

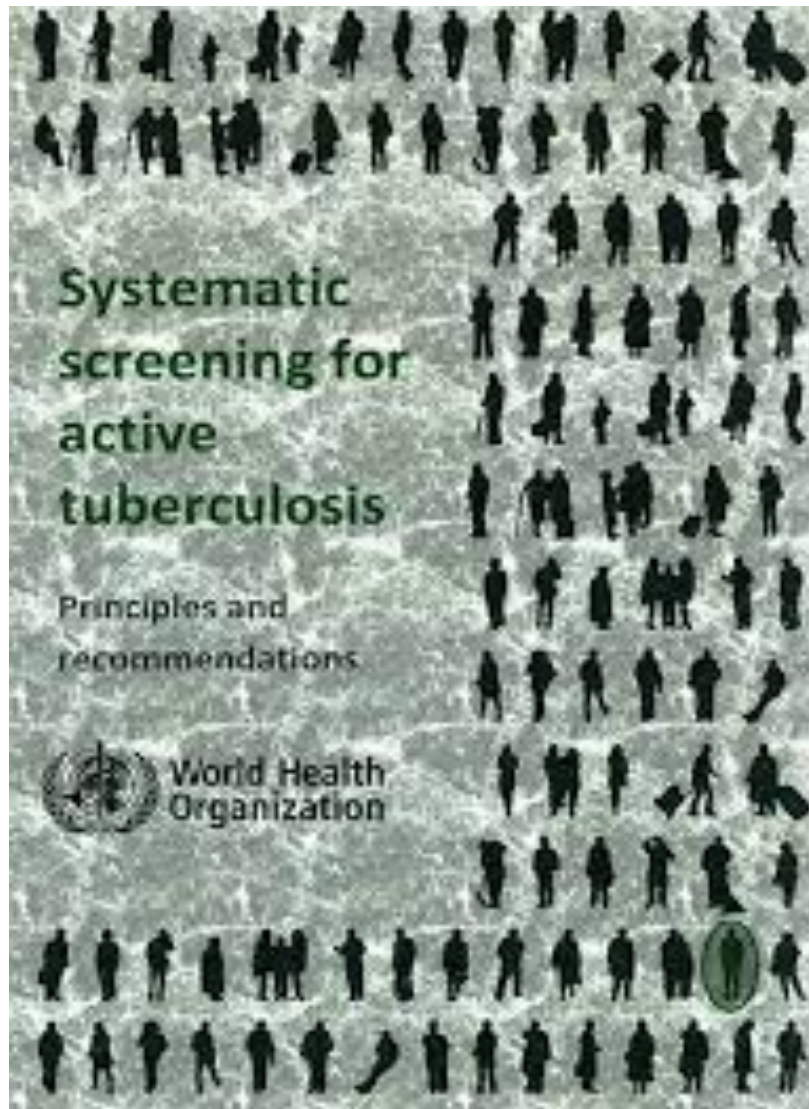


C-reactive protein-based TB screening

Advanced TB Diagnostics Workshop
June 22, 2017

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Systematic TB screening



Recommendations 1-3

Should be done:

- Household contacts
- PLHIV
- Silica-exposed workers

Recommendations 4-7

Should be considered:

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

How to screen?

Current options for TB screening:

1. Symptoms
2. CXR

TPP for a TB screening test:

1. Test characteristics (minimum):
 - Sensitivity $\geq 90\%$; Specificity $\geq 70\%$
2. Operational characteristics:
 - Low-cost, rapid, simple-to-perform

C-reactive protein (CRP)

Active TB causes significant rise in CRP (CRP \geq 10 mg/L)

- In **passive case detection**:
 - CRP has high sensitivity (>90%)
 - But low (<50%) specificity
- In **active case detection** (e.g., **systematic screening**):
 - Sensitivity comparable to symptom screen
 - But 2- to 4-fold greater specificity

Commercially available as a rapid, inexpensive, and easy-to-use point-of-care (POC) test

CRP: 2 studies

1. Systematic review/meta-analysis (SR/MA) to evaluate the accuracy of CRP for identifying active pulmonary TB (*in production*)
2. Prospective evaluation of the accuracy of CRP-based TB screening among PLHIV (*under revision*)

SR/MA: Objective

- To assess the diagnostic accuracy of CRP for active PTB by clinical setting (clinic vs. hospital)
- **Population:** Patients being screened for or undergoing evaluation for active PTB
- **Intervention:** CRP
- **Outcome:** Diagnostic accuracy (in reference to culture)

Methods: Study identification

Goal: Identify all studies that measured blood CRP levels in patients with TB

Databases (through January 31, 2015):

- PubMed, Embase, the Cochrane Library, and Web of Science
- Online search of Union Conference abstracts (2004 – 2015)

