



ZUCKERBERG
SAN FRANCISCO GENERAL
Hospital and Trauma Center



C-reactive protein-based TB screening

Advanced TB Diagnostics Workshop

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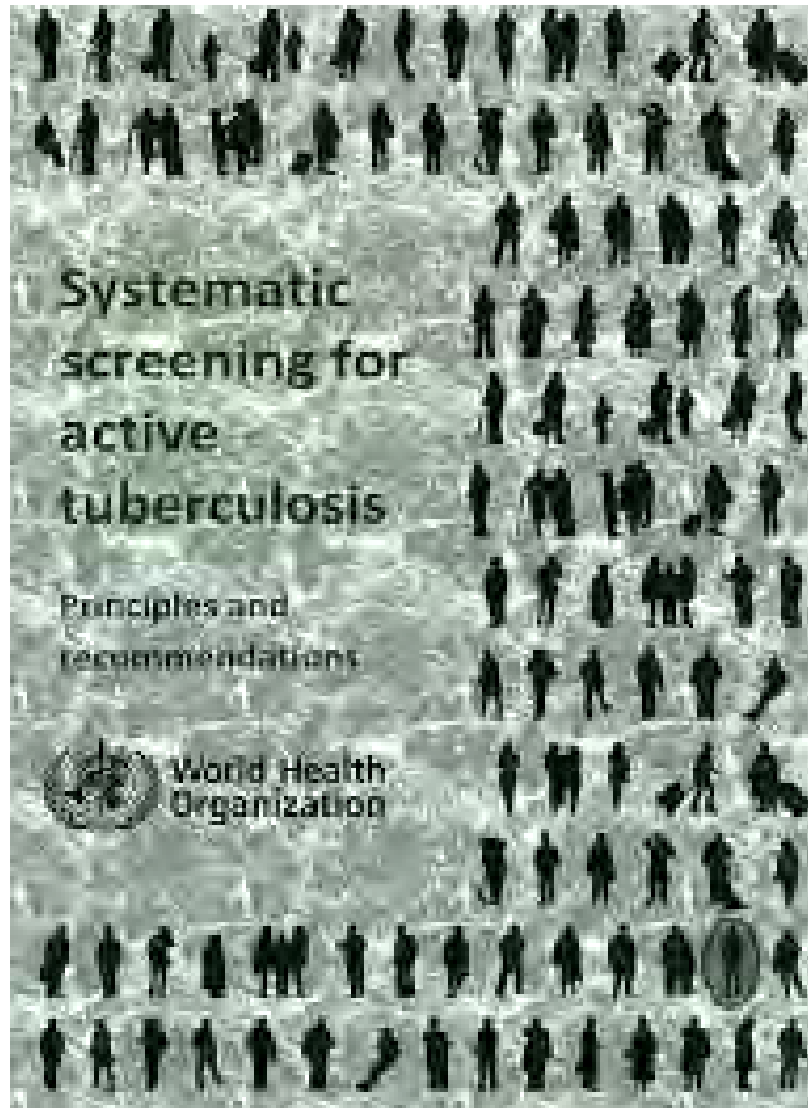
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Screening vs. Triage test: Definitions

- **Systematic screening** – provider-initiated TB screening, regardless of symptoms/ reason for presentation
- **Screening test** – a test applied to everyone for whom systematic screening is indicated to identify who needs confirmatory TB testing
- **Triage test** – 2° screening test, applied to screen-positive pts, to further reduce the proportion needing confirmatory TB testing
- Goals of screening and triage tests are similar: limit confirmatory testing to a smaller subset of high-risk pts
→ **Good triage tests may be good screening tests**

Who should be screened for active TB?



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 >100/100,000)
- Communities (prevalence 1%)

How to screen?

Current options for TB screening:

1. Symptoms
2. CXR

TPP for a TB screening (and triage) test:

1. Test characteristics (minimum):
 - Sensitivity $\geq 90\%$; Specificity $\geq 70\%$
2. Operational characteristics:
 - Low-cost (<\$2-5 per test), 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 (< \$2), and easy-to-use point-of-care (POC) test

