Xpert® MTB/RIF assay for TB detection in non-respiratory specimens: A systematic review and meta-analysis

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ORIGINAL ARTICLE
IN PRESS | CORRECTED PROOF

Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis

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BACKGROUND

Extrapulmonary TB & Diagnostics

- Extrapulmonary tuberculosis (EPTB) accounts for about 25% of all TB

- Existing diagnostics for detection of TB on non-respiratory samples are limited
  - in accuracy
  - time to diagnosis
  - resistance testing
  - and often require invasive procedures and special expertise

Peto 2009
Nelson 2004
Jones 1996
WHO Report 2012

What about Xpert?

- Xpert® MTB/RIF approved for pulmonary TB
- Xpert for detection of TB in non-respiratory specimens
  - neither approved by regulatory agencies
  - nor recommended by the manufacturer
- No SOP for non-respiratory specimens

WHO 2010
Cepheid

Review Question

In non-respiratory specimens,

- what is the diagnostic accuracy of Xpert for the detection of TB?
- what is the diagnostic accuracy of Xpert for detection of rifampicin resistance?
- what are factors that affect the diagnostic accuracy of Xpert?

METHODS

Search Methods

- Databases (searched through Dec 2012)
  - MEDLINE, Embase, Cochrane Register, Web of Knowledge
  - Reviewed bibliographies
  - Contacted authors with abstracts at major meetings
  - metaRegister of Controlled Trials (mRCT) and WHO International Clinical Trials Registry Platform
  - Contacted experts to find unpublished studies

- Inclusion Criteria:
  - All studies (included case-control)
  - All age-groups
  - All forms of TB, only TB suspects

Reference Standard

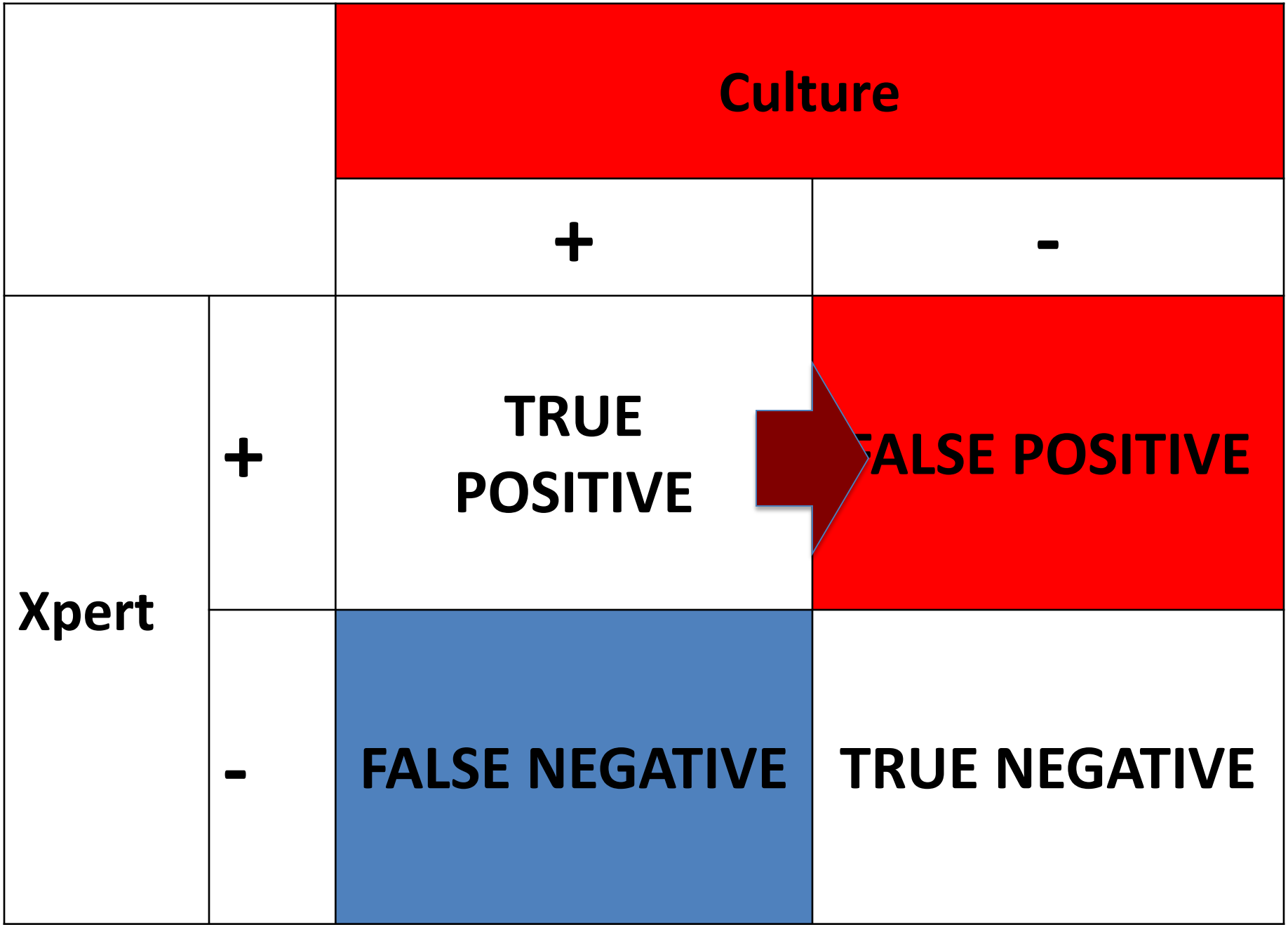
1. Mycobacterial culture (solid and liquid)

2. Composite reference standard (author-defined):
   - culture +/- NAAT, histology, smear
   - biochemical testing results
   - presenting signs
   - response to treatment with ATT

   → Limitations of reference standard: imperfect sensitivity and specificity

   → Comparison of the two reference standards will provide a plausible range for accuracy

		Perfect reference standard	
		+	-
Xpert	+	TRUE POSITIVE	FALSE POSITIVE
	-	FALSE NEGATIVE	TRUE NEGATIVE


