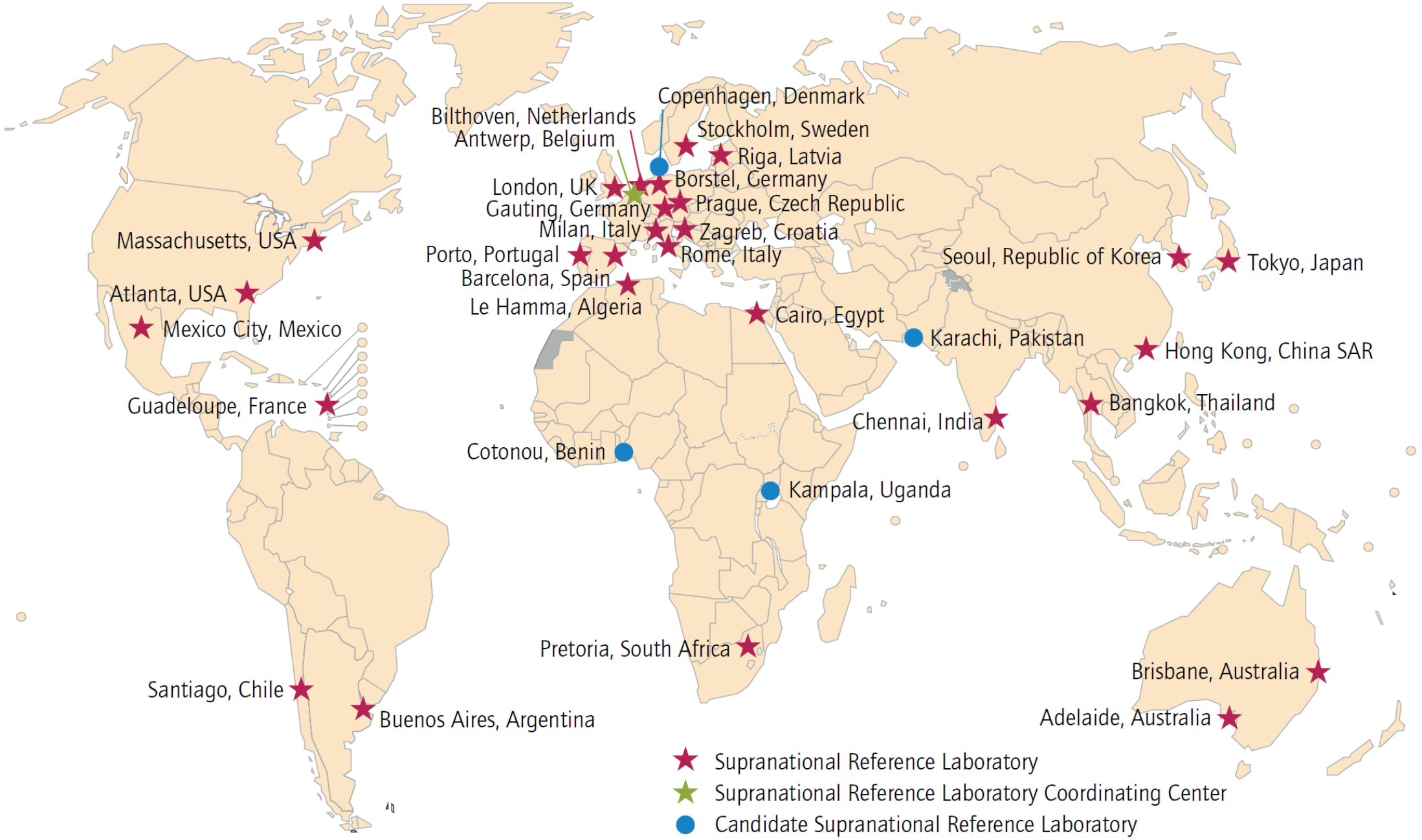
Laboratory capacity, 2011

	Smear microscopy: Laboratories per 100,000 population	Culture: Laboratories per 5 million population	DST: Laboratories per 5 million population	Line probe assay: Laboratories per 5 million population
22 high TB burden countries	1.1	1.5	0.4	<0.1
27 high MDR-TB burden countries	0.9	1.3	0.4	0.1
Global	1.1	3.9	0.8	0.2

- 15 of the 22 high TB burden countries have ≥1 microscopy centre per 100,000 population
- 17 of the 36 high TB / MDR-TB burden countries have ≥1 culture and DST laboratories per 5 million population

WHO/GLI Supranational Reference Laboratory Network



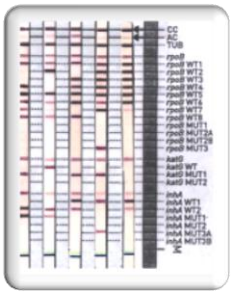
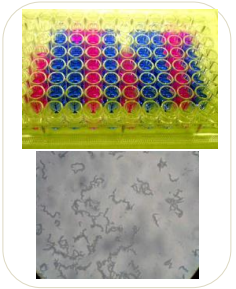
Organization