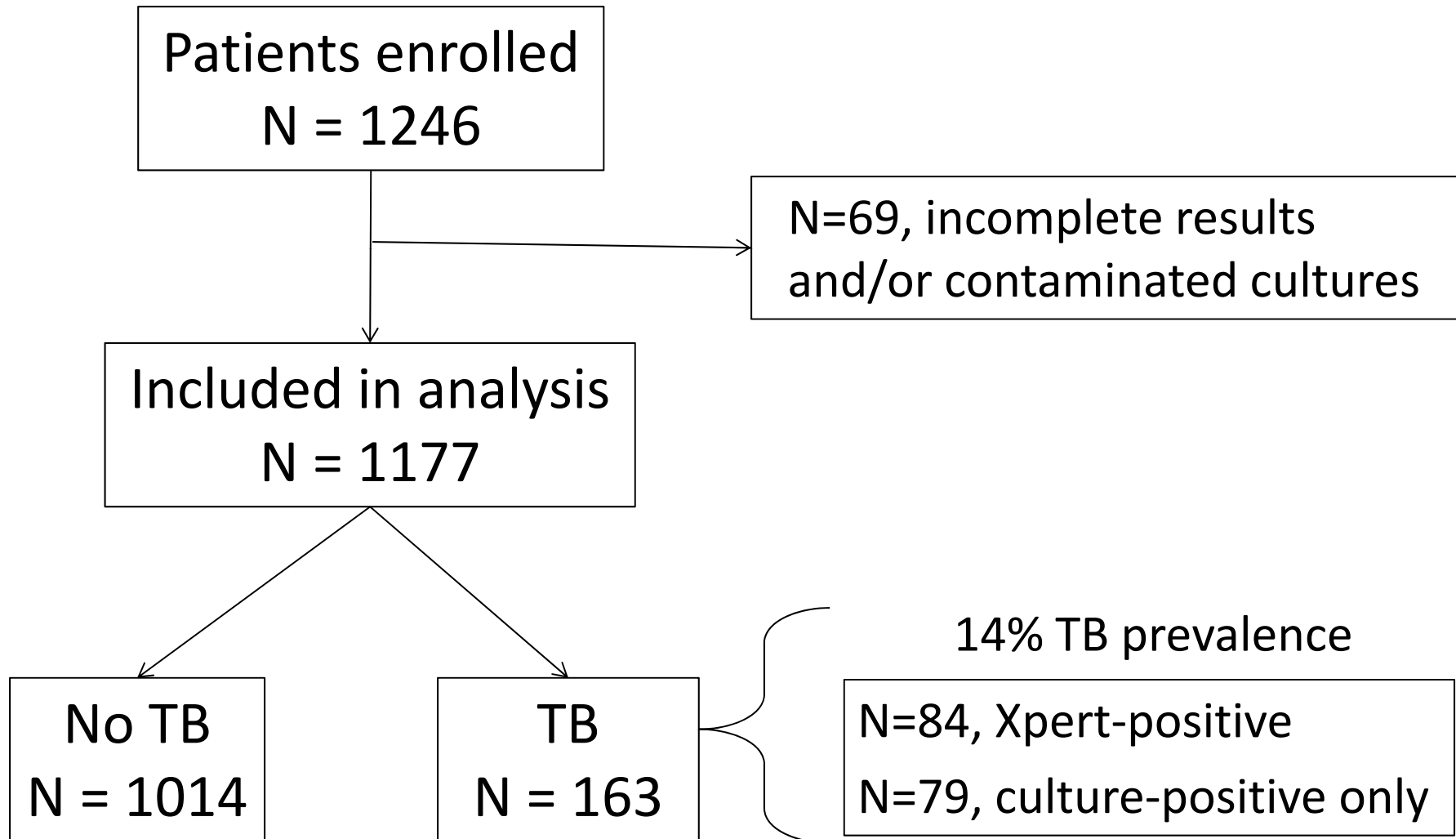
POC CRP: 2 studies in PLHIV

1. Diagnostic accuracy of POC CRP-based TB screening (Lancet ID, 2017)
2. Performance of POC CRP-based ICF algorithms (under revision)

Methods

- **Participants:** Consecutive HIV-infected adults with CD4 <350 initiating ART from 2 HIV clinics in Kampala, Uganda from 7/2013 to 12/2015
- **Procedures:**
 - **TB screening:** symptom screen assessment, POC CRP testing (normal < 10 mg/L)
 - **TB evaluation:** Xpert MTB/RIF (x1) and MGIT culture (x2)
- **Analysis:** sensitivity, specificity in reference to 1) culture (≥ 1 culture positive) and 2) Xpert MTB/RIF

