The Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults, a Cochrane Collaboration systematic review and meta-analysis

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Declarations of Interest

- Karen serves as Coordinator of the Evidence Synthesis and Policy Subgroup of Stop TB Partnership's New Diagnostics Working Group and is an Editor with the Cochrane Infectious Diseases Group

- Catharina is employed by the Foundation for Innovative New Diagnostics (FIND) and has conducted studies and published on Xpert MTB/RIF as part of a collaborative project between FIND, a Swiss non-profit, Cepheid, a US company, and academic partners

- Funding was provided by McGill University and the Cochrane Infectious Diseases Group which is funded by the Department for International Development, UK, for the benefit of low- and middle-income countries

- *This systematic review is currently undergoing review. The results should be considered preliminary until published by the Cochrane Collaboration*

Objectives

- I. **Xpert for TB detection**

  To determine summary estimates of the diagnostic accuracy of Xpert for pulmonary TB in adults

- **II. Xpert for rifampicin resistance detection**

  To determine summary estimates of the diagnostic accuracy of Xpert for rifampicin resistance detection in adults

Purpose of testing and setting of interest

- **I. Xpert for TB detection**

  - A. Xpert used as an initial test replacing smear microscopy

  - B. Xpert used as an add-on test following a negative smear microscopy result

- **II. Xpert for rifampicin resistance detection**

  - A. Xpert used as an initial test replacing conventional culture-based drug susceptibility testing as the initial test

- We were interested in how Xpert performed in patients who were evaluated in laboratories or health facilities in decentralized settings

Criteria for considering studies - 1

- **Types of studies** - randomized controlled trials, cross-sectional, and cohort studies
- **Participants**

  - adult or predominantly adult patients suspected of having pulmonary TB or MDR-TB

  - sputum and other respiratory specimens
- **Index test -** Xpert MTB/RIF test

Excluded

  - case-control studies

  - specimens obtained by gastric aspiration (because these are often used for investigating TB in children)

  - studies that evaluated the use of Xpert in children

Criteria for considering studies - 2

- **Reference standards**

  - **TB detection**: LJ, 7H10 or 7H11, or Ogawa media, and/or a commercial liquid culture system (such as BACTEC™ 460TB System or BACTEC™ MGIT™ 960)

  - **Rifampicin resistance detection**: culture-based drug susceptibility testing as recommended by WHO (WHO Interim policy guidance 2008)

Quality assessment and statistical analysis - 1

- Quality was assessed using QUADAS-2
- Data from 2-by-2 tables were used to calculate sensitivity and specificity estimates and 95% confidence intervals for individual studies
- Meta-analysis was performed using an adaptation of a bivariate random effects model (Reitsma 2005)

Quality assessment and statistical analysis - 2

- A diagnostic strategy using microscopy and Xpert concurrently was considered as a proxy for a strategy using Xpert as an add-on test following a negative smear microscopy result

- Data for indeterminates were excluded from primary analyses and analyzed separately

