Xpert MTB/RIF Ultra & GeneXpert OMNI: status update

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Outline

1. **Background**
   - GeneXpert instrument
   - Xpert MTB/RIF assay

2. **Ultra**
   - FIND study
   - WHO policy
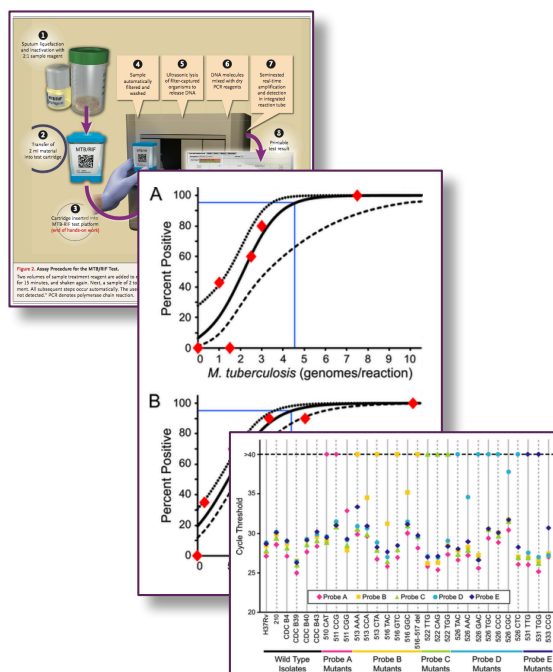   - GLI guide

3. **Omni**
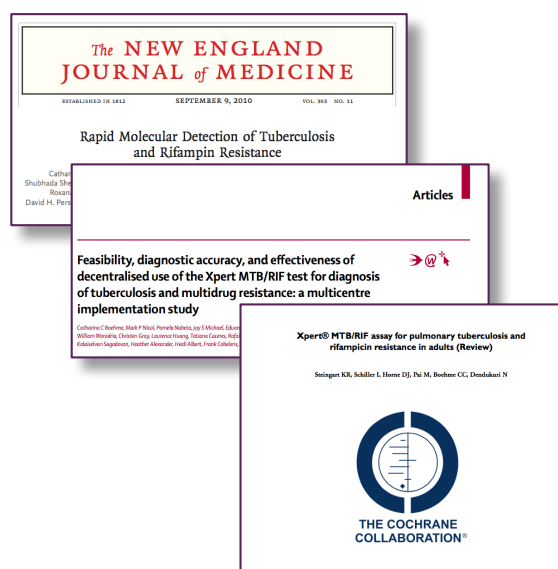   - Features
   - Planned trials

Background

Background
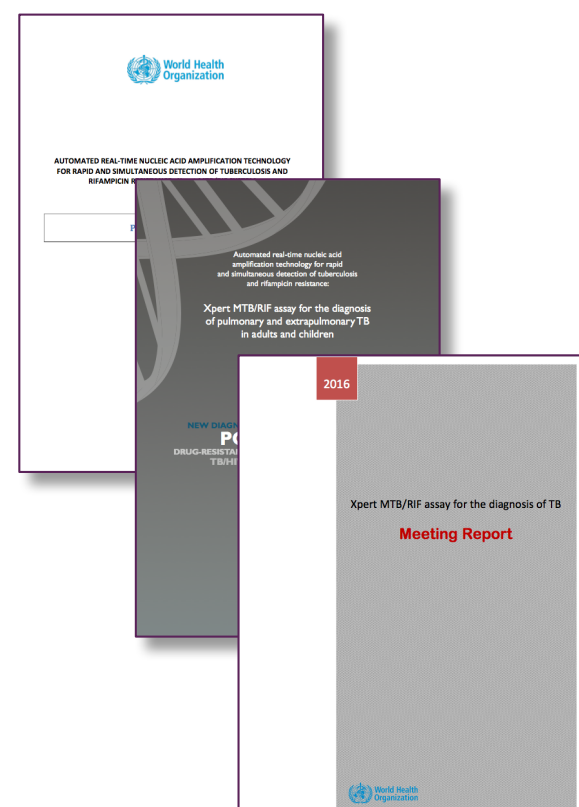## GeneXpert instrument and Xpert MTB/RIF assay

Development

Validation

Policy

Background
Limitations of the Xpert MTB/RIF cartridge

■ **Limitations of the Xpert MTB/RIF cartridge**

- Imperfect sensitivity for paucibacillary disease (HIV, early disease, children etc.)
- Imperfect specificity of RIF in patients with paucibacillary disease
- Imperfect sensitivity for RIF-resistance detection in case of heteroresistance
- Imperfect specificity for RIF-resistance detection due to silent mutation detection
- Imperfect specificity in NTMs (cross-reactivity)

■ **What remains unchanged Ultra vs. Xpert MTB/RIF**

- Cartridges run on the same instrument
- Simultaneous detection of MTB and RIF
- Price

