Sensitivity, specificity and predictive values of symptoms to detect tuberculosis in the ZAMSTAR community based prevalence studies

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CREATE

Consortium to Respond Effectively to the AIDS-TB Epidemic

An International Research Partnership

Supported by the Bill and Melinda Gates Foundation

http://www.tbhiv-create.org

TB/HIV NO RIO

ZAMSTAR

THIBELA
Team up against TB

A community randomised trial of two interventions delivered to ~1,200,000 people while strengthening the existing health systems

Baseline Prevalence Surveys

- 2 communities in Zambia and 2 in South Africa
- Sampling
  - Enumeration areas mapped and random order for sampling generated
- Recruitment
  - All households in EA visited and all consenting adults recruited
- Data collection
  - Questionnaire
  - Sputum sample

Prevalence Sites

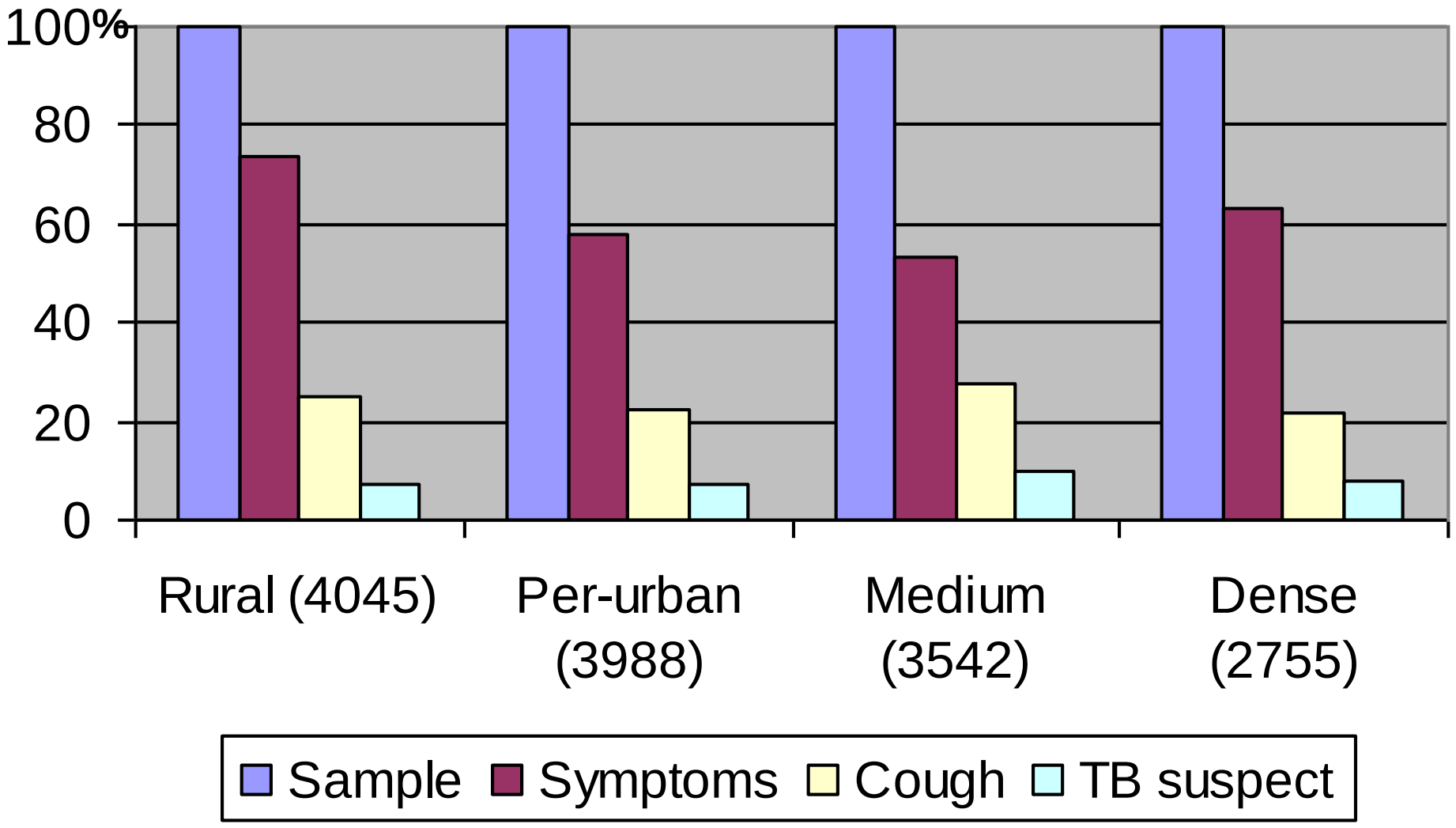
Rural Zambia

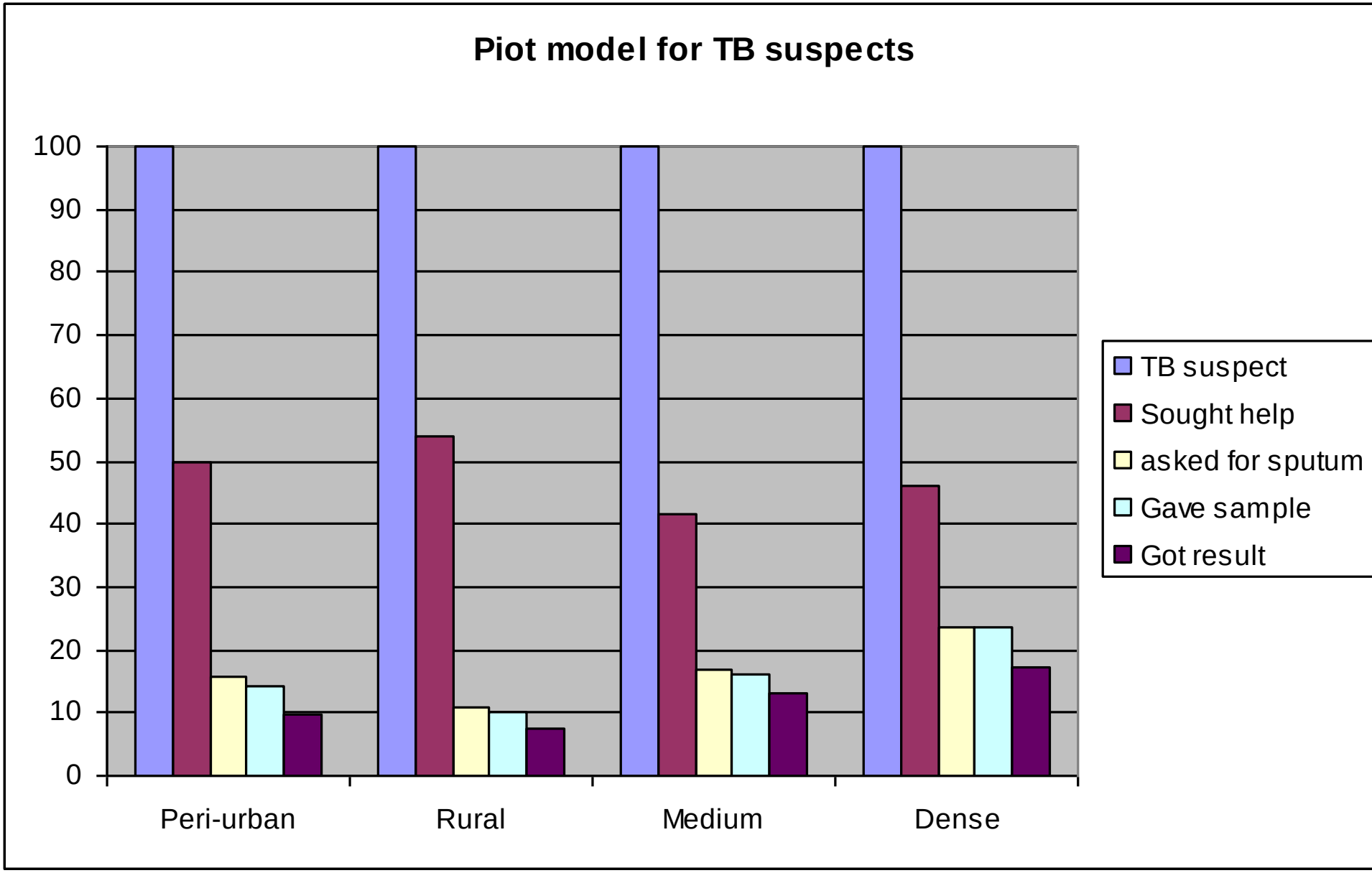
