Xpert® MTB/RIF for the diagnosis of tuberculosis in children

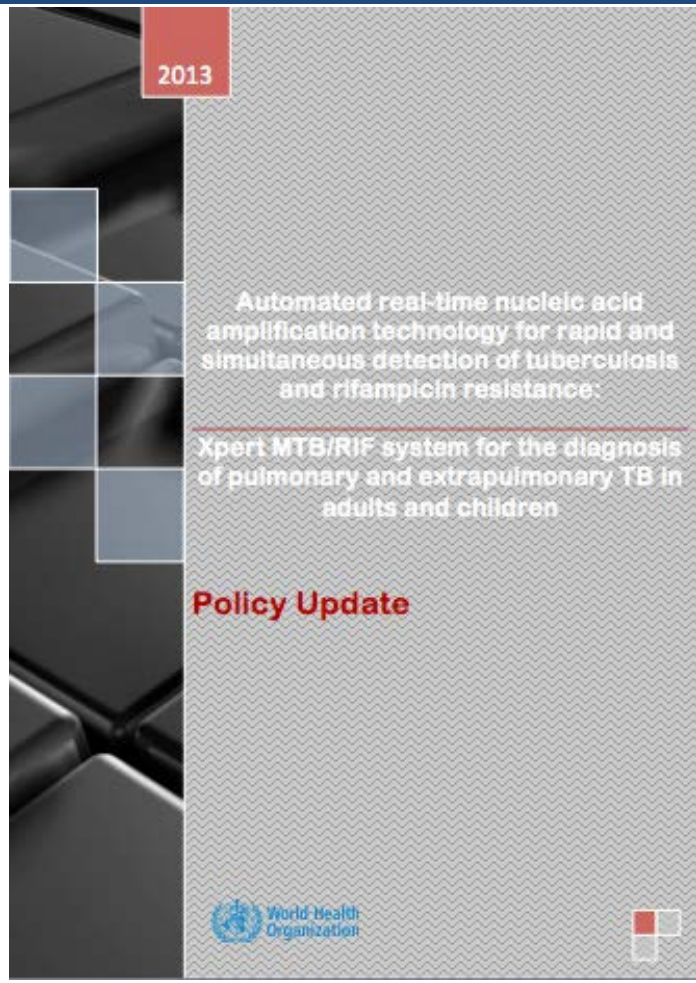
Anne Detjen, Andrew DiNardo, Jacinta Leyden, Karen Steingart, Dick Menzies, Ian Schiller, Nandini Dendukuri, Anna Mandalakas

International Union Against Tuberculosis and Lung Disease
Health solutions for the poor
BCM Baylor College of Medicine
Texas Children's Hospital
McGill

WHO Policy statement 2013

- Xpert MTB/RIF **should** be used rather than conventional microscopy, culture and DST **as the initial diagnostic test in children presumed to have MDR-TB or HIV-associated TB** (strong recommendation, very low-quality evidence).

- Xpert MTB/RIF **may** be used rather than conventional microscopy and culture **as the initial diagnostic test in all children presumed to have TB** (conditional recommendation acknowledging resource implications, very low-quality evidence).



- Xpert MTB/RIF **should** be used in preference to conventional microscopy and culture as the initial diagnostic test in testing **cerebrospinal fluid specimens from patients presumed to have TB meningitis** (strong recommendation given the urgency of rapid diagnosis, very low quality of evidence).

- Xpert MTB/RIF **may** be used as a replacement test for usual practice (including conventional microscopy, culture, and/or histopathology) for testing of specific non-respiratory specimens (**lymph nodes and other tissues**) from patients presumed to have extrapulmonary TB (conditional recommendation, very low quality of evidence).