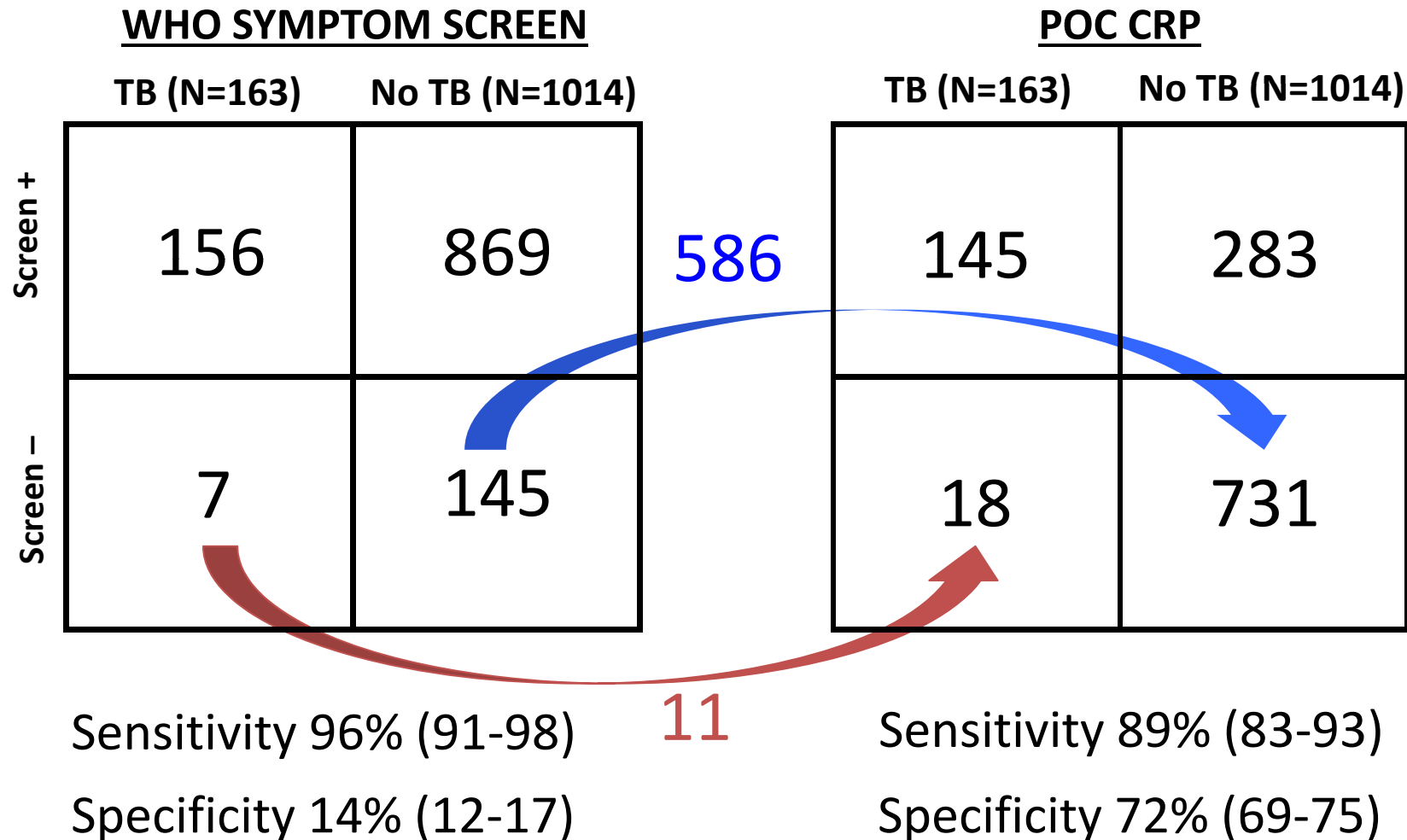
Patient flow diagram



Demographics and clinical characteristics

Characteristic, N (%)	Total (N=1177)
Age (years)	33 (27-40)
Female	626 (53%)
CD4 count (cells/ μ L) [†]	165 (75-271)
WHO symptom screen positive	1025 (87%)
Elevated POC-CRP	428 (36%)
POC CRP (mg/L)	4.6 (2.5-24.5)

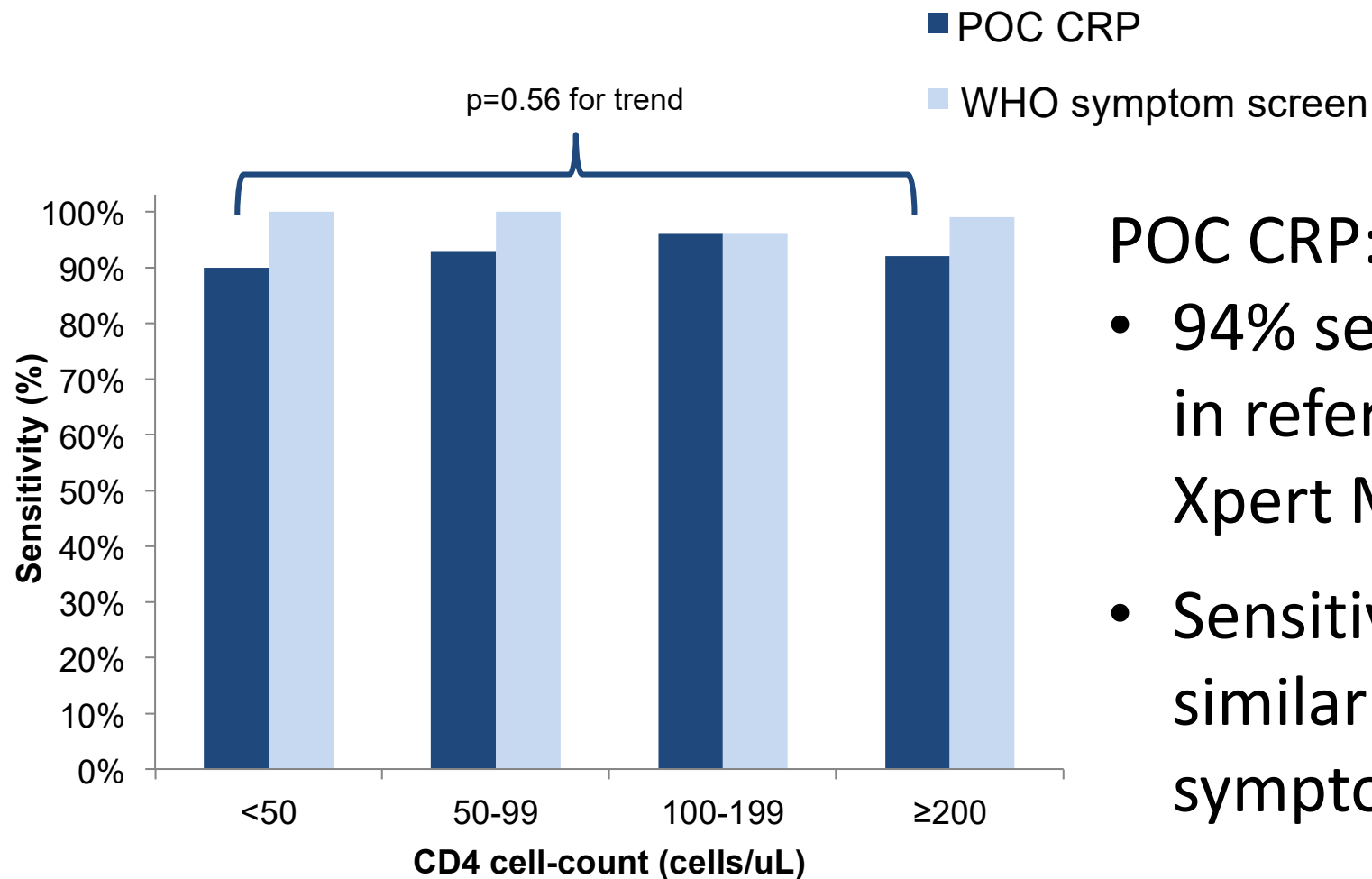
Diagnostic accuracy of TB screening tests (in reference to culture)