Tools in tiered heath services

Surveillance
Reference methods
Network supervision

Central Reference Level




Case finding
Treatment

District & Sub-district Level



Screening
Referral

Community Level

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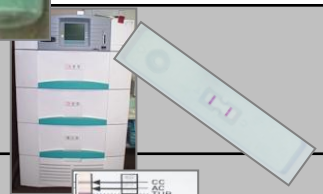
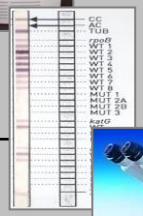
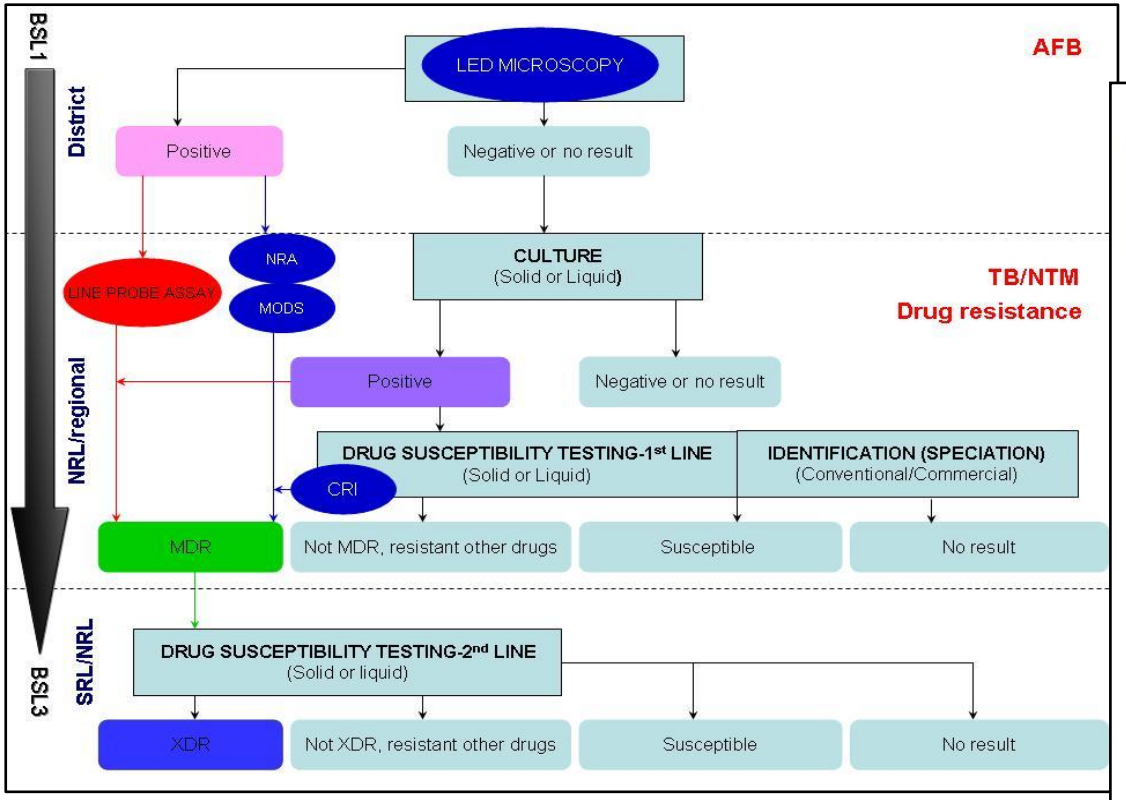
Tools in combination