Main Objectives

To determine summary estimates of the diagnostic accuracy (sensitivity and specificity) of Xpert® MTB/RIF for the detection of

1. **Pulmonary TB**
2. **RIF resistance** (in respiratory specimens)
3. **Peripheral lymph node TB** (in LN aspirates/biopsies)
4. **TB meningitis** (in CSF)

in children aged 0-15 years with presumed TB

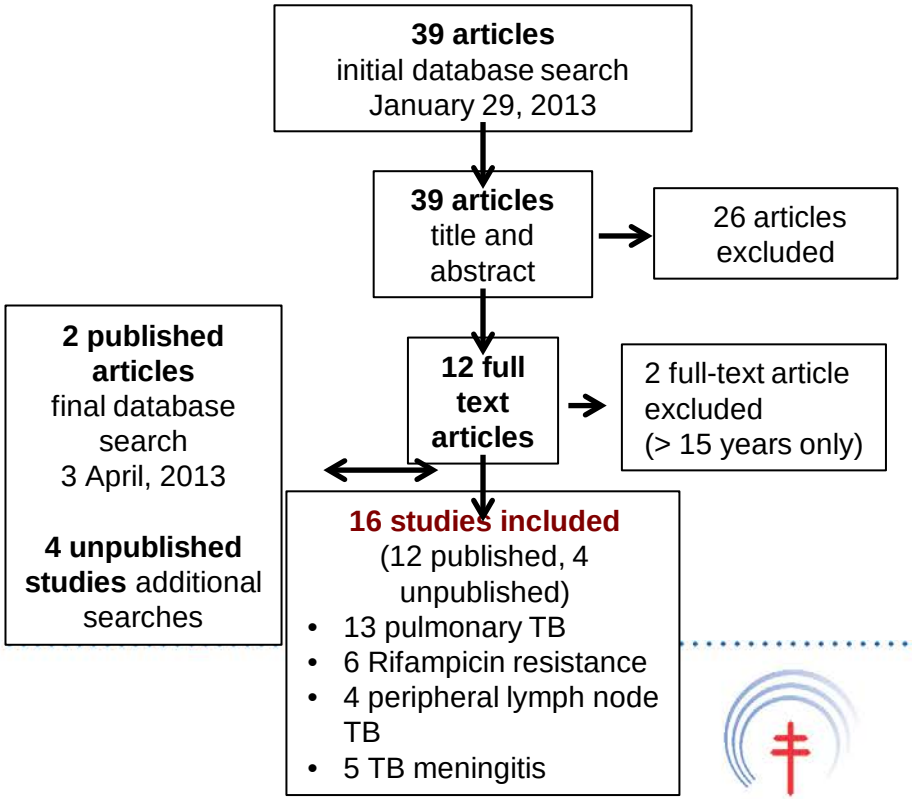
Methodology

Search strategy: published and unpublished

- Electronic databases (PubMed, Ovid, Web of Science)
- Reference lists of SRs, selected articles
- Authors of published articles and research networks

16 studies included

- 13 PTB
- 6 RIF resistance
- 4 pLN TB
- 5 TBM



Study characteristics

- 3 HIC, 6 UMIC (all South Africa), 3 LMIC, 4 LIC
- TB incidence rates 2.8 (Italy) to 993/100 000 (South Africa)
- Cross-sectional, cohort
- **All: higher-level care facilities** (tertiary level referral hospitals, university hospitals)
  - ➔ Inpatients (7 studies), In- and outpatients (6), Laboratory-based (3)
- Age: Median 36 months, mean 47 months
- HIV 0 to 54% (12 studies)

Analysis

- Sample size ≥ 5 children.
- Subgroup analysis with studies that provided data for all outcomes assessed

– Bivariate random effects model (Bayesian)
  - Pooled estimates of sensitivity and specificity with corresponding pooled 95% credible intervals
  - Subgroup analysis to investigate heterogeneity
- PTB
  – Meta-regression controlling for smear and HIV status

What is the diagnostic accuracy of Xpert for the detection of pulmonary TB against the reference standard culture?