Culture
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Xpert
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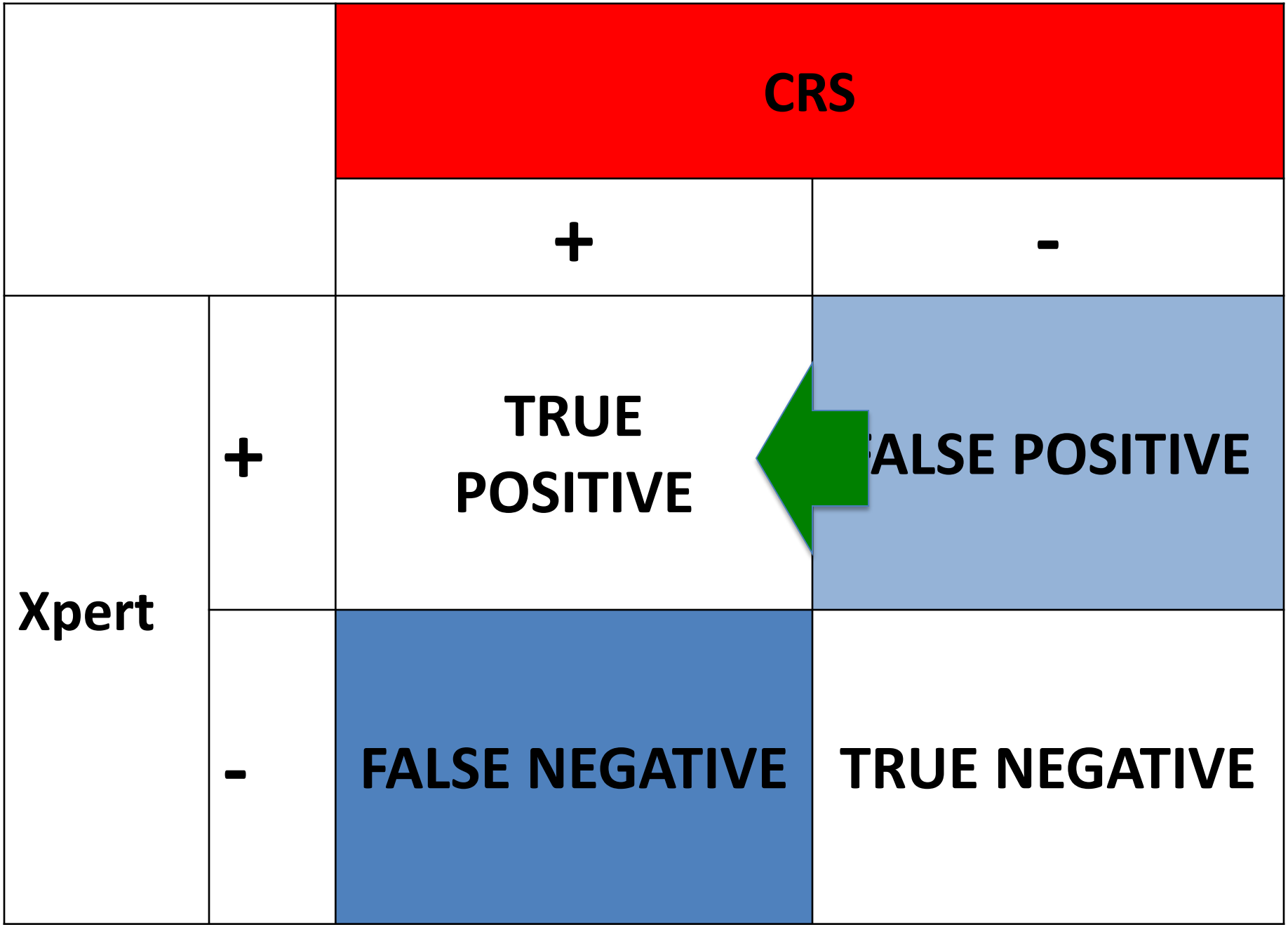
FALSE NEGATIVE
TRUE NEGATIVE


CRS
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Xpert
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TRUE POSITIVE
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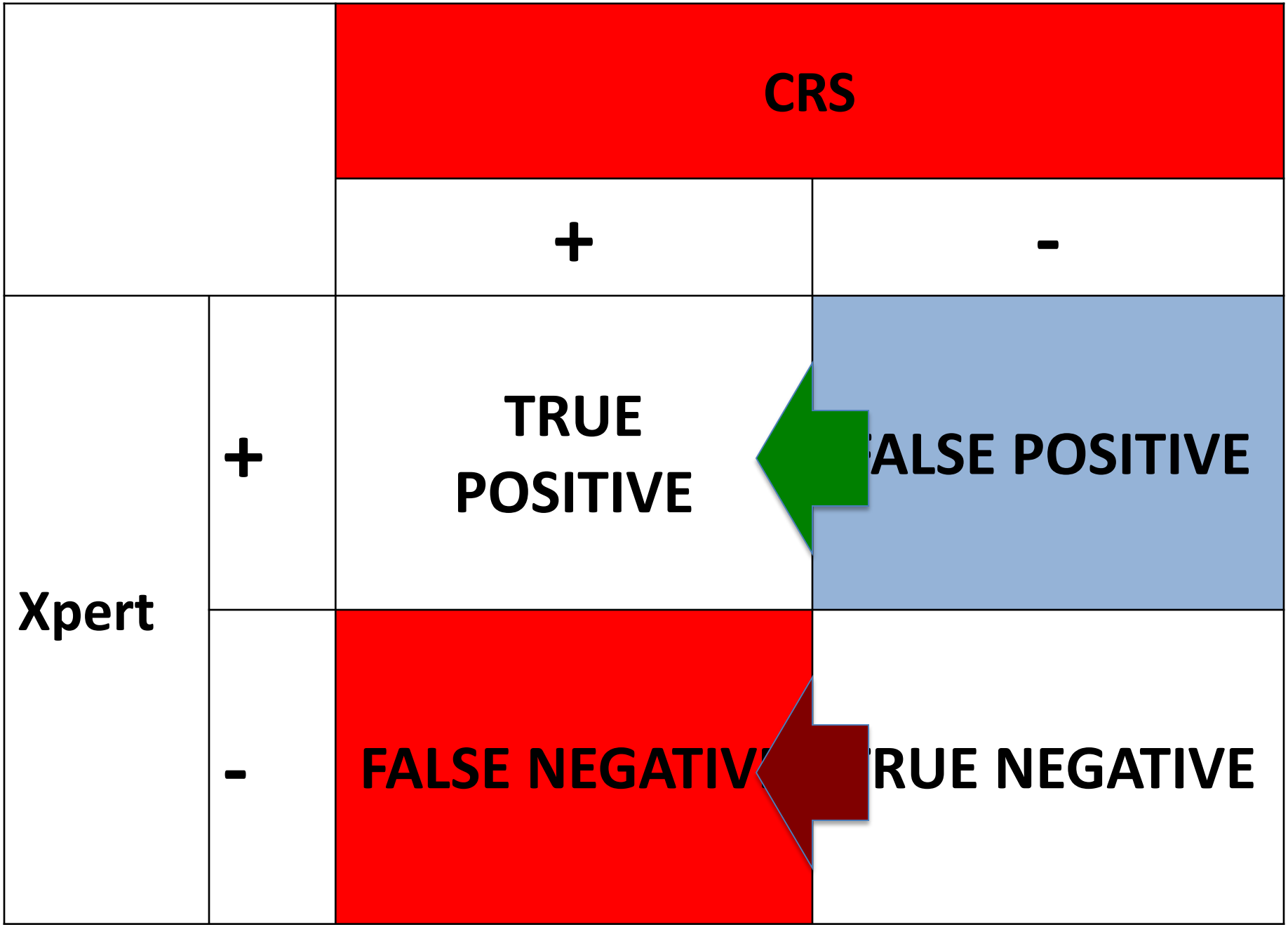
CRS
+
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Xpert
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TRUE POSITIVE
ALSE POSITIVE
FALSE NEGATIV
RUE NEGATIVE