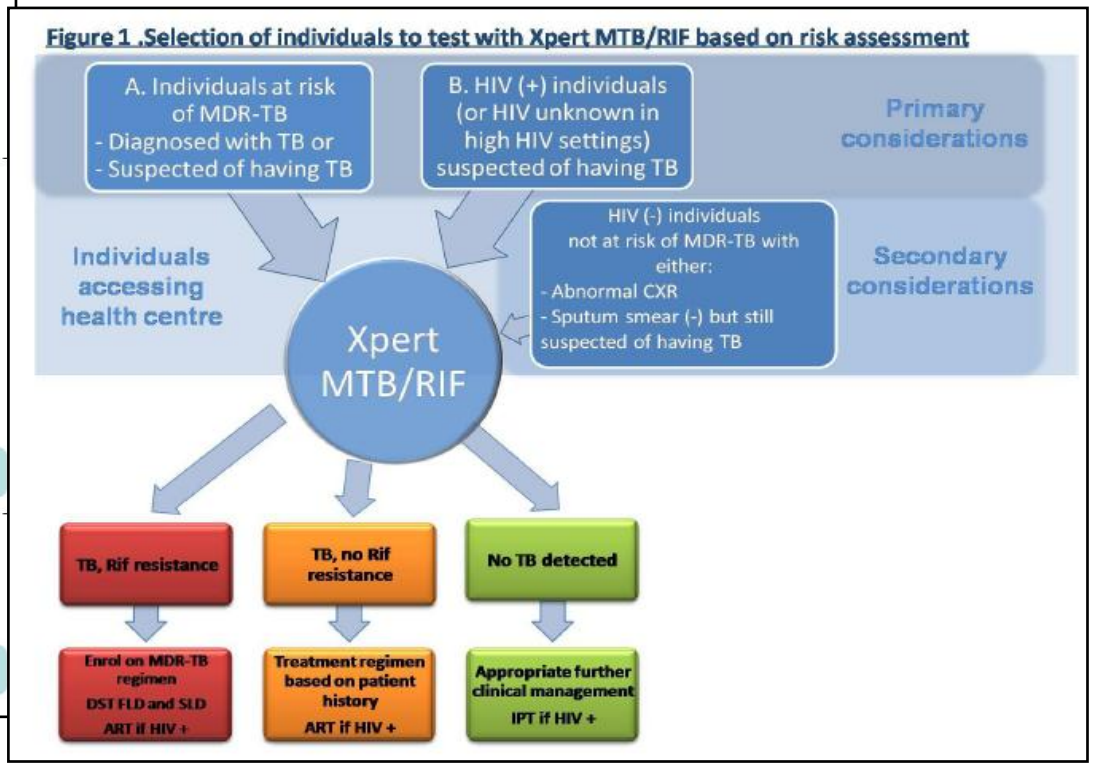
early diagnosis & care | smear-negative TB | rapid resistance detection


Year	Technology	Turnaround time	Sensitivity gain
Before 2007	ZN microscopy Solid Culture	2-3 days 30-60 days	Baseline
2007	Liquid Culture / DST Rapid speciation	15-30 days	+10% compared to LJ
2008	Line Probe Assay (1st line, Rif & INH)	2-4 days	S+ only
2009	LED-based FM	1-2 days	+10% compared to ZN
2009	In house DST (MODS, CRI, NRA)	15-30 days	1st line only
2010	Xpert MTB/RIF (TB, R resistance)	100 minutes	+40% compared to ZN

Tools in different algorithms





One size no longer fits all

WHO

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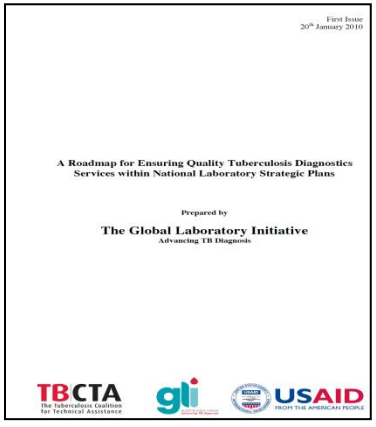
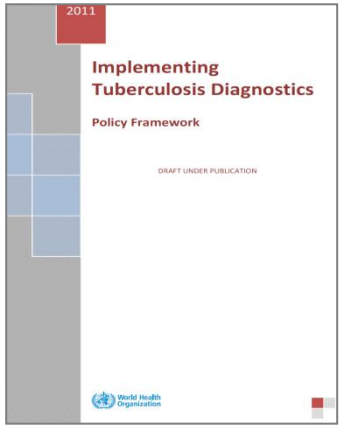
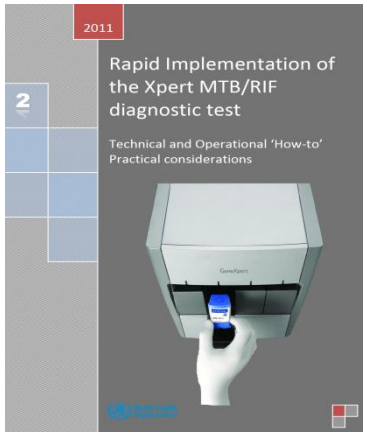
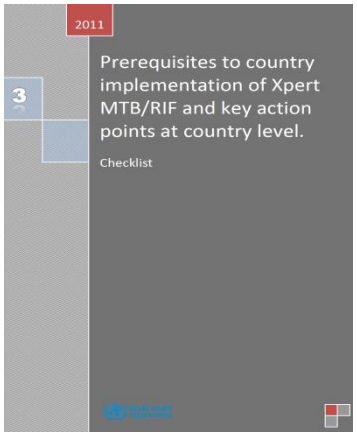
Guidance documents

- GLI Roadmap, Tools Set, Accreditation Guide
- WHO Policy Framework for Implementing TB Diagnostics
- WHO Fact Sheets
- ‘How to’ documents and online tracking
  - Xpert MTB/RIF Rapid Implementation Document
  - Xpert MTB/RIF Checklist
  - Xpert MTB/RIF Website and Online Data Collection Tool