Background
Limitations of the GeneXpert instrument

■ Limitations of the GeneXpert instrument

- Need for temperature control
- Need for constant power supply / UPS
- Dust issues
- Operated through laptop
- Not straightforward to get data out

■ What remains unchanged Omni vs GeneXpert

- All Cepheid cartridge will run on the Omni
- Run-times will initially be similar (to be shortened in the future)

Ultra

Acknowledgements

■ Study participants

■ Study sites
- Belarus - National Reference Laboratory Republican Scientific and Practical Centre for Pulmonology and Tuberculosis, Minsk (A. Skrahina)
- Brazil - Núcleo de Doenças Infecciosas, UFES Vitória (R. Dietze)
- Cape Town (ZA) - Division of Medical Microbiology, 5th floor, Falmouth Building, Health Sciences Faculty University of Cape Town (M. Nicol)
- China - President, Henan Provincial Chest Hospital Zhengzhou, Henan Province (Y. Xing)
- Georgia - National Center for Tuberculosis and Lung Diseases, Tbilisi (N. Tukvadze)
- Johannesburg (ZA) - National Health Laboratory Service (W. Stevens)
- Kenya - CDC-Kenya, Kenya Medical Research Institute / U.S. Centers for Disease Control and Prevention Research and Public Health Collaboration Kisumu (K. Cain)
- Mumbai - PD Hinduja Hospital and Medical Research Centre, Mumbai (C. Rodrigues)
- New Delhi - State TB Training & Demonstration Centre, New Delhi (KK. Chopra)
- Uganda - Infectious Diseases Institute-Makerere University, Mulago Hospital Complex, Kampala (L. Nakiyingi, Y. Manabe)

■ CDRC
- Johns Hopkins University
- Boston Medical Center
- Rutgers New Jersey Medical School

■ Funders (had no role in design, analysis and reporting)
- 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

■ Others
- Ospedale San Raffaele

Xpert vs Ultra

	Xpert	Ultra	Benefits
Target	Single copy rpoB	Multi-copy IS6110 & IS1081 + rpoB	Increased sensitivity: 20 CFU/ml vs 130 CFU/ml
Cartridge	25mcl tube	50 mcl tube	
Analysis	Real time PCR curves	Melt curve analysis	• Improved ability to detect mutations in mixtures. • Robust detection of all mutations associated to Rifampin resistance (i.e. rpoB 533 C to G mutations). • Avoid false + for Rifampin resistance in samples with low bacterial load

50uL tube   25uL tube

Rif -Susceptible

Rif-Resistant
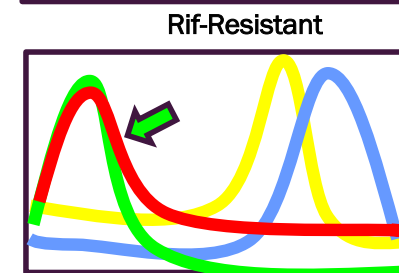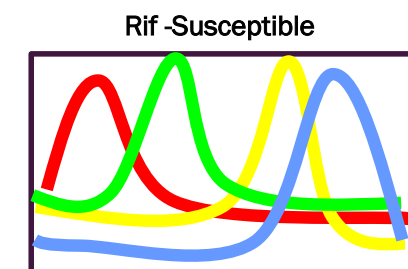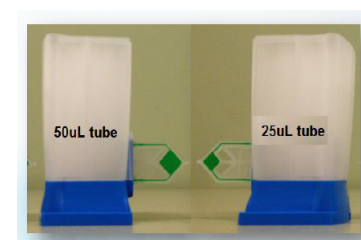
Methods

■ 10 sites in 8 countries

■ Reference standard: 4 cultures

■ Direct comparison Xpert vs Ultra

Map labels:
- Georgia ■ (FIND)
- Belarus ■ (FIND)
- China ■ (CDRC)
- India ■ ■ (FIND)
- Kenya ■ (CDRC)
- Uganda ■ (CDRC)
- Brazil ■ (CDRC)
- South Africa ■ ■ (FIND, CDRC)