Solid or liquid culture

positive = at least one positive culture

negative = no positive culture

Results PTB against culture

- **13 studies, 2603 participants**
- **Specimen types (participants):**
  - Expectorated (ES, 270) and Induced Sputum (IS,1279),
  - Gastric fluid (GLA, 1324)
  - Nasopharyngeal aspirates (NPA, 474)
- **Average sample size 69 (3-788)**
- **Bacteriologic yield (culture) 0-54.2%**

Main differences between studies

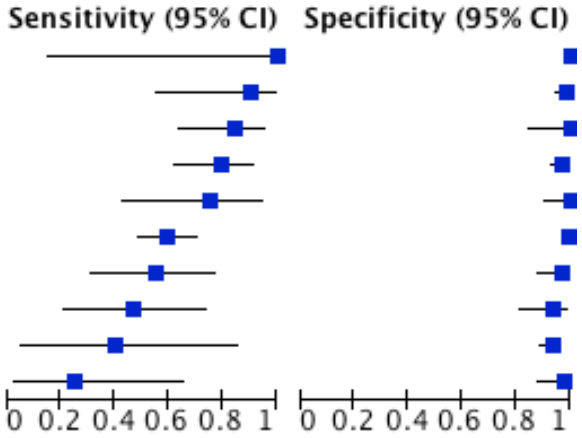
1. Inclusion criteria/Definition of TB suspect
   - Broad/unclear (7)
   - Rigorous (6)
2. Definition of clinical TB
3. Approach to confirm TB by culture
   - 1 culture (3 studies)
   - >1 (up to 6, 10 studies)

Tables 3 and 4 in Xpert report

PTB overall by specimen type

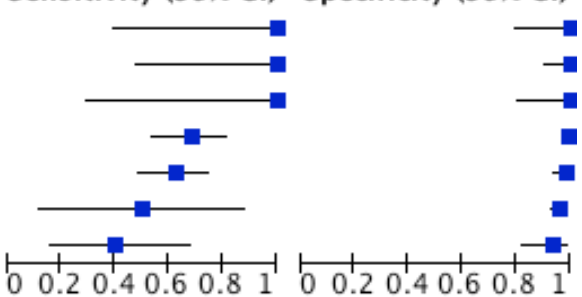
Expectorated/Induced Sputum: 10 (1546)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
ES_Unpublished	2	0	0	199	1.00 [0.16, 1.00]	1.00 [0.98, 1.00]
ES_Bates 2013	9	2	1	130	0.90 [0.55, 1.00]	0.98 [0.95, 1.00]
ES_Nhu 2013	21	0	4	22	0.84 [0.64, 0.95]	1.00 [0.85, 1.00]
IS_Sekkade 2013	27	7	7	194	0.79 [0.62, 0.91]	0.97 [0.93, 0.99]
IS_Nicol 2011	9	0	3	36	0.75 [0.43, 0.95]	1.00 [0.90, 1.00]
IS_Zar 2012	52	2	35	385	0.60 [0.49, 0.70]	0.99 [0.98, 1.00]
ES_Rachow 2012	11	2	9	56	0.55 [0.32, 0.77]	0.97 [0.88, 1.00]
IS_Unpublished	7	3	8	41	0.47 [0.21, 0.73]	0.93 [0.81, 0.99]
IS_Unpublished	2	14	3	192	0.40 [0.05, 0.85]	0.93 [0.89, 0.96]
IS_Rachow 2012	2	1	6	42	0.25 [0.03, 0.65]	0.98 [0.88, 1.00]



Gastric fluid: 7 (1319)