Methods: Study selection

Inclusion

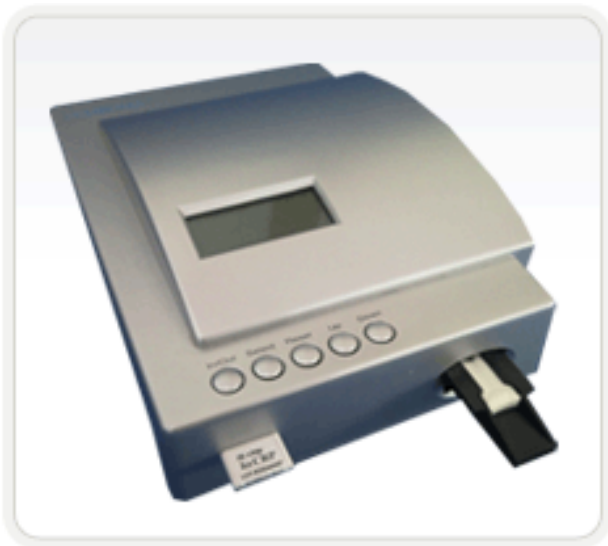
- Measured serum, plasma or whole blood CRP levels in children or adults being screened or evaluated for PTB
- Performed mycobacterial culture

Exclusion

- Non-English language studies
- Case-series/reports, review articles and letters to the editor
- Studies of only EPTB
- 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 PTB 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 provided/extracted using the 10 mg/L cut-point



Reference standard

- ≥ 1 solid and/or liquid sputum mycobacterial culture result
 - Studies excluded if data could not be extracted/ provided using only culture results as the reference standard