EXPanding Access to New Diagnostics for TB

UNITAID **$87M (total $350M)**

- Integrate tools in TB control
- Increase MDR diagnosis
- Improve market dynamics

Diagnose ~129,000 MDR patients

gli global laboratory initiative advancing TB diagnosis

FIND foundation for innovative new diagnostics

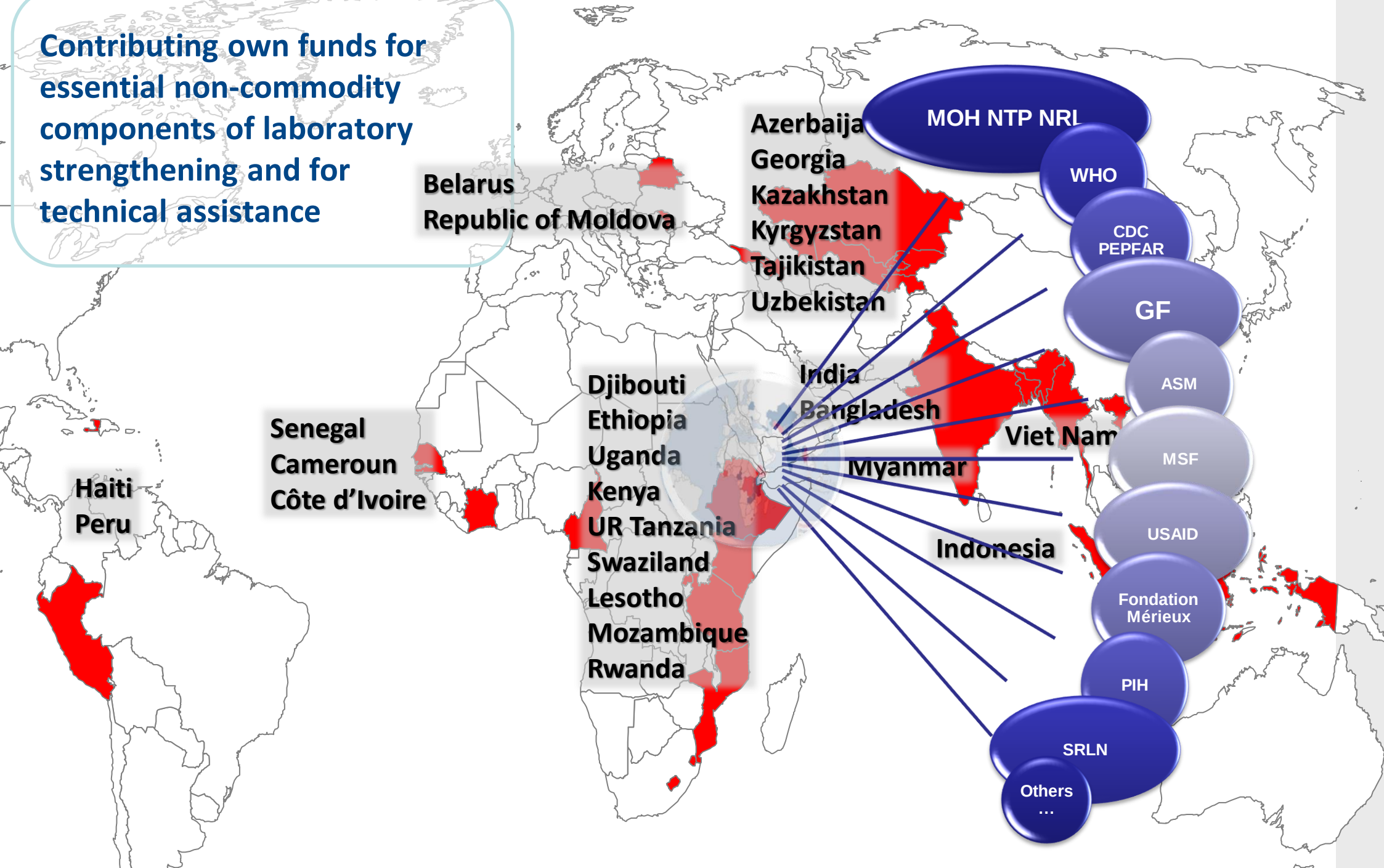
Stop TB Partnership GLOBAL DRUG FACILITY TB PROGRAMME

Strengthen >100 Labs

- Commodities
- Know-how

Project countries and partners

Contributing own funds for essential non-commodity components of laboratory strengthening and for technical assistance



Project Status

Laboratory preparedness

- Laboratory assessment
- Memorandum of Understanding
- Infrastructure upgrade
- Creation of SOPs
- Policy reform

18-24 months

- **Belarus**
- **Indonesia**
- **Kazakhstan**

Technology transfer

- Equipment and supplies
- Procurement
- Training
- Quality assurance
- Laboratory validation