Legend:
■ FIND sites
■ CDRC sites
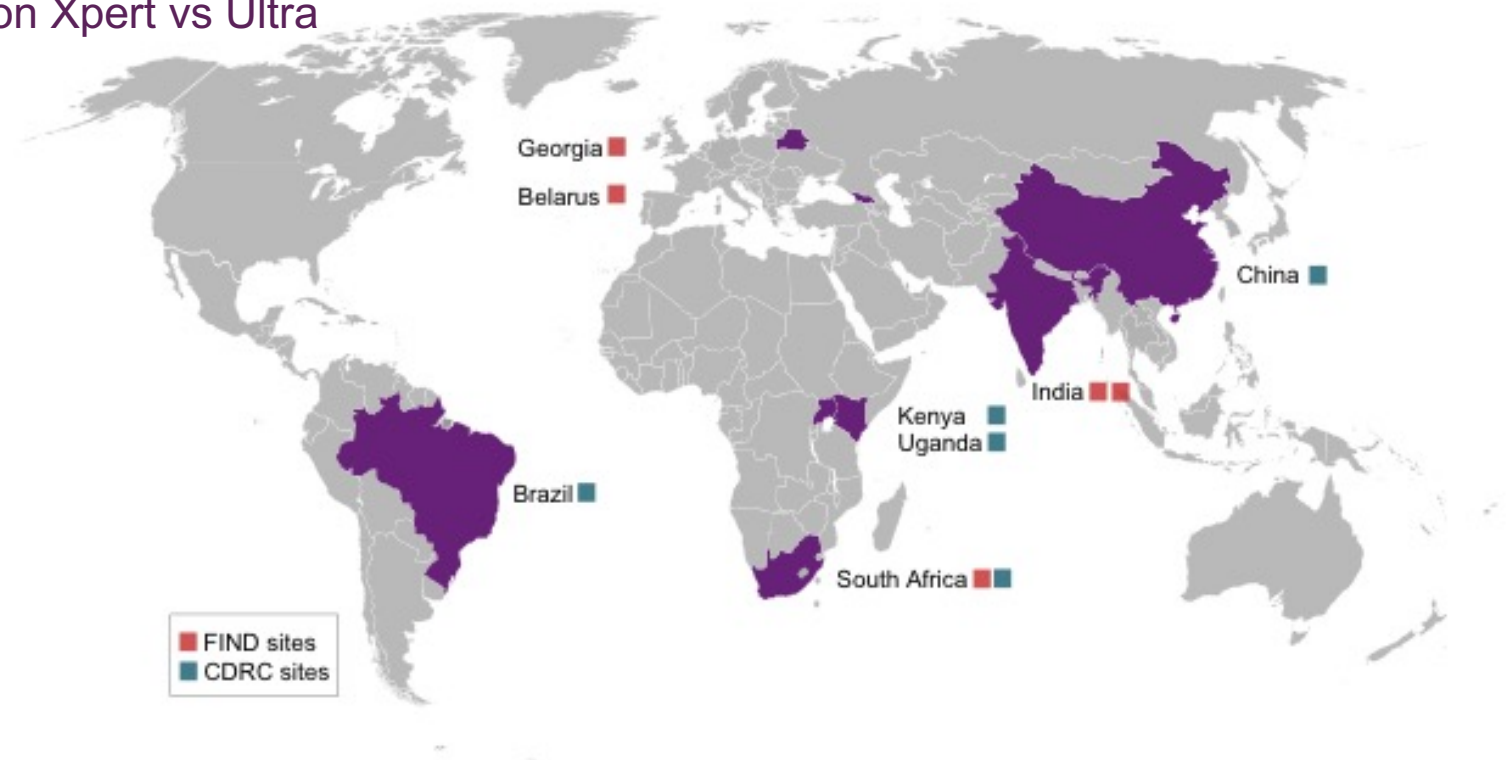
Results for RIF almost identical

11
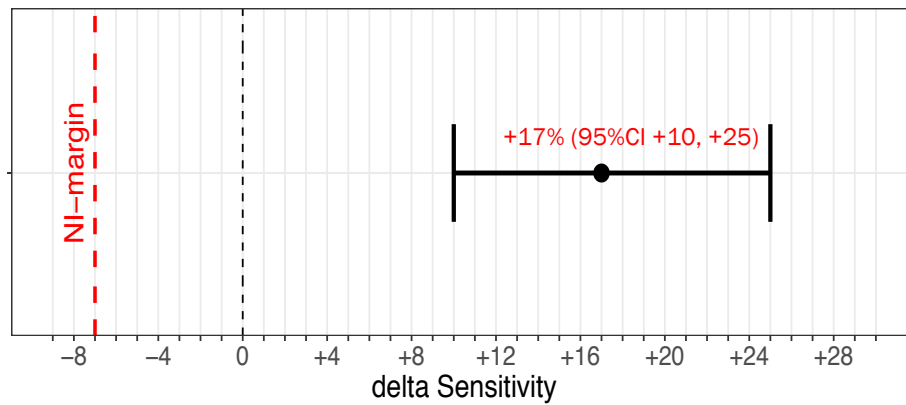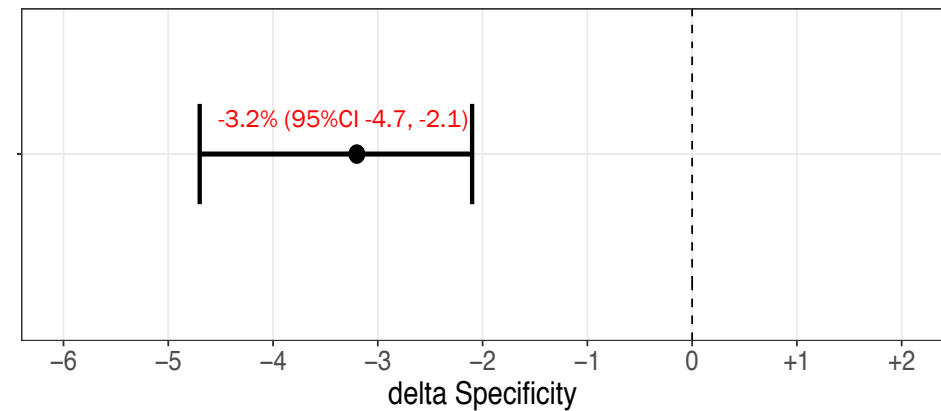
Root Cause Analysis: False-positives