- Data for NTM were summarized separately by determining the percent of false-positive Xpert results in samples that grew NTMs
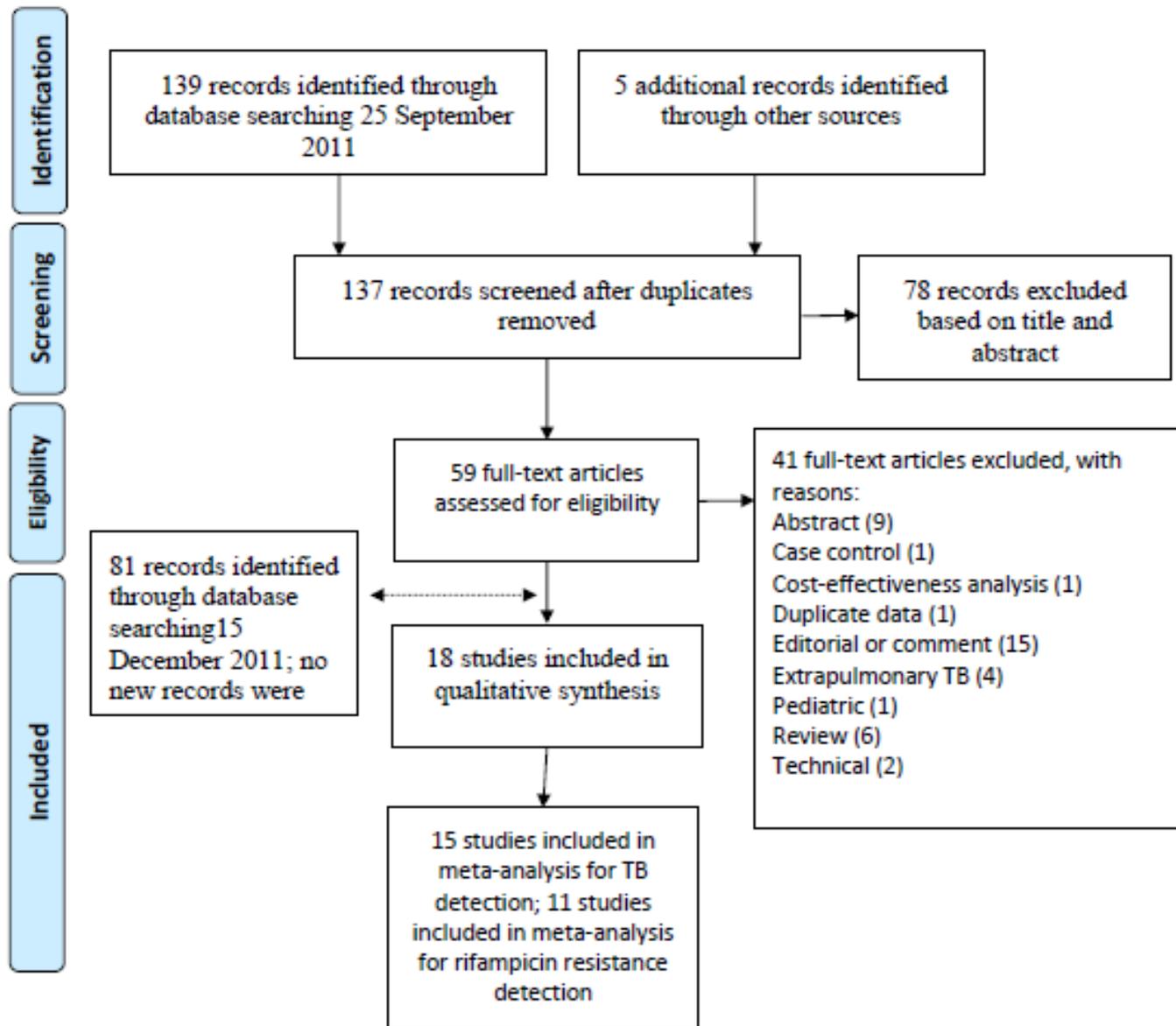
PRISMA diagram showing the flow of studies in the review

Results

- 18 included studies
  - 2 international multicentre studies
  - 1 study, conducted at 3 sites, presented accuracy data for all sites combined
- TB detection: 7816 participants
- Rifampicin resistance detection: 2340 participants
- 10 (56%) studies were performed in low-income and middle-income countries
- In 17 studies, Xpert was performed by trained technicians in reference laboratories
- In one study, Xpert was performed in decentralized laboratories associated with health clinics and provincial hospitals; no studies performed Xpert at the point of care