Analysis Plan

- Quality assessment – QUADAS 2

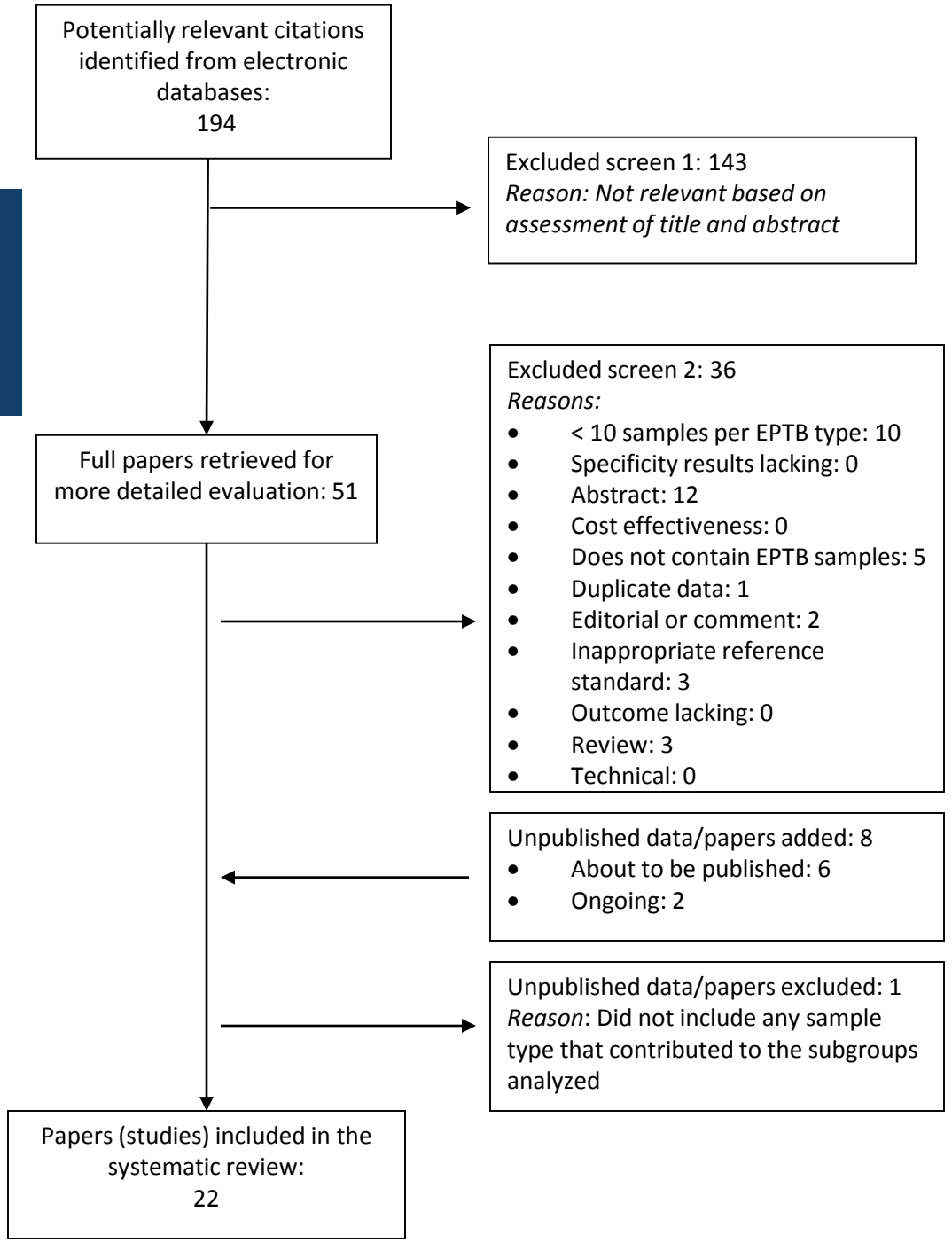
- Pre-specified subgroups by specimen type
  - Lymph node (aspirate and biopsy)
  - Pleural fluid
  - Cerebrospinal fluid
  - Gastric fluid
  - Vertebral bone tissue > limited > all tissue combined

- Further covariates for analysis:
  - Concentration step, sample condition, HIV prevalence

Analysis Plan

- ≥4 studies: bivariate random-effects meta-analysis
- <4 studies or limited events (i.e. TP+FN): summarized individual study results
- Univariate analysis separately if studies only contributed to sensitivity or specificity
- Sensitivity analysis
- Subgroup analysis and meta-regression

PRISMA


Potentially relevant citations identified from electronic databases: 194
Excluded screen 1: 143
Reason: Not relevant based on assessment of title and abstract
Full papers retrieved for more detailed evaluation: 51
Excluded screen 2: 36
Reasons:
< 10 samples per EPTB type: 10
Specificity results lacking: 0
Abstract: 12
Cost effectiveness: 0
Does not contain EPTB samples: 5
Duplicate data: 1
Editorial or comment: 2
Inappropriate reference standard: 3
Outcome lacking: 0
Review: 3
Technical: 0
Unpublished data/papers added: 8
About to be published: 6
Ongoing: 2
Unpublished data/papers excluded: 1
Reason: Did not include any sample type that contributed to the subgroups analyzed
Papers (studies) included in the systematic review: 22

RESULTS

Study Characteristics

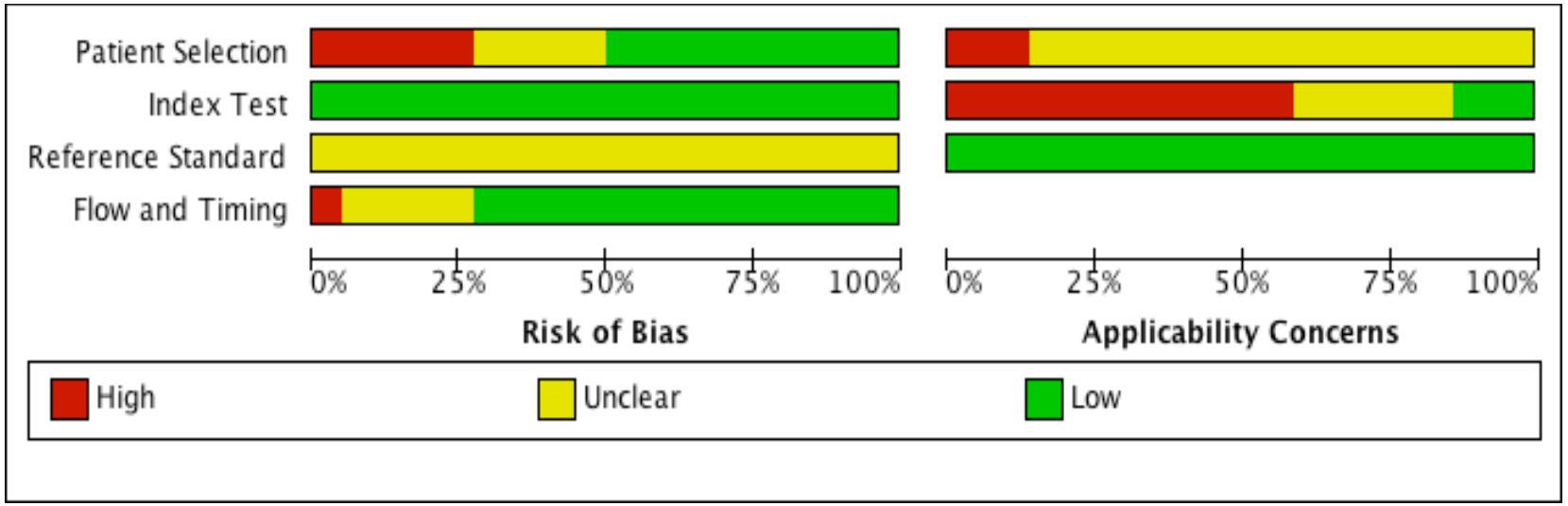
- 22 studies: 15 published, 7 unpublished
- 5,922 samples
- Low/middle income countries: 13 studies (59%)
- All in tertiary care hospitals or reference labs
- 14 studies with HIV+ patients: between 1-87%; 7 with more than 10%
- 13 studies with children: 2-34%; 2 with 100%

Sample Processing

- Only 4 studies used unprocessed samples
- Mechanical homogenization varied between studies (e.g. chopping into small pieces, vortexing or grinding)
- 12 studies used NALC-NaOH solution for specimen digestion and decontamination
- 14 studies reported a concentration step
- The ratio of the sample reagent volume to sample volume varied