Assay issue (false calls)
- Melt curves
- Sequencing

Cross-contamination
- NC, swabs
- Artificial sputum
- Analysis by time/site

False-positive cases

- Culture cont. Rate / S+C- rate
- S4 culture
- Follow-up visit

Imperfect ref. standard

- Analyses by TB Hx
- Follow-up visit

Non-viable/growing MTB
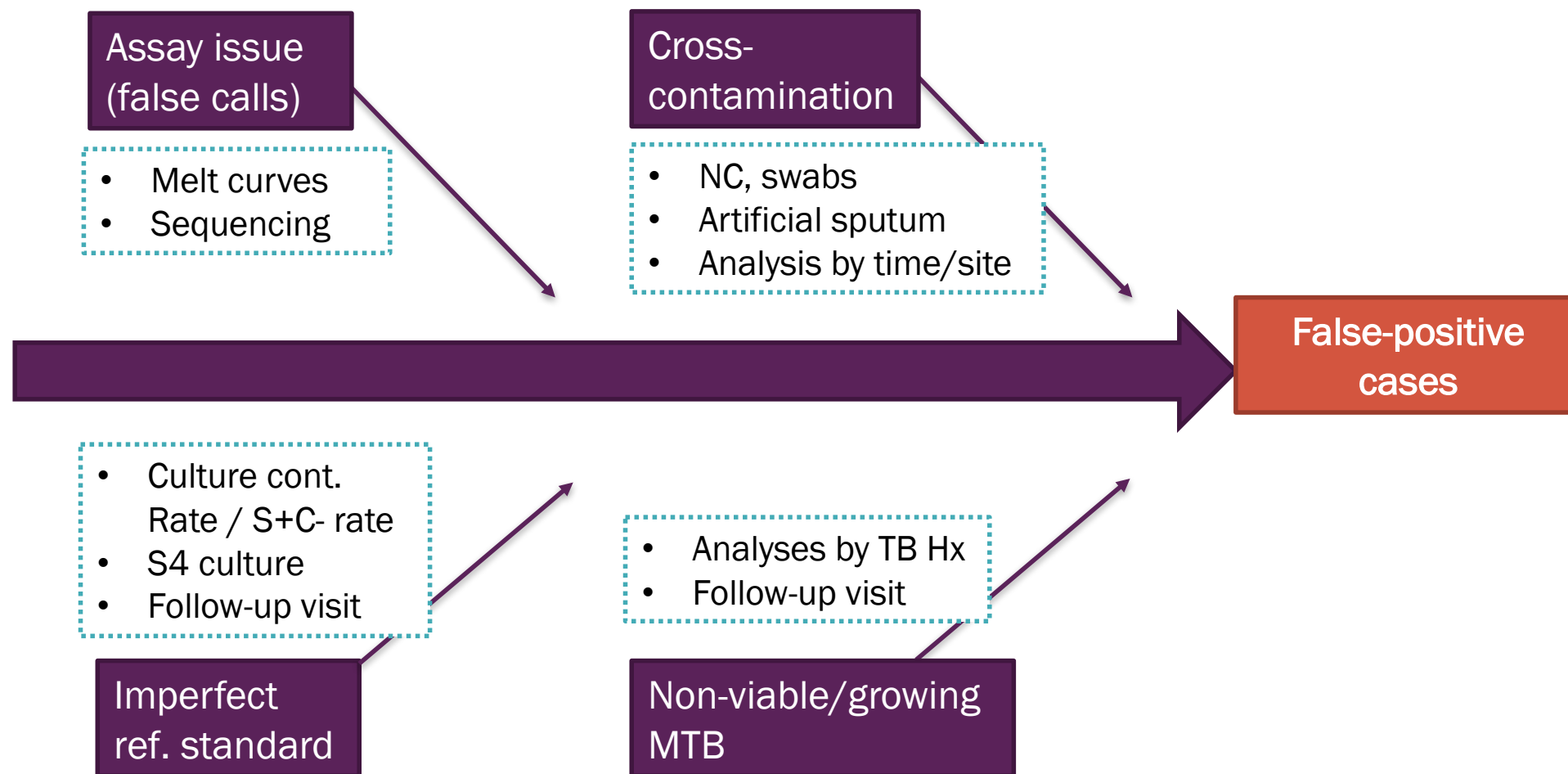
Specificity depending on prior TB history