6-12 months

- **Mozambique**
- **Rwanda**
- **Senegal**
- **Peru**
- **Viet Nam**

Routine testing and monitoring

- Monitoring and evaluation
- Impact assessment
- Market dynamics

Up to year 5

- **Azerbaijan**
- **Bangladesh**
- **Cameroon**
- **Côte d'Ivoire**
- **Djibouti**
- **Ethiopia**
- **Georgia**
- **India**
- **Uganda**
- **Haiti**
- **Kenya**
- **Kyrgyzstan**
- **Lesotho**
- **Myanmar**
- **Tajikistan**
- **Rep Moldova**
- **UR Tanzania**
- **Uzbekistan**
- **Swaziland**

- **Labs established: 58 out of 101**
- **19 countries reporting MDR-TB cases**
- **More that 21,000 MDR-TB cases already diagnosed**

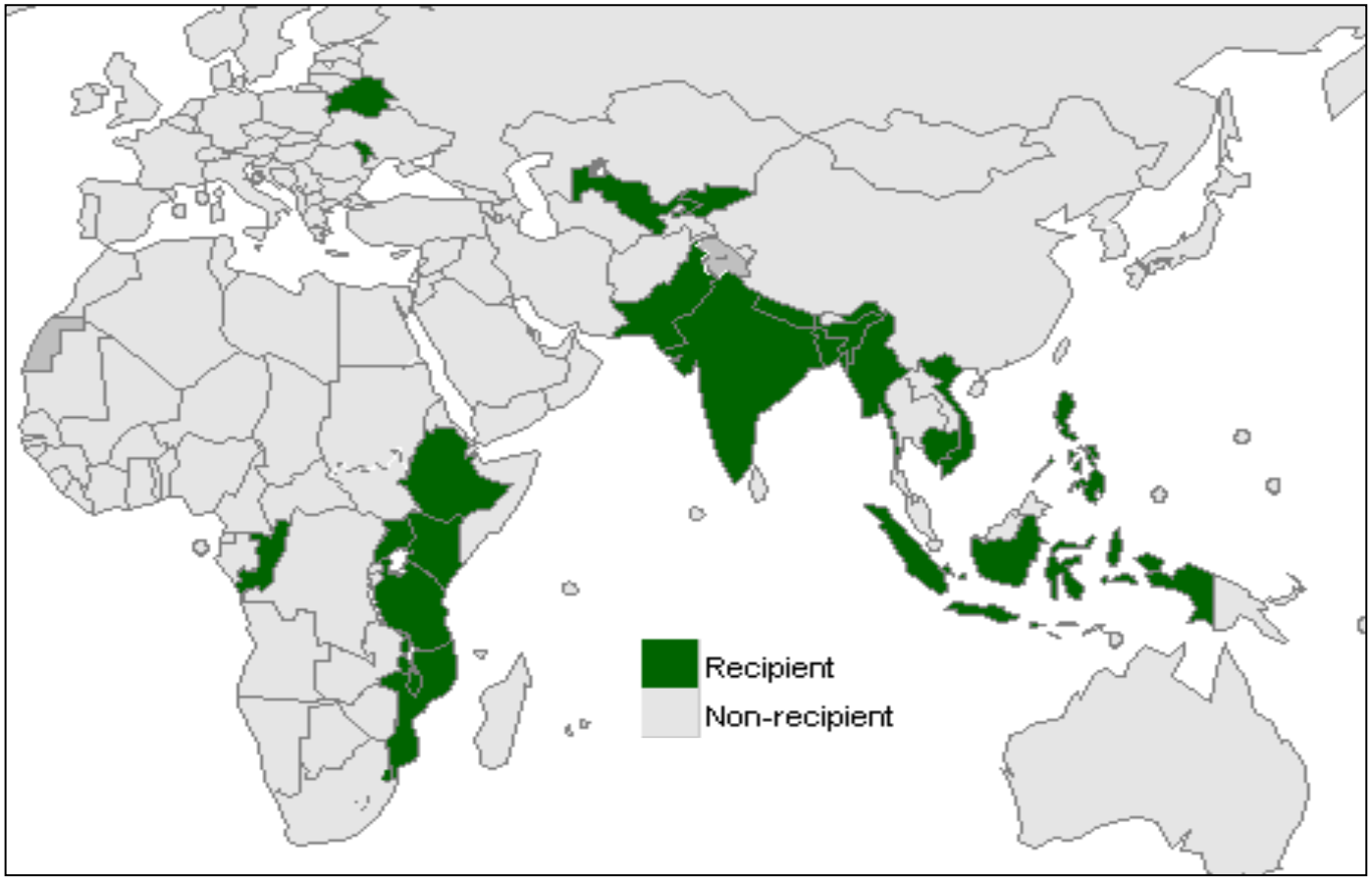
TBXpert Project

- **USD 25.9 million UNITAID-funded project for procurement of GeneXperts and Xpert MTB/RIF cartridges**
  - **Consortium: WHO Stop TB Department, Stop TB Partnership, Global Laboratory Initiative (GLI), TB REACH, EXPAND-TB, African Society for Laboratory Medicine (ASLM), Interactive Research and Development (IRD)**