Effect of alternate POC CRP cut-points on diagnostic accuracy

Table 3: Effect of varying point-of-care C-reactive protein threshold on diagnostic accuracy

Sensitivity, in reference to Xpert MTB/RIF



POC CRP:

- 94% sensitivity in reference to Xpert MTB/RIF
- Sensitivity similar to symptoms

Conclusions

- POC CRP meets the minimum criteria for a TB screening test among PLHIV with $CD4 \leq 350$ initiating ART
- Relative to symptom screening, POC CRP-based TB screening could improve the efficiency of ICF and scale-up of IPT

Performance of POC CRP-based ICF algorithms

Objectives:

1. To compare the *yield* of POC CRP-based ICF algorithms to the current ICF algorithm
2. To compare the *efficiency* of POC CRP-based ICF algorithms to the current ICF algorithm

Methods

Participants: Consecutive HIV-infected adults with CD4 <350 initiating ART from 2 HIV clinics in Kampala, Uganda from 4/2014 to 12/2016

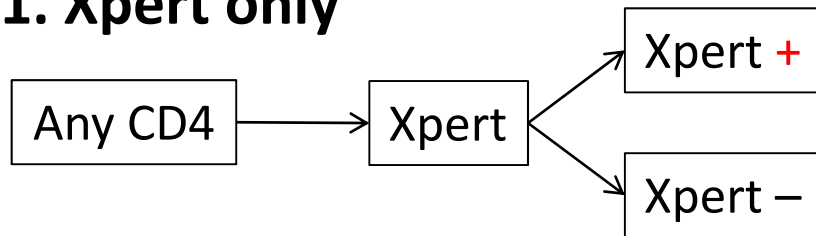
Procedures:

- **TB screening:** symptom screen assessment and POC CRP testing (**8 mg/L cut-point**)
- **TB confirmatory testing:** sputum Xpert (x1), sputum MGIT culture (x2) and **urine LAM** (if CD4 \leq 100 cells/ μ L; Grade 2 cut-point)

Analysis: diagnostic yield (incremental and diagnostic yield), efficiency (number of confirmatory tests used, NNT and costs per TB case detected)