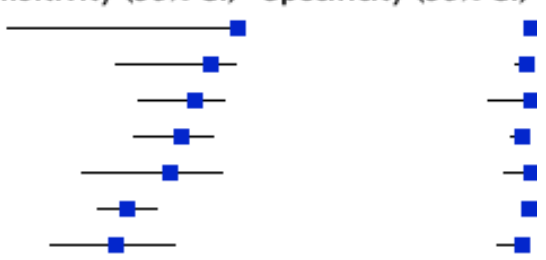
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
GLA_Nhu 2013	4	0	0	16	1.00 [0.40, 1.00]	1.00 [0.79, 1.00]
GLA_Causse 2012	5	0	0	38	1.00 [0.48, 1.00]	1.00 [0.91, 1.00]
GLA_Walters 2012	3	0	0	17	1.00 [0.29, 1.00]	1.00 [0.80, 1.00]
GLA_Bates 2013	33	5	15	735	0.69 [0.54, 0.81]	0.99 [0.98, 1.00]
GLA_Tortoli 2012	37	2	22	113	0.63 [0.49, 0.75]	0.98 [0.94, 1.00]
GLA_Unpublished	3	8	3	200	0.50 [0.12, 0.88]	0.96 [0.93, 0.98]
GLA_Unpublished	6	3	9	42	0.40 [0.16, 0.68]	0.93 [0.82, 0.99]



PTB overall by specimen type

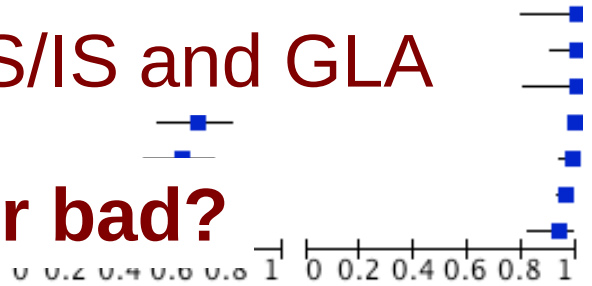
Overall ES/IS

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
ES_Unpublished	2	0	0	199	1.00 [0.16, 1.00]	1.00 [0.98, 1.00]
ES_Bates 2013	9	2	1	130	0.90 [0.55, 1.00]	0.98 [0.95, 1.00]
ES_Nhu 2013	21	0	4	22	0.84 [0.64, 0.95]	1.00 [0.85, 1.00]
IS_Sekkade 2013	27	7	7	194	0.79 [0.62, 0.91]	0.97 [0.93, 0.99]
IS_Nicol 2011	9	0	3	36	0.75 [0.43, 0.95]	1.00 [0.90, 1.00]
IS_Zar 2012	52	2	35	385	0.60 [0.49, 0.70]	0.99 [0.98, 1.00]
ES_Rachow 2012	11	2	9	56	0.55 [0.32, 0.77]	0.97 [0.88, 1.00]



	Pooled sensitivity (95%CrI)	Pooled specificity (95% CrI)
ES/IS	**66% (52, 77)**	**98% (96, 99)**
GLA	**66% (51, 81)**	**98 % (96, 99)**

