

**Global Forum of Xpert MTB/RIF Implementers:
Geneva, May 1st 2014**



Use of Xpert MTB/RIF for Diagnosing Extrapulmonary TB

Stephen D. Lawn

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



**Department of Clinical Research, London
School of Hygiene & Tropical Medicine,
London, UK**



Desmond Tutu HIV Centre
m a s i t h a n d a n e

**Desmond Tutu HIV Centre, University of Cape
Town, Cape Town, South Africa**

Improving health worldwide

www.lshtm.ac.uk

Outline



- **The problem of EPTB**
 - Frequency
 - Diagnostic challenge
- **Evidence base for use of Xpert MTB/RIF for EPTB diagnosis**
- **Further data needed**
- **New recommendations: policy update**

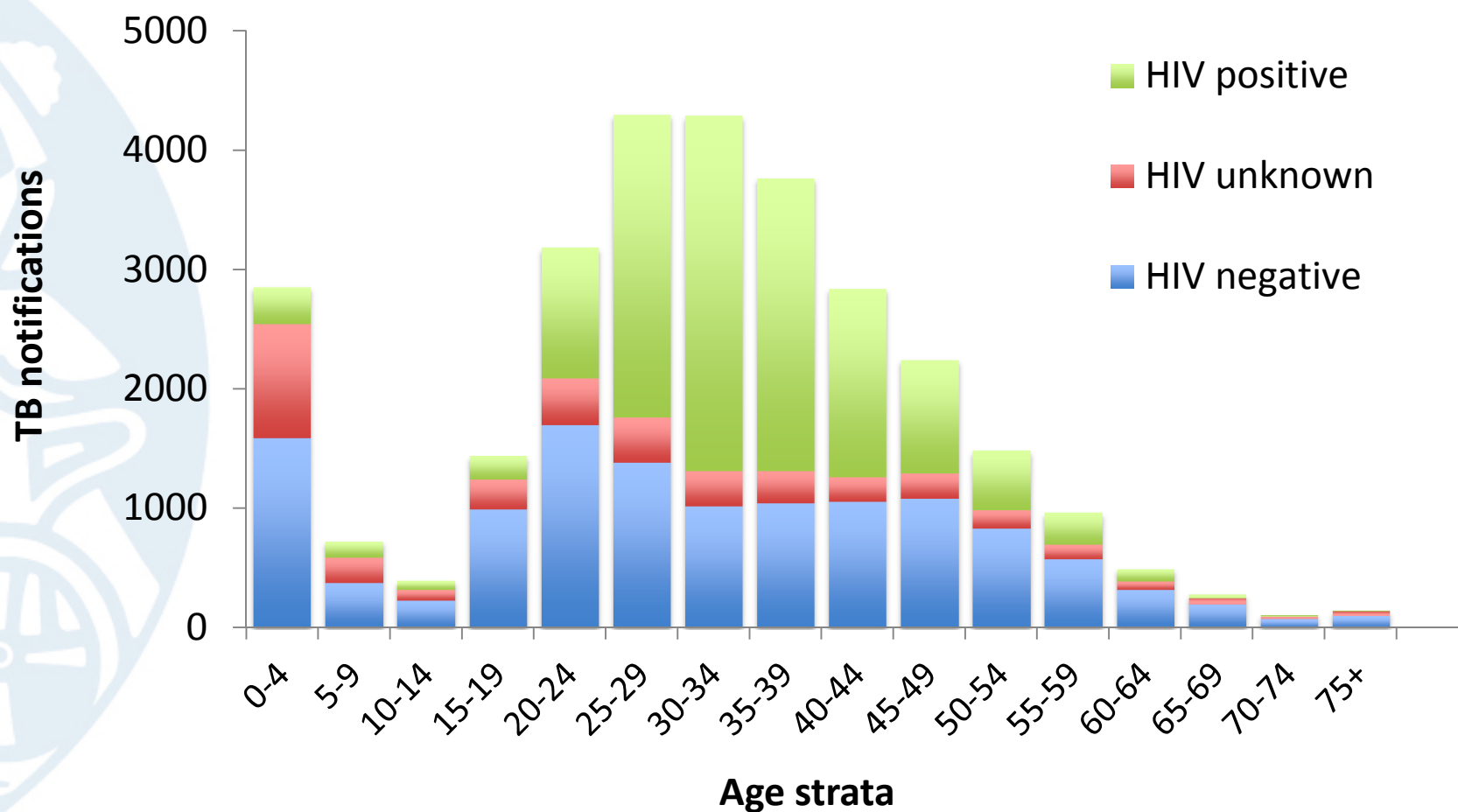
What proportion of TB is extrapulmonary?



- **ECDC EuroSurveillance report (Solovic I et al. 2013):**
 - Notified TB cases in the EU in 2011 (n=72,334)
 - 22% was EPTB
 - Range 4% to 48% in different countries (!)
- **WHO Global TB Control Report 2013**
 - 5.4 M notified new cases in 2012
 - 0.8 M (14.8%) had EPTB

TB Notifications in Cape Town in 2009 (n=29,478)

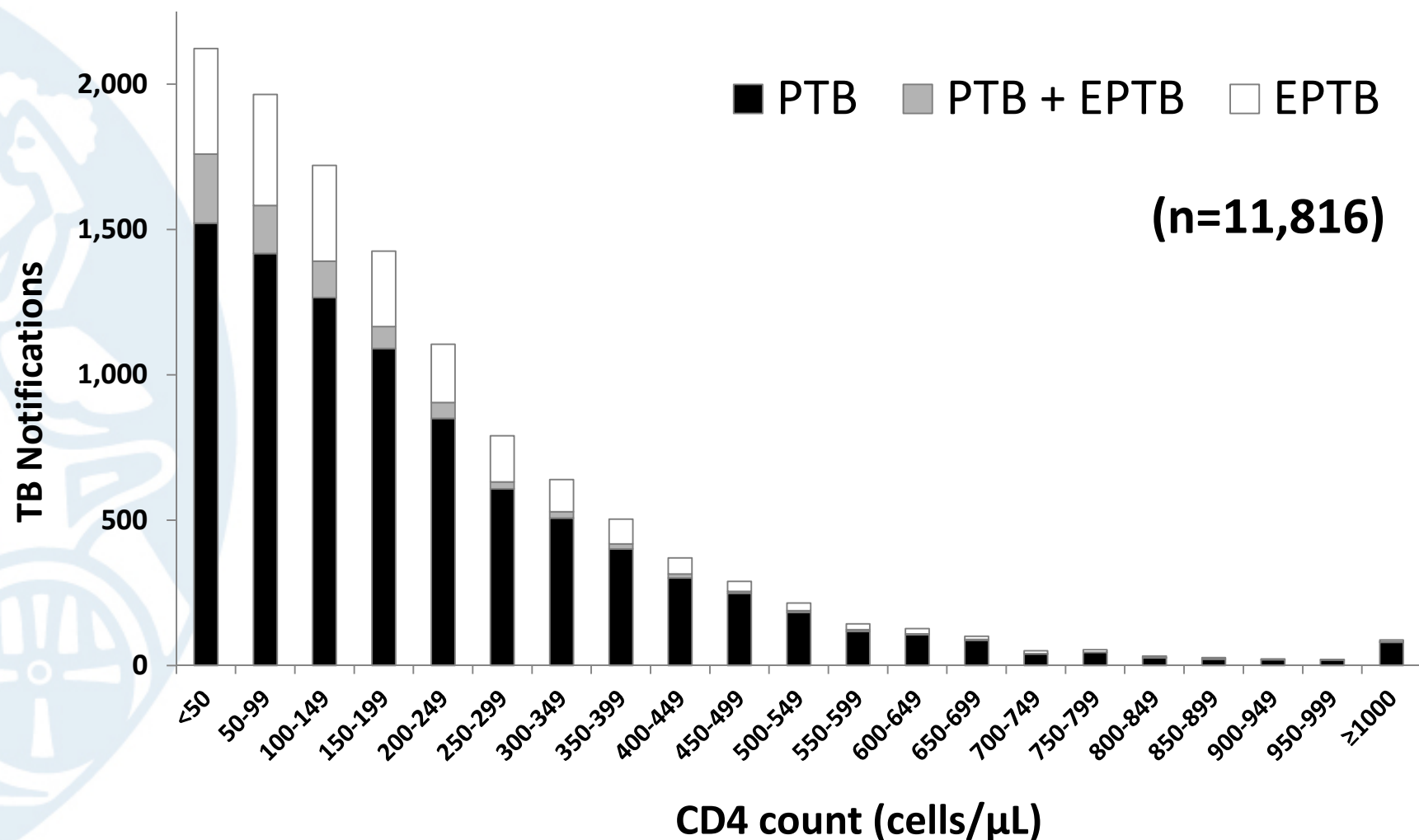
LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