Quality Assessment

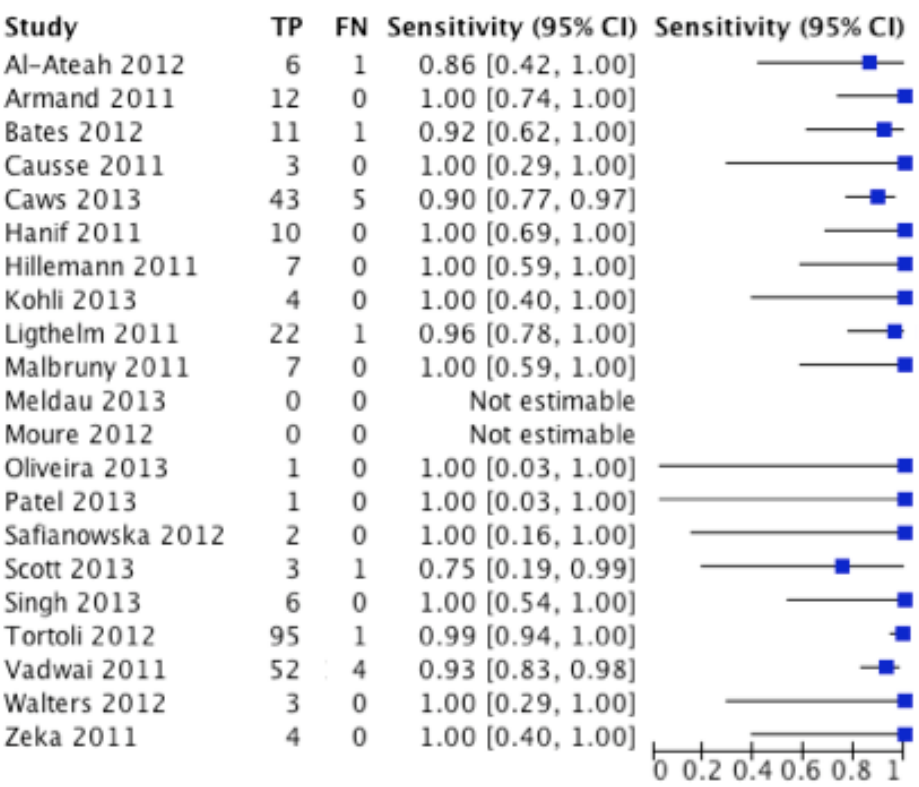
QUADAS-2



- Mostly consecutive sampling
- Mostly cross-sectional
- Concerns about imperfect reference standard
- Concerns about setting (tertiary care/reference labs)
- Concerns about sample processing

Sensitivity in Smear-positive samples

- Studies very diverse with respect to samples types + relative percentage tested
- No meaningful summary estimate overall
- Little heterogeneity in smear-positives (7% of all smear-tested)
- Overall small number of indeterminates (1.4%)



Study	TP	FN	Sensitivity (95% CI)
Al-Ateah 2012	6	1	0.86 [0.42, 1.00]
Armand 2011	12	0	1.00 [0.74, 1.00]
Bates 2012	11	1	0.92 [0.62, 1.00]
Causse 2011	3	0	1.00 [0.29, 1.00]
Caws 2013	43	5	0.90 [0.77, 0.97]
Hanif 2011	10	0	1.00 [0.69, 1.00]
Hillemann 2011	7	0	1.00 [0.59, 1.00]
Kohli 2013	4	0	1.00 [0.40, 1.00]
Ligthelm 2011	22	1	0.96 [0.78, 1.00]
Malbruny 2011	7	0	1.00 [0.59, 1.00]
Meldau 2013	0	0	Not estimable
Moure 2012	0	0	Not estimable
Oliveira 2013	1	0	1.00 [0.03, 1.00]
Patel 2013	1	0	1.00 [0.03, 1.00]
Safianowska 2012	2	0	1.00 [0.16, 1.00]
Scott 2013	3	1	0.75 [0.19, 0.99]
Singh 2013	6	0	1.00 [0.54, 1.00]
Tortoli 2012	95	1	0.99 [0.94, 1.00]
Vadwai 2011	52	4	0.93 [0.83, 0.98]
Walters 2012	3	0	1.00 [0.29, 1.00]
Zeka 2011	4	0	1.00 [0.40, 1.00]

Lymph node

Culture reference standard

- 14 studies, 849 samples
- Sensitivity 84.9% (CI: 72.1-92.4%)
- Specificity 92.5% (CI: 80.3-97.4%)

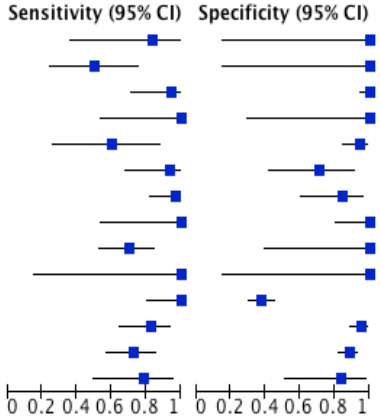
Composite reference standard

- 5 studies, 409 samples
- Sensitivity 83.7% (CI: 73.8-90.3)
- Specificity 99.2% (CI: 88.4-100%)

Lymph node

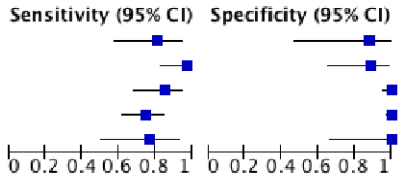
Culture reference standard

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Al-Ateah 2012	5	0	1	2	0.83 [0.36, 1.00]	1.00 [0.16, 1.00]
Armand 2011	8	0	8	2	0.50 [0.25, 0.75]	1.00 [0.16, 1.00]
Causse 2011	16	0	1	70	0.94 [0.71, 1.00]	1.00 [0.95, 1.00]
Hanif 2011	6	0	0	3	1.00 [0.54, 1.00]	1.00 [0.29, 1.00]
Hillemann 2011	6	3	4	52	0.60 [0.26, 0.88]	0.95 [0.85, 0.99]
Kohli 2013	14	4	1	10	0.93 [0.68, 1.00]	0.71 [0.42, 0.92]
Ligthelm 2011	28	3	1	16	0.97 [0.82, 1.00]	0.84 [0.60, 0.97]
Malbruny 2011	6	0	0	17	1.00 [0.54, 1.00]	1.00 [0.80, 1.00]
Moure 2012	24	0	10	4	0.71 [0.53, 0.85]	1.00 [0.40, 1.00]
Safianowska 2012	2	0	0	2	1.00 [0.16, 1.00]	1.00 [0.16, 1.00]
Singh 2013	17	108	0	65	1.00 [0.80, 1.00]	0.38 [0.30, 0.45]
Tortoli 2012	24	4	5	85	0.83 [0.64, 0.94]	0.96 [0.89, 0.99]
Vadwai 2011	32	17	12	127	0.73 [0.57, 0.85]	0.88 [0.82, 0.93]
Zeka 2011	11	2	3	10	0.79 [0.49, 0.95]	0.83 [0.52, 0.98]



Composite reference standard

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kohli 2013	17	1	4	7	0.81 [0.58, 0.95]	0.88 [0.47, 1.00]
Ligthelm 2011	29	2	1	16	0.97 [0.83, 1.00]	0.89 [0.65, 0.99]
Tortoli 2012	28	0	5	85	0.85 [0.68, 0.95]	1.00 [0.96, 1.00]
Vadwai 2011	49	0	17	122	0.74 [0.62, 0.84]	1.00 [0.97, 1.00]
Zeka 2011	13	0	4	9	0.76 [0.50, 0.93]	1.00 [0.66, 1.00]



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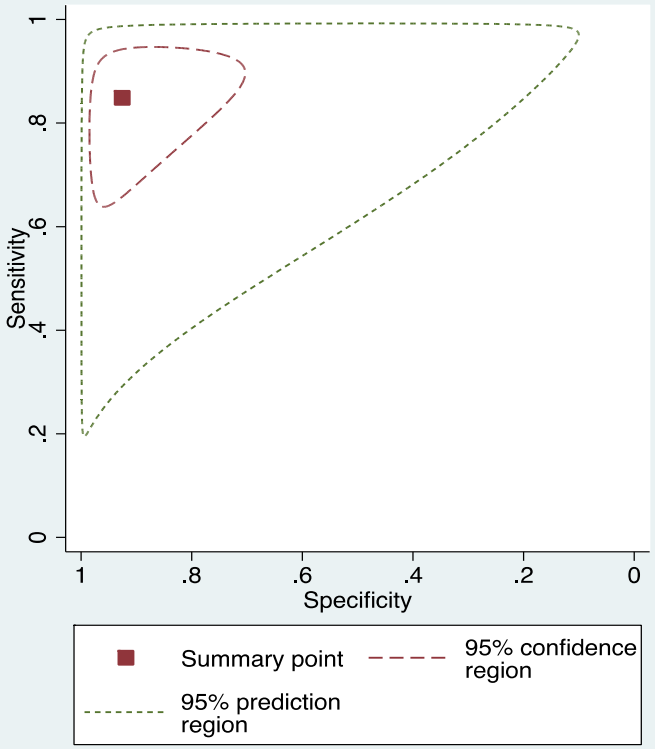


