Treating Patient, Not Disease: People-Centered Approach

7th TB Symposium — Ministry of Health of the Kyrgyz Republic and Médecins Sans Frontières

1-2 March , 2018, BISHKEK , KYRGYZSTAN

Results of Xpert MTB/RIF Ultra clinical study

Rusudan Aspindzelashvili,
Head of Tuberculosis Referral Laboratory
of National Center for Tuberculosis and Lung Diseases

MEDECINS SANS FRONTIERES

Study objective:

- Estimate the detection accuracy of **Xpert MTB/RIF Ultra** for TB and rifampicin resistance in geographically diverse populations

- *The study was presented at the World Health Organization meeting on 24 March 2017 in Geneva*

- Study results were cited by *The Lancet Infectious Diseases* in November 2017

Xpert MTB/RIF limitations:

- Imperfect sensitivity in case of low mycobacterial load (HIV coinfection, children)
- Imperfect specificity for RIF resistance in case of low mycobacteria concentration
- Imperfect detection of RIF resistance in case of heteroresistance
- Imperfect specificity for RIF resistance due to silent mutations
- Imperfect specificity in case of NTM (cross-reactivity)

Xpert MTB/RIF Ultra / Xpert MTB/RIF

Cartridge specifications

- Both cartridges can be used on the same machine
- Simultaneous detection of MTB and rifampicin resistance