Peri-urban Zambia

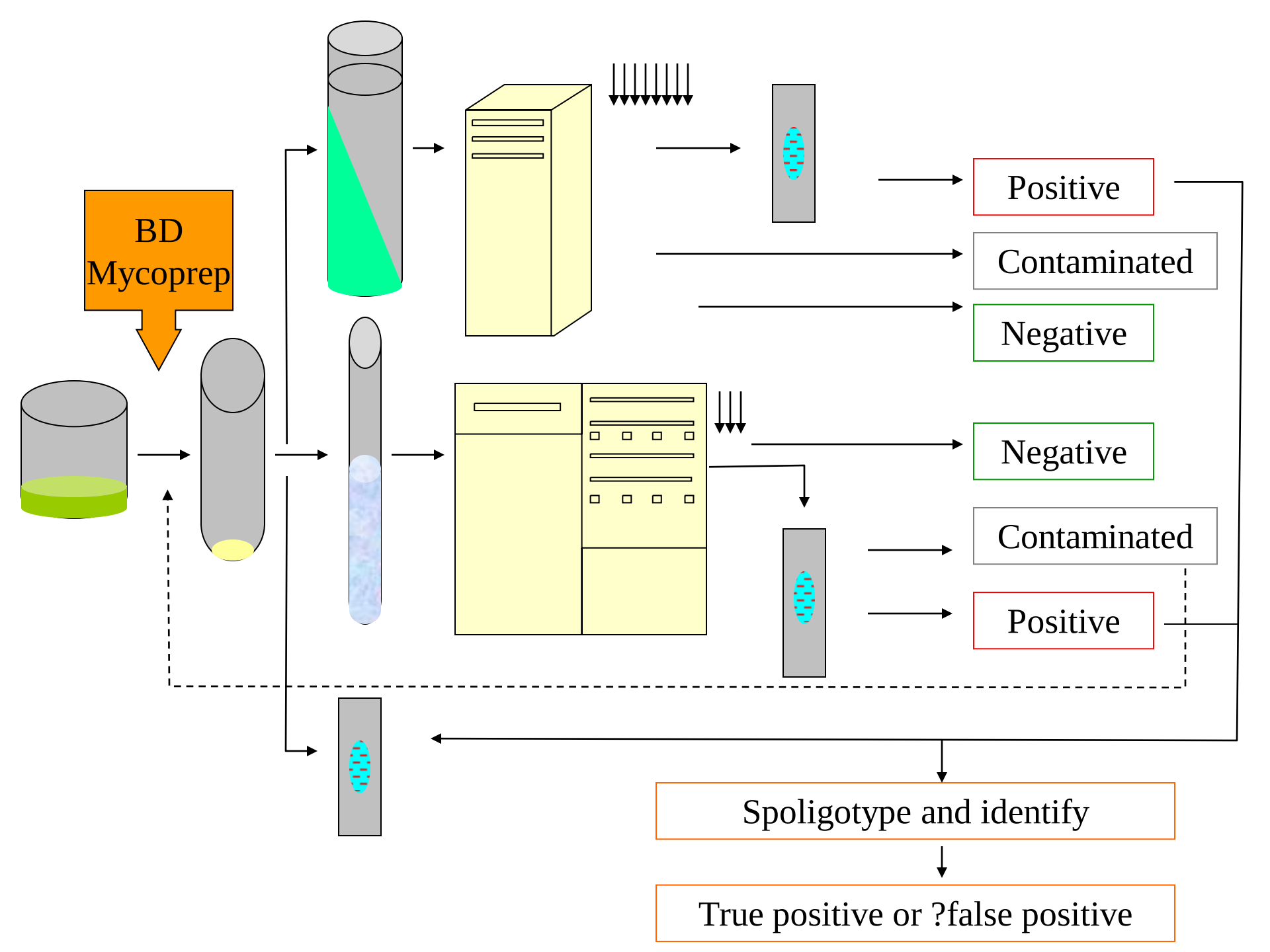
Dense South Africa

Medium South Africa

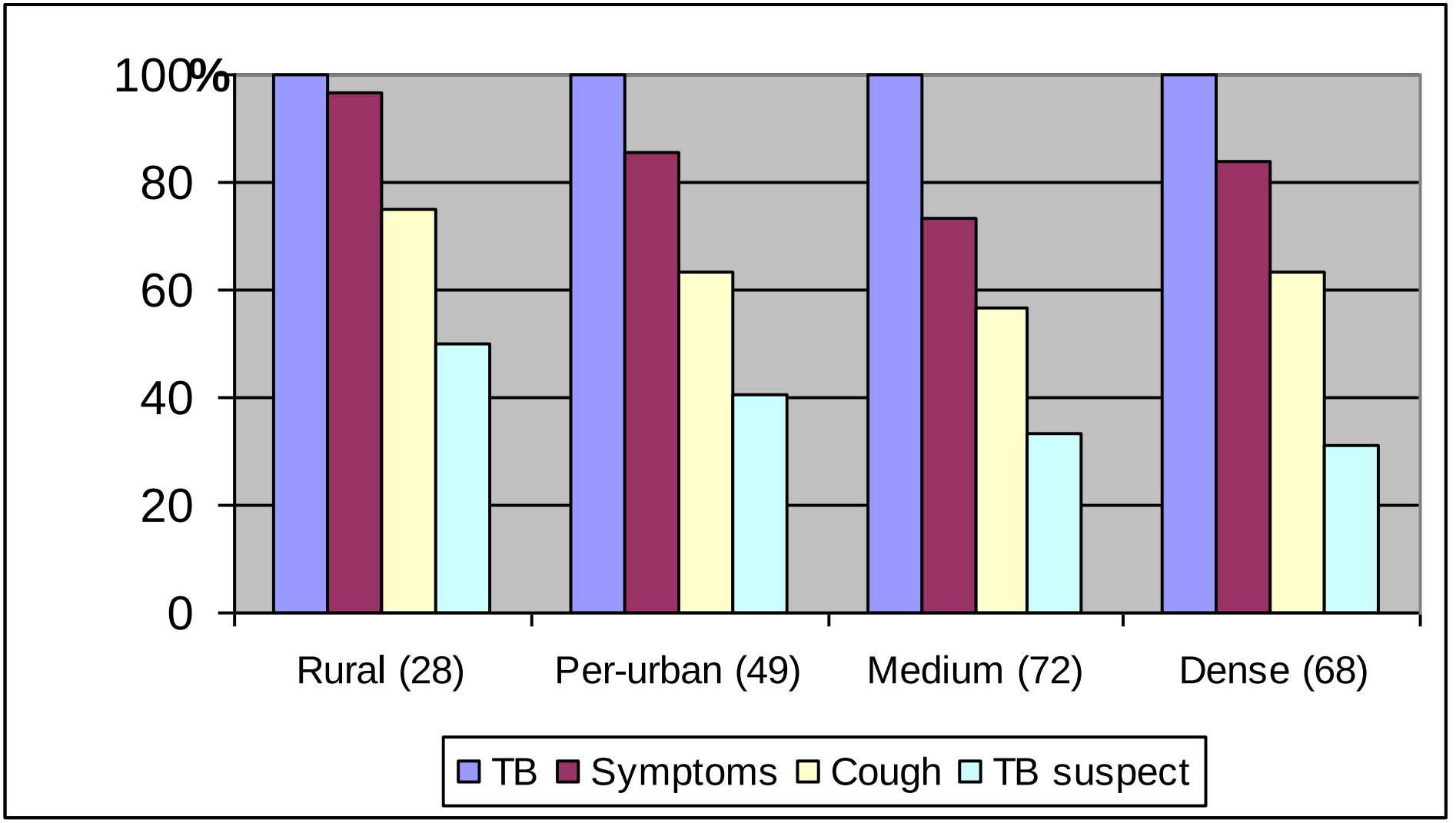
Symptoms by site




Piot model for TB suspects
100
90
80
70
60
50
40
30
20
10
0
Peri-urban
Rural
Medium
Dense
TB suspect
Sought help
asked for sputum
Gave sample
Got result