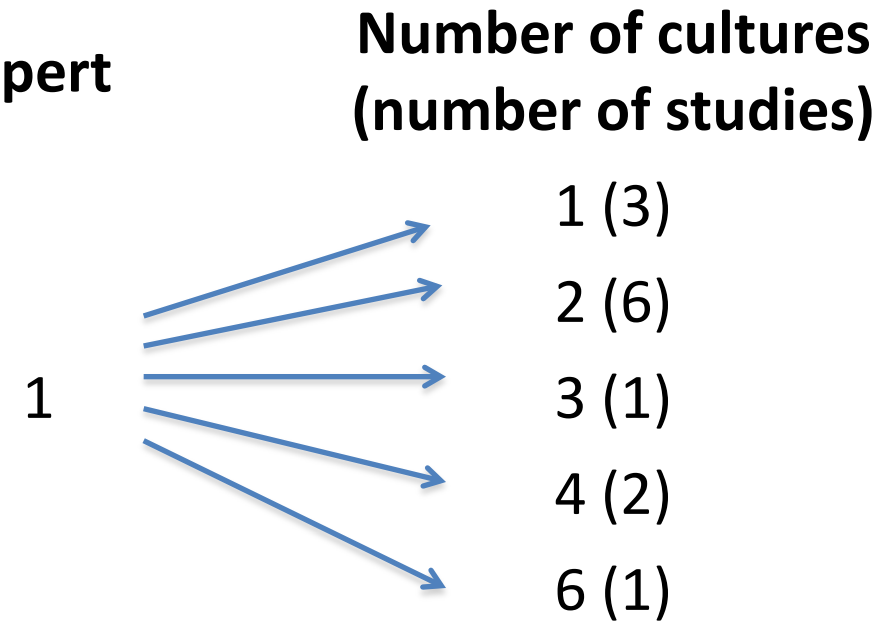
GLA_Nhu 2						
GLA_Causs						
GLA_Walte						
GLA_Bates 2013	33	5	15	735	0.69 [0.54, 0.81]	0.99 [0.98, 1.00]
GLA_Tortoli 2012	37					
GLA_Unpublished						
GLA_Unpublished						



➔Xpert performs similar in ES/IS and GLA

➔ **Sensitivity: good or bad?**

Xpert against culture, overall



Walters, unpublished

	Sensitivity	
	IS	**GLA**
1 Xpert vs. 1 culture	64%	50%
1 Xpert vs. up to 4 cultures	47%	40%

Incremental yield of multiple Xperts – 3 studies

2nd specimen ➔ 8.3 - 17.5%

3rd specimen ➔ 0 – 12.5%

Improved when additional specimens are taken on another day

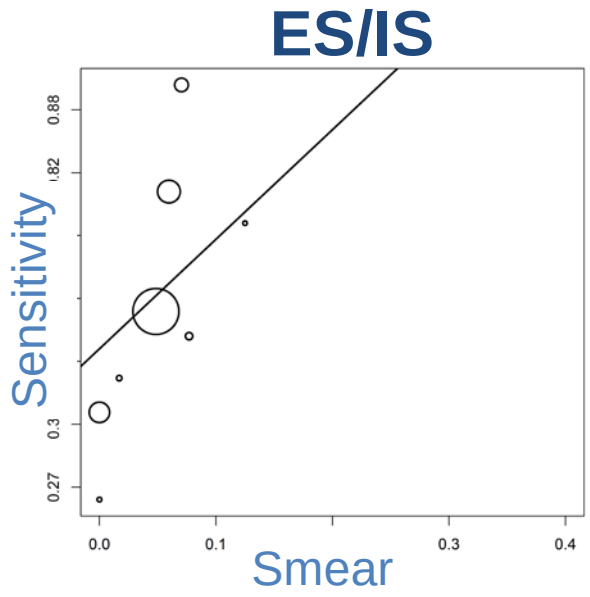
Incremental yield of culture in the same studies was 14.3 – 21.9%