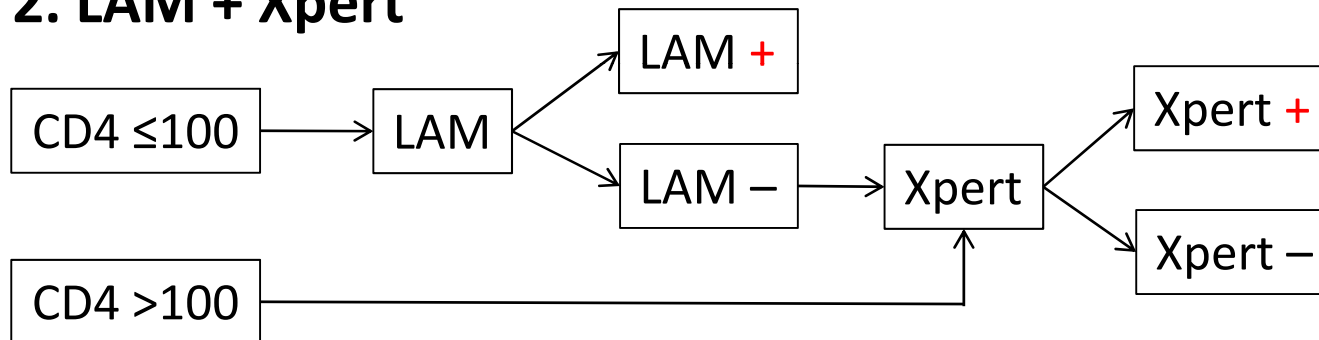
ICF algorithms evaluated

1. Xpert only

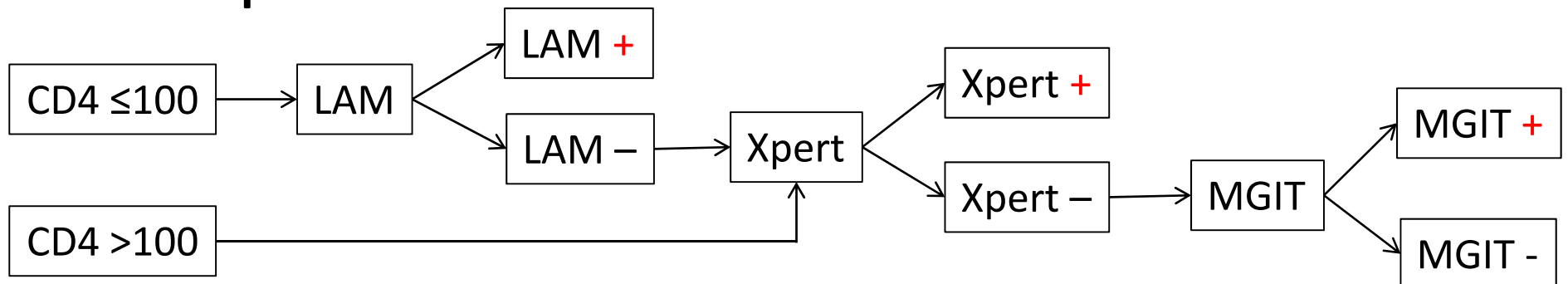


POC CRP or
WHO symptom screen
combined with...

2. LAM + Xpert



3. LAM + Xpert + MGIT



Demographics and clinical characteristics

Characteristic, N (%)	Total (N=1245)
Age (years) [†]	33 (27-40)
Female	648 (52%)
CD4 count (cells/ μ L) [†]	153 (67-252)
<i>CD4 \leq100 cells/μL</i>	439 (35%)
WHO symptom screen positive	1100 (88%)
POC CRP \geq8 mg/L	498 (40%)
POC CRP (mg/L)	4.0 (2.5-24.4)
Culture-positive TB	203 (16%)

Diagnostic accuracy of individual and combined confirmatory TB tests

Diagnostic accuracy of individual confirmatory TB tests.

Test	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	PPV (%, 95% CI)	NPV (%, 95% CI)
LAM	26% (18-35) 26/101	98% (96-99) 332/338	81% (64-93)	82% (78-85)
Xpert	60% (53-66) 121/203	99% (99-100) 1036/1042	95% (90-98)	93% (91-94)
Culture	79% (73-84) 160/203	100% (100-100) 1042/1042	100% (98-100)	96% (95-97)

Diagnostic accuracy of combined confirmatory TB testing strategies.

Test combinations	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	PPV (%, 95% CI)	NPV (%, 95% CI)
LAM + Xpert	63% (56-70) 128/203	99% (98-99) 1030/1042	91% (86-96)	93% (92-95)
LAM + Xpert + culture	88% (82-92) 178/203	99% (98-99) 1030/1042	94% (89-97)	98% (97-99)

Diagnostic yield, incremental yield and # of false-positives for each ICF algorithm

ICF strategy	Diagnostic yield # and % (95% CI) TB cases detected (N=203)	Incremental yield		Total # false-positives
		# add'l TB cases detected	% (95% CI) add'l TB cases detected	
WHO symptom screen +...				
Xpert (<i>current algorithm</i>)	119 (59%, 52-65)	REF	REF	7
LAM + Xpert	126 (62%, 55-69)	+7	+4% (0 to +7)	13
LAM + Xpert + culture	172 (85%, 79-89)	+53	+27% (+20 to +34)	13
POC CRP ≥8 mg/L + ...				
Xpert	114 (56%, 49-63)	-5	-2% (-5 to +1)	4
LAM + Xpert	121, (60%, 53-66)	+2	+1% (-3 to +5)	10
LAM + Xpert + culture	158, (78%, 71-83)	+39	+19% (+12 to +26)	10

Number of confirmatory tests used and NNT to detect one case of active TB

ICF algorithms	Number of confirmatory tests used			NNT to detect one case of active TB		
	LAM	Xpert	Culture	LAM	Xpert	Culture
WHO symptom screen +...						
Xpert	--	1,100	--	--	9	--
LAM + Xpert	411	1,062	--	16	11	--
LAM + Xpert + culture	411	1,062	956	16	11	21
POC CRP (≥ 8 mg/L) +...						
Xpert	--	498	--	--	4	--
LAM + Xpert	210	460	--	8	5	--
LAM + Xpert + culture	210	460	357	8	5	10

