

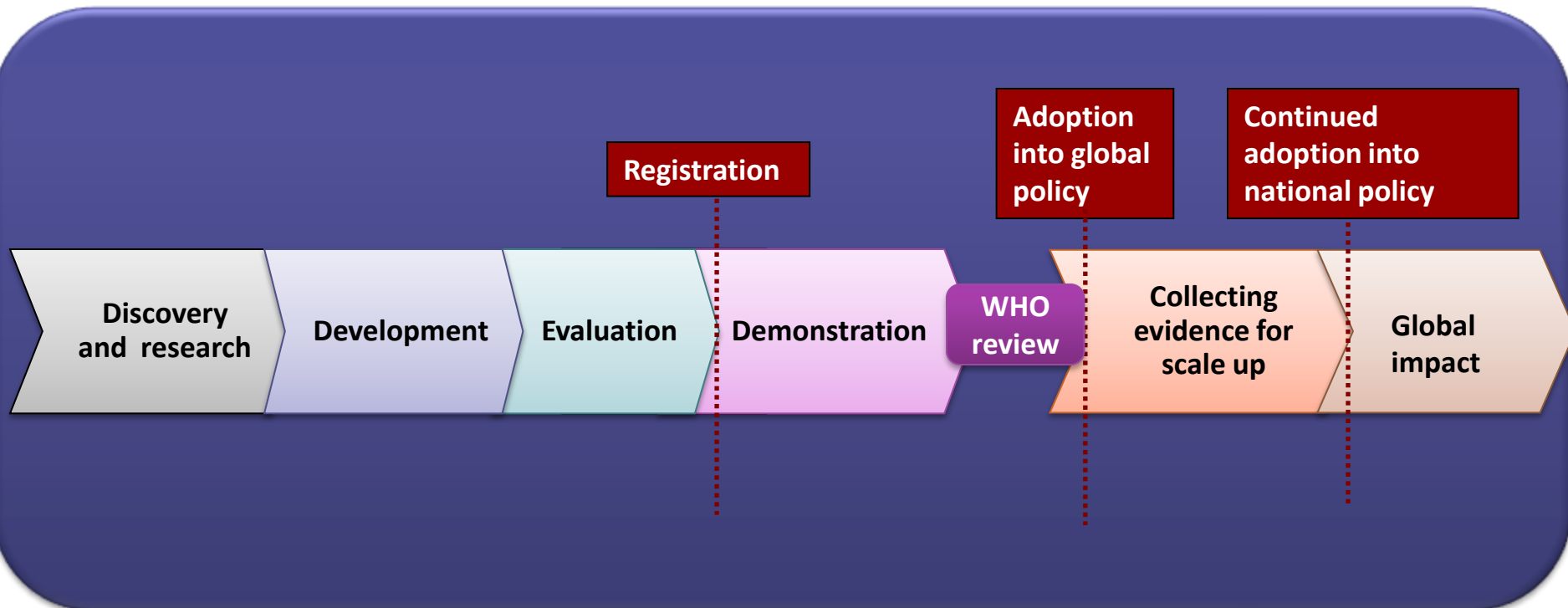


Xpert MTB/RIF: Evidence and operational considerations

*WHO Global Consultation
30 Nov – 2 Dec 2010
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Review of

1. Evaluation studies
2. Demonstration studies
3. Patient important outcomes
4. Operational performance & implementation issues



Multi-center evaluation study

- ❖ 5 reference laboratories with high quality gold standard
- ❖ Geographically diverse populations
- ❖ **1730** patients suspected of pulmonary TB or MDR-TB (4386 samples)