Analysis group (Culture- neg. cases)	Xpert Specificity (95%CI)	Ultra Specificity (95%CI)	Delta Specificity (95%CI)
Pooled (840)	98.0% (96.8, 98.8)	94.8% (93.0, 96.2)	-3.2% (-2.1%, -4.7%)
No History of TB (615)	98.4% (97.0, 99.2)	95.9% (94.1, 97.4)	-2.4% (-4.0%, -1.3%)
Any history of TB (224)	96.9% (93.7, 98.7)	91.5% (87.1, 94.8)	-5.4% (-9.1%, -3.1%)

Figure

Specificity depending on time since prior TB episode

Some of this may be mitigated through re-testing

Lines are running-line least squares (mean) smoothers using a bandwidth of 0.8 (Cleveland, JASA, 1979)
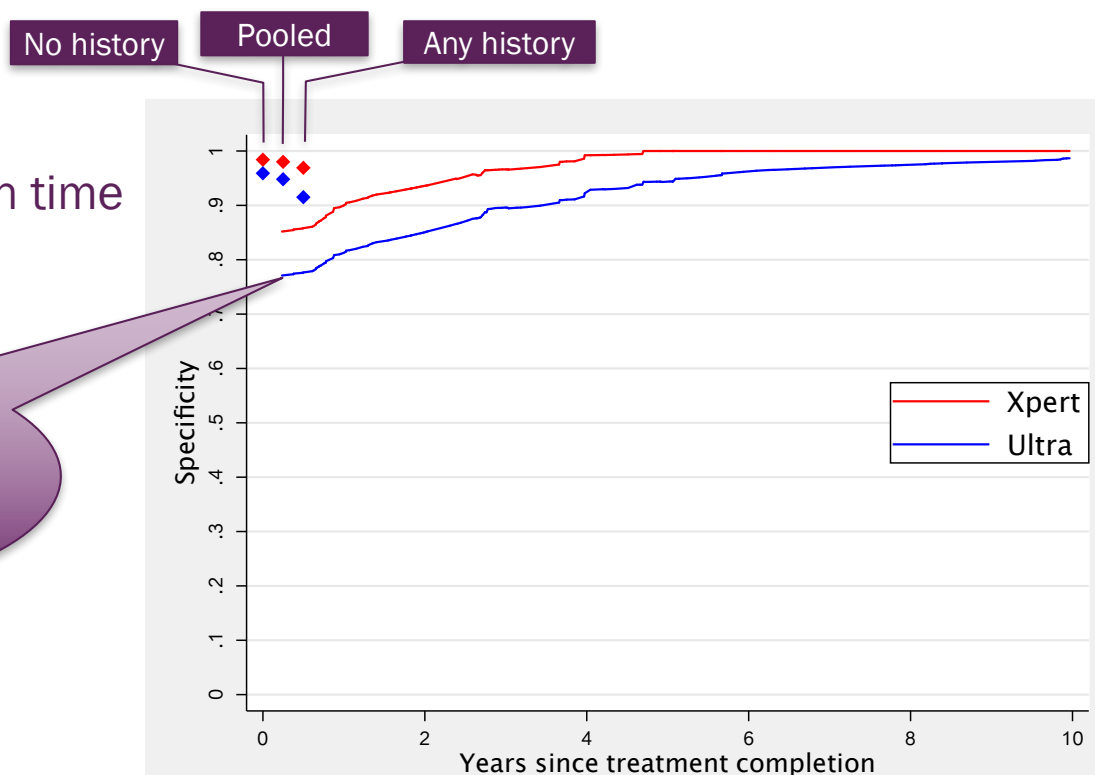
Results from additional studies

■ **Other populations showed great increases in sensitivity**

- Pediatric data
- CSF samples
- Non-HBDCs

CE-mark data, Cepheid

	Non-US		US	
	N	% (95% CI)	N	% (95% CI)
Sensitivity S+	367/369	99.5% (98.0, 99.9)	46/46	100% (92.3, 100)
Sensitivity S-	170/231	73.6% (67.6,78.9)	20/28	71.4% (52.9, 84.7)
Overall Sens	541/604	89.6% (86.9,91.8)	66/74	89.2% (80.1, 94.4)
Overall Spec	963/1014	95.0% (93.4, 96.2)	142/143	99.3% (96.1, 99.9)

Ultra has >99% specificity in US-population of adults

TB meningitis cohort, Uganda, D. Bouleware

TB Negative n=107

Ultra detected significantly more TB meningitis (95% sensitivity) than either Xpert (45% sens) or culture (45% sens) in a population of 129 patients with suspected meningitis in Uganda (17%, i.e. 22 with definite TBM). Adequate CSF testing volume is critical.

