



C-Reactive Protein for TB Screening

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Advanced TB Diagnostics Research Course

June 24, 2016



Recommendations 1-3

Should be done:

- Household contacts
- PLHIV
- Silica-exposed workers

Recommendations 4-7

Should be considered:

- Prisons
- Untreated fibrotic CXR lesions
(prevalence $>100/100000$)
- Healthcare settings
(prevalence 1%)

How to screen?

- TPP for a TB screening test
 - Minimum: Sensitivity >90%; Specificity >70%
 - Rapid, low-cost, simple-to-perform
- Current options for TB screening
 - Symptoms
 - CXR

C-Reactive Protein (CRP)

- Acute phase reactant synthesized by the liver in response to IL-6
 - Binds to surface of dead or dying cells
 - Activates complements, enhances phagocytosis
- Levels rise within 2 hours of onset of inflammation
 - Constant half life of 18 hours
 - Level determined by rate of production (*i.e.*, severity of underlying cause)
- Normal levels <10 mg/L

- Systematic review of the accuracy of CRP for identifying active pulmonary TB
- Prospective evaluation of the accuracy of CRP-based TB screening among PLHIV

Systematic Review Objective

- To assess the diagnostic accuracy of CRP among patients being screened or evaluated for pulmonary tuberculosis by clinical setting (outpatient clinic vs. hospital)
 - Population: Patients being screened for or suspected of having pulmonary TB
 - Intervention: C-reactive protein
 - Outcome: Diagnostic accuracy (in reference to mycobacterial culture)

Methods: Study identification

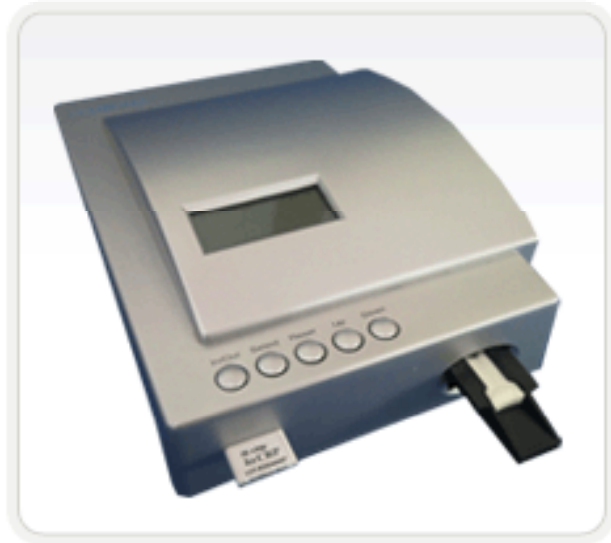
- Goal: Identify all studies that measured blood CRP levels in patients with TB
- Databases (through Jan 31, 2015)
 - PubMed, Embase, the Cochrane Library, and Web of Science
- Online search of Union Conference abstracts (2004 – 2015)

Methods: Study selection

- Inclusion
 - measured serum, plasma or whole blood CRP levels in children or adults being screened or evaluated for pulmonary TB
 - Performed mycobacterial culture
- Exclusion
 - non-English language studies
 - case-series/reports, review articles and letters to the editor
 - studies of only extra-pulmonary TB
 - studies that measured CRP using a non-quantitative assay
 - studies recruiting only patients with comorbid conditions associated with elevated CRP levels (*e.g.*, inflammatory bowel disease)
 - studies with <5 active pulmonary TB cases.

Index test: CRP

- quantitative lab-based and/or POC assays
- selected *a priori* a cut-point of 10 mg/L
 - studies excluded if data could not be extracted/not provided using the 10mg/L cut-point