	PERU
HIV	2%
TB (C+)	61%
MDR TB	7%



	AZERBAIJAN
HIV	5%
TB (C+)	42%
MDR TB	31%



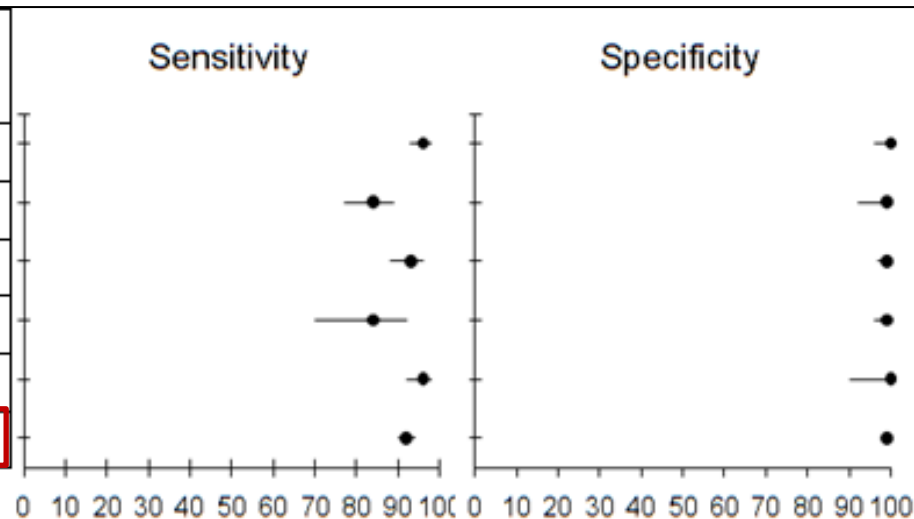
	SOUTH AFRICA	Cape Town	Durban
HIV	77%	72%	
TB (C+)	39%	13%	
MDR TB	10%	9%	



	INDIA
HIV	5%
TB (C+)	60%
MDR TB	67%

Single, direct Xpert: Performance similar to solid culture for MTB

Site	TP	FP	FN	TN	Sensitivity in C+ (95 CI)	Specificity in C- (95 CI)
Lima, Peru	201	0	8	101	96 (93-98)	100 (96-100)
Baku, Azerbaijan	123	1	24	68	84 (77-89)	99 (92-100)
Cape Town, SA	136	1	10	185	93 (88-96)	99 (97-100)
Durban, SA	36	3	7	215	84 (70-92)	99 (96-99)
Mumbai, India	179	0	8	35	96 (92-98)	100 (90-100)
Total	675	5	57	604	92 (90-94)	99 (98-100)



Patient group	Single LJ	Single MGIT	Single, direct Xpert
Smear-positive, Culture-positive	93.0% (1016/1092)	97.7% (1104/1130)	98.2% (551/561)
Smear-negative, Culture-positive	69.3% (205/296)	84.4% (276/327)	72.5% (124/171)
All Culture-positive	88.0% (1221/1388)	94.7% (1380/1457)	92.2% (675/732)

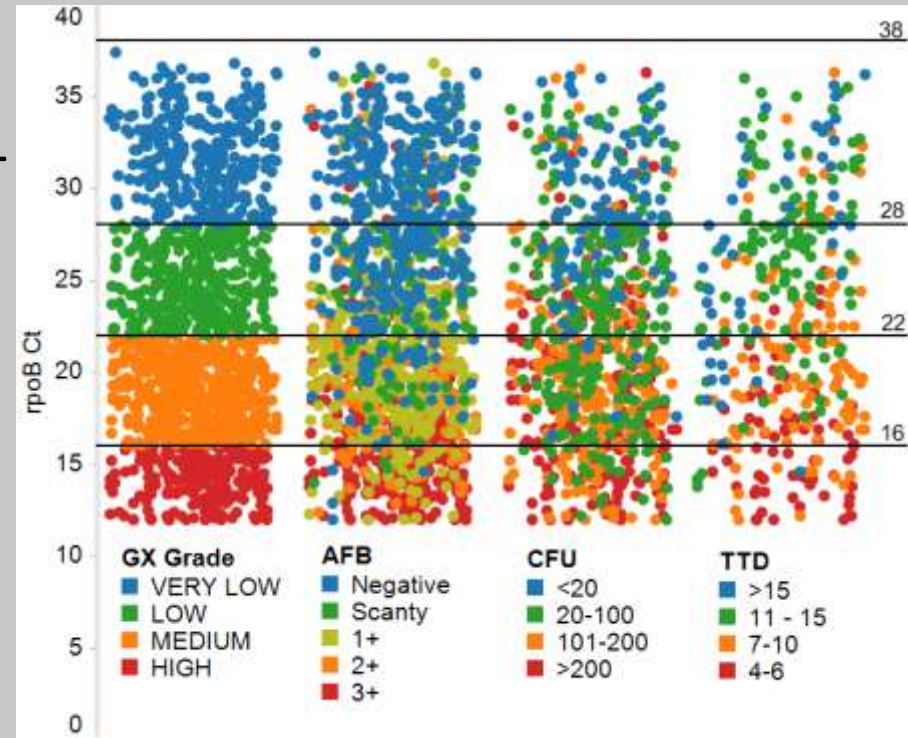
Rifampicin resistance detection by Xpert: Performance similar to phenotypic standard

