Clinical Validation of the CAD4TB v7 system for the detection of CXR abnormalities associated with TB:

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Investing In The Future – Impacting Real Lives

PRIME TB Project

PRIME TB

- Sponsored by the WHO STOP TB Partnership
- TBREACH funding mechanism (Wave 8)

Programmatic Aim:
To increase TB case-detection through engagement of private health providers in TB screening and diagnosis

Implementation Research Aim:

To clinically validate a new version of CAD4TB for the Ugandan population.

Stop TB Partnership

Introduction

- CXR has historically been one of the primary tools for diagnosing PTB.
- In the 1950-60s, developed countries held large scale screening campaigns using mobile Xray units to detect and treat patients with active TB disease.
- Mass screening campaigns were successful at detecting a large pool of prevalent TB cases, and resulted in significant reductions in TB burden
- However, these campaigns were expensive and once the burden of TB was significantly reduced, were abandoned in favour of symptom screening.
- Currently used only for selected places e.g. immigration centers

Introduction

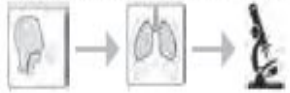
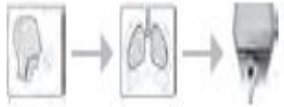
- In developing countries with high TB burdens, mass screening with CXR was too expensive and logistically challenging to implement.
- Moreover, CXR although highly sensitive has poor specificity and diverse intra- and inter-reader variability.
- Thus, the policy for TB screening in these countries is based on symptom screening combined with sputum microscopy/Xpert testing to establish a diagnosis.
- CXR was until recently, only recommended as a diagnostic tool to be used as part of clinical diagnosis for sputum negative TB.

Introduction

However, the pendulum is swinging back in favour of CXR for TB screening for a number of reasons

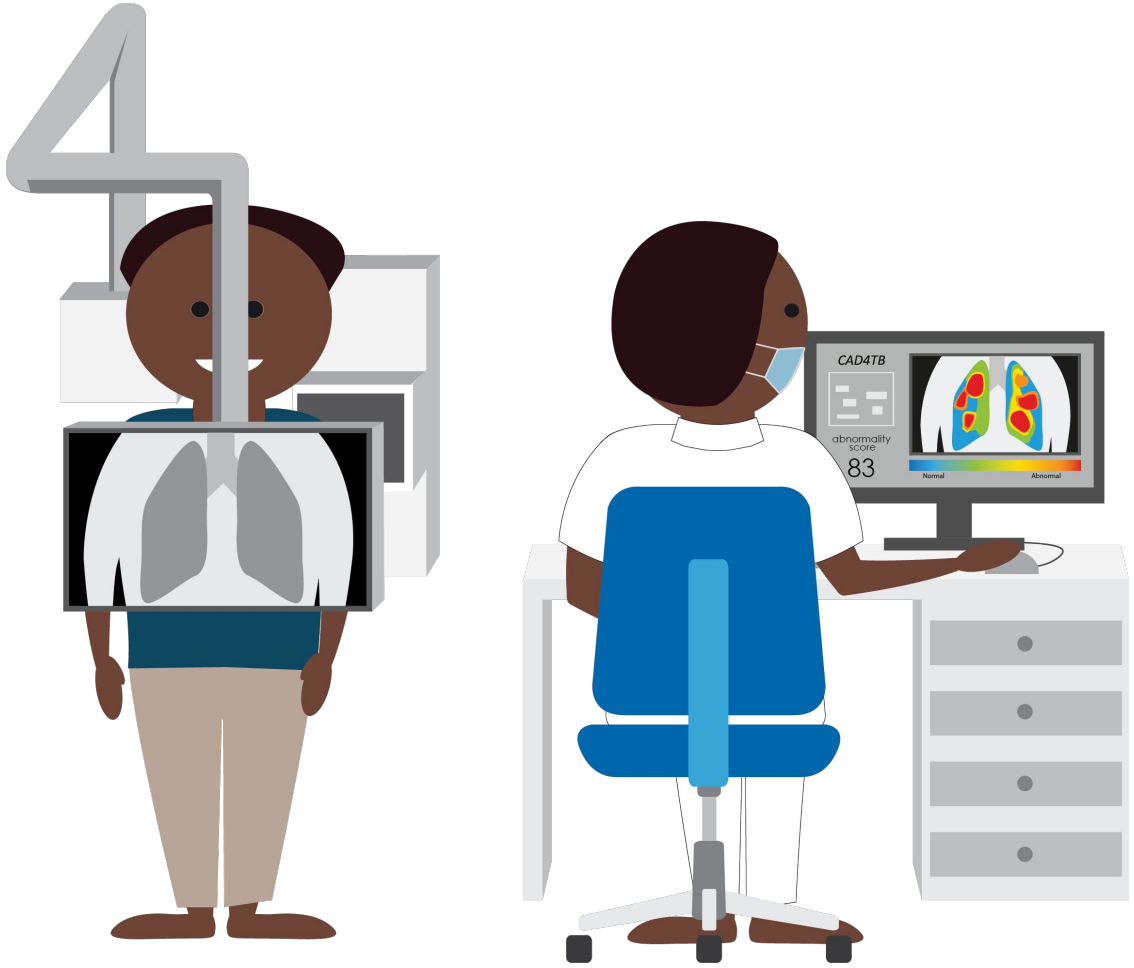
- Several prevalence surveys demonstrated that a significant proportion of TB cases are asymptomatic, but detectable through CXR.
- Global priorities shifted from finding the most infectious cases to early diagnosis of all TB cases (the END TB Strategy).
- Advancements in digital radiography have led to reduced costs, better image quality, lower radiation dosage, and digital image transfer for telemedicine.
- Innovations have led to the development of computer-aided detection (CAD) software programs which can standardize the interpretation of CXRs reducing inter-reader variability and error.