Individual test costs, ICF costs and costs per TB case detected

ICF algorithms	Individual test costs (USD)				ICF test costs (USD)	Cost per TB case detected (USD)
	POC CRP	LAM	Xpert	Culture		
WHO symptom screen +...						
Xpert	--	--	\$12,000	--	\$12,000	\$102
LAM + Xpert	--	\$1,644	\$11,682	--	\$13,326	\$106
LAM + Xpert + culture	--	\$1,644	\$11,682	\$16,252	\$29,578	\$172
POC CRP (≥8 mg/L) +...						
Xpert	\$2,490	--	\$5,478	--	\$7,968	\$70
LAM + Xpert	\$2,490	\$840	\$5,060	--	\$8,390	\$69
LAM + Xpert + culture	\$2,490	\$840	\$5,060	\$6,069	\$14,459	\$92

Assume \$2 per POC CRP assay, \$11 per Xpert assay, \$4 per LAM assay and \$17 per MGIT culture.

Conclusions

- Without compromising yield, POC CRP could:
 - Improve ICF efficiency
 - Reduce the cost of ICF
 - Improve scale-up of TB preventive therapy
- Costs saved from using POC CRP-based ICF, could be re-allocated to culture to substantially improve ICF yield

Conclusions

Future studies should evaluate:

- POC CRP-based *ICF* in combination with Xpert Ultra +/- culture
- POC CRP-based *screening* in other populations targeted for systematic screening
- POC CRP-based *triage* testing in populations not currently targeted for systematic screening

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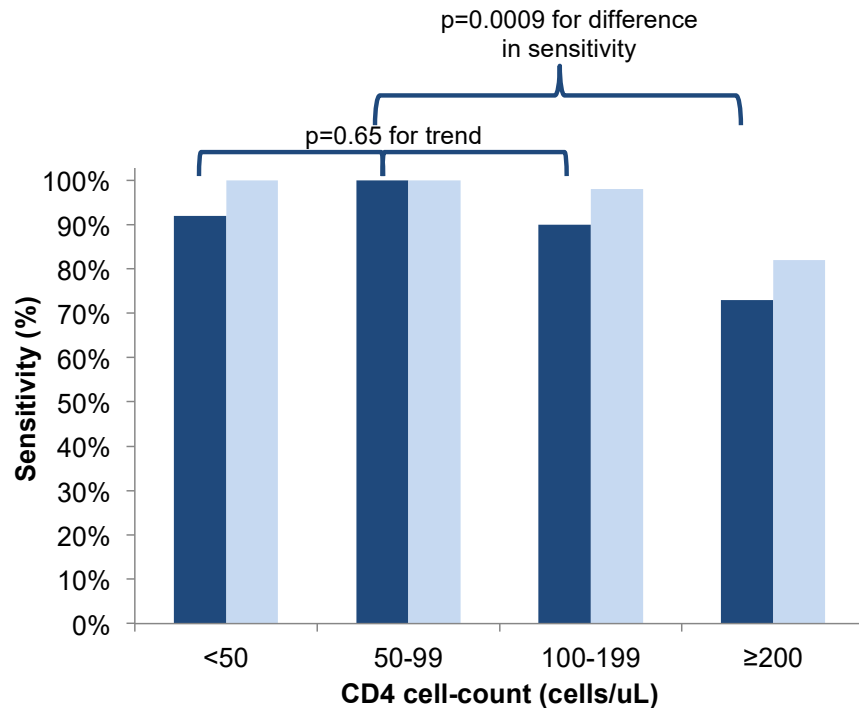
Diagnostic accuracy of combination TB screening strategies

	Any test positive	Both test positive
TP/Culture-positive	157/163	144/163
<i>% Sensitivity (95% CI)</i>	96% (92-99)	89% (82-92)
TN/Culture-negative	880/1014	742/1014
<i>% Specificity (95% CI)</i>	13% (11-16)	73% (70-76)
TN/(TN+FN)	134/140	742/762
<i>NPV (95% CI)</i>	96% (91-98)	97% (96-98)
TP/(TP+FP)	157/1038	144/416
<i>PPV (95% CI)</i>	15% (13-18)	35% (30-39)