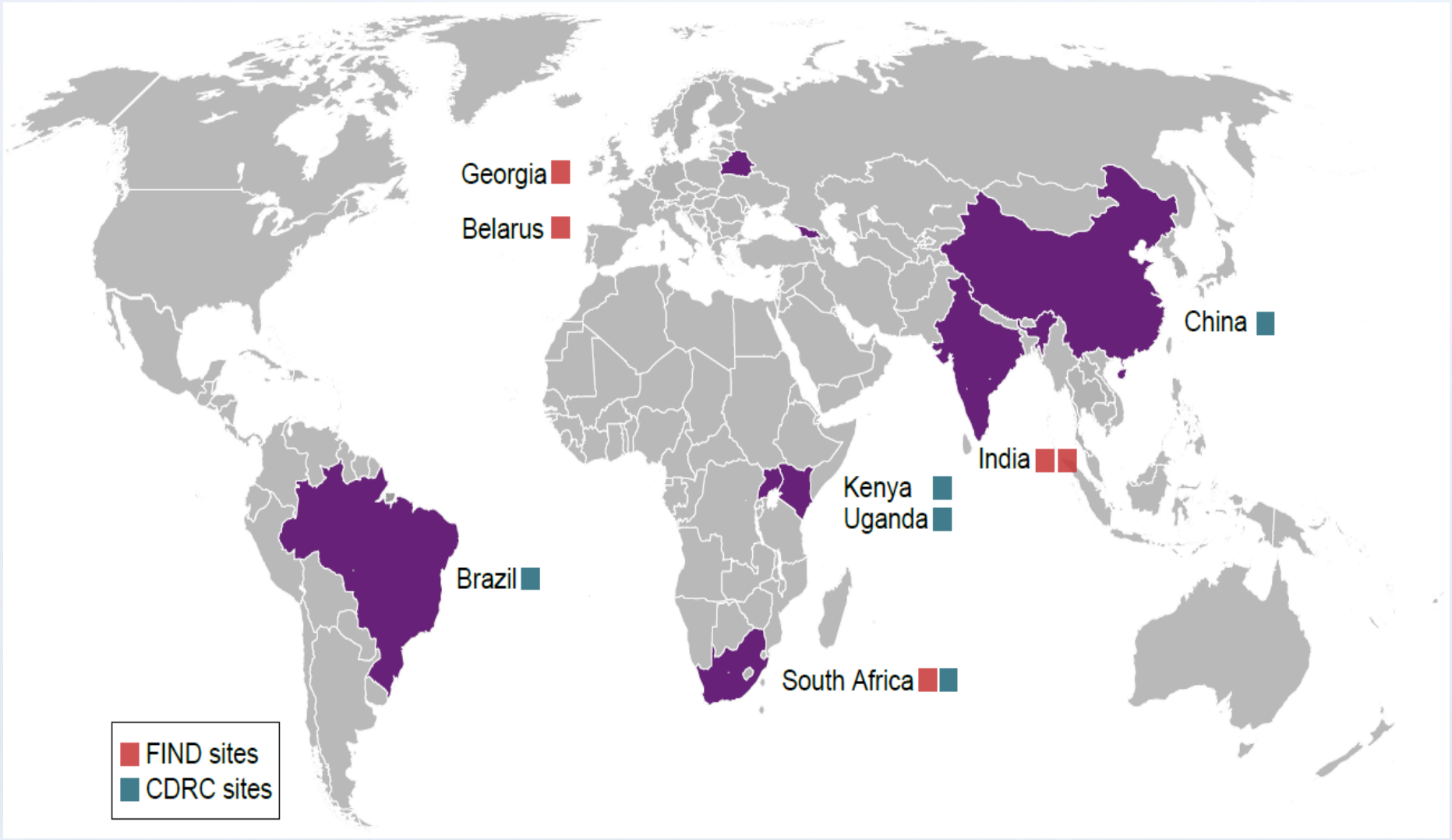
Xpert MTB/RIF Ultra / Xpert MTB/RIF

	Xpert	Ultra
Purpose	rpoB 1 copy	multiple copies IS6110 & IS1081 + rpoB
Cartridge	25 µl	50 µl
Enzymes		Enzyme optimization
Limit of detection	113.6 CFU/ml	15.5 CFU/ml
Time for detection of positive result	110 minutes	80 minutes
Time for detection of negative result	105–110 minutes	66 minutes

Study sponsors and collaborates

- FIND
- Cepheid
- Johns Hopkins University
- Boston Medical Center
- Rutgers New Jersey Medical School
- Bill & Melinda Gates Foundation
- Department for International Development, Government of the UK
- Department of Foreign Affairs and Trade, the Commonwealth of Australia
- National Institutes of Health

Study participating countries



Study design

- Multicenter prospective study
- Objective: estimate the detection sensitivity and specificity of **Ultra/Xpert** for TB and rifampicin resistance
- Two cohorts: case detection and MDR risk groups
- Reference standard: culture tests, drug sensitivity testing, sequencing