Pleural fluid

Culture reference standard

- 17 studies, 1385 samples, 217 culture-positive
- Sensitivity 43.7% (CI 24.8-64.7%)
- Specificity 98.1% (CI: 95.3-99.2%)
- Increased sensitivity in fresh samples (50%, CI: 36-64%) compared to frozen (26%, CI: 14-40%)

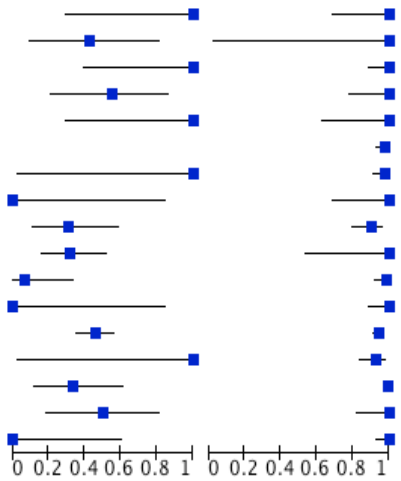
Composite reference standard

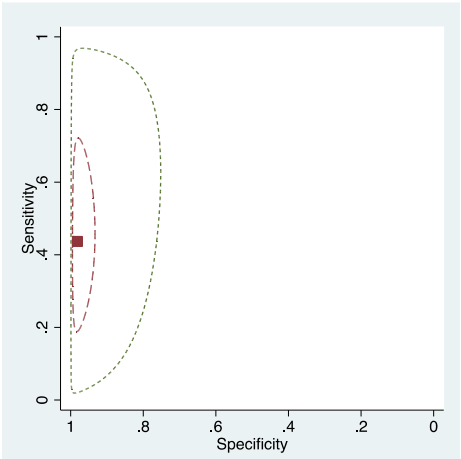
- 7 studies, 698 samples
- Sensitivity 17.0% (CI: 7.5% to 34.2%)
- Specificity 99.9% (CI: 93.7% to 100.0%)

Pleural fluid

Culture reference standard

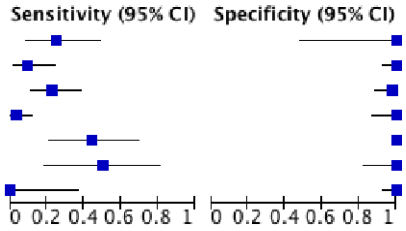
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Al-Ateah 2012	3	0	0	10	1.00 [0.29, 1.00]	1.00 [0.69, 1.00]
Armand 2011	3	0	4	1	0.43 [0.10, 0.82]	1.00 [0.03, 1.00]
Causse 2011	4	0	0	30	1.00 [0.40, 1.00]	1.00 [0.88, 1.00]
Friedrich 2011	5	0	4	15	0.56 [0.21, 0.86]	1.00 [0.78, 1.00]
Hanif 2011	3	0	0	8	1.00 [0.29, 1.00]	1.00 [0.63, 1.00]
Hillemann 2011	0	2	0	103	Not estimable	0.98 [0.93, 1.00]
Kohli 2013	1	2	0	81	1.00 [0.03, 1.00]	0.98 [0.92, 1.00]
Malbruny 2011	0	0	2	10	0.00 [0.00, 0.84]	1.00 [0.69, 1.00]
Meldau 2013	5	6	11	54	0.31 [0.11, 0.59]	0.90 [0.79, 0.96]
Moure 2012	9	0	19	6	0.32 [0.16, 0.52]	1.00 [0.54, 1.00]
Oliveira 2013	1	1	13	68	0.07 [0.00, 0.34]	0.99 [0.92, 1.00]
Safianowska 2012	0	0	2	30	0.00 [0.00, 0.84]	1.00 [0.88, 1.00]
Scott 2013	45	15	53	270	0.46 [0.36, 0.56]	0.95 [0.91, 0.97]
Singh 2013	1	5	0	64	1.00 [0.03, 1.00]	0.93 [0.84, 0.98]
Tortoli 2012	5	3	10	312	0.33 [0.12, 0.62]	0.99 [0.97, 1.00]
Vadwai 2011	5	0	5	19	0.50 [0.19, 0.81]	1.00 [0.82, 1.00]
Zeka 2011	0	0	4	52	0.00 [0.00, 0.60]	1.00 [0.93, 1.00]

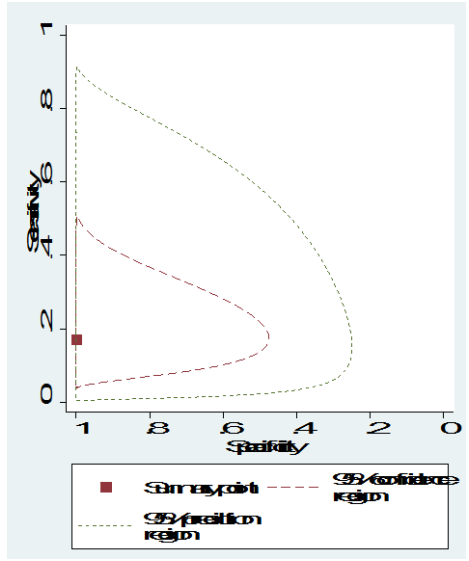




Composite reference standard

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Friedrich 2011	5	0	15	5	0.25 [0.09, 0.49]	1.00 [0.48, 1.00]
Kohli 2013	3	0	30	51	0.09 [0.02, 0.24]	1.00 [0.93, 1.00]
Meldau 2013	9	1	31	48	0.23 [0.11, 0.38]	0.98 [0.89, 1.00]
Oliveira 2013	2	0	57	26	0.03 [0.00, 0.12]	1.00 [0.87, 1.00]
Tortoli 2012	8	0	10	312	0.44 [0.22, 0.69]	1.00 [0.99, 1.00]
Vadwai 2011	5	0	5	19	0.50 [0.19, 0.81]	1.00 [0.82, 1.00]
Zeka 2011	0	0	8	48	0.00 [0.00, 0.37]	1.00 [0.93, 1.00]





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Cerebrospinal fluid

Culture reference standard

- 16 studies, 709 samples, 117 culture-positive
- Sensitivity 79.5% (CI: 62.0-90.2%)
- Specificity 98.6% (CI: 95.8-99.6%)
- Concentration step resulted in increased sensitivity: 82%, CI:71-93% vs 56%, CI: 36-77%

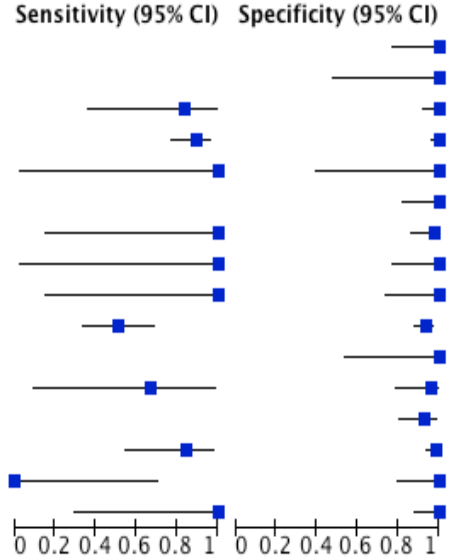
Composite reference standard

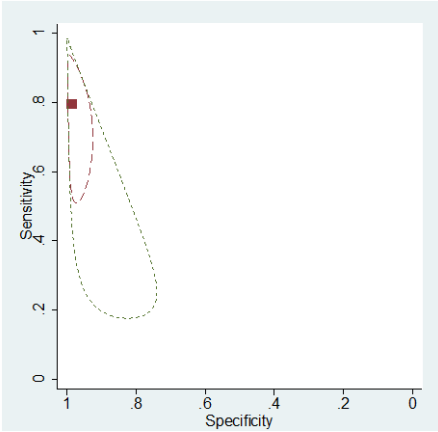
- 6 studies, 512 samples
- Sensitivity 55.5% (CI: 44.2-66.3)
- Specificity 98.8 (CI: 94.5-99.8%)