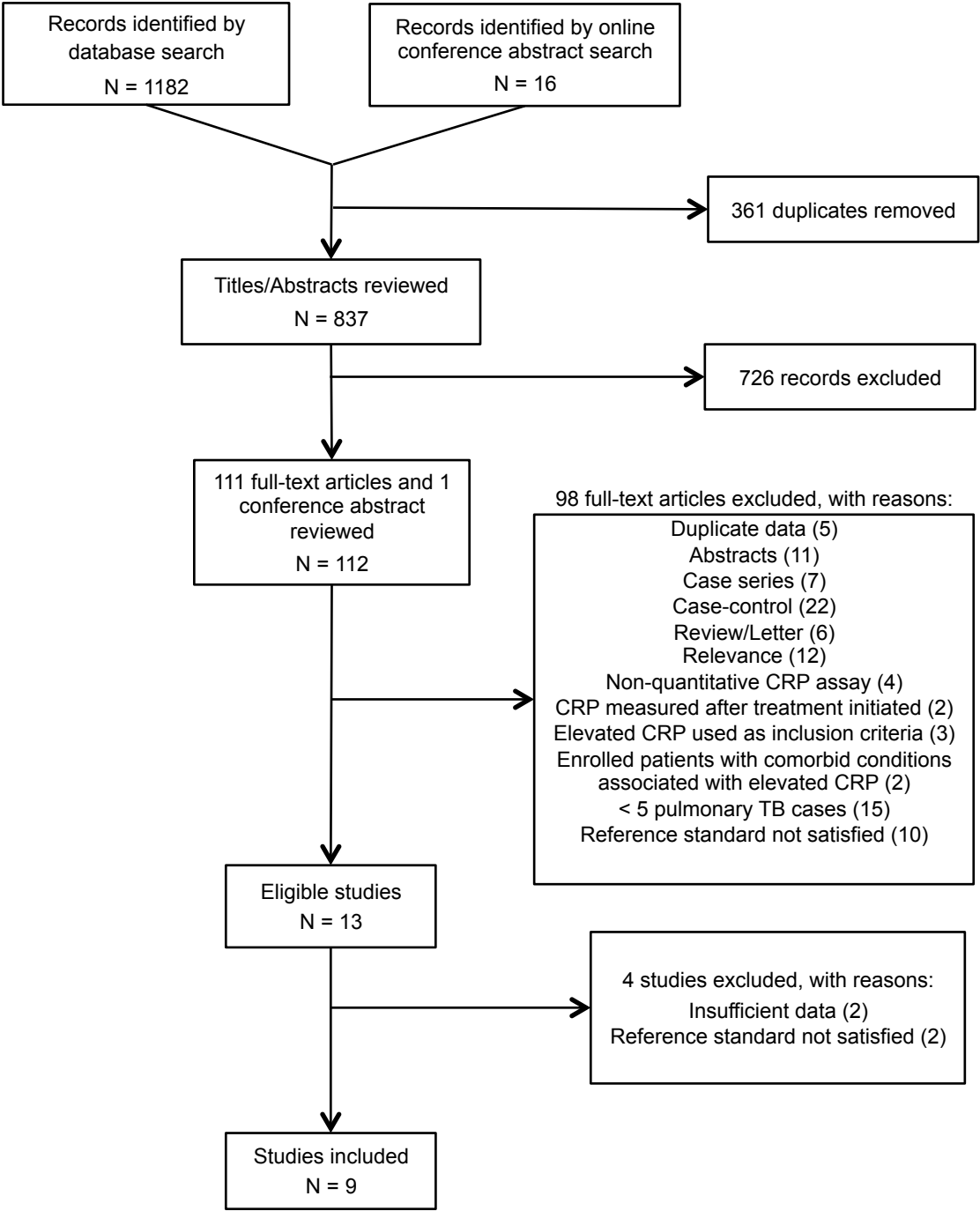
Methods: Analysis plan

Quality assessment: QUADAS-2

Heterogeneity: visually using forest plots and statistically using χ^2 and I^2 tests

Pooled sensitivity, specificity: HSROC analysis

- Separately for outpatient & inpatient studies
- ≥ 4 studies, each with ≥ 10 patients
- Sub-group analyses:
 - Screening vs. diagnosis-seeking patients
 - HIV+ vs. HIV- patients






Outpatient studies

Study	Country	Setting	N (% HIV)	TB n (%)	CRP assay	Culture
Lawn, 2013	S. Africa	ART-initiation	496 (100)	81 (16)	Lab-based	MGIT
Yoon, 2014	Uganda	ART-initiation	271 (100)	27 (10)	POC (iCHROMA)	MGIT
Drain, 2014	S. Africa	Smear-negative	76 (100)	30 (39)	POC (NycoCard)	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: Outpatients

	<u>Risk of Bias</u>				<u>Applicability Concerns</u>		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Lawn 2013 (S. Africa)	+	+	+	+	+	+	+
Yoon 2014 (Uganda)	+	+	+	+	+	+	+
Drain 2014 (S. Africa)	+	+	+	+	-	+	+
Wilson 2006 (S. Africa)	-	+	+	+	-	+	+
Wilson 2011 (S. Africa)	-	+	+	-	-	+	+

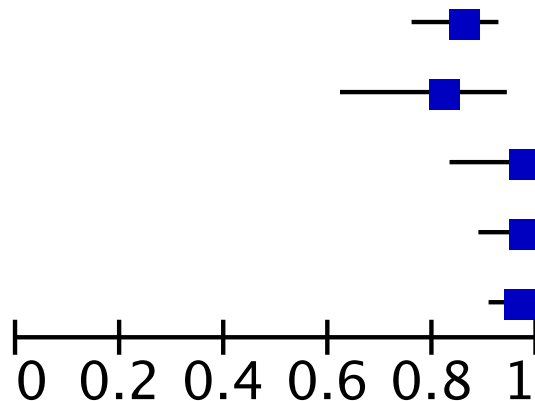
 High	 Unclear	 Low
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Heterogeneity: Outpatients

Study

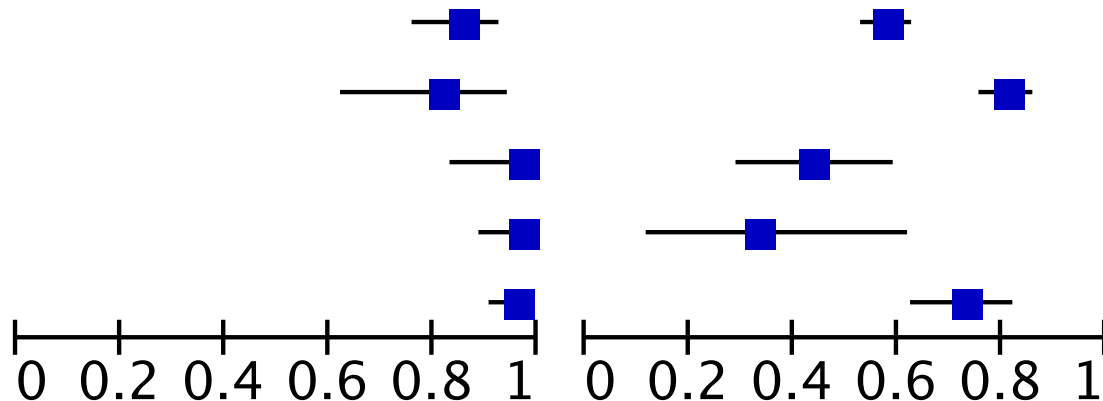
Lawn 2013 (S. Africa)
Yoon 2014 (Uganda)
Drain 2014 (S. Africa)
Wilson 2006 (S. Africa)
Wilson 2011 (S. Africa)

Sensitivity (95% CI)