Quality assessment
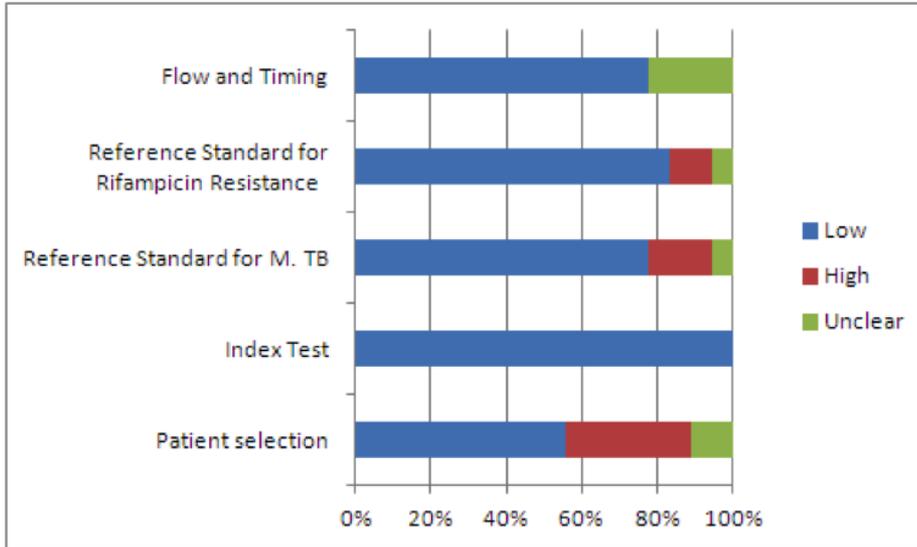
A. Risk of bias

B. Applicability
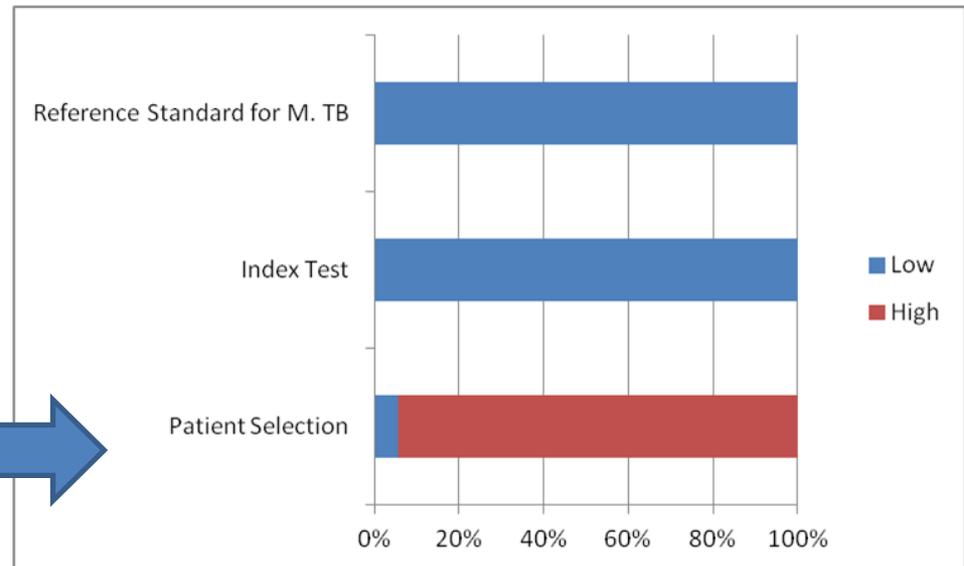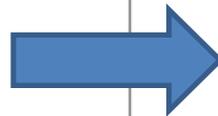
TB Detection, Xpert used as an initial test replacing smear microscopy
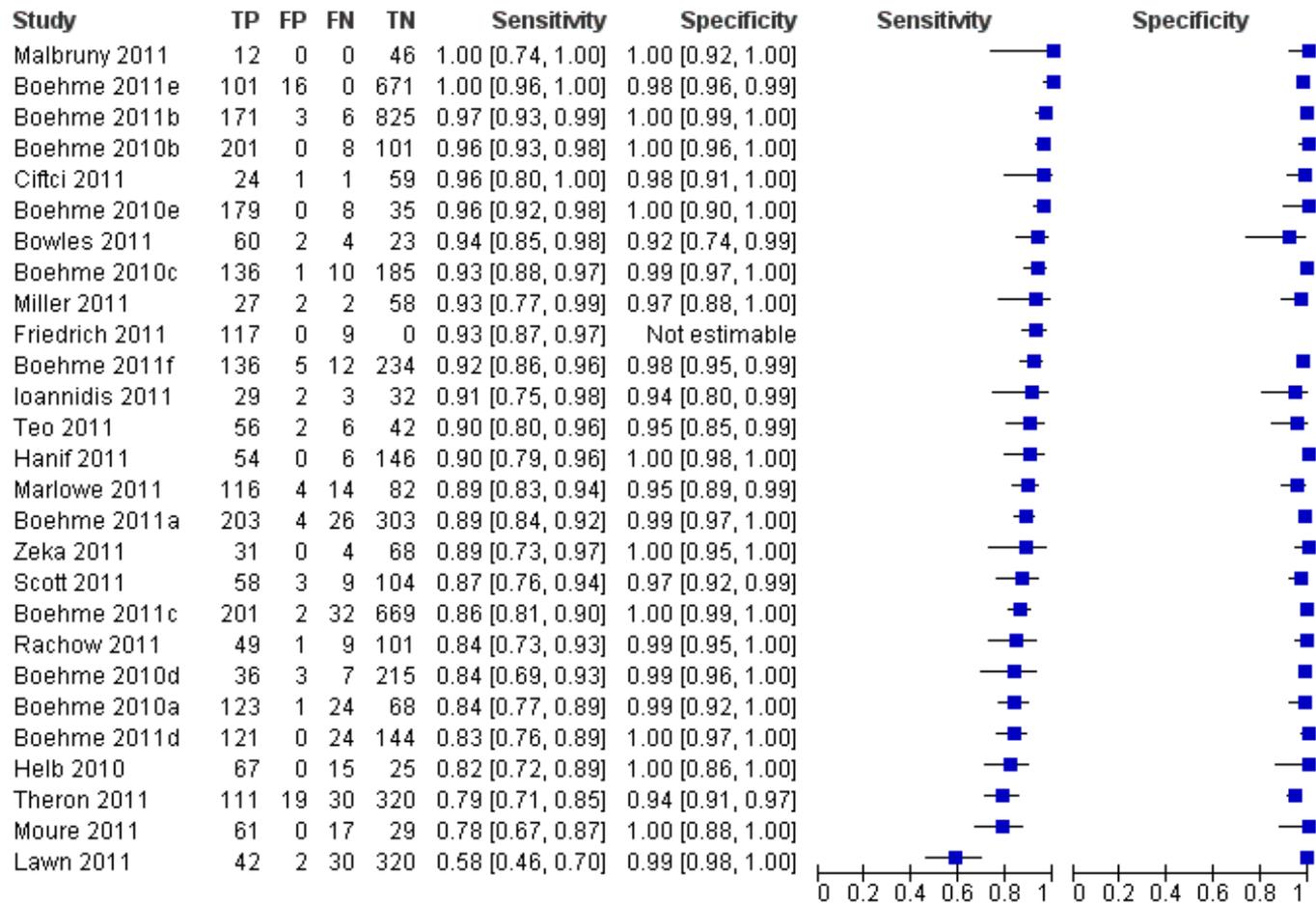
Fig 1. Forest plots of the included studies, Xpert for TB detection, Xpert used as an initial test