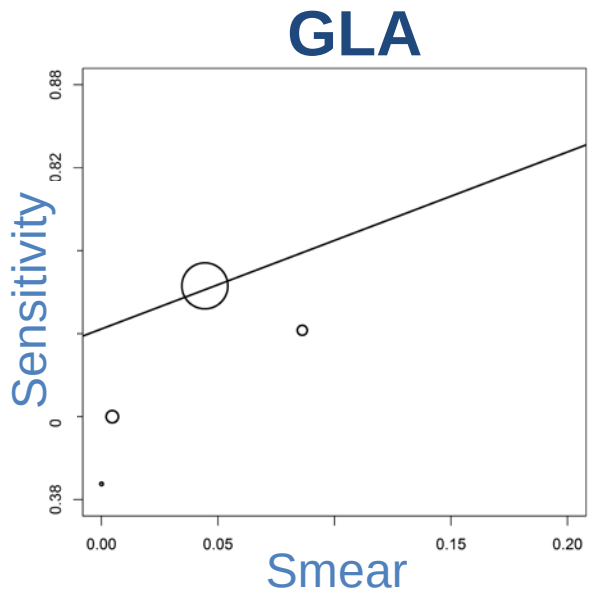
Nhu 2013, Rachow 2012, Zar 2012

Subgroup analysis

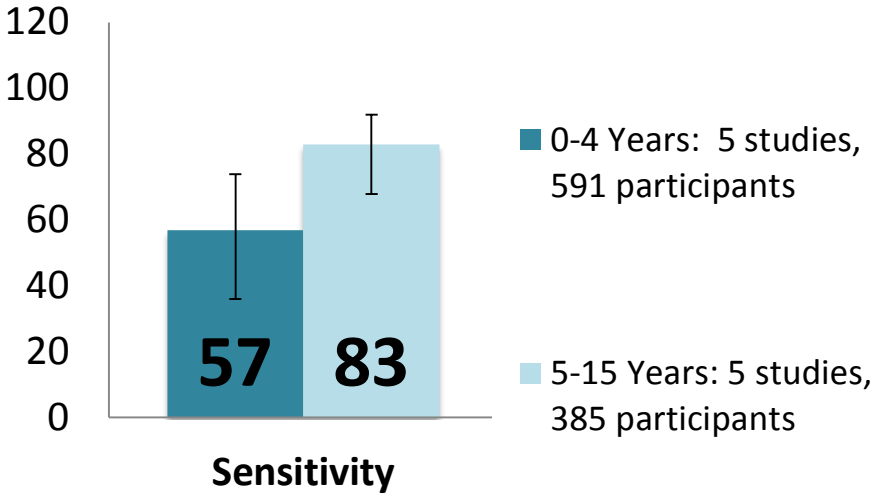
Sensitivity by smear status

Specimen	Smear positive	Smear negative
ES/IS	96% (90, 99)	55% (41, 69)
GLA	95% (83, 99)	62% (44, 80)

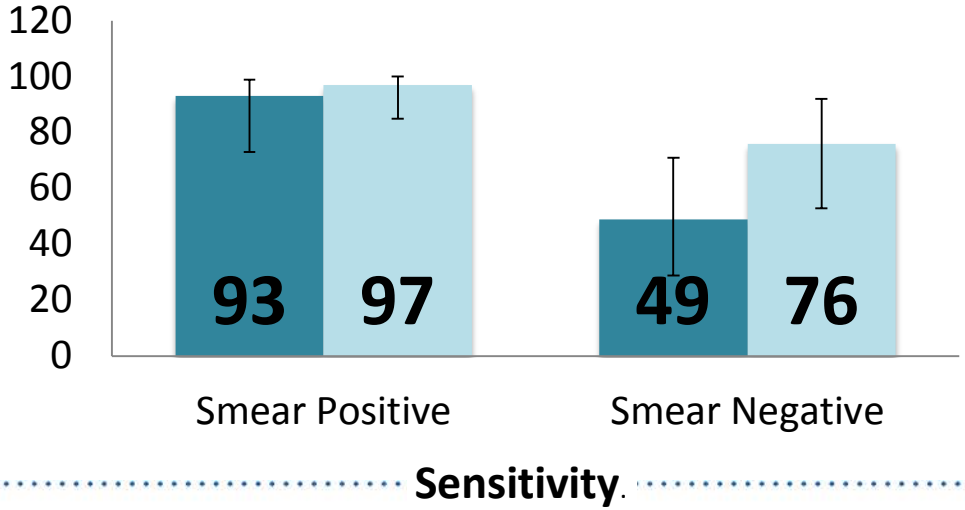




Age (ES/IS)