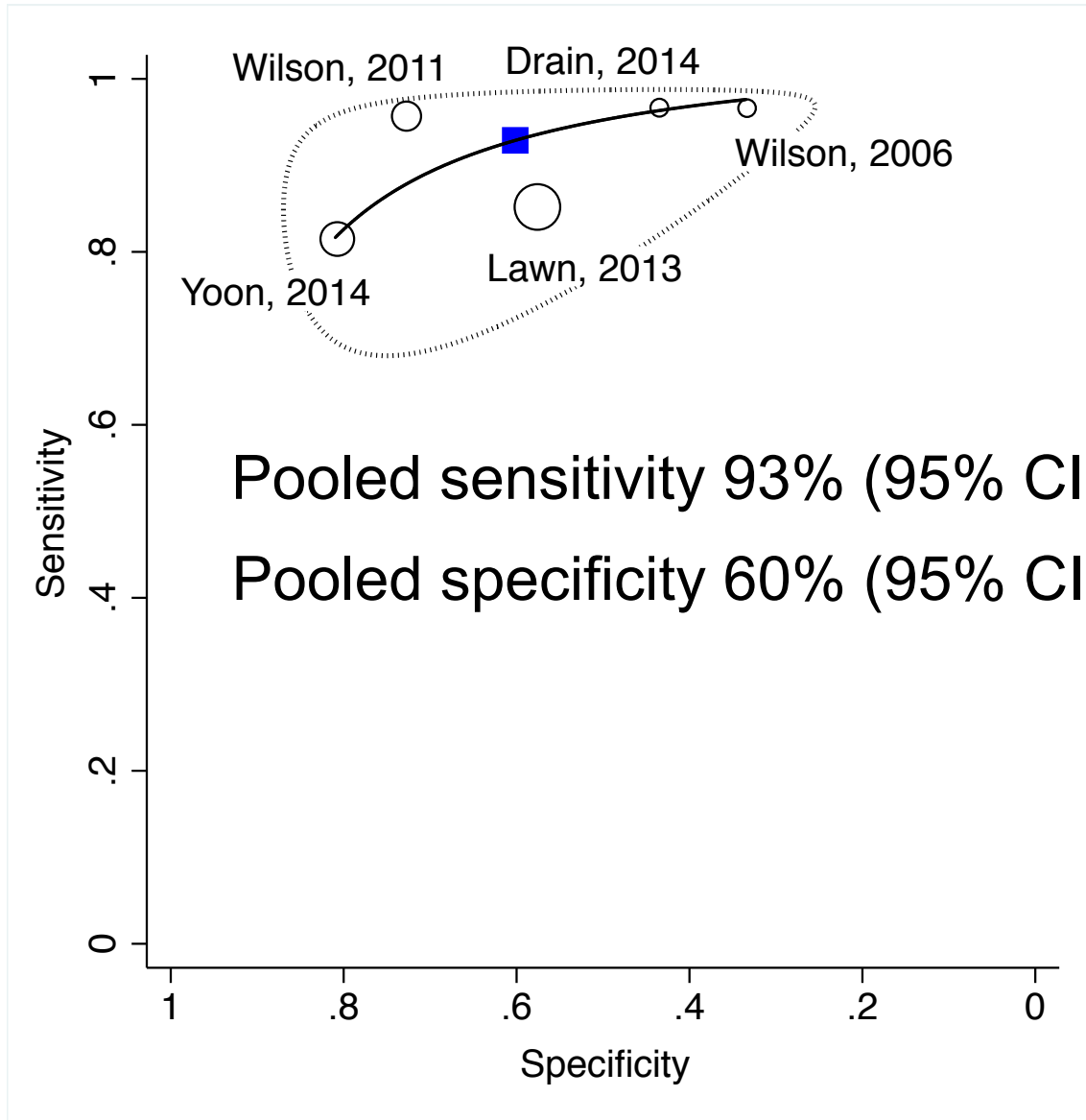
$I^2 = 53\%$, $p=0.07$

Specificity (95% CI)



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

Pooled estimates: Outpatients



Sub-group analyses

	# of studies	Pooled sensitivity	Pooled specificity
Outpatient			
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	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 PLHIV

Conclusions

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

Acknowledgments

UCSF

- Isabel E. Allen
- Adithya Cattamanchi
- Laurence Huang
- George Rutherford
- Gloria Won

Johns Hopkins University

- Derek Armstrong
- Lelia Chaisson
- David Dowdy

University of Washington

- Paul Drain

Yale University

- J. Luke Davis

University of KwaZulu-Natal

- Doug Wilson

Makerere University

- Alfred Andama
- Lucy Asege
- Elly Atuhumuza
- Jane Katende
- Moses Kanya
- Sandra Mwebe
- Martha Nakaye
- Fred Semitala

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