- **Project objectives:**
  - **To reduce the cartridge price from 16.86 USD to 9.98 USD to generate demand and create a sustainable market**
  - **To rapidly scale-up implementation of Xpert MTB/RIF in target countries using effective diagnostic algorithms**
  - **To develop and establish innovative PPM models to accelerate uptake and increase demand**

TBXpert Project

- **>200 GeneXpert devices and 1.4 million Xpert MTB/RIF cartridges in 21 countries, 2013-2015**



Impact of Xpert MTB/RIF

- **Early** and **rapid** case detection
- **Increase** in number of TB and R-resistant cases
- Reduced need (**but not eliminated**) for conventional laboratory services
- **Urgent need to match diagnosis with treatment and care delivery**

Rapid TB test with higher sensitivity, used widely

Allow for rapid detection of TB patients with lower bacteria load

More TB patients are found earlier in the course

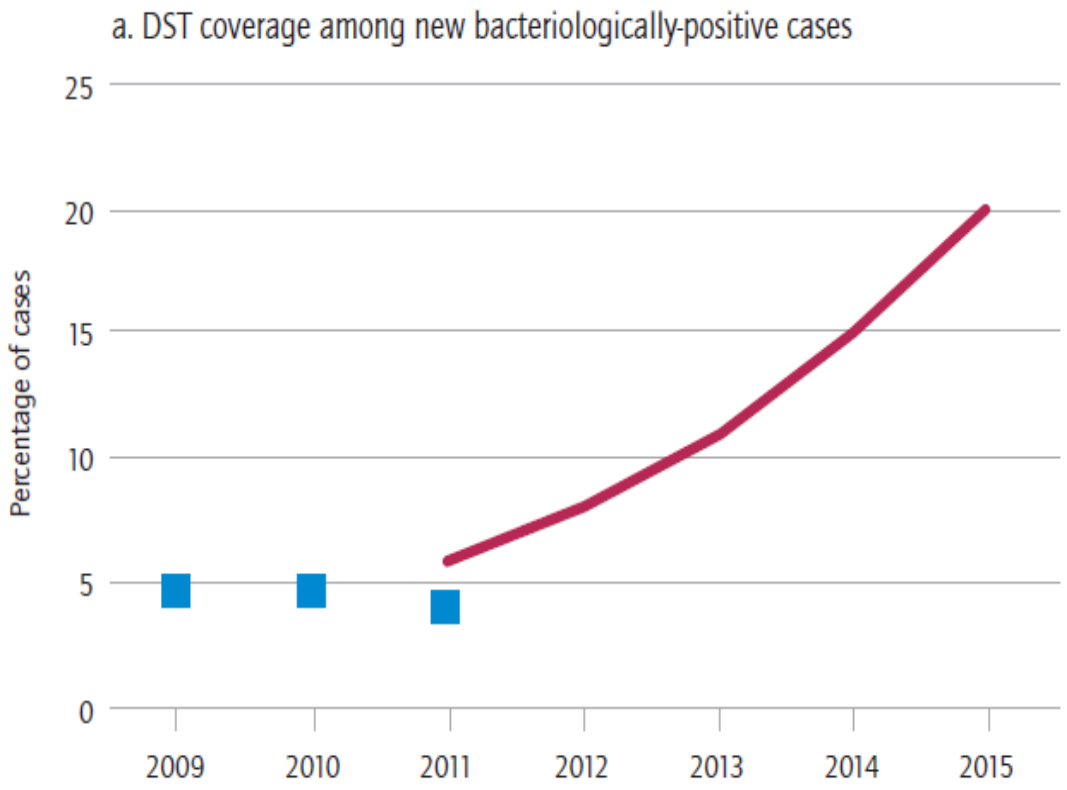
Early and rapid case finding allows earlier intervention and