Wood and Lawn PLoS ONE 2011

HIV-Associated TB in Cape Town

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



Gupta / Lawn 2012; IJTLD 2013

TB Diagnosis in Unselected HIV+ Medical Admissions in Cape Town

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



427 new admissions

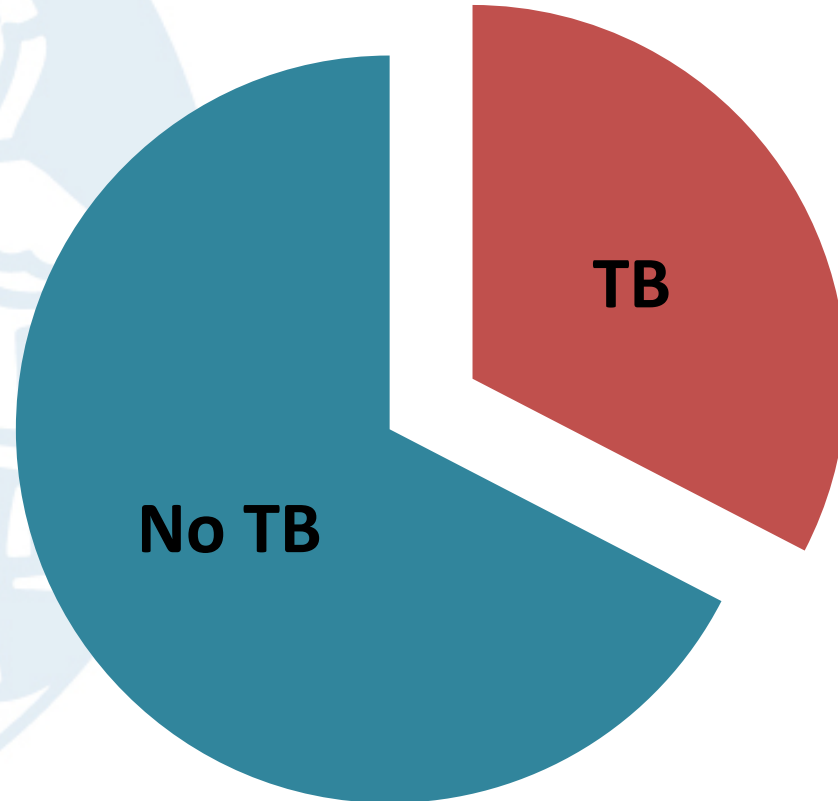
2,391 samples (median – 3 body compartments)

3,471 diagnostic tests for TB

Lawn et al CROI 2014

TB Prevalence

- TB diagnoses = 139 (Xpert or culture of any sample)
- TB Prevalence = 32.6% (28.1-37.2)



**Median CD4 Count in
TB cases = 80 cells/ μ L**

**Cough >2 weeks
in just 13% of TB cases**

**WHO symptom screen
NOT predictive for TB**

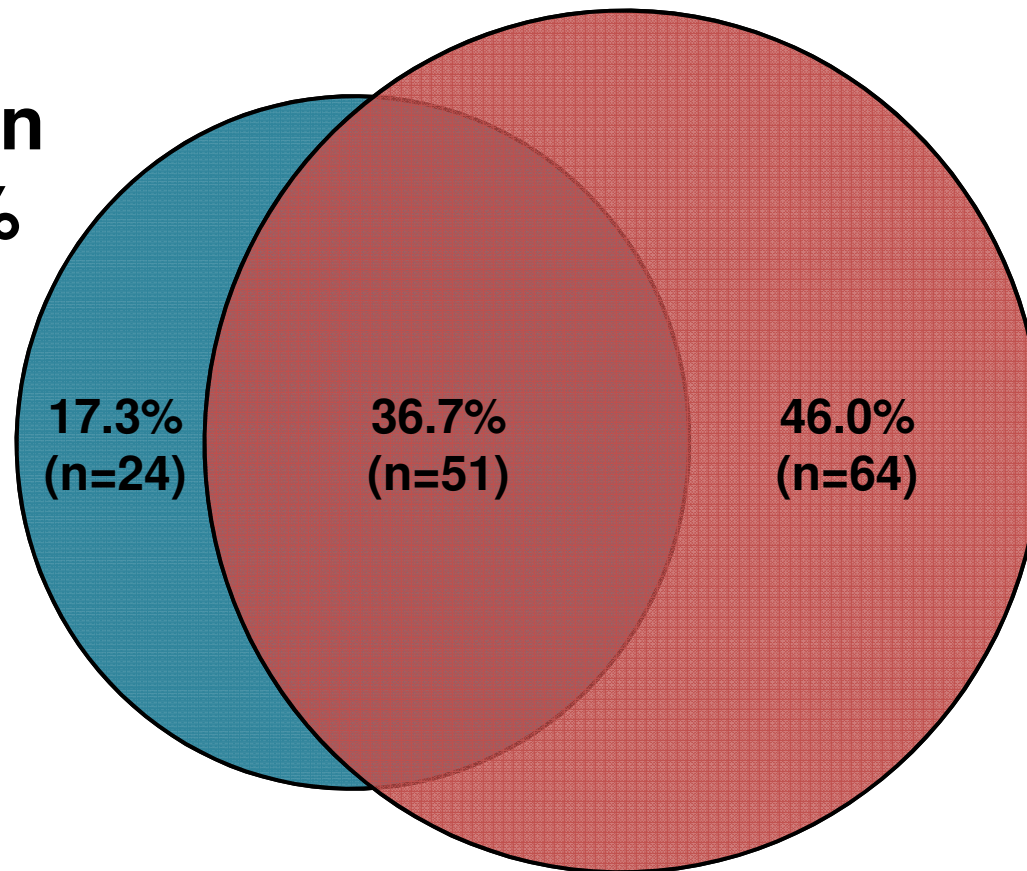
Pulmonary vs Extrapulmonary Disease

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



**PTB in
54.0%**

**EPTB in
82.7%**



Lawn et al CROI 2014

Challenges in EPTB Diagnosis



- **Sampling**
 - **invasive procedures**
 - **special expertise**
- **Frequently paucibacillary**
 - **Mostly smear-negative**
 - **Limited sensitivity of all microbiological tests**
 - **Prolonged time to culture-positivity**
 - **DST even further delayed**
- **Reliance on histology and imaging**
- **Empirical treatment**

Xpert MTB/RIF Testing of Non-Respiratory Samples

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



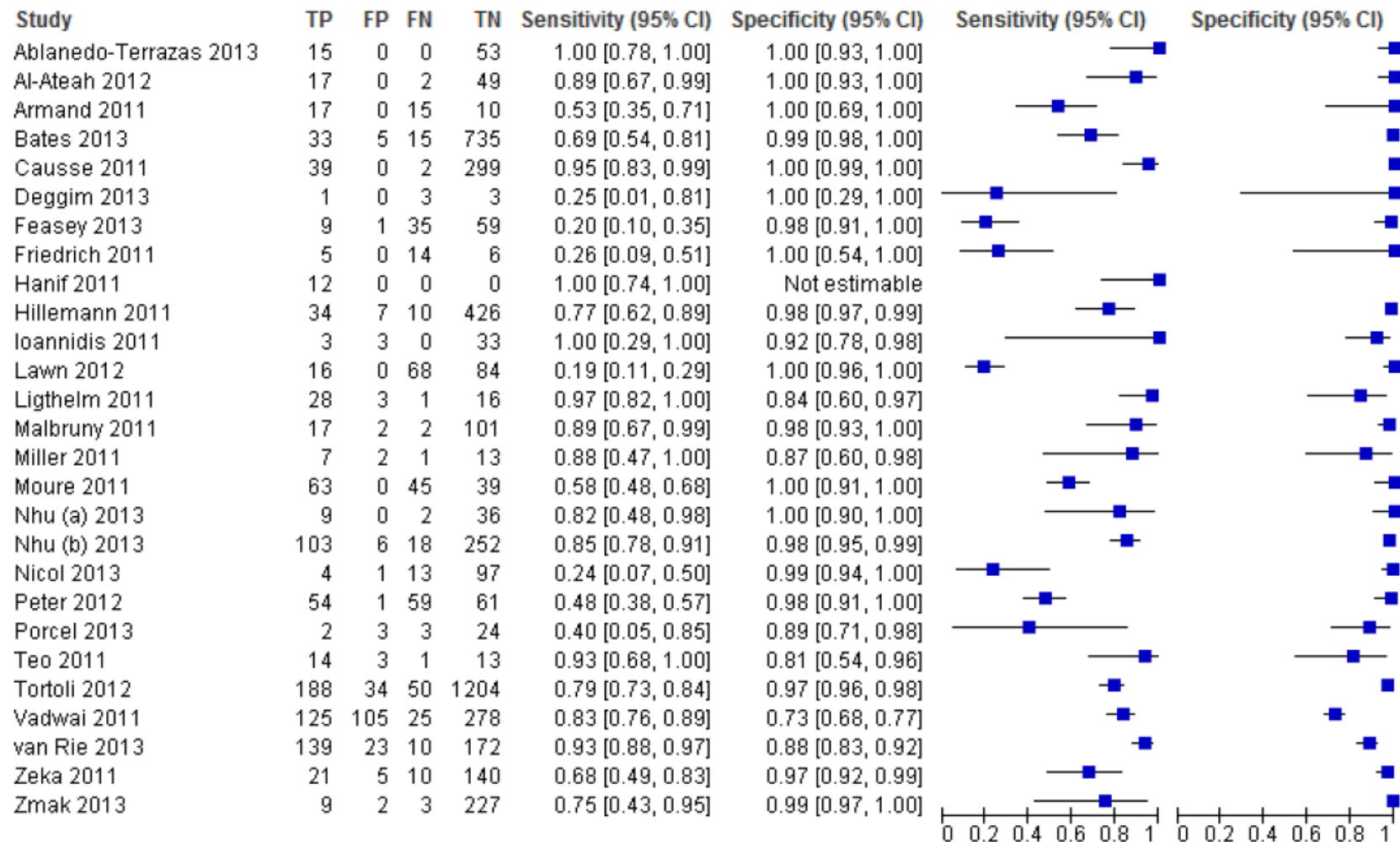
- 1. Testing non-respiratory samples to diagnose pulmonary TB, especially in children**
- 2. Diagnosis of TB at extrapulmonary sites ✓**