Meta-analysis: pooled sensitivity = 88% (83, 92)
pooled specificity = 98% (97, 99)

TB Detection, Xpert used as an add-on test following a negative smear microscopy result
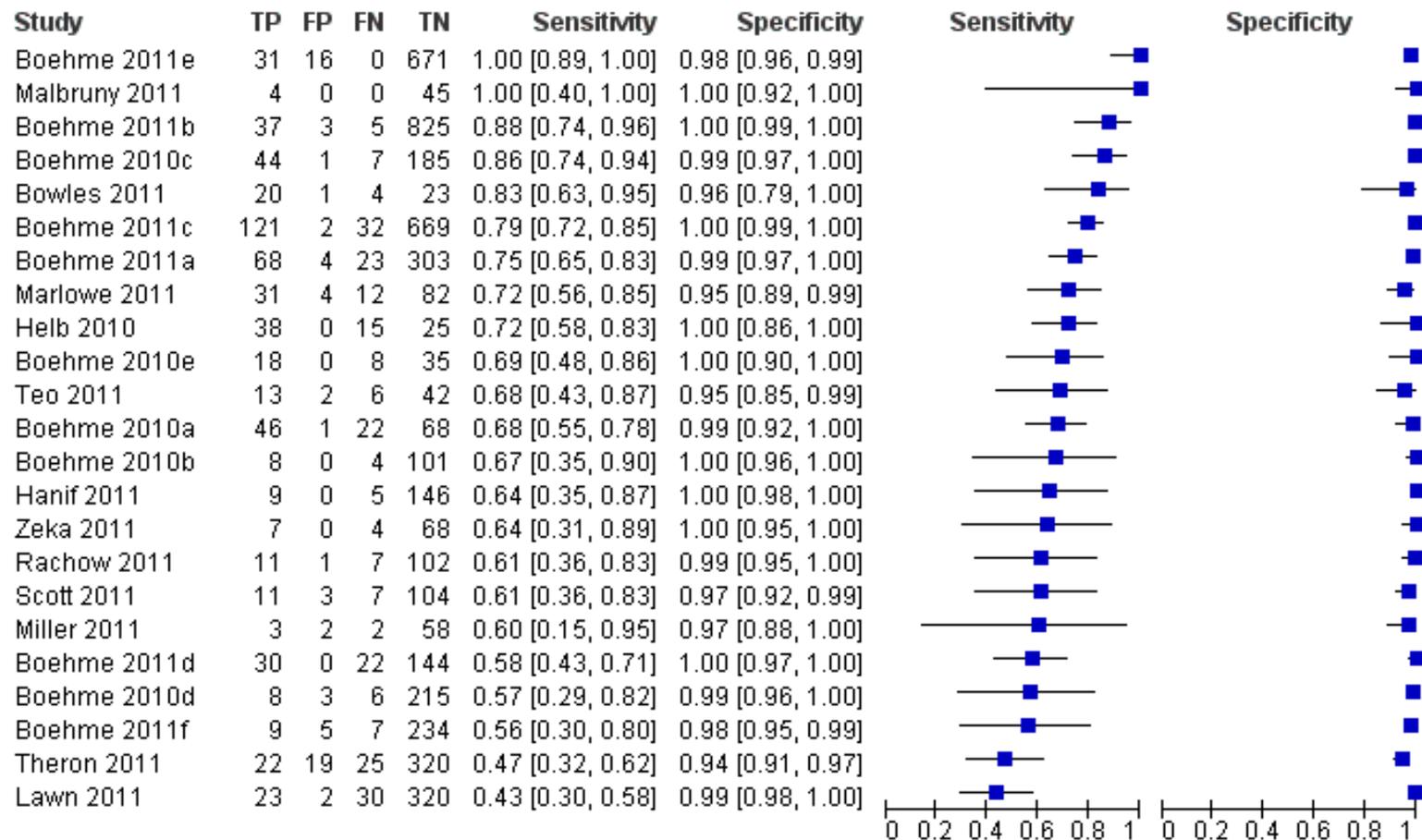
Fig 2. Forest plots of the included studies, Xpert for TB detection
Xpert used as an add-on test following microscopy