Pediatric studies in African setting

UCT, M. Nicol South Africa	N = 391	SENSITIVITY	SPECIFICITY
	ULTRA	56/74 (75.7%) (64.3 – 84.9)	306/317 (96.5%) (93.9 – 98.3)

10 children with Ultra pos, MGIT neg: 7/10 with probable/possible TB (NIH classification); 3 from not treated children: 2 recovered and 1 is LTFU (all 'trace' positive)

Mbeya, A. Rachow Tanzania	N = 146	SENSITIVITY	SPECIFICITY
	Ultra results	12/17=71% (CI 44-89%)	129/129=100% (CI 97-100%)
	Xpert results	8/17=47% (CI 23-72%)	129/129=100% (CI 97-100%)

Screening of Refugees & Asylum seekers, Milano, Italy, D. Cirillo

N=139	Xpert MTB/RIF	Xpert Ultra
Positive	3/139 (2,1%)	10/139 (7,2%)
Estim. incidence	291/100000	972/100000
Error	1/145 (0,7%)	5/146 (3,4%)

- 3 positive samples Xpert MTB/RIF were positive with Ultra.
- 4 positive Xpert Ultra scoring trace had negative result on a 2nd Ultra test performed on the same sample (cultures ongoing)
- 2 Ultra culture positive were G4 negative

■ **Modelling**

- Suggested that trade-offs will vary depending on context

Reported as median (95% uncertainty interval), per 1000 individuals evaluated for suspected TB

India	Xpert	Ultra (with trace)	Difference, Ultra – Xpert	Unnecessary treatments per TB death prevented	Additional cases identified
TB deaths	10.6 (7.3, 14.4)	10.1 (7.4, 13.6)	-0.4 (-1.7, 0)	66 (12, *)	3
Unnecessary treatments	58 (46, 135)	82 (12, 159)	24 (12, 37)		

South Africa	Xpert	Ultra (with trace)	Difference, Ultra – Xpert	Unnecessary treatments per TB death prevented	
TB deaths	15.6 (10.7, 21.6)	14.3 (9.9, 19.0)	-1.3 (-3.7, -0.2)	11 (3, 83)	9
Unnecessary treatments	363 (229, 497)	377 (246, 508)	14 (6, 24)		

China	Xpert	Ultra (with trace)	Difference, Ultra – Xpert	Unnecessary treatments per TB death prevented	
TB deaths	2.2 (1.5, 2.9)	2.1 (1.4, 2.9)	-0.04 (-0.26, 0.04)	530 (70, *)	2
Unnecessary treatments	17 (10, 26)	41 (31, 54)	24 (11, 39)		

* 5% of simulations of in Indian cohort and 26% of simulations in Chinese cohort had no incremental prevented deaths

Conclusions of the Technical Expert Consultation

WHO Meeting Report of a Technical Expert Consultation: Non-inferiority analysis of Xpert MTB/RIF Ultra compared to Xpert MTB/RIF

GeneXpert
Xpert® MTB/RIF Ultra

World Health Organization

2017

"The current WHO recommendations for the use of Xpert MTB/RIF also apply to the use of Ultra as the initial diagnostic test for all adults and children with signs and symptoms of TB and in the testing of selected extrapulmonary specimens (CSF, lymph nodes and tissue specimens)"

"The following implementation considerations apply to Ultra:" (summarized)