Diagnostic Accuracy of Xpert MTB/RIF When Testing Non-Respiratory Samples vs Culture

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



(n=27 studies with 6026 samples)



Challenges in Assessing Literature on Diagnostic Accuracy for EPTB

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



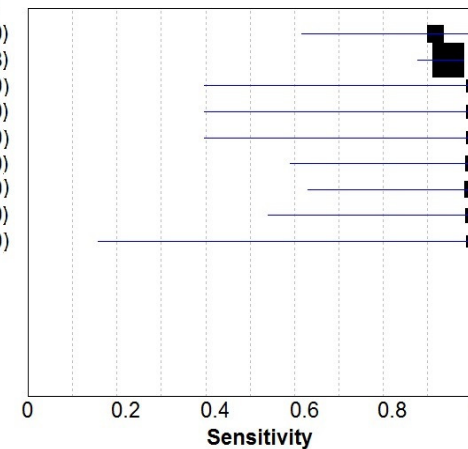
- **Laboratory-based studies with convenience sampling + mixture of studies with prospective clinical recruitment + a few case control**
- **Range in size (range 7 – 1476 samples)**
- **Range in TB prevalence: 0% - 81%**
- **Multiple sample types**
- **Variations in sample processing**
- **Reference standard: microbiological vs composite**
- **Disaggregation of data by sample type / age / HIV-status not always possible**

Sensitivity stratified by smear status



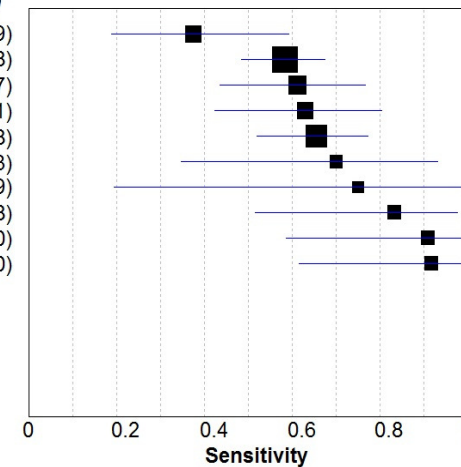
(A) Smear Positive

	TP	FP	FN	TN	Sensitivity (95% CI)	
Bates	11	0	1	0	0.92	(0.62 - 1.00)
Vadwai	87	0	5	0	0.95	(0.88 - 0.98)
Miller	4	0	0	0	1.00	(0.40 - 1.00)
Zeka	4	0	0	0	1.00	(0.40 - 1.00)
Teo	4	2	0	0	1.00	(0.40 - 1.00)
Malbruny	7	0	0	1	1.00	(0.59 - 1.00)
Armand	8	0	0	0	1.00	(0.63 - 1.00)
Al-Ateah	6	0	0	0	1.00	(0.54 - 1.00)
Zmak	2	0	0	0	1.00	(0.16 - 1.00)



(B) Smear Negative

	TP	FP	FN	TN	Sensitivity (95% CI)	
Armand	9	0	15	0	0.38	(0.19 - 0.59)
Moure	63	0	45	39	0.58	(0.48 - 0.68)
Bates	22	0	14	0	0.61	(0.43 - 0.77)
Zeka	17	5	10	140	0.63	(0.42 - 0.81)
Vadwai	38	0	20	0	0.66	(0.52 - 0.78)
Zmak	7	2	3	227	0.70	(0.35 - 0.93)
Miller	3	0	1	0	0.75	(0.19 - 0.99)
Malbruny	10	2	2	100	0.83	(0.52 - 0.98)
Teo	10	1	1	13	0.91	(0.59 - 1.00)
Al-Ateah	11	0	1	49	0.92	(0.62 - 1.00)



Systematic Review

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



ORIGINAL ARTICLE
IN PRESS | CORRECTED PROOF

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

Claudia M. Denking^{1,2}, Samuel G. Schumacher², Catharina C. Boehme⁴, Nandini Dendukuri^{2,3}, Madhukar Pai^{2,3} and Karen R. Steingart⁵

Affiliations: ¹Division of Infectious Disease, Beth Israel Deaconess Medical Centre, Boston, MA, USA. ²McGill International TB Centre, and Dept of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, QC, Canada. ³Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, Montreal, QC, Canada. ⁴Foundation for Innovative New Diagnostics, Geneva, Switzerland. ⁵Portland, OR, USA.

Correspondence: Claudia M. Denking, McGill International TB Centre, Dept of Epidemiology and Biostatistics, 3650 Saint-Urbain, K-3.09, Montreal, QC H2X 2P4, Canada.
E-mail: claudia.denking@mail.mcgill.ca

European Respiratory Journal 2014



Search Methods

- **Databases (searched through Oct 15 2013)**
 - 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 study types (including case-control)
 - All age-groups
 - All types of non-respiratory sample

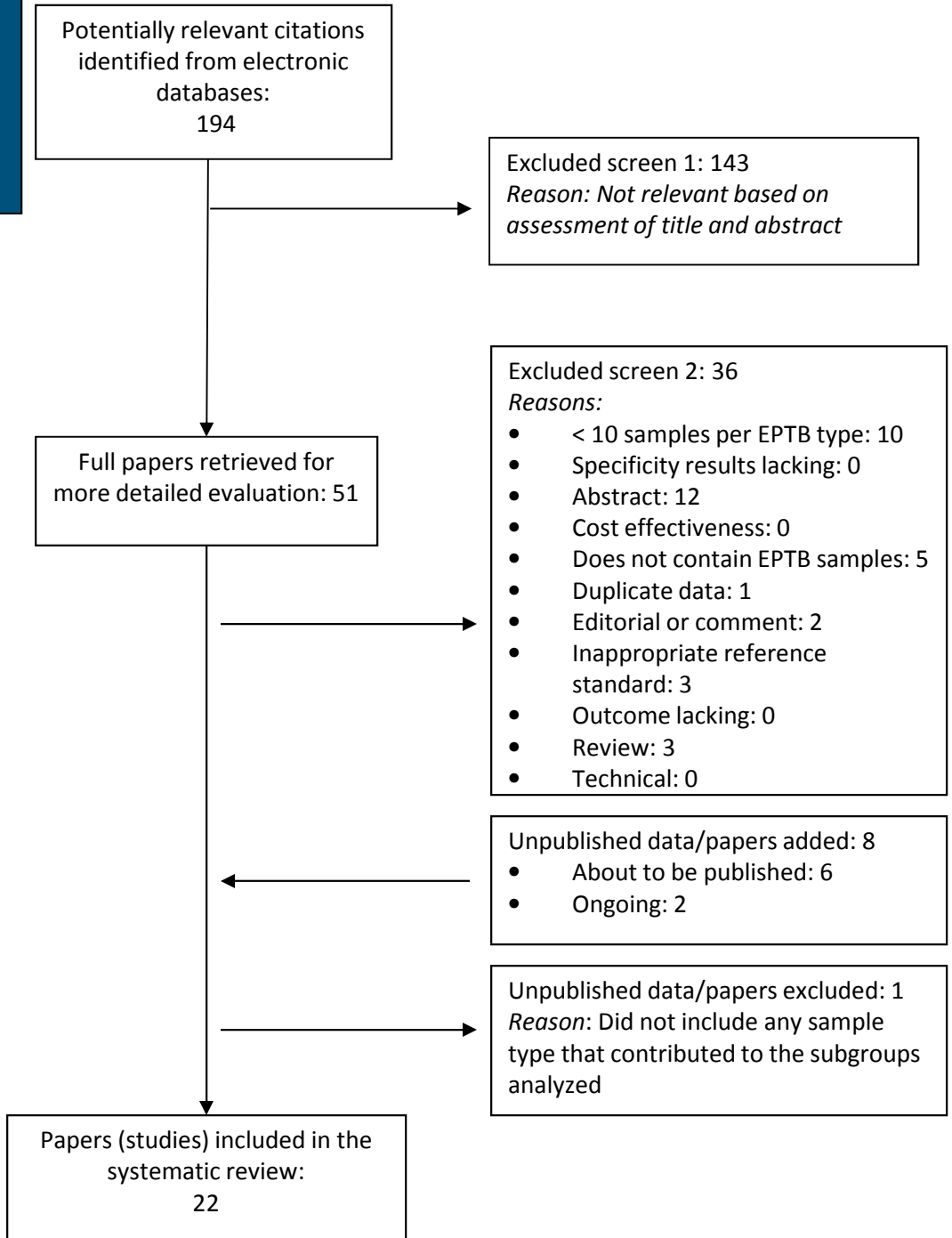
Reference Standard

- **Mycobacterial culture (solid and liquid)**
- **An author-defined composite reference standard (CRS): culture +/- NAAT, histology, smear, biochemical testing, clinical signs, response to TB treatment**
 - **Limitations of reference standard: imperfect sensitivity and specificity**
 - **Comparison of the two reference standards: assess plausible range for accuracy**