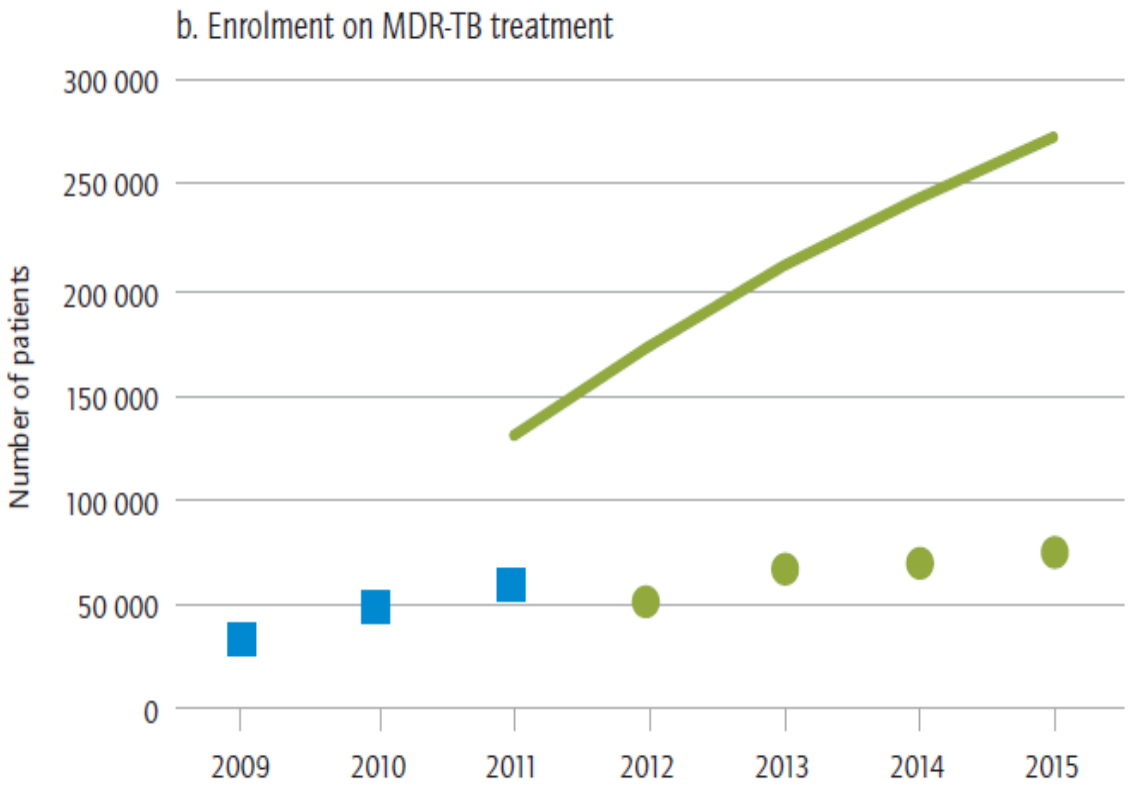
Reduction in mortality, suffering from and disease transmission

- Low bio-safety requirement
- Sensitivity close to culture
- High specificity
- Rapid (< 2 hrs)
- Portable
- Easy to use

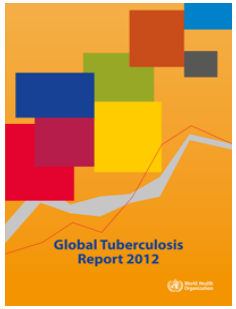
- Running costs
- Infrastructure needs
- R resistance ≠ MDR-TB
- No use for treatment monitoring