- Interpretation of Ultra results same as for Xpert with the exception of 'trace'
- Interpret 'trace' calls as follows:
  - HIV+, children, extrapulm. specimens: interpret 'trace' as true positive
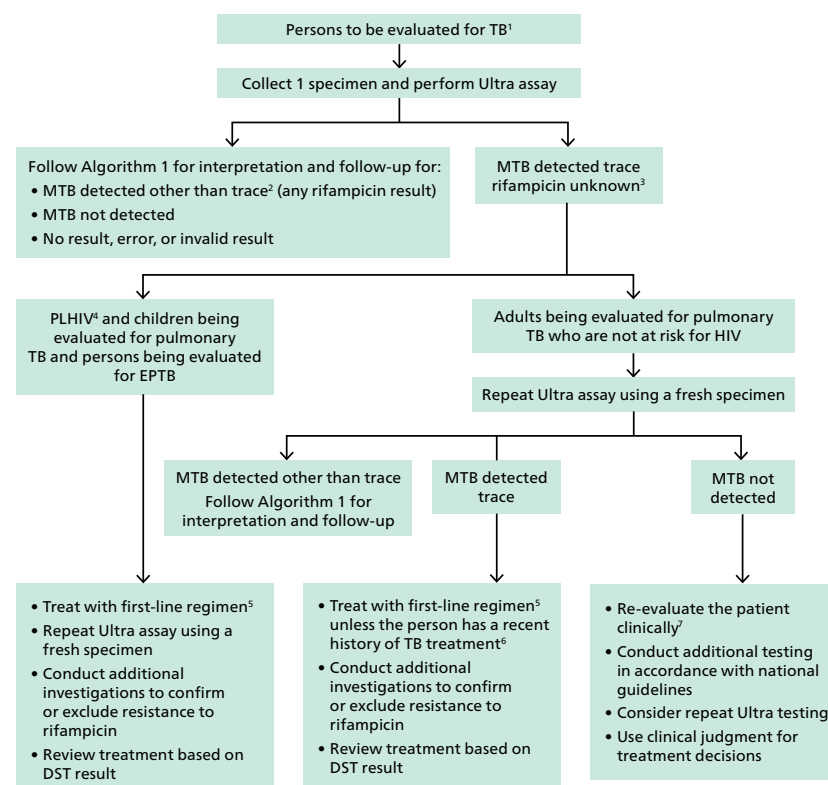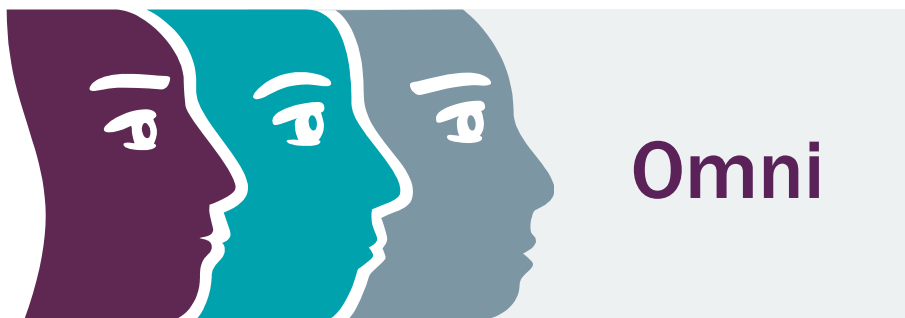 - Others: get fresh specimen and test with Ultra; use 2nd Ultra result

Planning for country transition to Xpert® MTB/RIF Ultra Cartridges

Algorithm 1a. **Algorithm for universal patient access to rapid testing to detect MTB and rifampicin resistance incorporating Xpert MTB/RIF Ultra**

Persons to be evaluated for TB[1]

↓

Collect 1 specimen and perform Ultra assay

Follow Algorithm 1 for interpretation and follow-up for:
- MTB detected other than trace[2] (any rifampicin result)
- MTB not detected
- No result, error, or invalid result

MTB detected trace rifampicin unknown[3]

PLHIV[4] and children being evaluated for pulmonary TB and persons being evaluated for EPTB

Adults being evaluated for pulmonary TB who are not at risk for HIV

↓

Repeat Ultra assay using a fresh specimen

MTB detected other than trace Follow Algorithm 1 for interpretation and follow-up

MTB detected trace

MTB not detected

- Treat with first-line regimen[5]
- Repeat Ultra assay using a fresh specimen
- Conduct additional investigations to confirm or exclude resistance to rifampicin
- Review treatment based on DST result

- Treat with first-line regimen[5] unless the person has a recent history of TB treatment[6]
- Conduct additional investigations to confirm or exclude resistance to rifampicin
- Review treatment based on DST result

- Re-evaluate the patient clinically[7]
- Conduct additional testing in accordance with national guidelines
- Consider repeat Ultra testing
- Use clinical judgment for treatment decisions

Omni

TB: The need for a patient-centred approach to diagnosis

LEVEL 3: 0% seek care here
High TB diagnostics capacity, including drug sensitivity

LPA
Culture
DST

LEVEL 2: 10% seek care here
Some TB diagnostics capacity
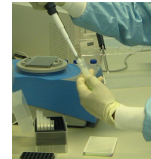
Gene Xpert
Established in LMICs
>21'600 installed modules

LEVEL 1: 53% seek care here
Extremely limited TB diagnostics

Smear Microscopy
diagnosis of majority of TB cases

Omni

LEVEL 0: 30% seek care here
No TB diagnostics or sample referral capacity

Improvements on the Cepheid platform

Tuberculosis Patient

Level 0 — Community/POC
Level 1 — Microscopy centre
Level 2 — District hospital
Level 3 — Reference centre