Analysis Plan

- **Quality assessment – QUADAS 2**
- **Pre-specified subgroups by specimen type**
 - **Lymph node (aspirate and biopsy)**
 - **Pleural fluid**
 - **Cerebrospinal fluid**
 - **All other tissues combined**
- **Further covariates of interest:**
 - **Concentration step**
 - **Sample storage**
 - **HIV prevalence**

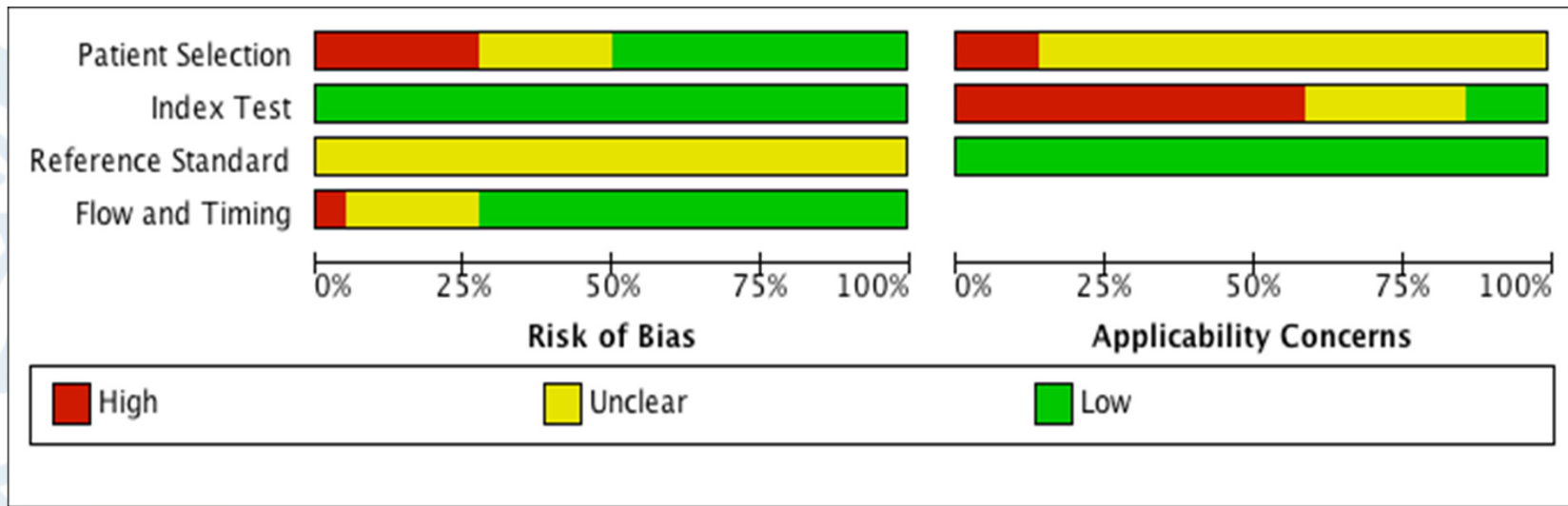
PRISMA



Sample Processing

- **Unprocessed samples: only 4 studies**
- **Mechanical homogenization varied (e.g. chopping into small pieces, vortexing or grinding)**
- **NALC-NaOH digestion and decontamination: 12 studies**
- **Concentration step: 14 studies**
- **Sample : SR volume ratio varied (2:1 vs 3:1)**

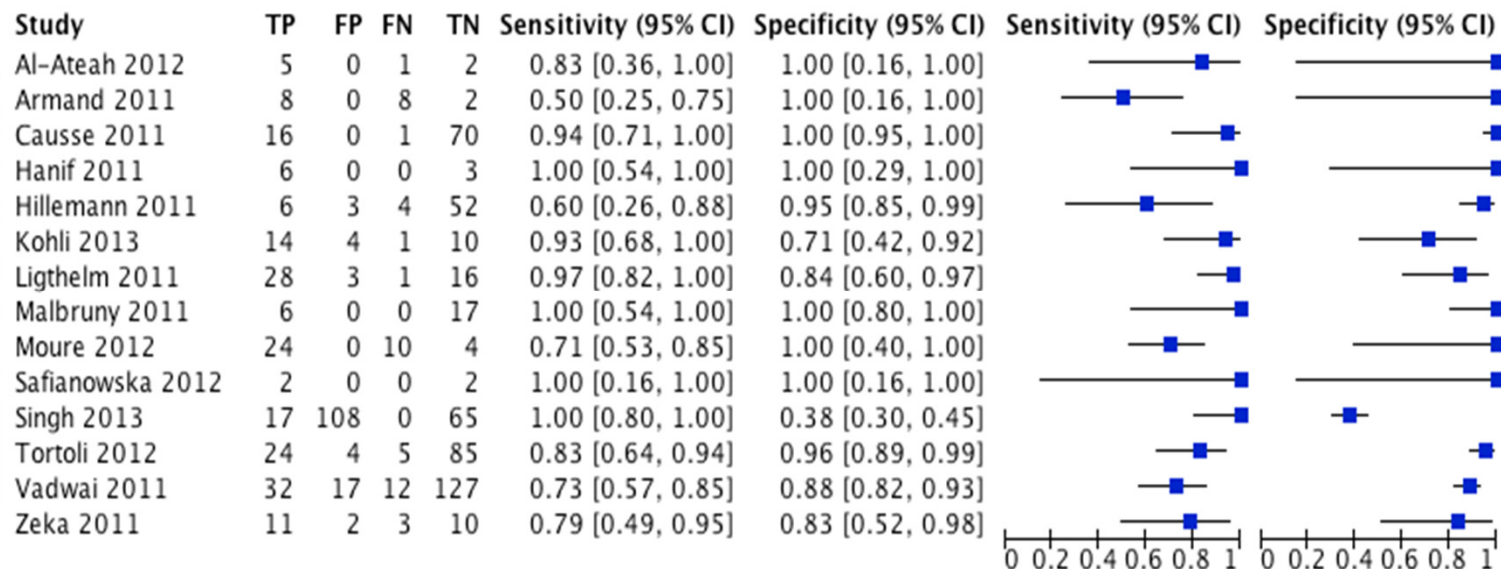
QUADAS 2



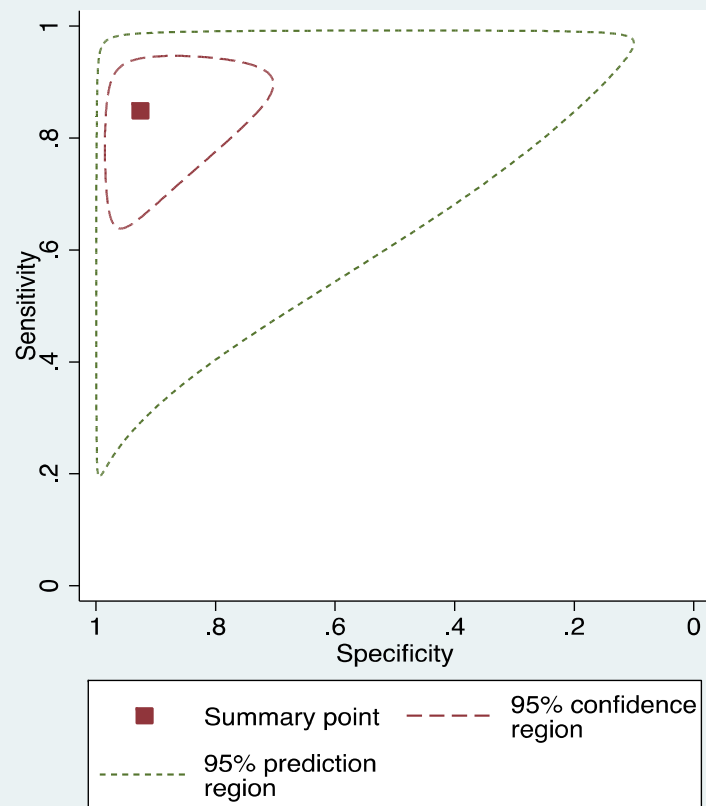
- **Mostly consecutive sampling / cross-sectional**
- **Concerns about imperfect reference standard**
- **Concerns about setting (tertiary care/reference labs)**
- **Concerns about sample processing**
- **Uninterpretable results: only 1.2%**

Lymph node (FNA or biopsy)