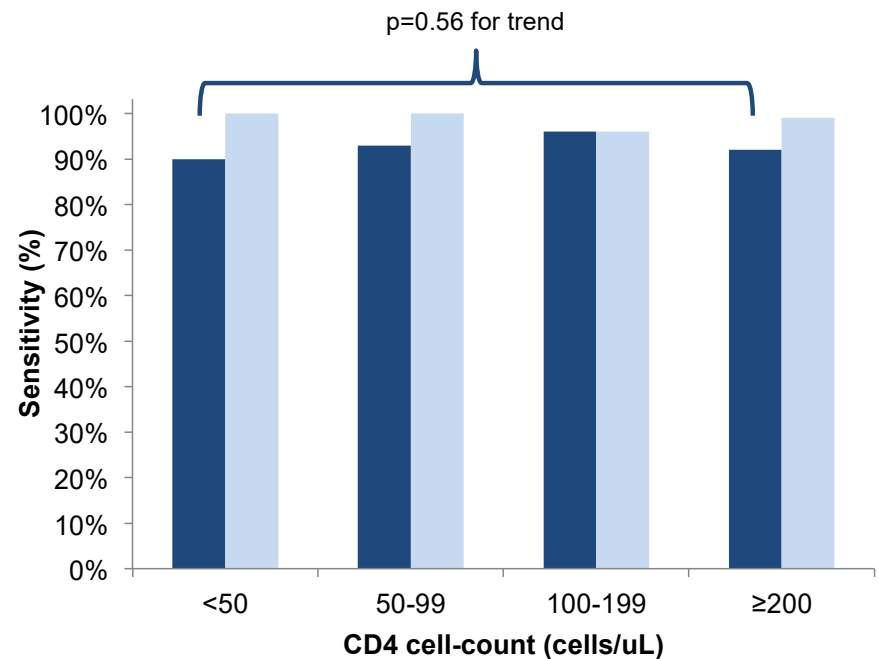
Sensitivity, stratified by CD4 strata

- POC CRP
- WHO symptom screen

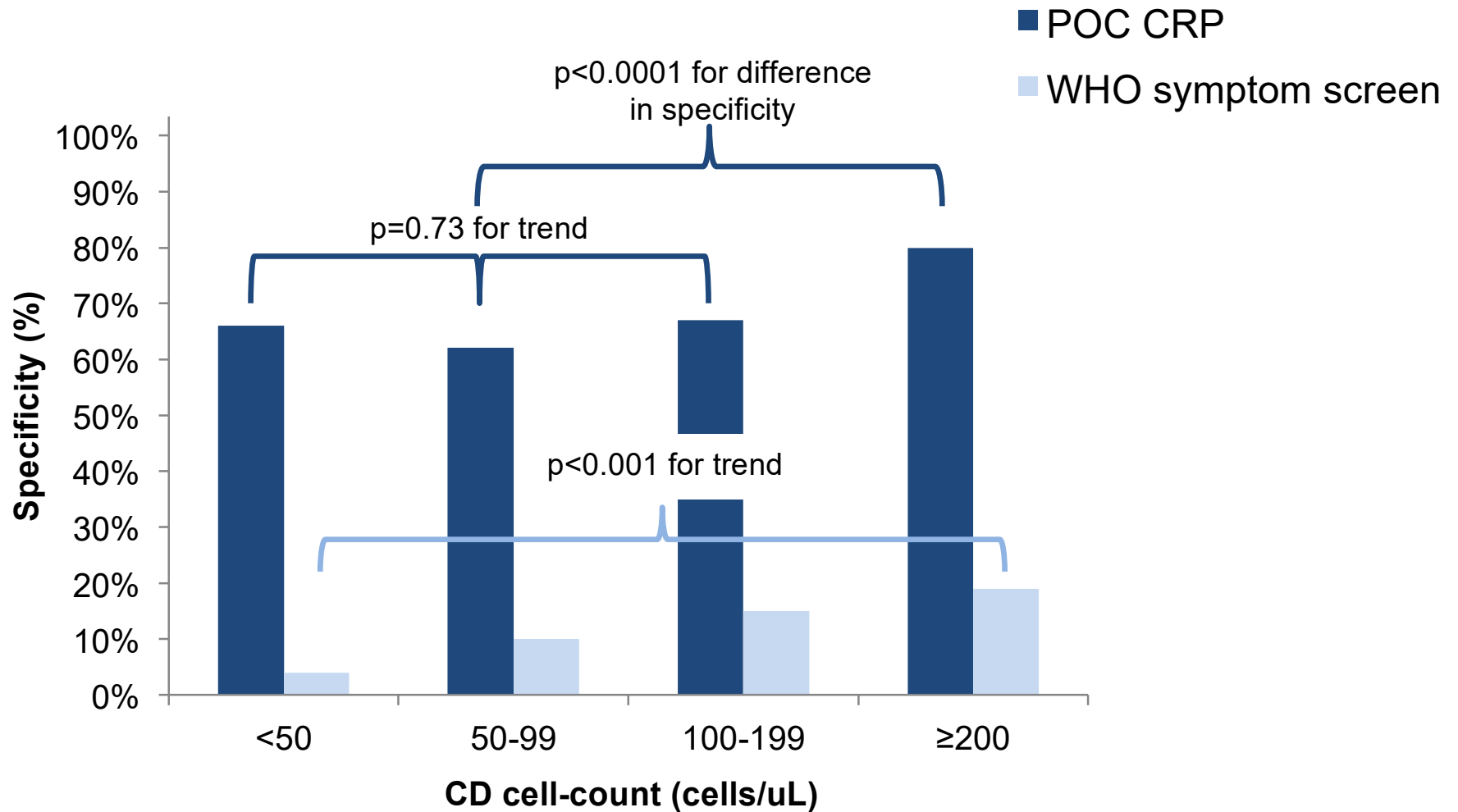
In reference to culture



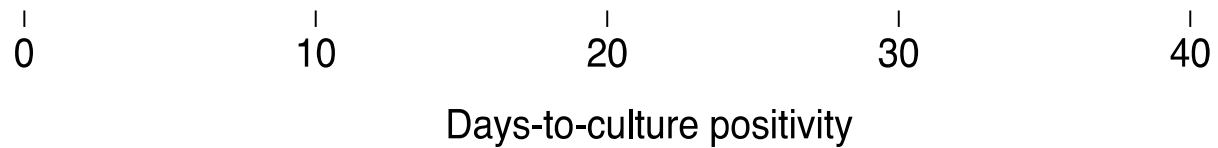