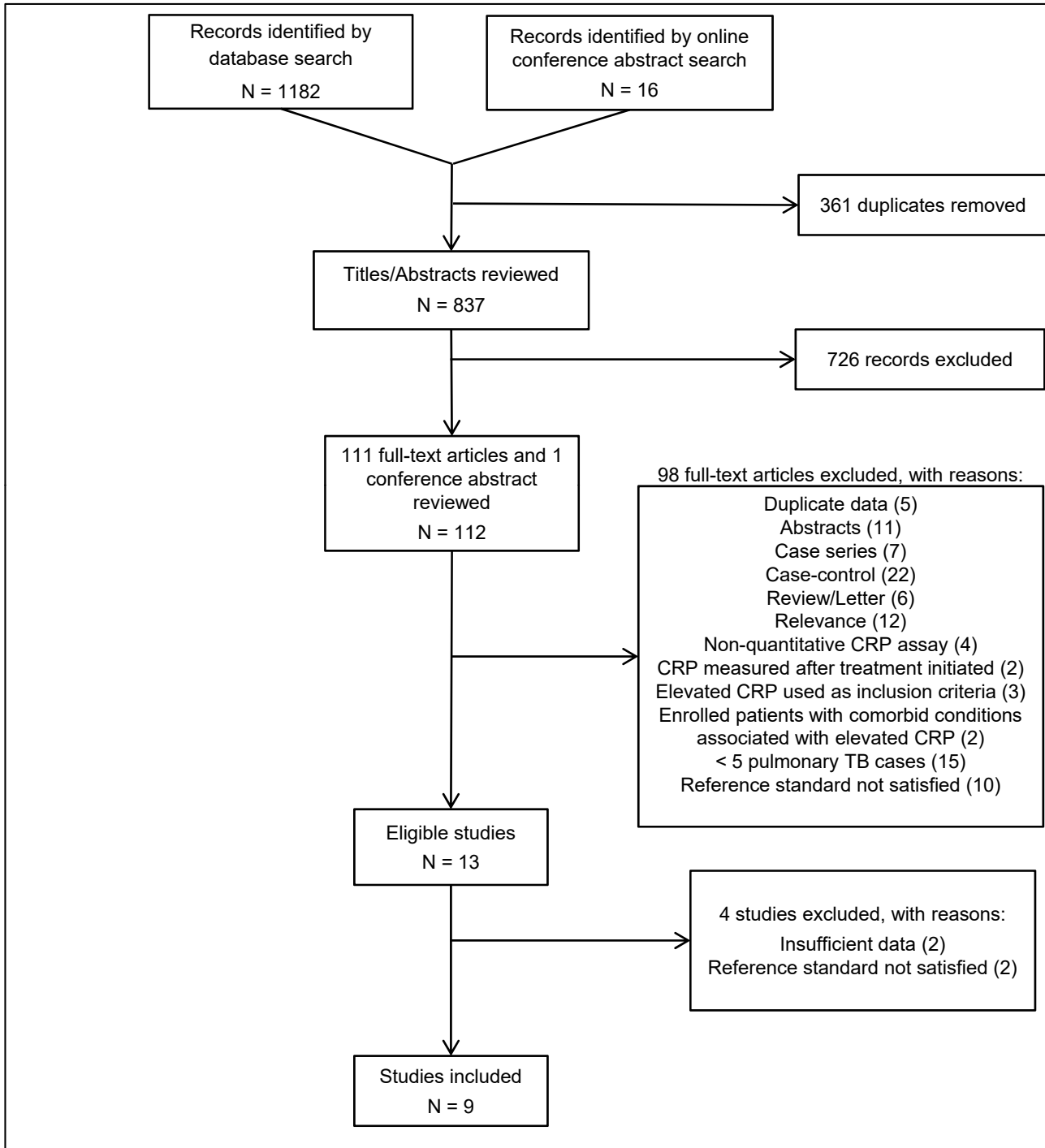


Reference standard

- ≥ 1 solid and/or liquid sputum mycobacterial culture result

Methods: Analysis plan

- Quality assessment: QUADAS-2
- Heterogeneity: visually using forest plots and statistically using χ^2 and I^2 tests
- Pooled sensitivity/specificity: HSROC analysis
 - ≥ 4 studies, each with ≥ 10 patients
 - Separately for inpatient & outpatient studies
 - Pre-specified sub-group analyses
 - Screening vs. Diagnosis-seeking patients
 - HIV-infected vs. HIV-uninfected patients