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

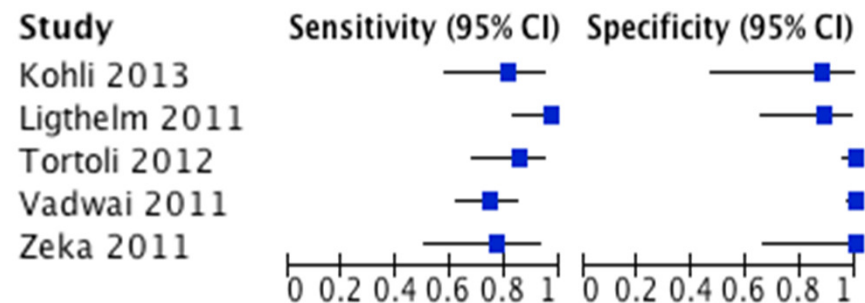


Lymph node



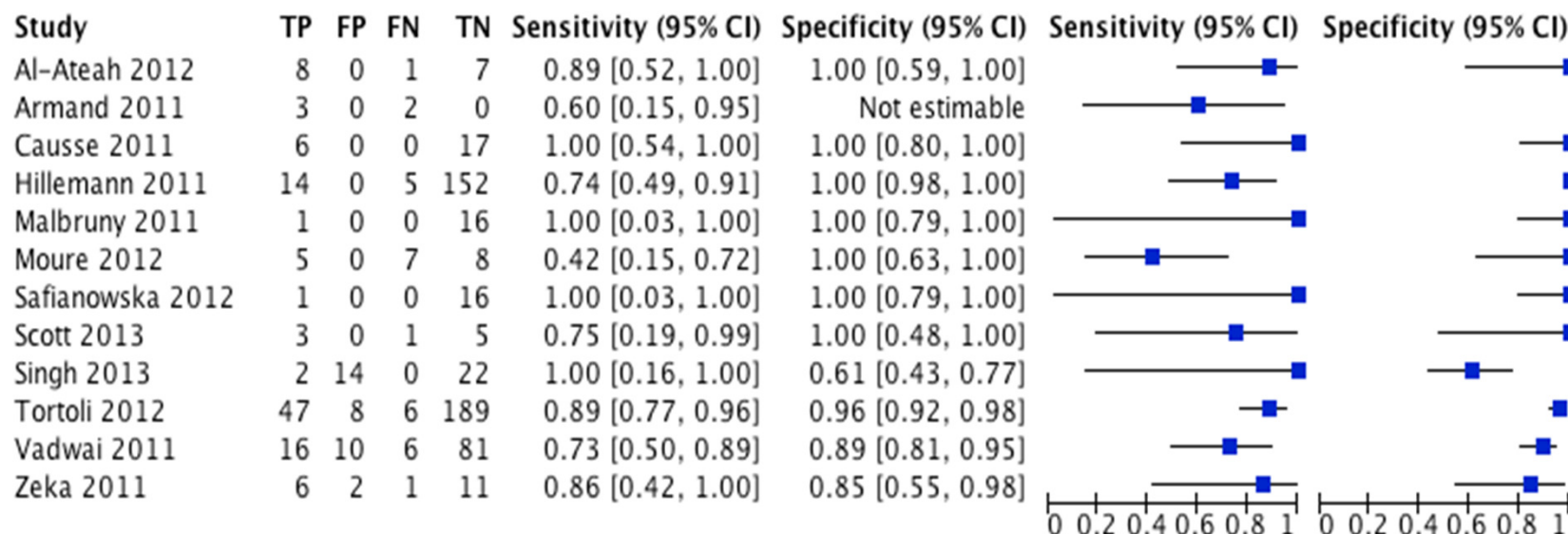
For composite reference standard:

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

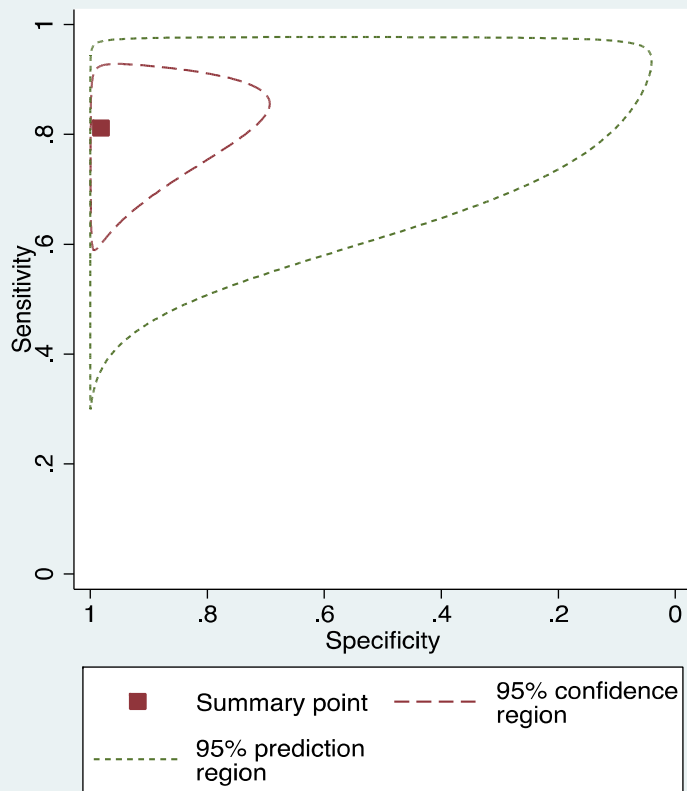


Tissue (other than lymph node)

- 12 studies, 699 samples
- Culture reference standard:
 - **Sensitivity 81.2%** (CI: 67.7-89.9%)
 - **Specificity 98.1%** (CI: 87.0-99.8%)



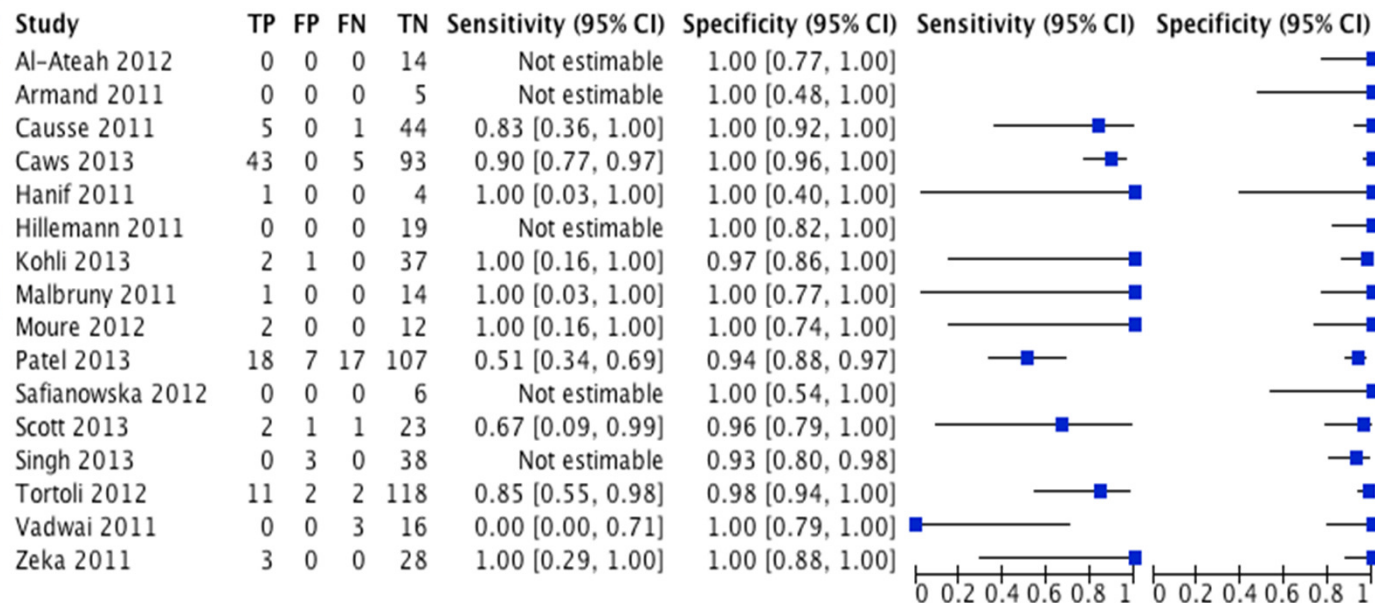
Tissue (other than lymph node)



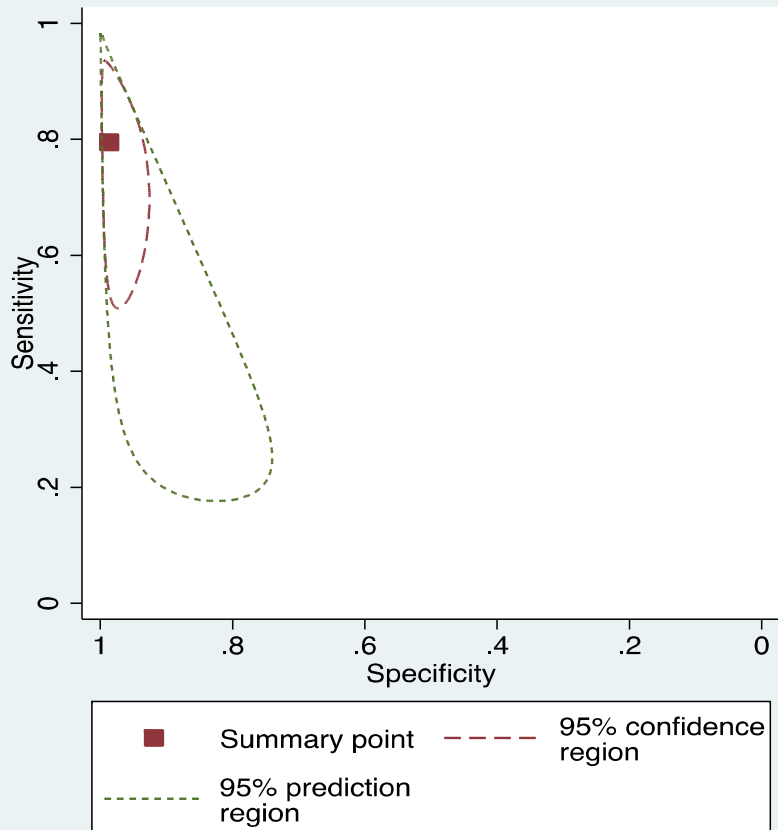
Analysis of sensitivity
excluding one study that
had >10% HIV: 84.1% (CI:
76.1-89.8%)