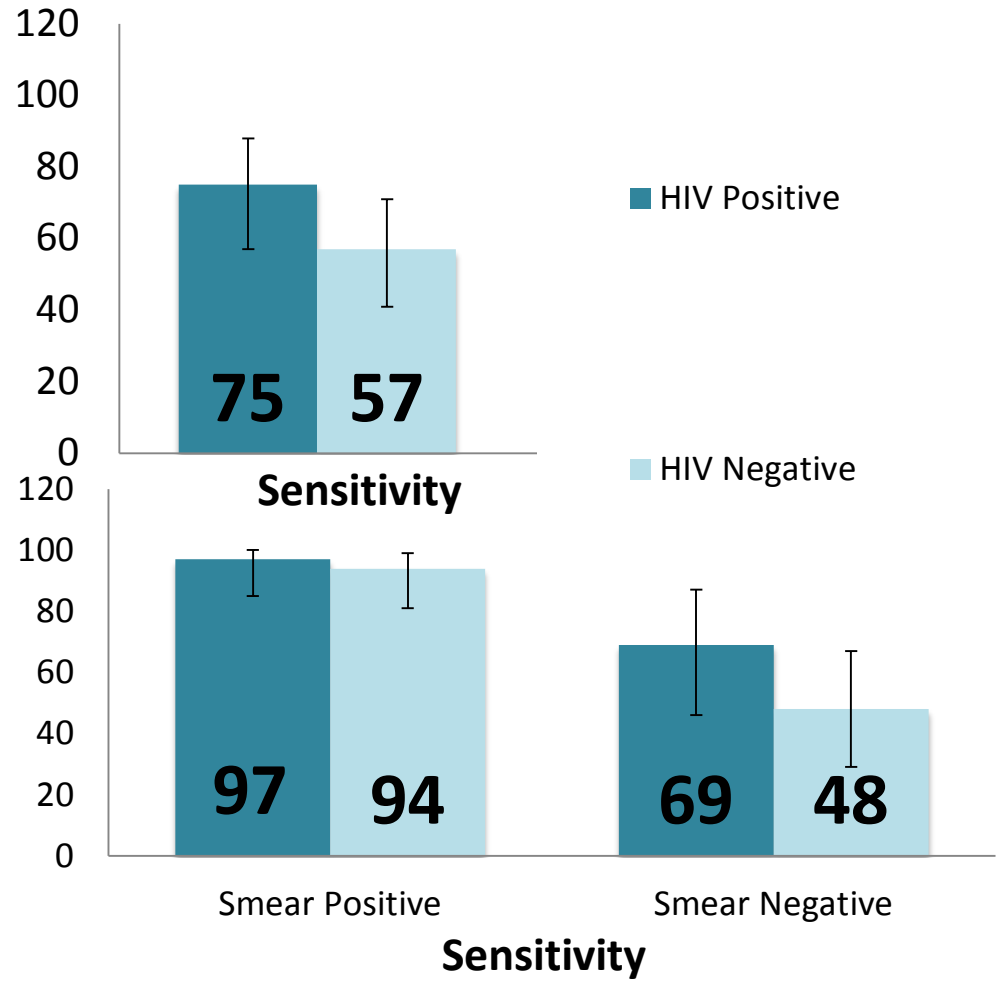


➔ Point estimate for sensitivity of Xpert is higher in older compared to younger children?



➔ Xpert performs better in smear positive children (older children are more likely to be smear +)

HIV status (ES/IS)



➔ Sensitivity of Xpert is higher in HIV-infected than uninfected children

➔???