BD
Mycoprep
Positive
Contaminated
Negative
Negative
Contaminated
Positive
Spoligotype and identify
True positive or ?false positive

Sensitivity of symptoms



Sensitivity and specificity of different screens

Sensitivity	Total	SA	Zambia	HIV-ve	HIV+ve
Number	*14330*	*6297*	*8033*	*5666*	*2297*
Any symptom	82.8	79.1	89.9	83.3	95.3
Any cough	61.7	58.8	67.1	66.7	67.4
Prolonged cough	33.5	28.4	43		
TB suspect	34.8	30.4	43	36.1	48.8
TB suspect or any other 2 symptoms	67.8	64.1	74.7	69.4	79.1

Specificity	Total	SA	Zambia	HIV-ve	HIV+ve
Number	*14330*	*6297*	*8033*	*5666*	*2297*
Any symptom	37.9	42.6	34.1	35.8	29.4
Any cough	76.1	75.5	76.6	77.8	73.1
Prolonged cough	93.4	92.2	94.2		
TB suspect	92.4	91.4	93.1	94	90.7
TB suspect or any other 2 symptoms	62.6	67.5	58.8	61	53

Kevin Cain CROI 2008

				Sensitivity	Specificity
Day	899	Miners 35/44 cult+ve	Cough 2/52	13.6%	88%
			Symptom screen	59.1%	76%
Mohamed	129	Stage 3 or 4 10/11 cult+ve	Cough 2/52	81.8%	79%
			Symptom screen	100.0%	79%
Kimerling	441	Home based care cult +ve	Cough 3/52	65.9%	33%
			Symptom screen	95.1%	10%
Kimerling	496	VCT HIV -ve and +ve, cult +ve	Cough 2/52	58.6%	50%
			Symptom screen	100.0%	27%
Shah	438	Newly diagnosed cult +ve	Cough	43.8%	76%
			Symptom screen	75.0%	57%
Kain	927	Mixed clinical stages Cult +ve	Cough 2/52	28.8%	85%
			Symptom screen	90.9%	34%

Diagnostic tests, screens and the 2I's

- Screen to decide who to give IPT to.
  - Negative predictive value
- Screen to decide who to culture/test
  - Positive predictive value

Screening for IPT

- Negative predictive value – if the screen says that this person doesn't have tuberculosis, how certain are we that he doesn't?
- Yield of screen – what proportion of people who could benefit get through the screen?

How high is a high negative predictive value?

- 98%? 99% ? 99.9%?
- How dangerous is it to start a person (with few enough symptoms to get through the screen) on isoniazid montherapy?
- For each 100 people who start isoniazid, how many cases of HIV-related tuberculosis will be prevented? (? 6 over the next three years – of whom 1 might die and 1 might default/fail treatment in many weak programmes)