Cerebrospinal fluid

Culture reference standard

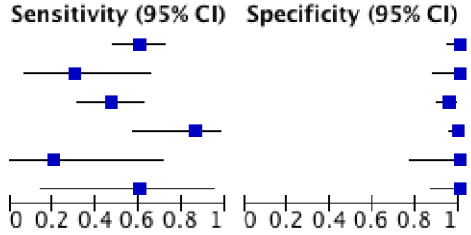
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Al-Ateah 2012	0	0	0	14	Not estimable	1.00 [0.77, 1.00]
Armand 2011	0	0	0	5	Not estimable	1.00 [0.48, 1.00]
Causse 2011	5	0	1	44	0.83 [0.36, 1.00]	1.00 [0.92, 1.00]
Caws 2013	43	0	5	93	0.90 [0.77, 0.97]	1.00 [0.96, 1.00]
Hanif 2011	1	0	0	4	1.00 [0.03, 1.00]	1.00 [0.40, 1.00]
Hillemann 2011	0	0	0	19	Not estimable	1.00 [0.82, 1.00]
Kohli 2013	2	1	0	37	1.00 [0.16, 1.00]	0.97 [0.86, 1.00]
Malbruny 2011	1	0	0	14	1.00 [0.03, 1.00]	1.00 [0.77, 1.00]
Moure 2012	2	0	0	12	1.00 [0.16, 1.00]	1.00 [0.74, 1.00]
Patel 2013	18	7	17	107	0.51 [0.34, 0.69]	0.94 [0.88, 0.97]
Safianowska 2012	0	0	0	6	Not estimable	1.00 [0.54, 1.00]
Scott 2013	2	1	1	23	0.67 [0.09, 0.99]	0.96 [0.79, 1.00]
Singh 2013	0	3	0	38	Not estimable	0.93 [0.80, 0.98]
Tortoli 2012	11	2	2	118	0.85 [0.55, 0.98]	0.98 [0.94, 1.00]
Vadwai 2011	0	0	3	16	0.00 [0.00, 0.71]	1.00 [0.79, 1.00]
Zeka 2011	3	0	0	28	1.00 [0.29, 1.00]	1.00 [0.88, 1.00]

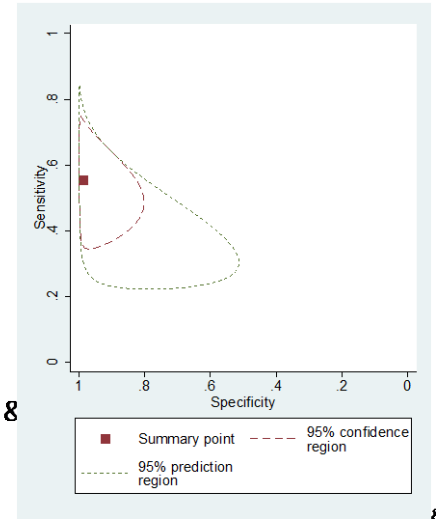




Composite reference standard

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Caws 2013	43	0	28	70	0.61 [0.48, 0.72]	1.00 [0.95, 1.00]
Kohli 2013	3	0	7	29	0.30 [0.07, 0.65]	1.00 [0.88, 1.00]
Patel 2013	20	5	23	101	0.47 [0.31, 0.62]	0.95 [0.89, 0.98]
Tortoli 2012	12	1	2	118	0.86 [0.57, 0.98]	0.99 [0.95, 1.00]
Vadwai 2011	1	0	4	14	0.20 [0.01, 0.72]	1.00 [0.77, 1.00]
Zeka 2011	3	0	2	26	0.60 [0.15, 0.95]	1.00 [0.87, 1.00]





Gastric fluid

Culture reference standard

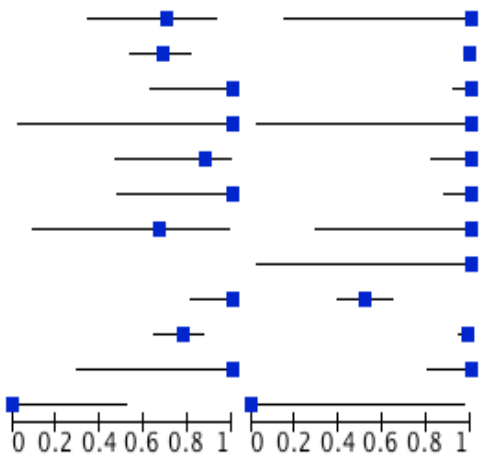
- 12 studies, 1258 samples
- Sensitivity 83.8% (CI: 65.9-93.2%)
- Specificity 98.1% (CI: 92.3-99.5%)
- Increase in univariate analysis of sensitivity if the one study with >10% HIV excluded (90.9%, CI: 80.6-100%)

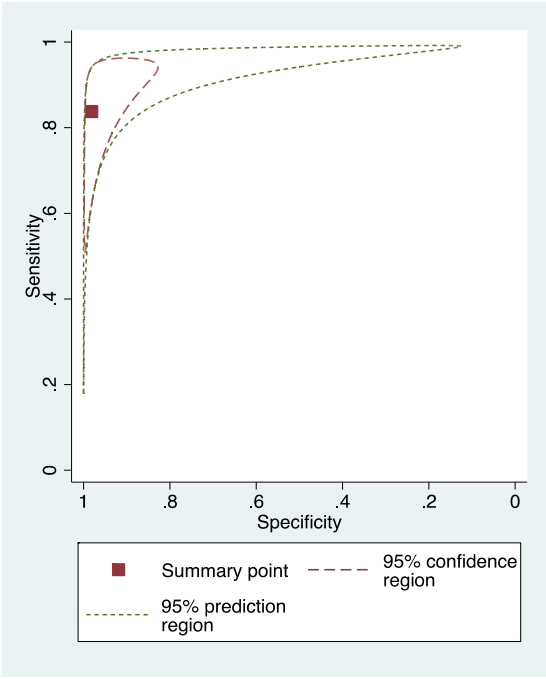
- All studies included a concentration step

Gastric fluid

Culture reference standard

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Armand 2011	7	0	3	2	0.70 [0.35, 0.93]	1.00 [0.16, 1.00]
Bates 2012	33	5	15	735	0.69 [0.54, 0.81]	0.99 [0.98, 1.00]
Causse 2011	8	0	0	46	1.00 [0.63, 1.00]	1.00 [0.92, 1.00]
Hanif 2011	1	0	0	1	1.00 [0.03, 1.00]	1.00 [0.03, 1.00]
Hillemann 2011	7	0	1	19	0.88 [0.47, 1.00]	1.00 [0.82, 1.00]
Malbruny 2011	5	0	0	28	1.00 [0.48, 1.00]	1.00 [0.88, 1.00]
Moure 2012	2	0	1	3	0.67 [0.09, 0.99]	1.00 [0.29, 1.00]
Scott 2013	0	0	0	1	Not estimable	1.00 [0.03, 1.00]
Singh 2013	18	32	0	35	1.00 [0.81, 1.00]	0.52 [0.40, 0.65]
Tortoli 2012	45	3	13	163	0.78 [0.65, 0.87]	0.98 [0.95, 1.00]
Walters 2012	3	0	0	17	1.00 [0.29, 1.00]	1.00 [0.80, 1.00]
Zeka 2011	0	1	5	0	0.00 [0.00, 0.52]	0.00 [0.00, 0.97]