Site	TP	FP	FN	TN	Sensitivity (95 CI)	Specificity (95 CI)
Lima, Peru	16	3	0	190	100	98
Baku, Azerbaijan	47	4	2	90	96	96
Cape Town, SA	15	0	1	126	94	100
Durban, SA	3	0	0	38	100	100
Mumbai, India	119	3	2	61	100	100
Total	200	10	5	505	98 (94-99)	98 (96-99)

- ❖ Compared to sequencing: 99% sensitivity, 100% specificity.
- ❖ 98% of RIF resistant cases were confirmed MDR-TB.

Other take-away messages from evaluation study

- ❖ Performance from NaOH-treated pellet – equivalent to raw sputum
- ❖ Moderate sensitivity gain in S-C+ with 2nd (+13%) & 3rd test (+5%)
- ❖ Low indeterminate rate



Correlation of semi-quantitative results

Multi-center implementation studies

- ❖ 9 settings of intended use in 6 countries
 - ❖ District/sub-district (3), microscopy centers (3), MDR screening / ER (3)
- ❖ **Diverse** laboratory conditions (temp up to 42C, space, staff background)
- ❖ **7000** TB or MDR-TB suspected patients screened from diverse populations

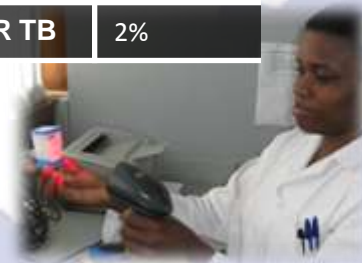


Lima	Peru
HIV	3%
TB (C+)	17%
MDR TB	8%

Kampala	Uganda
HIV	100%
TB (C+)	42%
MDR TB	2%



Baku	Azerbaijan
HIV	6%
TB (C+)	47%
MDR TB	22%



Cape Town	South Africa
HIV	77% (K), 30% (P)
TB (C+)	26%
MDR TB	4%



Vellore	India
HIV	<1%
TB (C+)	10%
MDR TB	7%



Manila	Philippines
HIV	<1%
TB (C+)	20%
MDR TB	54%



Manila	Philippines
HIV	<1%
TB (C+)	20%
MDR TB	54%

Partners and study design