Predictive values of different screens

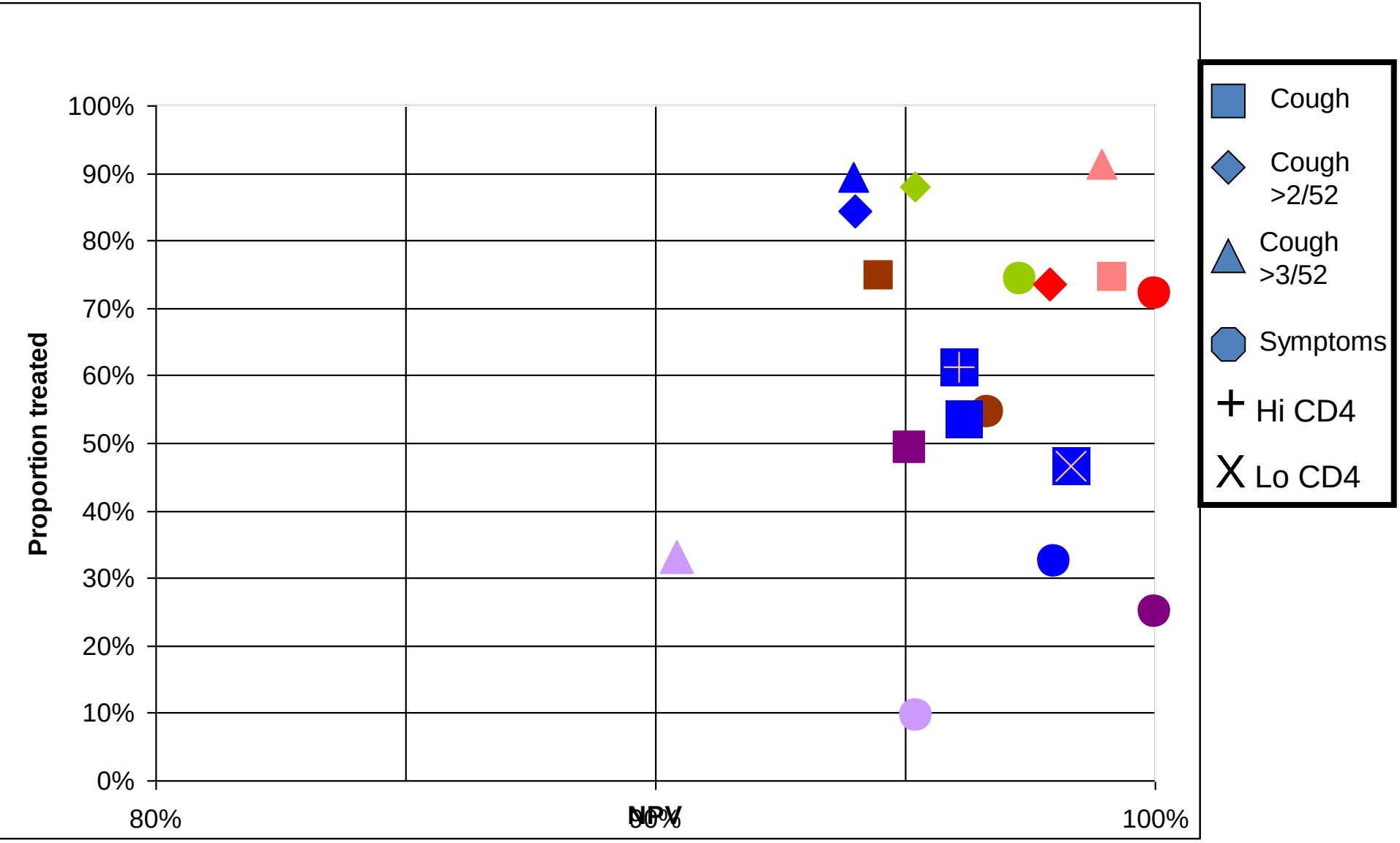
NPV	Total	SA	Zambia	HIV-ve	HIV+ve
Number	*14330*	*6297*	*8033*	*5666*	*2297*
Any symptom	99.3	98.8	99.7	99.7	99.7
Any cough	99.2	98.7	99.6	99.7	99.2
Prolonged cough	98.9	98.2	99.4		
TB suspect	98.9	98.2	99.4	99.6	98.9
TB suspect or any other 2 symptoms	99.2	98.7	99.6	99.7	99.3

PPV	Total	SA	Zambia	HIV-ve	HIV+ve
Number	*14330*	*6297*	*8033*	*5666*	*2297*
Any symptom	2.1	3.2	1.3	0.8	2.5
Any cough	4.0	5.5	2.8	1.9	4.6
Prolonged cough	7.5	8.1	6.9		
TB suspect	6.9	7.9	5.9	3.7	9.1
TB suspect or any other 2 symptoms	2.8	4.5	1.8	1.1	3.1