Tissue

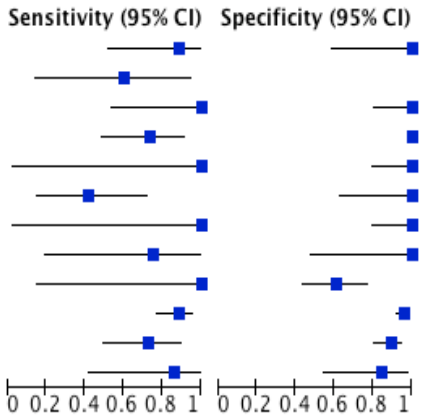
Culture reference standard

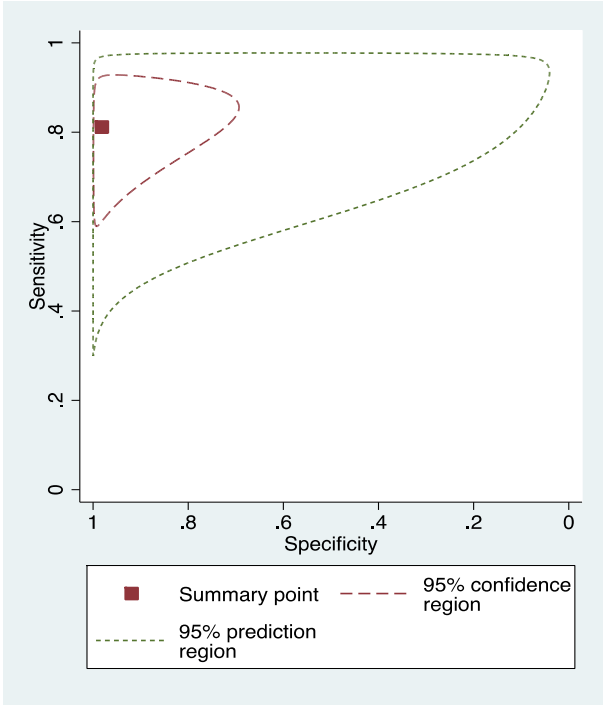
- 12 studies, 699 samples
- Sensitivity 81.2% (CI: 67.7-89.9%)
- Specificity 98.1% (CI: 87.0-99.8%
- Analysis of sensitivity excluding one study that had >10% HIV: 84.1% (CI: 76.1-89.8%)
  - Sensitivity slightly higher
  - CI narrowed
- Condition of sample without effect

Tissue

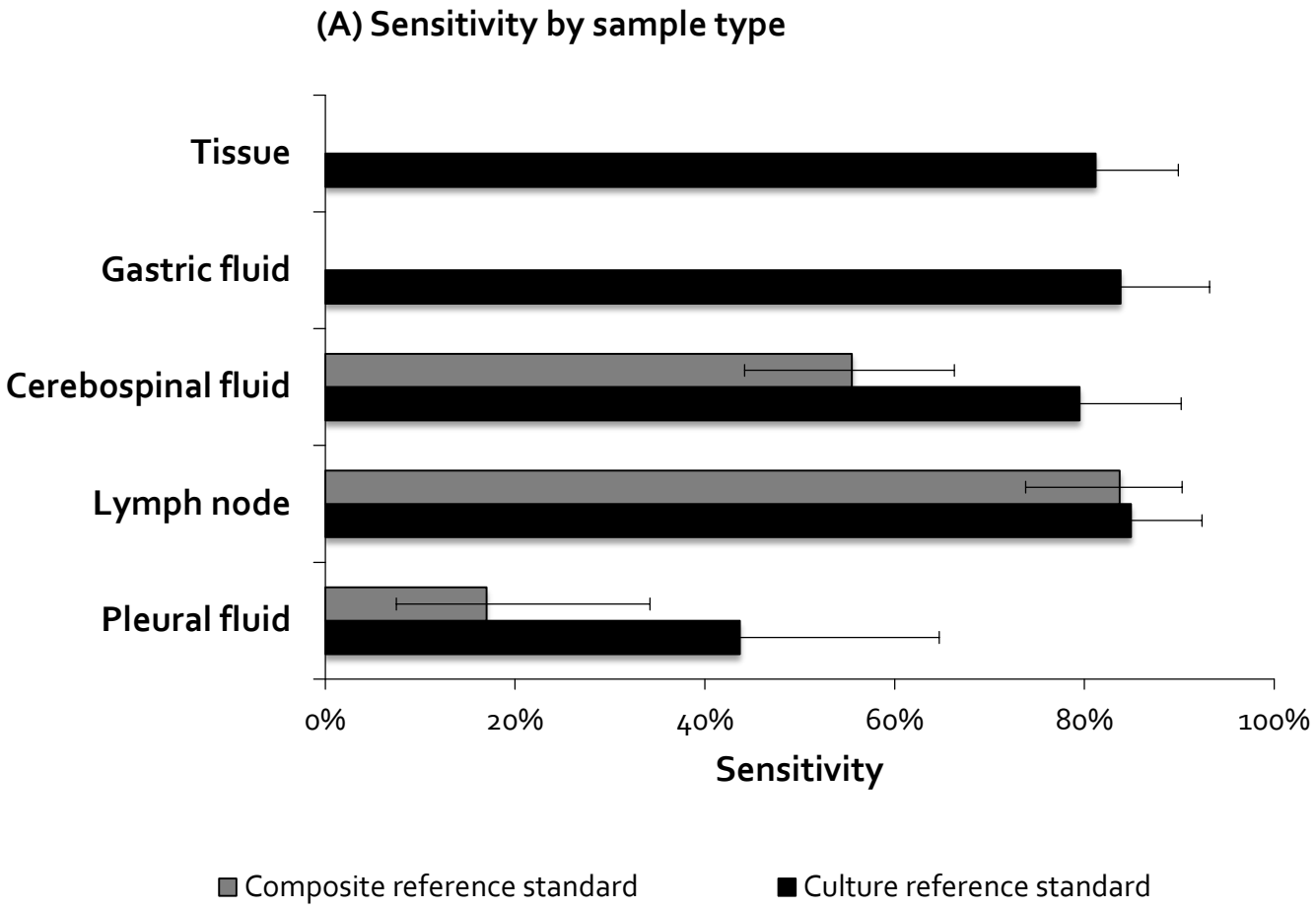
Culture reference standard

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Al-Ateah 2012	8	0	1	7	0.89 [0.52, 1.00]	1.00 [0.59, 1.00]
Armand 2011	3	0	2	0	0.60 [0.15, 0.95]	Not estimable
Causse 2011	6	0	0	17	1.00 [0.54, 1.00]	1.00 [0.80, 1.00]
Hillemann 2011	14	0	5	152	0.74 [0.49, 0.91]	1.00 [0.98, 1.00]
Malbruny 2011	1	0	0	16	1.00 [0.03, 1.00]	1.00 [0.79, 1.00]
Moure 2012	5	0	7	8	0.42 [0.15, 0.72]	1.00 [0.63, 1.00]
Safianowska 2012	1	0	0	16	1.00 [0.03, 1.00]	1.00 [0.79, 1.00]
Scott 2013	3	0	1	5	0.75 [0.19, 0.99]	1.00 [0.48, 1.00]
Singh 2013	2	14	0	22	1.00 [0.16, 1.00]	0.61 [0.43, 0.77]
Tortoli 2012	47	8	6	189	0.89 [0.77, 0.96]	0.96 [0.92, 0.98]
Vadwai 2011	16	10	6	81	0.73 [0.50, 0.89]	0.89 [0.81, 0.95]
Zeka 2011	6	2	1	11	0.86 [0.42, 1.00]	0.85 [0.55, 0.98]