Inclusion criteria

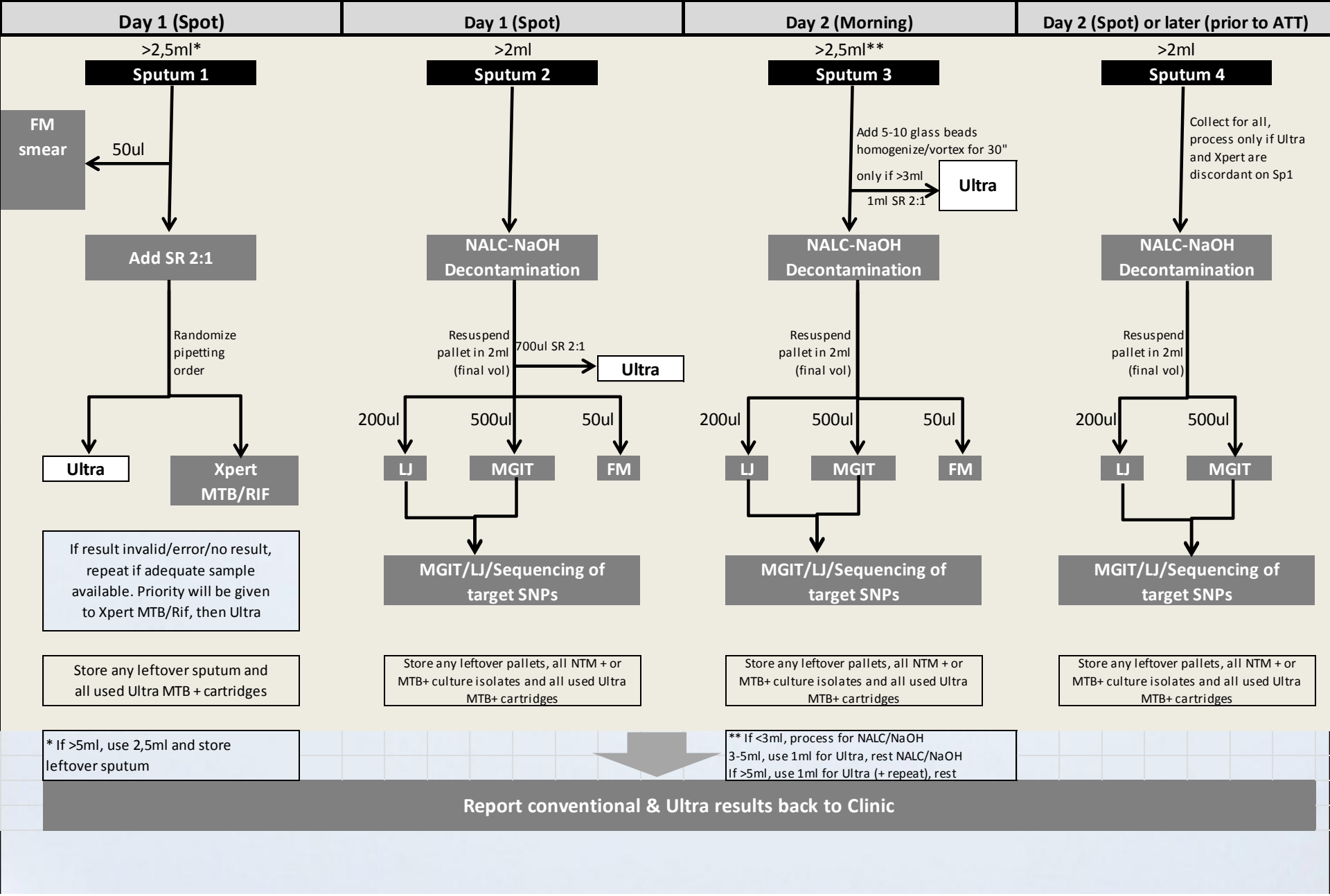
	Case detection group	MDR risk group
Inclusion	• Age: ≥18 • Informed consent • Presumptive pulmonary TB, cough lasting for over 2 weeks + a typical sign of TB	• Age: ≥18 • Informed consent • Presumptive pulmonary TB, cough lasting for over 2 weeks + a typical sign of TB

Inclusion criteria

	Case detection group	MDR risk group
Inclusion	• Consent to submit 4 sputum samples • Follow-up visit in 42–70 days after the enrolment	• Consent to submit 4 sputum samples • One or more of the following criteria are met: microbiologically confirmed TB/RIF resistance; history of TB; previous treatment failure; previous treatment with any TB drugs ≥ 3 months

Inclusion criteria

	Case detection group	MDR risk group
Exclusion	Previous treatment with any TB drugs 6 months prior to enrolment	


Day 1 (Spot)
Day 1 (Spot)
Day 2 (Morning)
Day 2 (Spot) or later (prior to ATT)
>2,5ml*
Sputum 1
FM smear
50ul
Add SR 2:1
Randomize pipetting order
Ultra
Xpert MTB/RIF
If result invalid/error/no result, repeat if adequate sample available. Priority will be given to Xpert MTB/Rif, then Ultra
Store any leftover sputum and all used Ultra MTB + cartridges
* If >5ml, use 2,5ml and store leftover sputum
>2ml
Sputum 2
NALC-NaOH Decontamination
Resuspend pallet in 2ml (final vol)
700ul SR 2:1
Ultra
200ul
500ul
50ul
LJ
MGIT
FM
MGIT/LJ/Sequencing of target SNPs
Store any leftover pallets, all NTM + or MTB+ culture isolates and all used Ultra MTB+ cartridges
>2,5ml**
Sputum 3
Add 5-10 glass beads homogenize/vortex for 30"
only if >3ml
1ml SR 2:1
Ultra
NALC-NaOH Decontamination
Resuspend pallet in 2ml (final vol)
200ul
500ul
50ul
LJ
MGIT
FM
MGIT/LJ/Sequencing of target SNPs
Store any leftover pallets, all NTM + or MTB+ culture isolates and all used Ultra MTB+ cartridges
** If <3ml, process for NALC/NaOH
3-5ml, use 1ml for Ultra, rest NALC/NaOH
If >5ml, use 1ml for Ultra (+ repeat), rest
>2ml
Sputum 4
Collect for all, process only if Ultra and Xpert are discordant on Sp1
NALC-NaOH Decontamination
Resuspend pallet in 2ml (final vol)
200ul
500ul
LJ
MGIT
MGIT/LJ/Sequencing of target SNPs
Store any leftover pallets, all NTM + or MTB+ culture isolates and all used Ultra MTB+ cartridges
Report conventional & Ultra results back to Clinic