Outpatient studies

Study	Country	Setting	N (% HIV)	TB n (%)	CRP assay	Culture
Lawn 2013	S. Africa	ART-initiation	496 (100)	81 (16)	Quantikine (ELISA)	MGIT
Yoon 2014	Uganda	ART-initiation	271 (100)	27 (10)	iCHROMA (POC)	MGIT
Drain 2014	S. Africa	Smear-negative	76 (100)	30 (39)	NycoCard (POC)	LJ and MGIT
Wilson 2006	S. Africa	Smear-negative	74 (100)	59 (80)	Lab-based	LJ and MGIT
Wilson 2011	S. Africa	Smear-negative	204 (44)	116 (57)	Lab-based	MGIT

Study quality



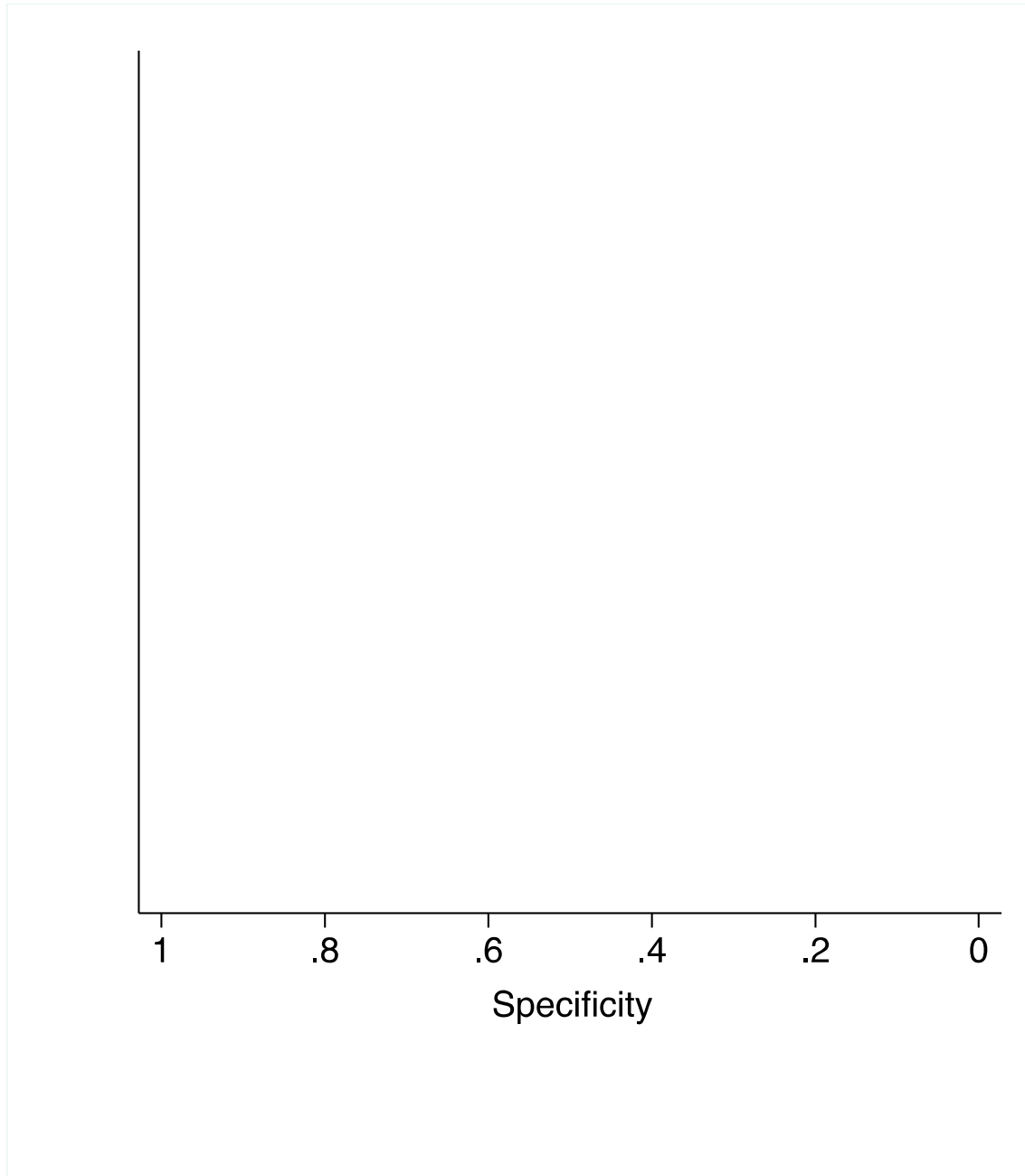
Heterogeneity

0 0.2 0.4 0.6 0.8 1 0 0.2 0.4 0.6 0.8 1

$I^2 = 53\%$, $p=0.07$

$I^2 = 93\%$, $p<0.001$

Pooled estimates



88-98)

44-75)

Sub-group analyses

Sub-group	# of studies	Pooled sensitivity	Pooled specificity
Screening	2	Range: 81-85%	Range: 58-81%
Diagnosis	3	Range: 96-97%	Range: 33-73%
HIV-positive	5	93% (95% CI: 88-98)	61% (95% CI: 45-77)
HIV-negative	1	100%	85%

Inpatient studies

# of studies	Pooled sensitivity	Pooled specificity
5	78% (95% CI: 58-90)	21% (95% CI: 6-52)

Limitations

- Significant heterogeneity in specificity (but not sensitivity) estimates
- Only 2 studies evaluated CRP in the context of TB screening
- No studies in high-risk populations other than people living with HIV

Conclusions

- CRP shows promise as a TB screening tool
- CRP should be further evaluated in populations targeted for systematic screening

- Systematic review of the accuracy of CRP for identifying active pulmonary TB
- Prospective evaluation of the accuracy of CRP-based TB screening among PLHIV

Study design

- Setting: 2 prototypical HIV clinics in Kampala
- Participants: Consecutive clients initiating ART
- Procedures