Cerebrospinal fluid

- 16 studies, 709 samples, 117 culture-positive
- Culture reference standard:
 - **Sensitivity 79.5%** (CI: 62.0-90.2%),
 - **Specificity 98.6%** (CI: 95.8-99.6%)
- Concentration step (10 studies) resulted in increased sensitivity: 82%, CI:71-93% versus 56%, CI: 36-77%

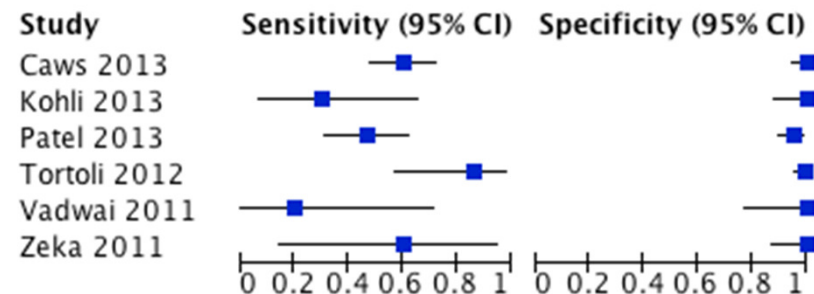


Cerebrospinal fluid



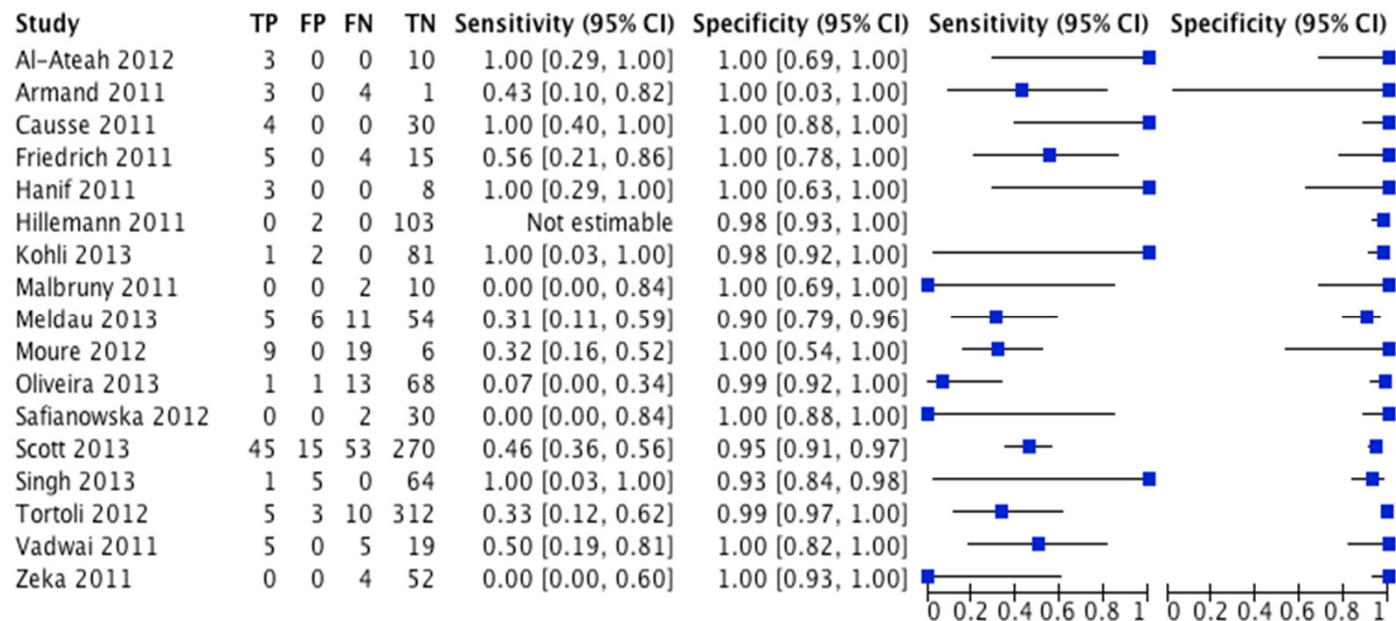
For composite reference standard:

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

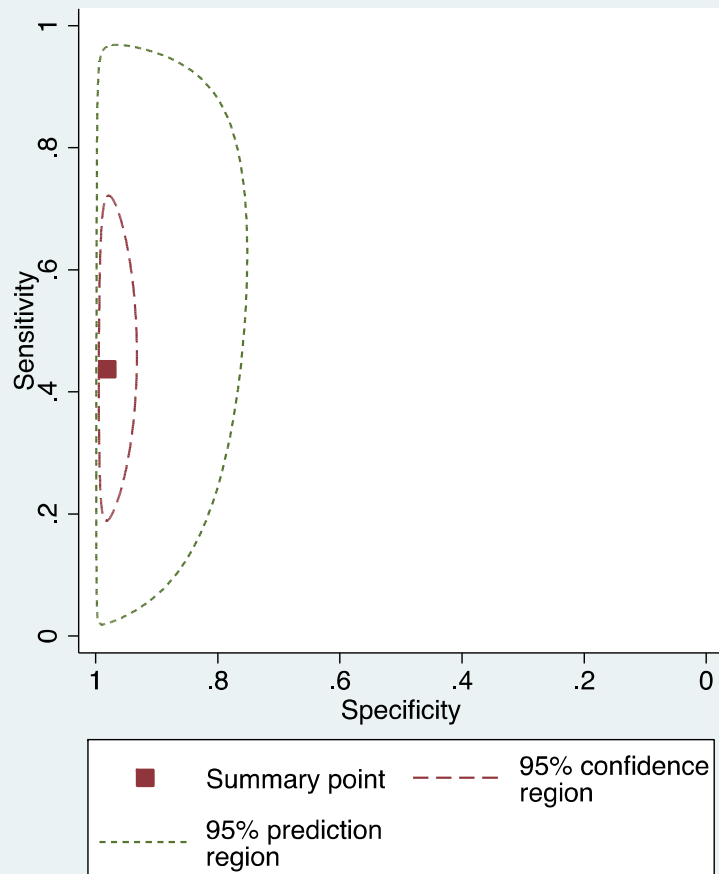


Pleural fluid (excl pleural bx)

- 17 studies, 1385 samples, 217 culture-positive
- Culture reference standard:
 - **Sensitivity 43.7%** (CI 24.8-64.7%)
 - **Specificity 98.1%** (CI: 95.3-99.2%)