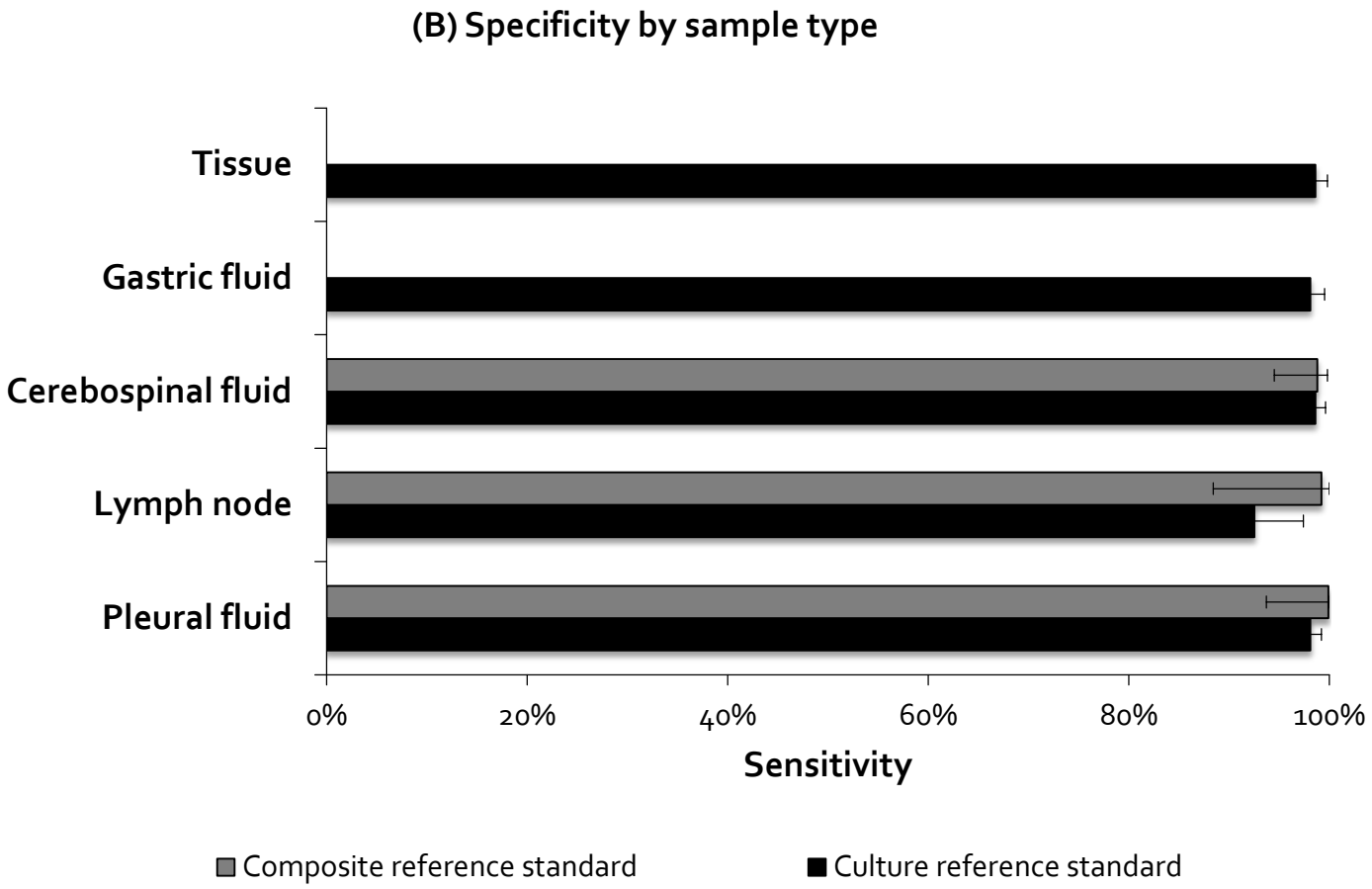




Summary - Sensitivity



Summary - Specificity



Rifampicin resistance detection

- Only published studies that DST tested all samples
- 566 samples, 13 studies
- 37 confirmed RIF-resistant on DST
- Average prevalence of RIF resistance 5.4%
- Xpert false-negative in 2 samples
- 6 FP on Xpert > However, 4/5 with rpoB gene mutation in codon 533 (on sequencing)
- Only 3 indeterminate results on RIF testing

Publication & Policy Update

WHO's policy recommendations

Box 2. Using Xpert MTB/RIF to diagnose extrapulmonary TB and rifampicin resistance in adults and children

These recommendations should be read in conjunction with the remarks in section 5.2.

- Xpert MTB/RIF should be used in preference to conventional microscopy and culture as the initial diagnostic test for CSF specimens from patients suspected of having TB meningitis (strong recommendation given the urgency for rapid diagnosis, very low-quality evidence).
- Xpert MTB/RIF may be used as a replacement test for usual practice (including conventional microscopy, culture or histopathology) for testing specific nonrespiratory specimens (lymph nodes and other tissues) from patients suspected of having extrapulmonary TB (conditional recommendation, very low-quality evidence).

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ORIGINAL ARTICLE
IN PRESS | CORRECTED PROOF

Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis

Claudia M. Denkinger[1,2], Samuel G. Schumacher[2], Catharina C. Boehme[4], Nandini Dendukuri[2,3], Madhukar Pai[2,3] and Karen R. Steingart[5]

CONCLUSIONS

Conclusions

- Xpert sensitivity varied widely across different sample types if the smear-result was negative
- Good sensitivity on smear-positive samples
- Xpert had good sensitivity compared with culture in
  - lymph node tissues or aspirates
  - gastric fluid
  - CSF
  - other tissue samples
- Xpert had poor sensitivity in pleural fluid

Conclusions

- Comparison between culture and CRS provided a plausible range
- Few indeterminate results
- Substantial heterogeneity even within subgroups classified by sample type

  → Caution with interpretation
- Concentration step might increase sensitivity if analyzing CSF
- Fresh samples might provide better results

Limitations

- Limited number of studies and samples
- Residual substantial heterogeneity
  - Varied sample processing
  - Diverse population (selection, different prevalence settings)
  - Difference in reference standard (LJ, MGIT; CRS)
- Imperfect reference standard > Residual verification bias
- High level of care (tertiary care, reference)
- Nine studies in low prevalence settings

Suggestions for further research

- Optimized sample processing
  - Focus on individual sample types
  - Assess individual steps (lab-based research)
  - ? Expert committee suggestions for studies in routine care
- Accuracy in high-risk subgroups (e.g. HIV)
- Impact on patient important outcomes

Thank you!

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- David Alland

Questions?

Table 1. Meta-analysis of the sensitivity and specificity of Xpert MTB/RIF in diagnosing extrapulmonary TB and rifampicin resistance in adults and children compared against culture as a reference standard as well as against a composite reference standard, by type of extrapulmonary specimen

Specimen type	Comparison (No. of studies, No. of samples)	Median (%) pooled sensitivity (pooled 95% CrI)	Median (%) pooled specificity (pooled 95% CrI)
Lymph node tissue and aspirate	Xpert MTB/RIF compared against culture (14 studies, 849 samples)	84.9 (72–92)	92.5 (80–97)
	Xpert MTB/RIF compared against a composite reference standard (5 studies, 1 unpublished)	83.7 (74–90)	99.2 (88–100)
Cerebrospinal fluid	Xpert MTB/RIF compared against culture (16 studies, 709 samples)	79.5 (62–90)	98.6 (96–100)
	Xpert MTB/RIF compared against a composite reference standard (6 studies, 512 samples)	55.5 (51–81)	98.8 (95–100)
Pleural fluid	Xpert MTB/RIF compared against culture (17 studies, 1385 samples)	43.7 (25–65)	98.1 (95–99)
	Xpert MTB/RIF compared against a composite reference standard (7 studies, 698 samples)	17 (8–34)	99.9 (94–100)
Gastric lavage and aspirate	Xpert MTB/RIF compared against culture (12 studies, 1258 samples)	83.8 (66–93)	98.1 (92–100)
Other tissue samples	Xpert MTB/RIF compared against culture (12 studies, 699 samples)	81.2 (68–90)	98.1 (87–100)

CrI, credible interval; the CrI is the Bayesian equivalent of the confidence interval.

The data for additional sample types (such as, ascitic fluid, pericardial fluid, urine, blood and stool) were limited and therefore not considered in the analysis.