DST coverage and enrolment on MDR-TB treatment compared to Global Plan

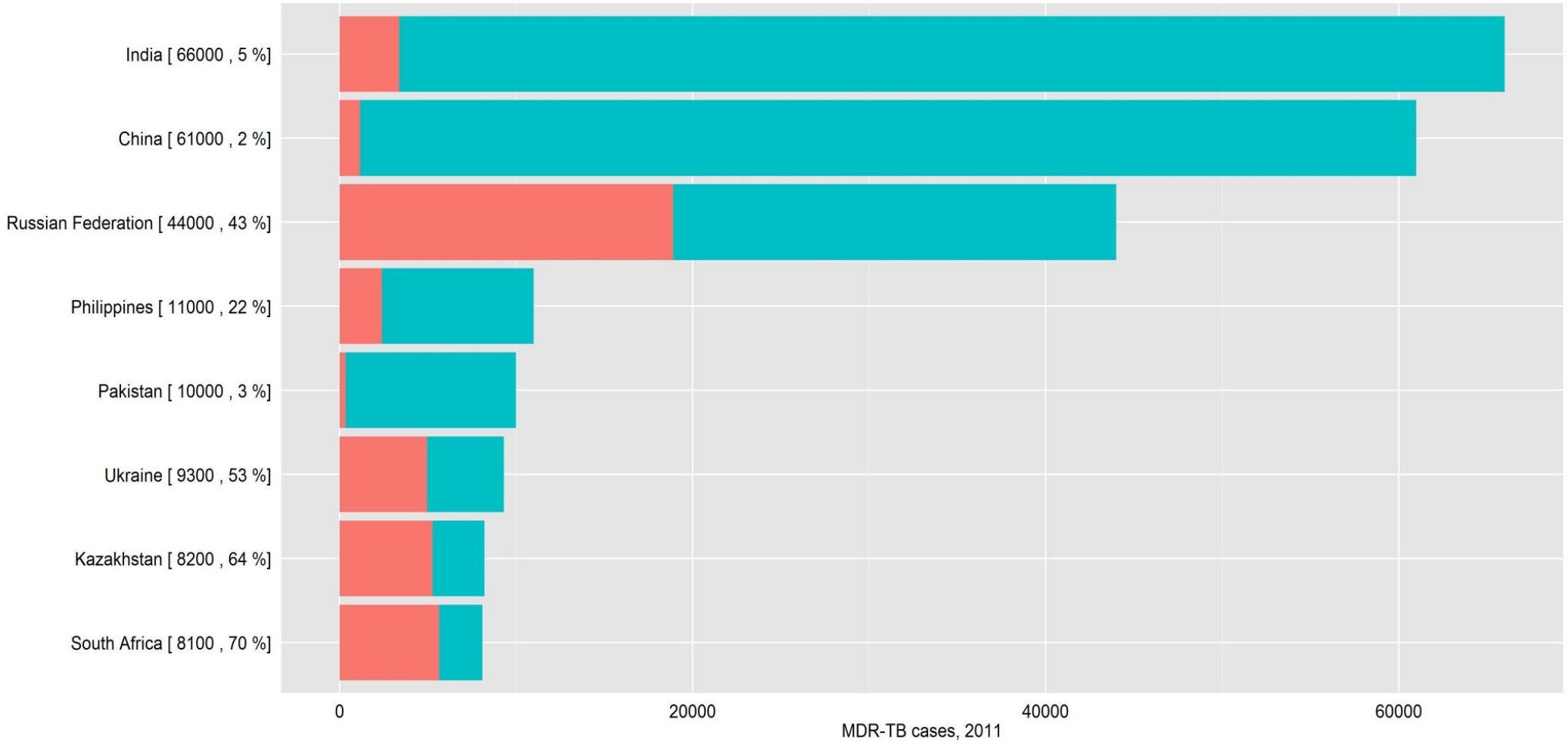




Coverage among new cases and enrollment on MDR-TB treatment compared with the targets in the Global Plan to Stop TB, 2011-2015
Lines indicate the planned targets, blue squares show the situation in 2009-2011 and green circles the projected enrolments 2012-2015



Enrolment on MDR-TB treatment, 2011

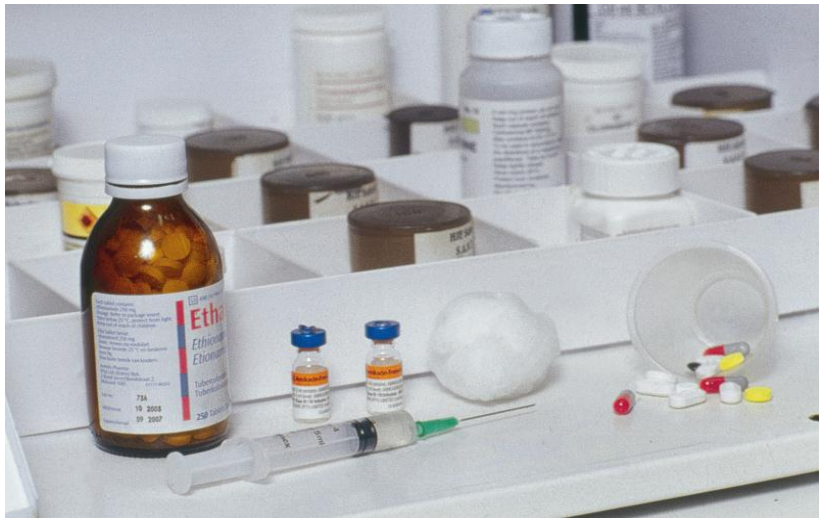


World Health Organization

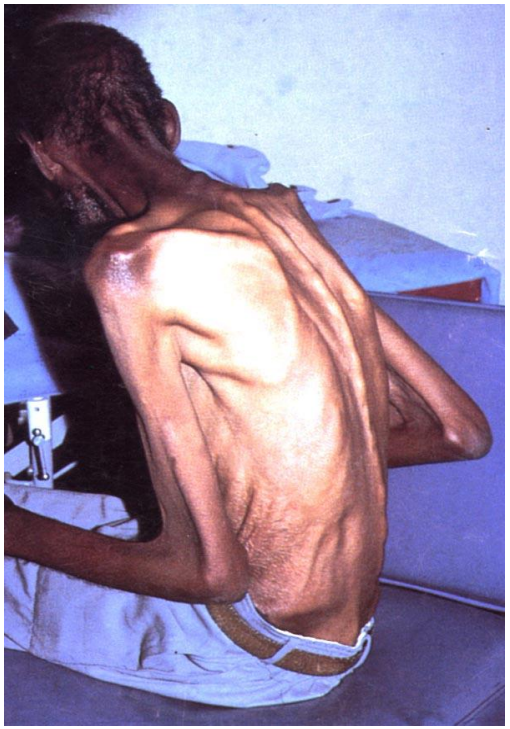
Scaling up quality management of MDR-TB

- Only if all pieces fit together -

Diagnostics



Drugs



Patient care