Lima, Peru

- ❖ INS
- ❖ NTP / DISA IV Lima Este
- ❖ Instituto A. v. Humboldt
- ❖ UPCH



Vellore, India

- ❖ Central TB Division
- ❖ Community Health Dep.
- ❖ Christian Medical College

Manila, Philippines

- ❖ Lung Institute
- ❖ TDF
- ❖ CDC



Kampala, Uganda

- ❖ NRL
- ❖ Makerere University
- ❖ Mulago Hospital
- ❖ University of California

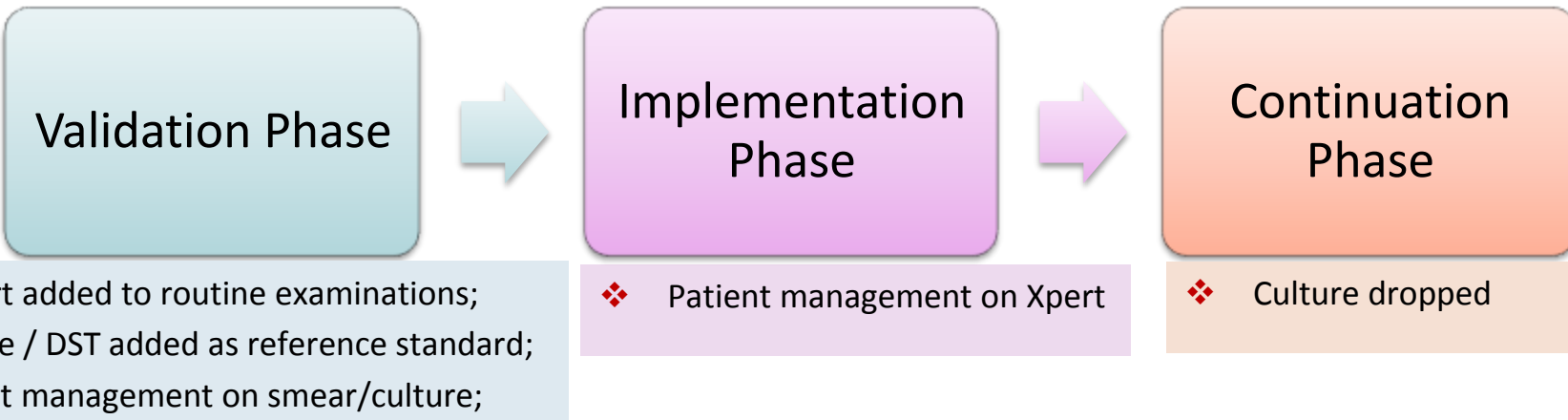
Cape Town, South Africa

- ❖ MOH / NTP
- ❖ NHLS
- ❖ MSF
- ❖ UCT

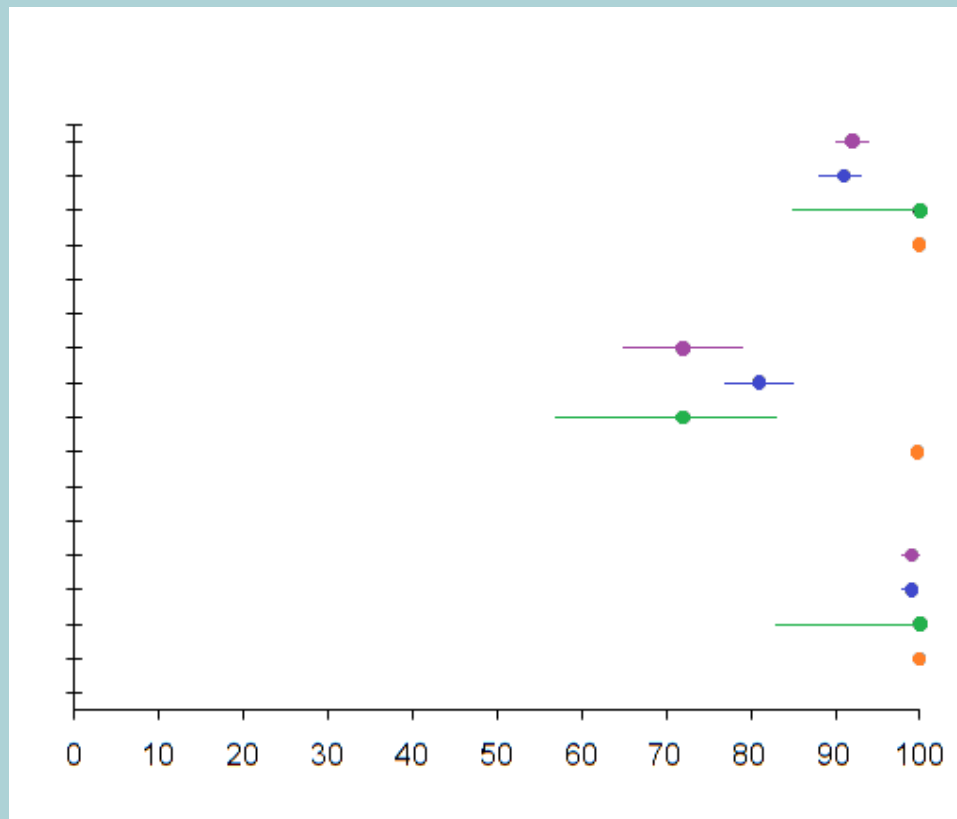


Baku, Azerbaijan

- ❖ MOH
- ❖ MOJ
- ❖ STI/Main Medical Dep.



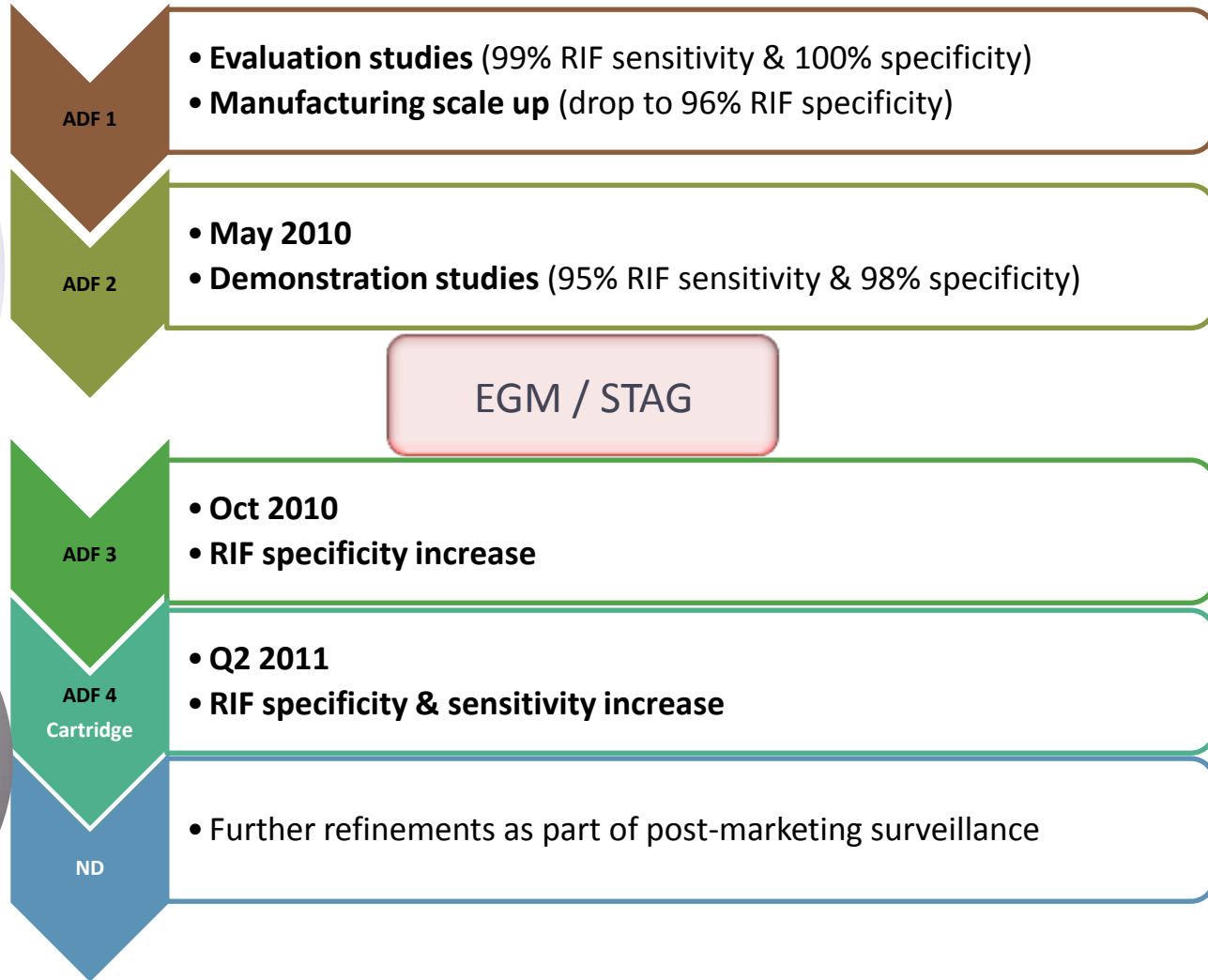
Xpert case detection estimates during implementation in line with published evaluation results