➔ Xpert performs better in smear positive children

Meta regression model: smear and HIV status

Node		Mean	SD	MC error	2.5%	Median	97.5%
BETA 0		0.06201	0.385	0.0054	-0.8159	-0.06399	0.7059
BETA 1 (HIV)		0.5863	0.5551	0.008862	-0.4919	0.5789	1.705
BETA 2 (Smear)		3.98	1.076	0.02855	2.159	3.878	6.399
Pooled Sensit.	SM-/HIV-	0.485	0.09264	0.0013	0.3066	0.484	0.6695
	Sm+/HIV-	0.9694	0.03031	6.402E-4	0.8873	0.9785	0.9983
	Sm-/HIV+	0.6213	0.1101	0.001197	0.3944	0.6257	0.8216
	Sm+/HIV +	0.9818	0.01977	3.951E-4	0.9284	0.9879	0.9991

Odds of test positivity

- **is 4 fold greater in smear + compared to smear -**
- **is not significantly higher for HIV + versus HIV -**

Xpert versus smear microscopy

- **Xpert as a replacement**

	Pooled Sensitivity (95% CrI)	Pooled Specificity (CrI)
Smear microscopy	29% (16, 42)	100% (99, 100)
Xpert (ES/IS)	66% (52, 77)	98% (96, 99)

- **Xpert as add-on** (analysis in smear negatives)

	Pooled Sensitivity (95% CrI)
Smear microscopy	0%
Xpert (ES/IS)	55 % (41, 69)

➔ **Xpert has a clear advantage over smear microscopy**

What is the diagnostic accuracy of Xpert for the detection pulmonary TB in culture negative children against a clinical reference standard?

The pragmatic approach:

TB = **started on ATT**

Not TB = no ATT, other diagnosis, improvement after at least 1 month

Xpert against Clinical Reference standard in culture negative children

	Pooled sensitivity (95%CrI)	Pooled specificity (95% CrI)
ES/IS	4% (1, 12)	100% (99, 100)
GLA	15% (5, 31)	99 % (96, 100)

➔ Does Xpert perform badly **OR** are many children overdiagnosed?

Xpert against clinical TB

Consider:

1.Clinical reference standard TB = all culture negative children initiated on treatment

➔How would Xpert perform against a more strictly defined clinical reference standard **(irrespective of culture)**

2. Limit of detection

Culture: 10-100 CFU/ml

Xpert: 131 CFU/ml*

➔ **Xpert does not detect culture negative children with paucibacillary TB**

Helb D., JCM 2009, van Zyl-Smit R., PloSOne 2011

Xpert for RIF resistance, pLN TB, TBM

Pooled sensitivity (95%CrI)	Pooled specificity (95% CrI)	Pooled sensitivity other reviews for WHO
RIF resistance (3 studies, 176 participants)		17 studies, 555/2624 specimens
86% (53, 98)	**98% (94, 100)**	**95% (90, 97)**
pLN TB (3 studies, 172 children)		14 studies, 849 samples
86% (65, 96)	**81% (54, 93)**	**84.9% (72, 92)**
TBM (3 studies, 51 children)		16 studies, 709 samples
-	**95% (81, 99)**	**79.5 (62, 90)**

Summary

- Xpert shows similar performance in ES/IS and GLA
- Xpert results are associated with smear status

  (Smear status is a proxy for severity/extent of disease?)
- Xpert has an advantage over smear microscopy
- 20-60 % of children with TB are confirmed by culture ➔ **40-80% of childhood TB cases will be Xpert negative**
- Performing > 1 Xpert increases the number of identified TB cases (but: $$$)

Scale up of Xpert

- Increased access to TB diagnostics
  - Need to optimize referral systems
- **Motivation to get pediatric specimens**
- Increased number of confirmed TB cases
- **Clear need to emphasize to interpret negative results cautiously – diagnosis remains a composite in the context of contact history, signs and symptoms, other diagnostic tools**

Future research

- Research studies need to apply clear criteria for inclusion of TB suspects as well as clinical case definitions
- The impact of disease severity on test accuracy
- Performance of Xpert in outpatient settings (uncomplicated disease)
- Integration: **Xpert in non-traditional TB settings** (e.g. malnutrition units)
- **Routine program data**
- Type of specimen and specimen collection technique (including less invasive specimens)
- Patient important outcomes for children: time to diagnosis, time to treatment initiation, cost

Thank you

To all that contributed to this review!