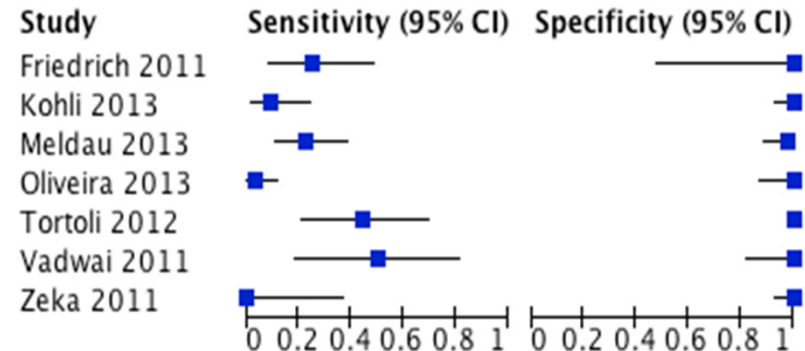


Pleural fluid

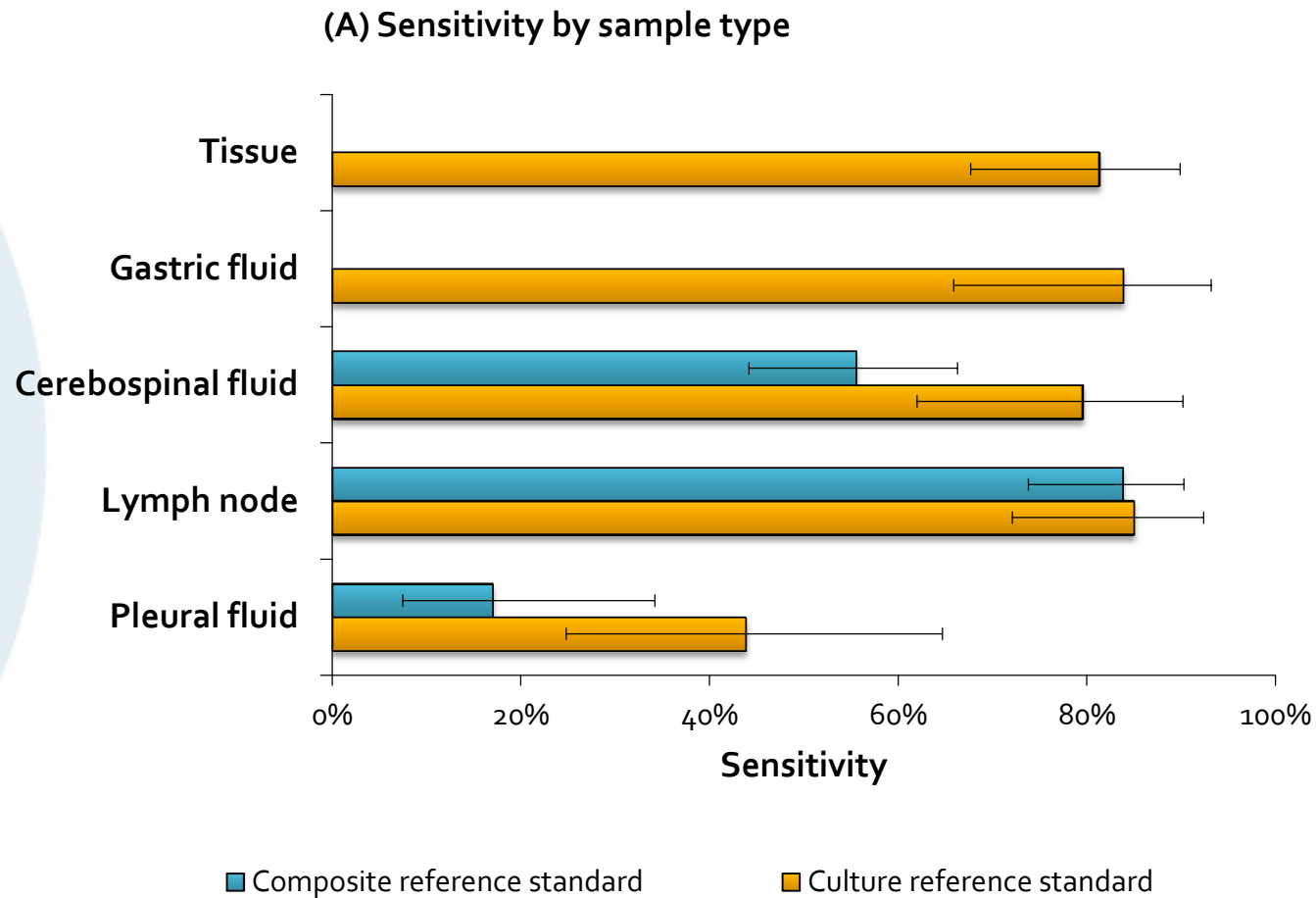


For composite reference standard:

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



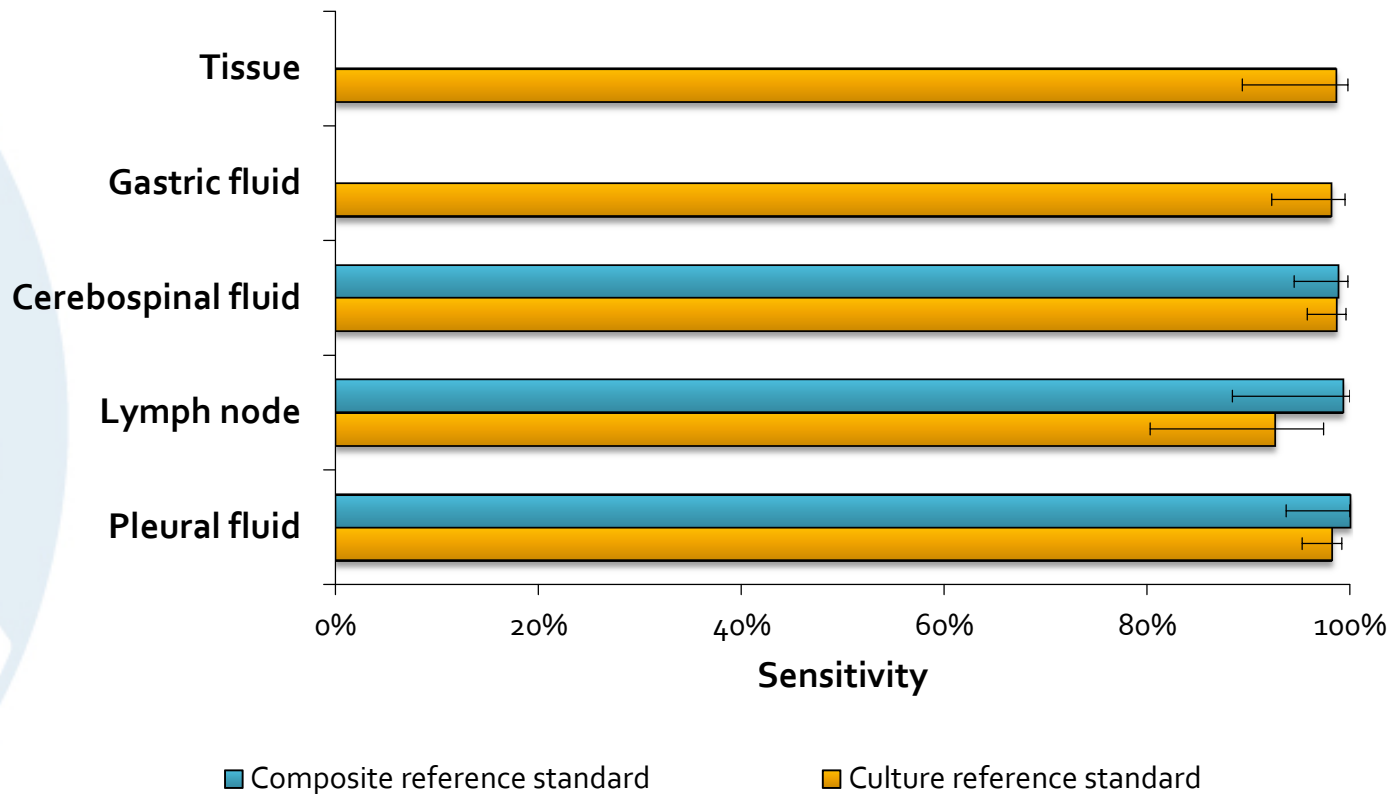
Summary



NB. Different numbers of studies in paired comparisons

Summary

(B) Specificity by sample type



**Using composite reference standard:
specificity >98.7% across all sample types**

Other variables



Data are limited:

- Sample concentration:
 - sensitivity in CSF improved
- Fresh vs frozen samples:
 - Possible effect on sensitivity in pleural fluid
- HIV
 - inconclusive

Rifampicin resistance detection

- Only published studies that all samples had DST
- 566 samples, 13 studies
 - Only 3 indeterminate results for RIF testing
 - Xpert true-positive (vs phenotypic DST) in 37 samples
 - Xpert false-negative in 2 samples (ie approx 95% detected; no pooled estimate)
 - 6 FP on Xpert: 5 were sequenced and 4 had rpoB gene mutation in codon 533
- G3 vs G4 cartridges?

Conclusions

- Sensitivity extremely heterogeneous
 - Strongly related to smear result
 - Varied widely between sample types
- Xpert had good sensitivity compared with culture in:
 - Lymph node tissues or aspirates
 - Other tissue samples
 - CSF
- Xpert had poor sensitivity in pleural fluid

Conclusions

- Comparison between culture and CRS provided a plausible range
- Few indeterminate results
- Substantial heterogeneity even within sample types: must interpret pooled estimates with caution
- Concentration step might increase sensitivity if analyzing CSF

Limitations

- Limited number of studies and samples
- Residual substantial heterogeneity in sub-groups
 - Varied sample processing
 - Diverse populations
 - Differences in reference standard
- Imperfect reference standard
- High level of care (tertiary care, reference)
- Nine studies in low prevalence settings

Further research

- **Further studies focused on specific sample types**
- **To optimize sample processing**
- **Define accuracy in subgroups eg HIV status; adults vs children**
- **Operational feasibility in resource-limited settings**
- **Impact on patient important outcomes**

WHO Policy Update

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



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 of 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).

WHO Policy Update

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



Remarks

Individuals suspected of having extrapulmonary TB but who have had a single negative result from Xpert MTB/RIF should undergo further diagnostic testing, and those for whom there is a high clinical suspicion for TB (especially children) should be treated even if an Xpert MTB/RIF result is negative or if the test is not available.

These recommendations do not apply to samples of stool, urine or blood, given the lack of data on the utility of Xpert MTB/RIF for these specimens.