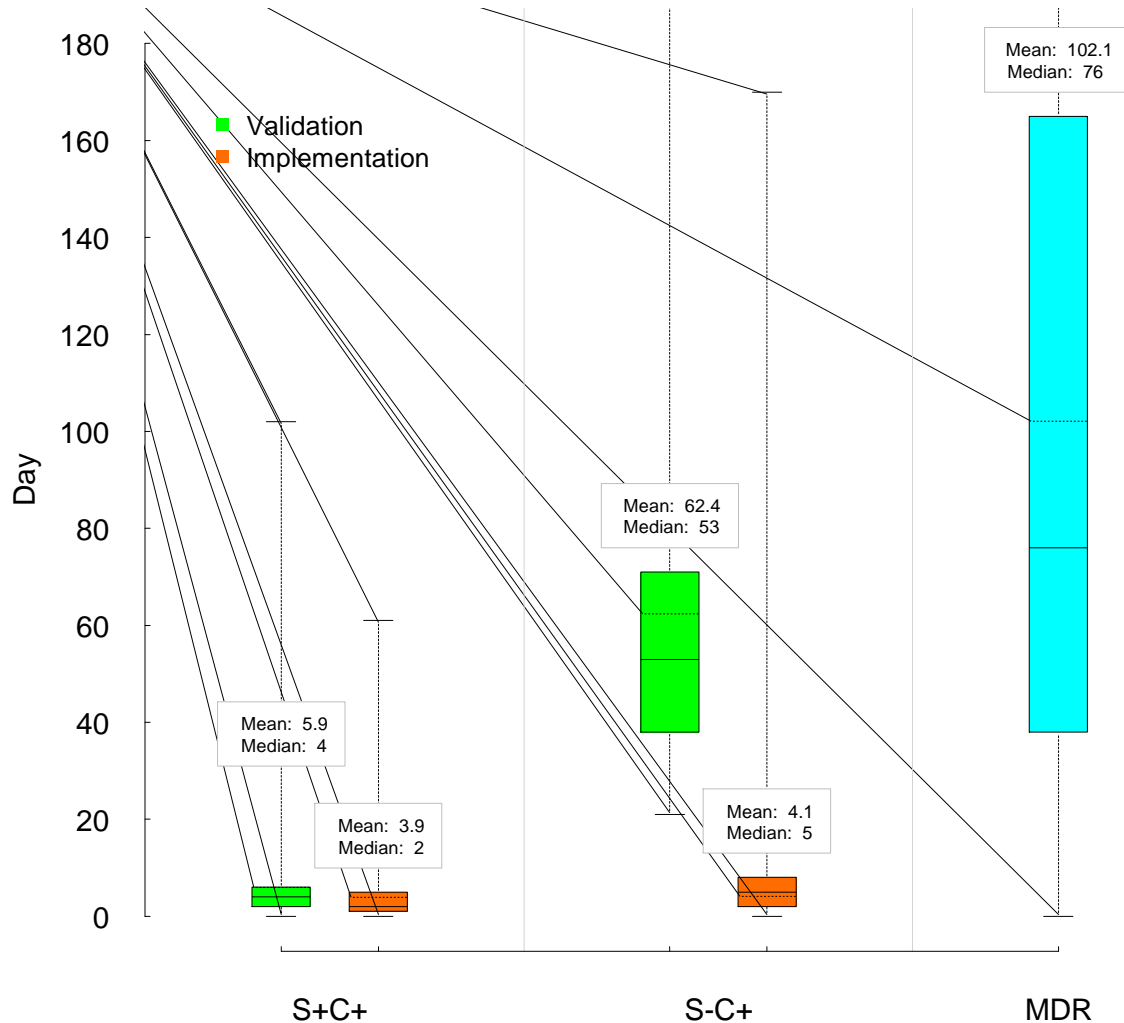
Sensitivity in culture +	
92.2% (675/732)	90.0 – 93.9
90.7% (641/707)	88.3 – 92.6
100.0% (29/29)	85.4 – 100.0
99.9% (4675/4682)	99.7 – 99.9
Sensitivity in smear-,culture +	
72.5% (124/171)	65.4 – 78.7
81.2% (263/324)	76.6 – 85.1
71.5% (38/53)	57.4 – 82.8
99.7% (2540/2547)	99.4 – 99.9
Specificity in smear-,culture -	
99.2% (604/609)	98.1 – 99.7
98.5% (1938/1968)	97.8 – 98.9
100.0% (25/25)	83.4 – 100.0
99.9% (7567/7568)	99.9 – 100.0