Study results

Clinical and demographic profile of patients

Site	Case detection	MDR risk	Total	Median age (IQR)	Female sex [%]	HIV [%]	TB history [%][4]	Cult.+ [%][4]	SSM-Cult.+ [%][4,5]	RIF-r new [%]	RIF-r retr. [%]
Belarus	41	62	**103**	42 (29-56)	41%	≤4.0%[1]	12%	54%	59%	56%	100%
Brazil	127	0	**127**	50 (37-59)	36%	5%	7%	27%	15%	3%	NE
Cape Town	150	2	**152**	41 (34-49)	59%	57%	39%	18%	52%	5%	20%
China	33	68	**101**	47 (34-57)	25%	0%	3%	79%	15%	20%	70%
Georgia	290	23	**313**	45 (34-56)	28%	≤4.0%[1]	29%	29%	36%	19%	79%
Jo'burg	142	0	**142**	34 (29-43)	38%	68%[2]	28%	34%	31%	3%	0%
Kenya	136	0	**136**	34 (27-44)	49%	58%	15%	21%	21%	0%	0%
Mumbai	42	121	**163**	30 (22-45)	45%	4.0%[1]	13%	69%	31%	46%	73%
New Delhi	101	1	**102**	30 (21-45)	42%	4.0%[1]	26%	38%	19%	28%	25%
Uganda	181	0	**181**	30 (26-39)	36%	46%	8%	37%	24%	0%	0%
Total	**1,243**	**277**	**1,520**	**38 (28-50)**	**39%**	**25%**[3]	**21%**	**32%**	**30%**	**19%**	**64%**

Comparative analysis of TB detection

	Sensitivity				Specificity
	Culture+	Smear-	HIV-	HIV+	
Xpert	82.9% 78.8– 86.4	44.5% 35.4– 53.9	89.3% 83.1– 93.7	75.5% 65.8– 83.6	98%
Ultra	87.8% 84.2– 90.9	61.3% 52.0– 70.1	90.6% 84.7– 94.8	87.8% 79.6– 93.5	94.8% 93, 96.2
Difference (Ultra–Xpert)	5.0% +2.7, +7.8	17% +10, +25	1.3% -1.9, +5.2	12% +4.9, +21	-3.2% -4.7, - 2.1

Detection of rifampicin resistance

	Sensitivity	Specificity
Xpert	95.5% 90.9–98.2	97.9% 95.7–99.1
Ultra	94.8% 90.1–97.7	98.2% 96.1–99.3
Difference (Ultra–Xpert)	-0.6% -3.6%, +1.8%	+0.3% -0.9%, +1.7%

Preliminary results

- Sensitivity of **Ulta** is 17% higher than that of **Xpert** in smear-negative microbiologically confirmed TB cases

- Sensitivity of **Ulta** is 5% higher than that of **Xpert** in all TB cases

- Specificity of **Ulta** is 3% lower than that of **Xpert**

Preliminary results

- No false positive results for rifampicin resistance in case of low concentration of mycobacteria
- Detection of heteroresistance
- Detection of NTM

Thank you for your attention!