Meta-analysis: pooled sensitivity = 67% (58, 74)
pooled specificity = 98% (97, 99)

Rifampicin resistance detection, Xpert used as an initial test, replacing conventional culture-based drug susceptibility testing as the initial test

Study	TP	FP	FN	TN	Sensitivity	Specificity
Boehme 2010b	16	3	0	190	1.00 [0.79, 1.00]	0.98 [0.96, 1.00]
Bowles 2011	8	0	0	81	1.00 [0.63, 1.00]	1.00 [0.96, 1.00]
Lawn 2011	4	3	0	48	1.00 [0.40, 1.00]	0.94 [0.84, 0.99]
Boehme 2010d	3	0	0	38	1.00 [0.29, 1.00]	1.00 [0.91, 1.00]
Friedrich 2011	3	0	0	90	1.00 [0.29, 1.00]	1.00 [0.96, 1.00]
Teo 2011	1	0	0	130	1.00 [0.03, 1.00]	1.00 [0.97, 1.00]
Zeka 2011	1	0	0	34	1.00 [0.03, 1.00]	1.00 [0.90, 1.00]
Malbruny 2011	1	0	0	16	1.00 [0.03, 1.00]	1.00 [0.79, 1.00]
Boehme 2010e	119	3	2	61	0.98 [0.94, 1.00]	0.95 [0.87, 0.99]
Boehme 2011f	149	6	5	97	0.97 [0.93, 0.99]	0.94 [0.88, 0.98]
Boehme 2010a	47	4	2	90	0.96 [0.86, 1.00]	0.96 [0.89, 0.99]
Boehme 2011b	22	1	1	161	0.96 [0.78, 1.00]	0.99 [0.97, 1.00]
Boehme 2011a	47	1	3	160	0.94 [0.83, 0.99]	0.99 [0.97, 1.00]
Boehme 2010c	15	0	1	126	0.94 [0.70, 1.00]	1.00 [0.97, 1.00]
Boehme 2011c	9	3	1	175	0.90 [0.55, 1.00]	0.98 [0.95, 1.00]
Boehme 2011e	8	2	2	91	0.80 [0.44, 0.97]	0.98 [0.92, 1.00]
Scott 2011	4	2	1	10	0.80 [0.28, 0.99]	0.83 [0.52, 0.98]
Ioannidis 2011	4	0	1	27	0.80 [0.28, 0.99]	1.00 [0.87, 1.00]
Theron 2011	1	5	1	84	0.50 [0.01, 0.99]	0.94 [0.87, 0.98]
Boehme 2011d	1	1	2	112	0.33 [0.01, 0.91]	0.99 [0.95, 1.00]