Established in LMICs
>21'600 installed modules

Data reporting

Omni

GeneXpert

Xpert cartridges

Expanded portfolio: Xpert, Ultra, XDR, other diseases (HIV, HCV, NG/CT, Ebola)
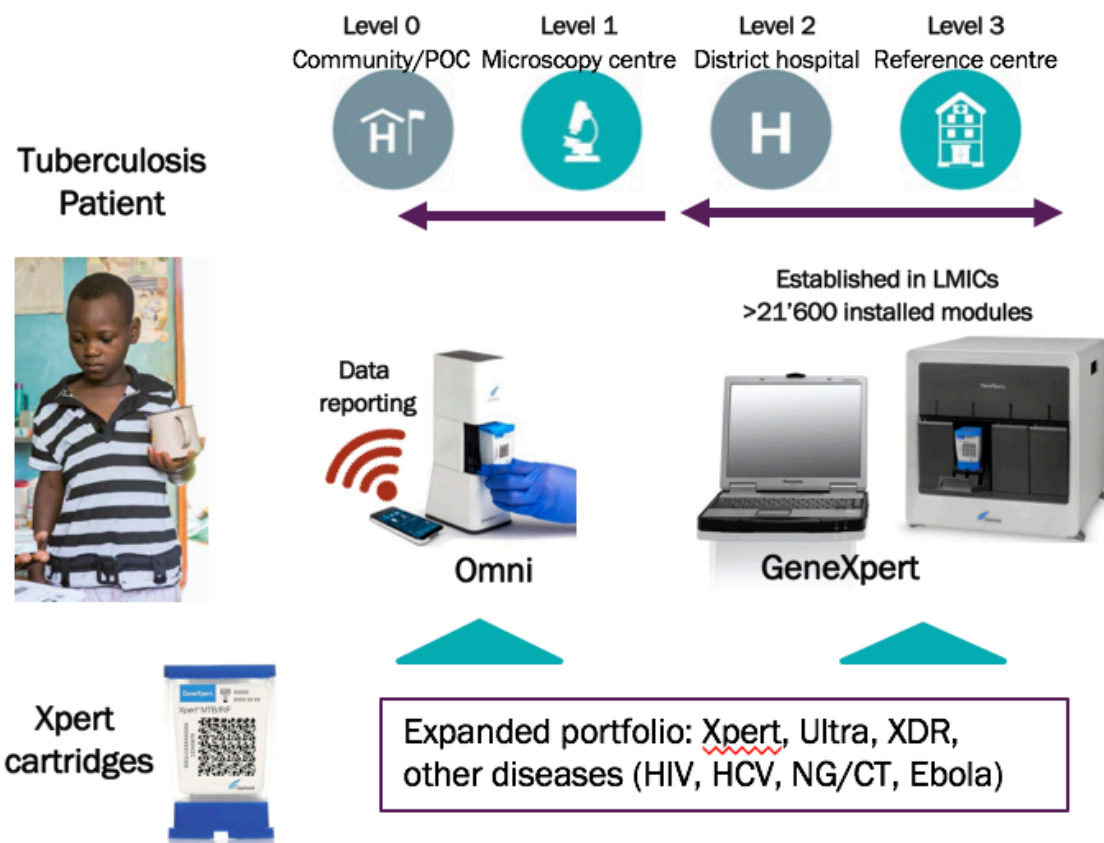
- Battery operated
- Robust to dust and high temperatures
- Mobile phone interface
- Connectivity enabled
- Significantly lower cost

Trial aim, designs and outcomes

■ **General aim**
- Generate high-quality evidence on feasibility and impact of Omni on patient outcomes to drive global uptake

■ **Two categories of studies**
- Use of Omni for passive case finding (PCF) vs standard of care
- Use of Omni for active Case finding (ACF):
  - (i) community-based,
  - (ii) facility-based or
  - (iii) household contact screening
- Additional modelling and cost-effectiveness studies planned

■ **Study designs and outcomes**
- 11/13 are randomized trials
- Outcomes for PCF studies*
  - Primary: proportion rapidly diagnosed and treated
  - Key secondary: all-cause mortality at 6 months
- Outcomes for ACF studies
  - Varying by study (including feasibility, time to diagnosis/treatment, case yield etc.)

* These two outcomes and key study design features have been harmonized between studies to allow for a global analysis across all sites.
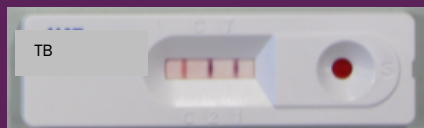
Vision for TB diagnostics in 2020

Case finding –
first point of contact

1. Triage tests

Further work up & treatment –
dedicated unit

2. Confirmation & rapid drug susceptibility testing (critical drugs)

Surveillance, QA, training –
specialized unit

3. Comprehensive, rapid drug susceptibility testing

E-Health supported solutions

Thank you/ Questions?

FIND
Claudia Denkinger
Pamela Nabeta
Timothy Rodwell
Catharina Boehme

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