Kevin Cain CROI 2008 updated

				Sensitivity	Specificity	NPV	Prevalence
Day	899	Miners 35/44 cult+ve	Cough 2/52	13.6%	88%	95.19%	5%
			Symptom screen	59.1%	76%	97.31%	
Mohamed	129	Stage 3 or 4 10/11 cult+ve	Cough 2/52	81.8%	79%	97.89%	9%
			Symptom screen	100.0%	79%	100.00%	
Kimerling	441	Home based care cult +ve	Cough 3/52	65.9%	33%	90.41%	9%
			Symptom screen	95.1%	10%	95.24%	
Kimerling	496	VCT HIV -ve and +ve, cult +ve	Cough 2/52	58.6%	50%	95.10%	6%
			Symptom screen	100.0%	27%	100.00%	
Shah	438	Newly diagnosed cult +ve	Cough	43.8%	76%	94.50%	7%
			Symptom screen	75.0%	57%	96.65%	
Kain	927	Mixed clinical stages Cult +ve	Cough 2/52	28.8%	85%	96.18%	7%
			Symptom screen	90.9%	34%	98.00%	
Ayles	2239	Population based Cult +ve	Cough	66.7%	77.8%	99.16%	2%
			Cough 3/52	36.1%	94%	98.92%	
			Symptom screen	69.4%	61%	99.30%	

To exclude TB we need high NPV and we want as many as possible to benefit from IPT



Sensitivity and specificity of algorithms, stratified by CD4 count (courtesy of Cain CROI 2008)

Algorithm	CD4 < 250				CD4 >250			
	Sens	Spec	NPV	Benefit	Sens	Spec	NPV	Benefit
Day	97	31	98.9%	28.2	70	39	97.7%	38.7
Mohammed	92	51	98.3%	46.7	48	67	97.7%	66.6
Kimerling	92	35	97.5%	32.3	67	54	98.1%	53.4
Shah	95	37	98.5%	33.8	81	47	98.8%	46.2
Pre-IPT	92	51	98.3%	46.7	52	64	97.7%	63.5
Cough/fever /wt. loss	97	27	98.8%	24.6	81	37	98.4%	36.5

Screening for ICF

- How many samples can the laboratory handle?
- What is an acceptable yield of positive diagnoses?

Kevin Cain CROI 2008 updated

				Sensitivity	Specificity	PPV	Prevalence
Day	899	Miners 35/44 cult+ve	Cough 2/52	13.6%	88%	6%	5%
			Symptom screen	59.1%	76%	11%	
Mohamed	129	Stage 3 or 4 10/11 cult+ve	Cough 2/52	81.8%	79%	26%	9%
			Symptom screen	100.0%	79%	31%	
Kimerling	441	Home based care cult +ve	Cough 3/52	65.9%	33%	9%	9%
			Symptom screen	95.1%	10%	10%	
Kimerling	496	VCT HIV -ve and +ve, cult +ve	Cough 2/52	58.6%	50%	7%	6%
			Symptom screen	100.0%	27%	8%	
Shah	438	Newly diagnosed cult +ve	Cough	43.8%	76%	13%	7%
			Symptom screen	75.0%	57%	12%	
Kain	927	Mixed clinical stages Cult +ve	Cough 2/52	28.8%	85%	11%	7%
			Symptom screen	90.9%	34%	10%	
Ayles	2239	Population based Cult +ve	Cough	66.7%	77.8%	5%	2%
			Cough 3/52	36.1%	94%	9%	
			Symptom screen	69.4%	61%	3%	

Conclusions - IPT

- We need consensus on how high NPV needs to be.
- NPV depends on prevalence as much as on sensitivity.
- Simple screens with higher sensitivity (and lower specificity) will allow fewer people to benefit from IPT.
- In the ZAMSTAR community based surveys, absence of cough is probably a good enough screen.
- In more clinical settings, more sensitive screens are needed.
- No screen will have 100% sensitivity, so if prevalence is too high, it may not be possible to reach a high enough NPV to offer IPT without first doing a culture.

Conclusions - ICF

- Laboratory capacity is currently a limiting step
- PPV tells us about relative workload, sensitivity tells us how many cases will be missed.
- 1/PPV is the number needed to culture to confirm one case.
- In ZAMSTAR community surveys, traditional TB suspect (PPV=9%) is probably the only feasible option with current tools, but will still miss more than half the cases.
- In several of the clinical settings, prevalence approaches 9%, so it may be efficient to culture every patient.

Conclusions – if we can't culture everyone in clinical settings, then what?

- Until we have better diagnostic tools, capable of high throughput, speed and accuracy, should we consider treating all HIV-infected people with multi-drug TB therapy, either as presumptive treatment or as preventive therapy?