Fig 3. Forest plots of the included studies, Xpert for rifampicin resistance detection Xpert used as an initial test

Meta-analysis: pooled sensitivity = 94% (87, 97)
pooled specificity = 98% (97, 99)

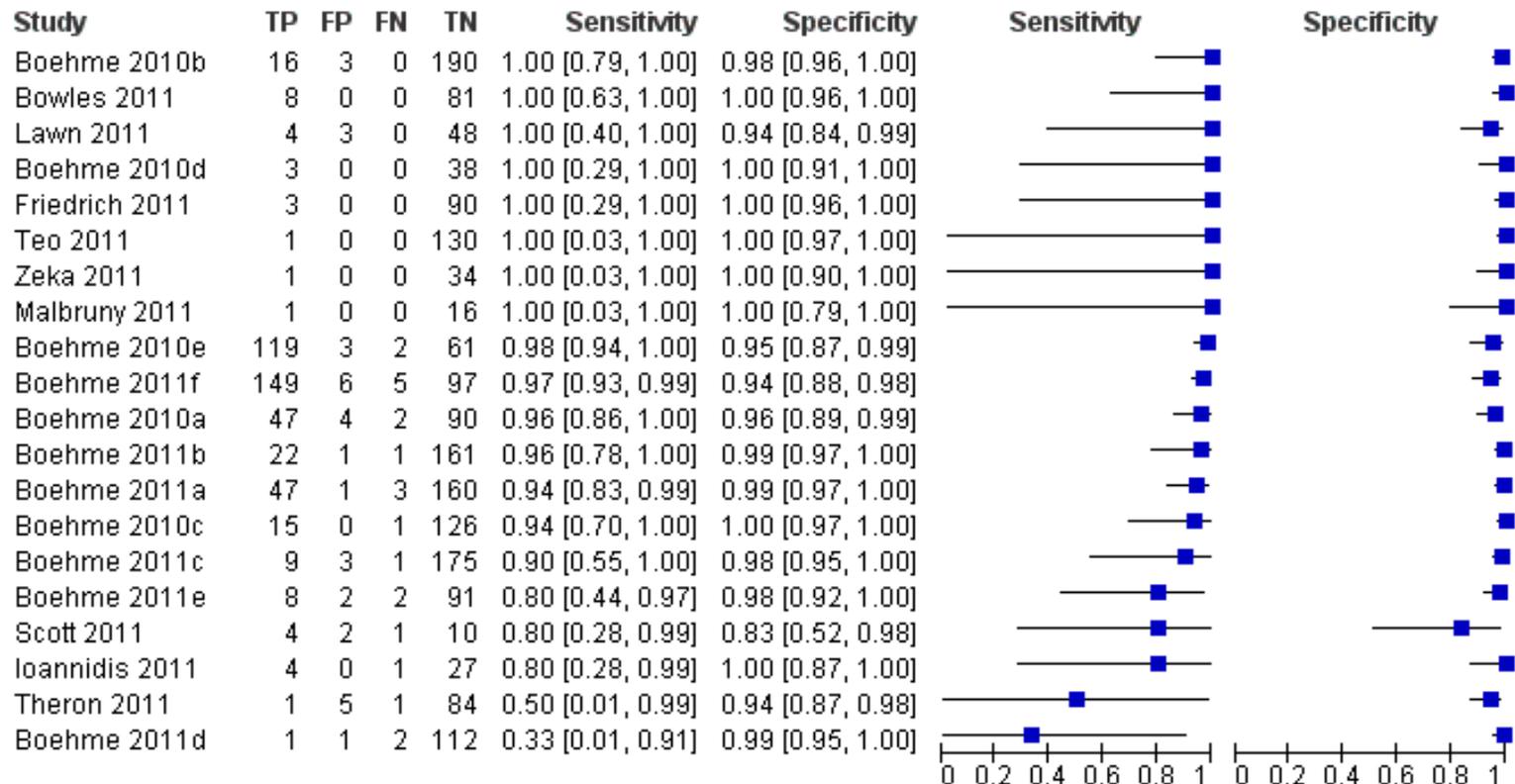# TB Detection, Investigations of heterogeneity