- Boehme et al. 2010 (Evaluation)
- Demonstration studies
- Helb et al. 2010
- Naidoo 2010

Summary: Rifampicin Resistance



Xpert implementation translates into shortened time to treatment



- ❖ Validation → Tx based on routine tests.
- ❖ Implementation → Tx based on Xpert.
- ❖ MDR → conventional DST (or LPA).

Operational performance and robustness

Variable	Performance / outcome
Indeterminate rate	2.5% and 0.3% after repetition. Culture indeterminate rate 4.7%.
DNA contamination events	None observed (swabs, neg controls)
Batching / Pellet / Smear	OK / OK / NO
Operating and short term storage temperature	High lab temperature = no effect on performance.
Training needs	2 days for non-experienced lab techs.
User appraisal	Less difficult than microscopy; user friendly; user-independent read-out.



Considerations for implementation

Variable	Performance / outcome
Preventive maintenance	Annual calibration (logistics and costs)
Storage	2-28°C; cartridges require substantial storage space
Electrical supply and back-up power	power outage reported; uninterruptable power supply with UPS (400 VA) for 20 min. Serial car batteries tested.
Biosafety requirements	Same as smear microscopy*.
Waste management	As for sputum containers; additional waste volume compared to smear microscopy.

*Banada PP., et al. Containment of bioaerosol infection risk by the Xpert MTB/RIF assay and its applicability to point-of-care settings. J Clin Microbiol 2010; 48 (10): 3551-7



Conclusions

- ❖ Consistently high sensitivity and specificity for TB detection
- ❖ Good performance for RIF resistance, confirmatory testing to be considered in low MDR-TB prevalence areas
- ❖ Study data likely to be globally applicable
- ❖ Implementation successful after minimal training
- ❖ Impact for patients shown to be significant

Future R&D needs

1. Assessing feasibility of further decentralization (rural areas)
2. Further evaluation in pediatric and extra-pulmonary TB
3. Study optimal positioning in existing diagnostic algorithms
4. Accelerate development of a 2nd generation RIF/INH assay
5. Accelerate development of a 1st generation FG/AG assay

**Thank you to
all partners
who generated
and shared this
evidence for
WHO review**