 - WHO symptom screen and POC CRP (iChroma)
 - Xpert MTB/RIF x 1, liquid culture x 2
- Analysis
 - Sensitivity/specificity in reference to culture results
 - Sensitivity in reference to Xpert MTB/RIF

Study population

Characteristic, N (%)	Total (N=1177)
Age (years)*	33 (27-40)
Female	626 (53%)
CD4 count (cells/ μ L)*	165 (75-271)
BMI (kg/m ²)*	21.2 (18.9-24.0)
Culture-positive TB	163 (14%)
Positive symptom screen	1025 (87%)
Elevated POC-CRP (>10mg/L)	428 (36%)

Diagnostic accuracy (in reference to culture)

Parameter	POC-CRP	WHO symptom screen	% Difference
<i>Sensitivity</i>	89% (83-93%)	96% (91-98%)	-7% (-12 to -2%)
<i>Specificity</i>	72% (69-75%)	14% (12-17%)	+58% (+55 to +61%)
<i>NPV</i>	98% (96-99%)	95% (91-98%)	
<i>PPV</i>	34% (29-39%)	15% (13-18%)	

Diagnostic accuracy (in reference to Xpert)

Parameter	POC-CRP	WHO symptom screen	% Difference
<i>Sensitivity</i>	94% (87-98)	99% (94-100)	-5% (-12 to +2%)
<i>NPV</i>	99% (98-100)	99% (96-100)	

Conclusions

- POC CRP has much higher accuracy than symptoms
- POC CRP meets the minimum criteria for a TB screening test among PLHIV initiating ART
- Further studies are needed in other populations targeted for systematic screening

Acknowledgements

UCSF/Curry International TB Center

Isabel E. Allen

Lelia Chaisson

Sweta Patel

Payam Nahid

George Rutherford

Gloria Won

Yale University

Luke Davis

Harvard University

Paul Drain

University of KwaZulu-Natal

Doug Wilson

Makerere University

Fred Semitala

Moses Kamya

Elly Atuhumuza

Jane Katende

Sandra Mwebe

Lucy Asege

Makerere University Joint

AIDS Programme

Jennifer Namusobya

Funding: NIH/NIAID; UCSF Nina Ireland Program in Lung Health