In reference to Xpert



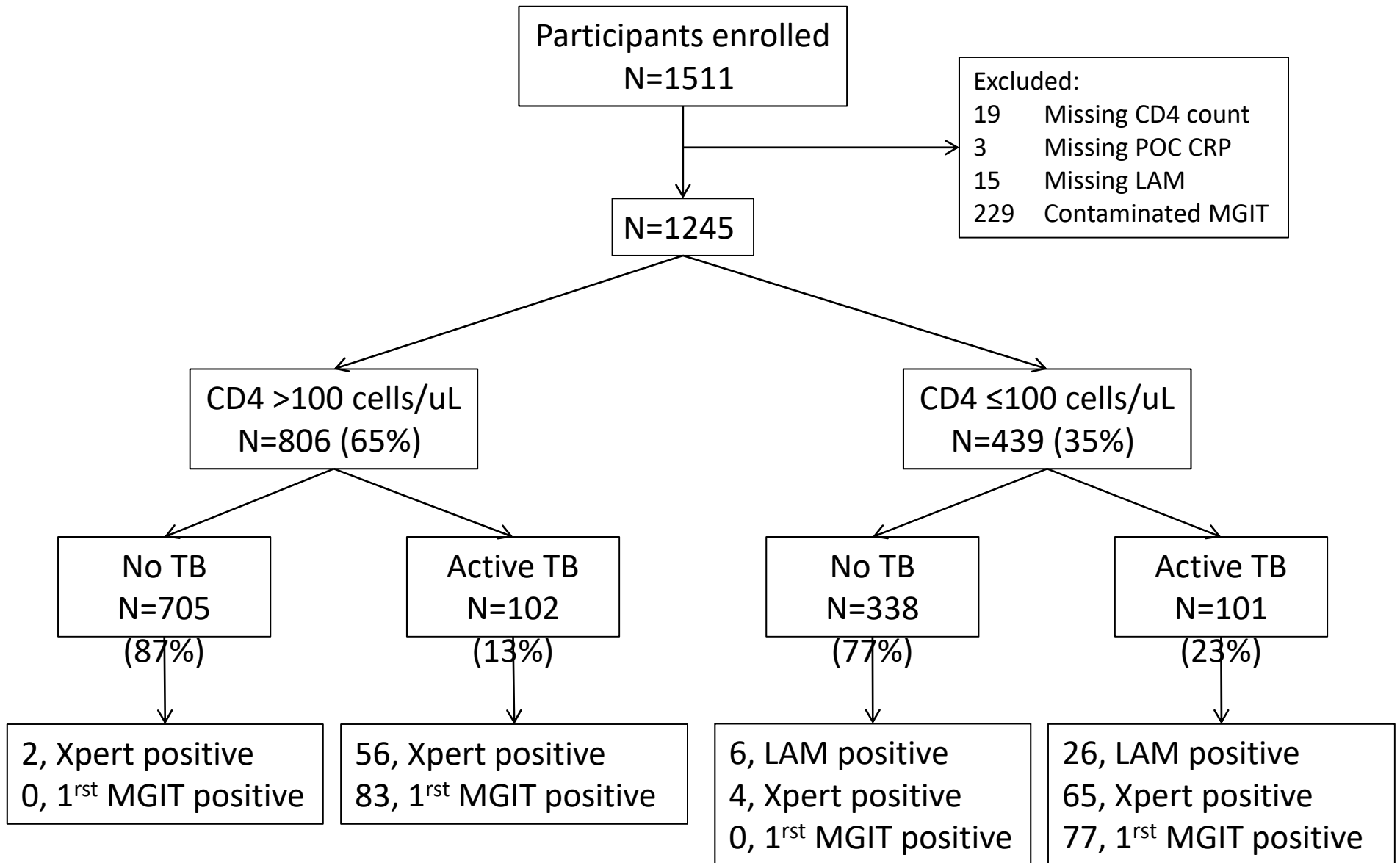
Specificity, stratified by CD4 strata



Scatter plot of POC CRP, by days to culture-positivity



Patient flow diagram



Probability of 3-month survival