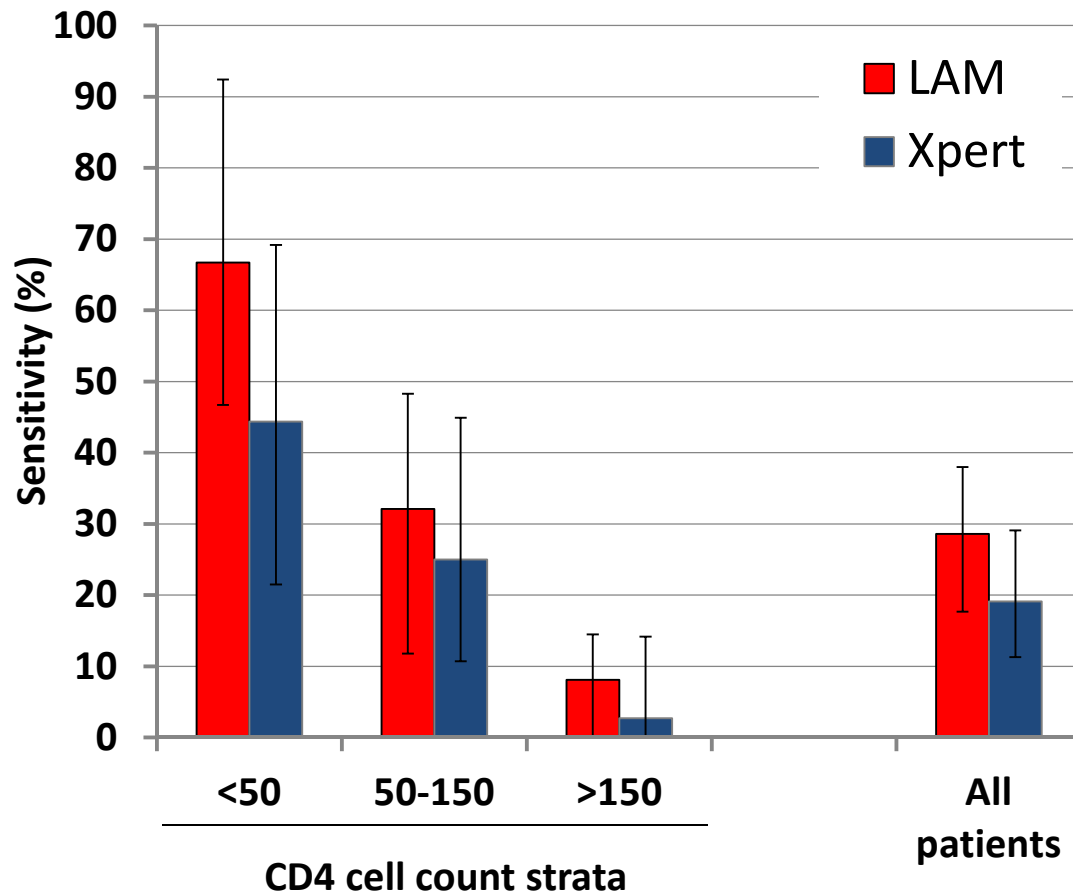
Acknowledgements



- **Systematic Review:** Claudia Denking, Samuel Schumacher, Catharina Boehme, Nandini Dendukuri, Madhu Pai, Karen Steingart.
- **LSHTM Colleagues:** Laura Maynard-Smith, Natasha Larke
- **Cape Town Colleagues:** Andrew Kerkhoff, Graeme Meintjes, Rosie Burton, Mark Nicol et al.

High Diagnostic Yield of Tuberculosis From Screening Urine Samples From HIV-infected Patients with Advanced Immunodeficiency Using The Xpert MTB/RIF Assay

Stephen D. Lawn, MBBS, MRCP, MD, DTM&H,† Andrew D. Kerkhoff, MSc,*‡
Monica Vogt, DipMedTech,* and Robin Wood, MMed, FCP**



Lawn et al. JAIDS 2012

TB Diagnosis in Unselected HIV+ Medical Admissions in Cape Town

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



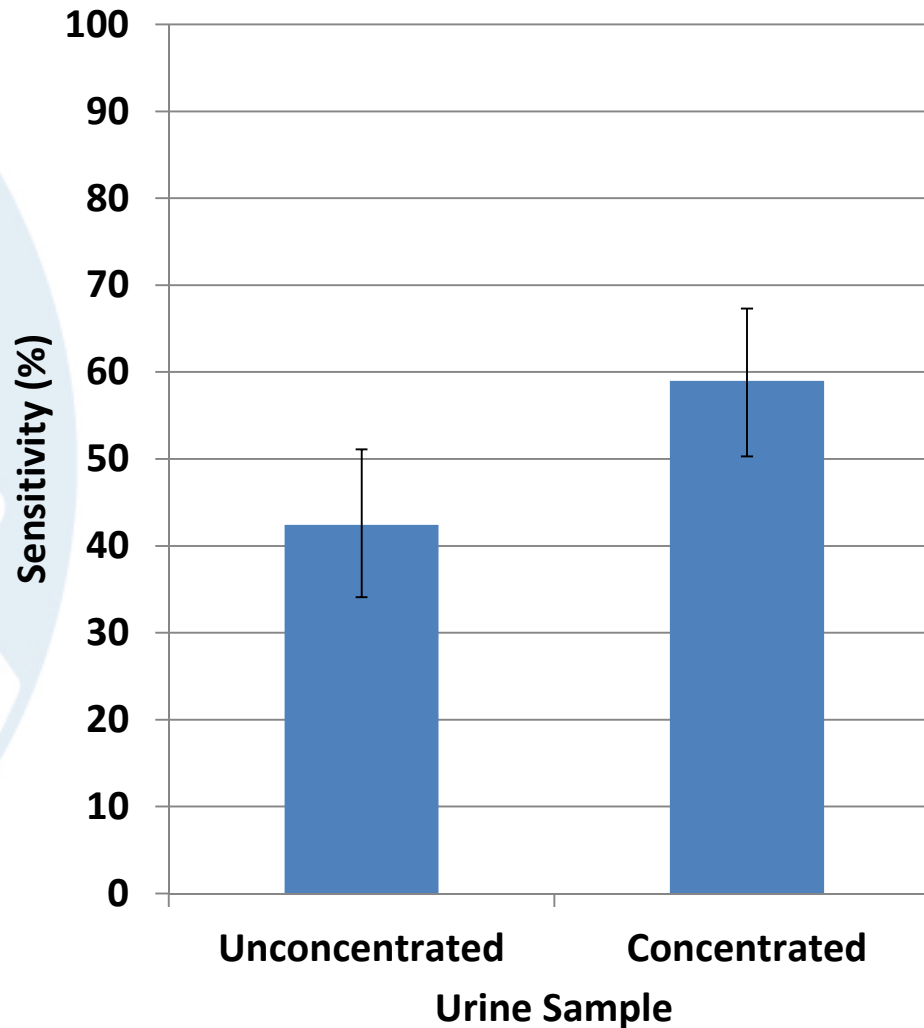
427 new admissions

2,391 samples (median – 3 body compartments)

3,471 diagnostic tests for TB

Lawn et al CROI 2014

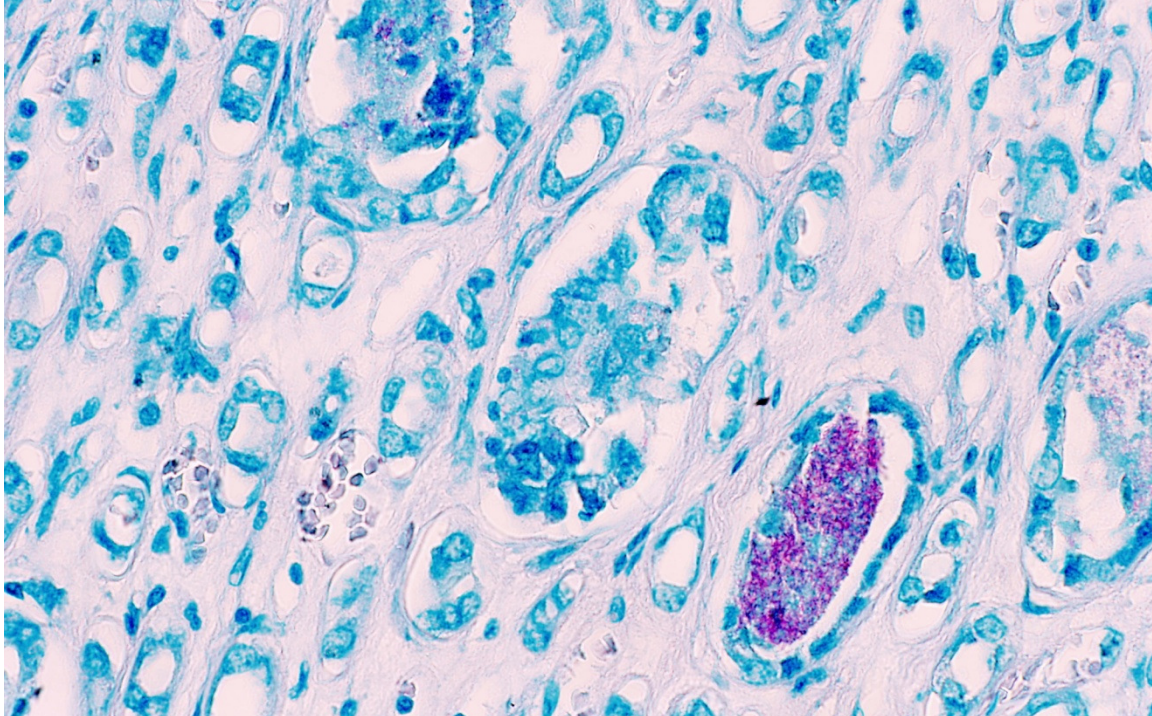
Urine for HIV-Associated TB



**Centrifugation
of 30-40 mls
urine increased
absolute yield
by 17%**



Of those with
generalised TB,
65.2% had
evidence of renal
involvement



**New analysis of
Lucas *et al.* AIDS 1993**