Type of Analysis (Number of Studies)	Pooled Sensitivity Median (95% Credible Interval*)	Pooled Specificity Median (95% Credible Interval*)
HIV-negative subgroup (4)	89% (81, 94)	99% (96, 99)
HIV-positive subgroup (4)	80% (67, 88)	97% (93, 99)

Table 1. Xpert MTB/RIF for TB detection, investigations of heterogeneity -1

Type of Analysis (Number of Studies)	Pooled Sensitivity Median (95% Credible Interval)	Pooled Specificity Median (95% Credible Interval)
Unprocessed specimens (5)	92% (87, 96)	99% (97,99)
Processed specimens (10)	85% (79, 90)	98% (96, 99)
High-income countries (5)	92% (86, 96)	98% (95, 99)
Low/middle-income countries (10)	85% (79, 90)	99% (97, 99)

Table 1. Xpert MTB/RIF for TB detection, investigations of heterogeneity - 2

Other analyses

- **Indeterminate results:**

  - Of 13,308 tests performed, the pooled proportion of indeterminate tests was very low, 0.01 (0.00, 0.02)

- **Nontuberculous mycobacteria (NTM)**:

  - 8 studies provided data on a variety of NTM that grew from the specimens tested

  - Among these studies, comprising 139 NTM, Xpert was positive in only one (0.7%) specimen that grew NTMs

Summary of findings

- Xpert sensitivity for smear-positive, culture-positive TB was very high and consistent (98%); Xpert sensitivity for smear-negative, culture-positive TB was lower and more variable (68%)

- Xpert detected 80% of pulmonary TB cases in people living with HIV and 89% of pulmonary TB cases in people without HIV infection

- When used as an initial test replacing conventional drug susceptibility testing, Xpert detected 94% of rifampicin-resistant TB with high specificity (98%)

- The proportion of indeterminate Xpert results was very low (.01)

Conclusions

- The findings in this systematic review lend support to the WHO recommendations on the use of Xpert as an initial diagnostic test for TB detection and rifampicin resistance detection in patients suspected of having MDR-TB and HIV-associated TB

- An Xpert result that is positive for rifampicin resistance should be carefully interpreted with consideration of the expected prevalence of MDR-TB in a given setting.

- It is anticipated that ongoing roll-out of Xpert in high burden countries will generate evidence on patient outcomes and cost-effectiveness in routine programmatic and decentralized settings, in particular at the point of care

Weaknesses of this systematic review

- Rapidly growing evidence body (another 17 accuracy studies for pulmonary TB in adults published so far in 2012)

- There were no studies of the current version of Xpert, G4, included in this review. It is possible that the performance of Xpert G4 will be different.

✓ Cochrane Review to be updated asap

Detection of extrapulmonary TB

Reference	Tissue	Lymph Node	CSF	Gastric	Pleural	Urine	Cavitary fluid	Pericardial fluid	Stool	Pus	Other	Total Sensitivity
Ligthelm et al. [1]		28/29 (97%)										28/29 (97%)
Hillemann et al. [2]	20/29 (69%)			7/8 (87.5%)		5 /5 (100%)			2/2 (100%)			35/44 (77.3%)
Teo et al. [3]			2/3 (66%)	4/4 (100%)			1/1 (100%)				7/7 (100%)	14/15 (93.3%)
Vadwai et al. [4]	54/70 (77%)		1/3 (33%)*	Body fluids 16/21 (76%)						54/56 (96%)		125/150 (83%)
Miller et al. [5]												7/8 (88%)
Zeka et al. [6]					0/4 (0%)							21/31 (68%)
Causse et al. [7]												39/41 (95%)
Friedrich et al. [8]					5/20 (25%)							5/20 (25%)
Hanif et al. [9]												12/12 (100%)
Armand et al. [10]	3/5 (60%)	8/16 (50%)			3/7 (43%)	0/1 (0%)				3/3 (100%)		17/32 (53%)
Moure et al. [11]	5/12 (42%)	24/34 (71%)	2/2 (100%)	2/3 (67%)	7/26 (27%)	2/3 (67%)		1/1 (100%)	2/2 (100%)	13/17 (76%)	5/8 (63%)	63/108 (58%)
Tortoli et al. [12]			11/13 (85%)	45/58 (78%)	5/15 (33%)	11/13 (85%)	40/47 (85%)	5/10 (50%)		71/82 (87%)		188/238 (79%)

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Thank you!