Considerations for use of CXR in TB screening

Triage algorithm	Cost per true case detected / Yield of true-positive results / Yield of false-positive results
1. Cough followed by microscopy 	$ / + / + +
2. Cough followed by CXR followed by microscopy 	$ $ / + / +
3. Any TB symptom followed by microscopy 	$ $ / + + + / + + + + +
4. Any TB symptom followed by CXR followed by microscopy 	$ $ $ / + + + / +
5. CXR followed by microscopy 	$ $ $ $ $ / + + + / + + + +
6. Cough followed by Xpert MTB/RIF testing 	$ $ / + + / +
7. Cough followed by CXR followed by Xpert MTB/RIF testing 	$ $ / + + / +
8. Any TB symptom followed by Xpert MTB/RIF testing 	$ $ $ $ / + + + + / + + +
9. Any TB symptom followed by CXR, followed by Xpert MTB/RIF testing 	$ $ $ / + + + + / + +
10. CXR followed by Xpert MTB/RIF testing 	$ $ $ $ $ / + + + + + / + + +

CXR: chest X-ray.

Computer Aided Detection



Computer aided detection (CAD) systems detect three categories of radiographic abnormalities compatible with TB:

- textural abnormalities - diffuse changes in the lung parenchyma;
- shape abnormalities- changes in the boundaries of the lung and
- focal abnormalities- well-defined local lesions e.g. cavities.

Abnormality scores in each category are combined to produce an overall score for the presence/absence of active TB diseas

Score range is **0-100.** Higher scores signify greater likelihood of TB.

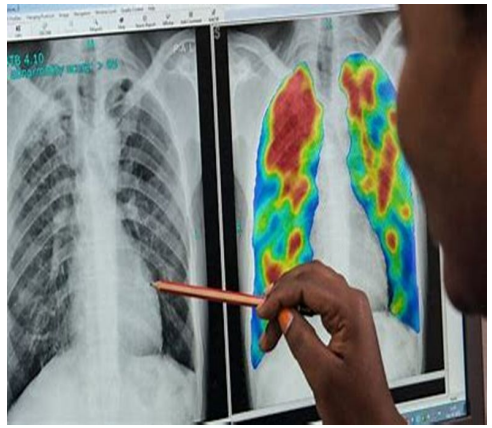
Study Objective

Why CAD Calibration?

- TB Pathophysiology leads to a large diversity of pathologic changes in the lungs which vary with age, co-infection with HIV and severity of TB disease.
- This leads to different patterns of abnormalities across populations.
- Adequate utilisation of the CAD4TB system therefore requires adaptation of abnormality scores to individual populations with their own specific characteristics.
- CAD Calibration before use in a specific setting is essential to ensure the accuracy, predictive values, overall yield, and requirements for further diagnostic testing are as expected.
- Individuals recruited into the calibration study/studies must be representative of the population in which CAD will be implemented.

Study Objective

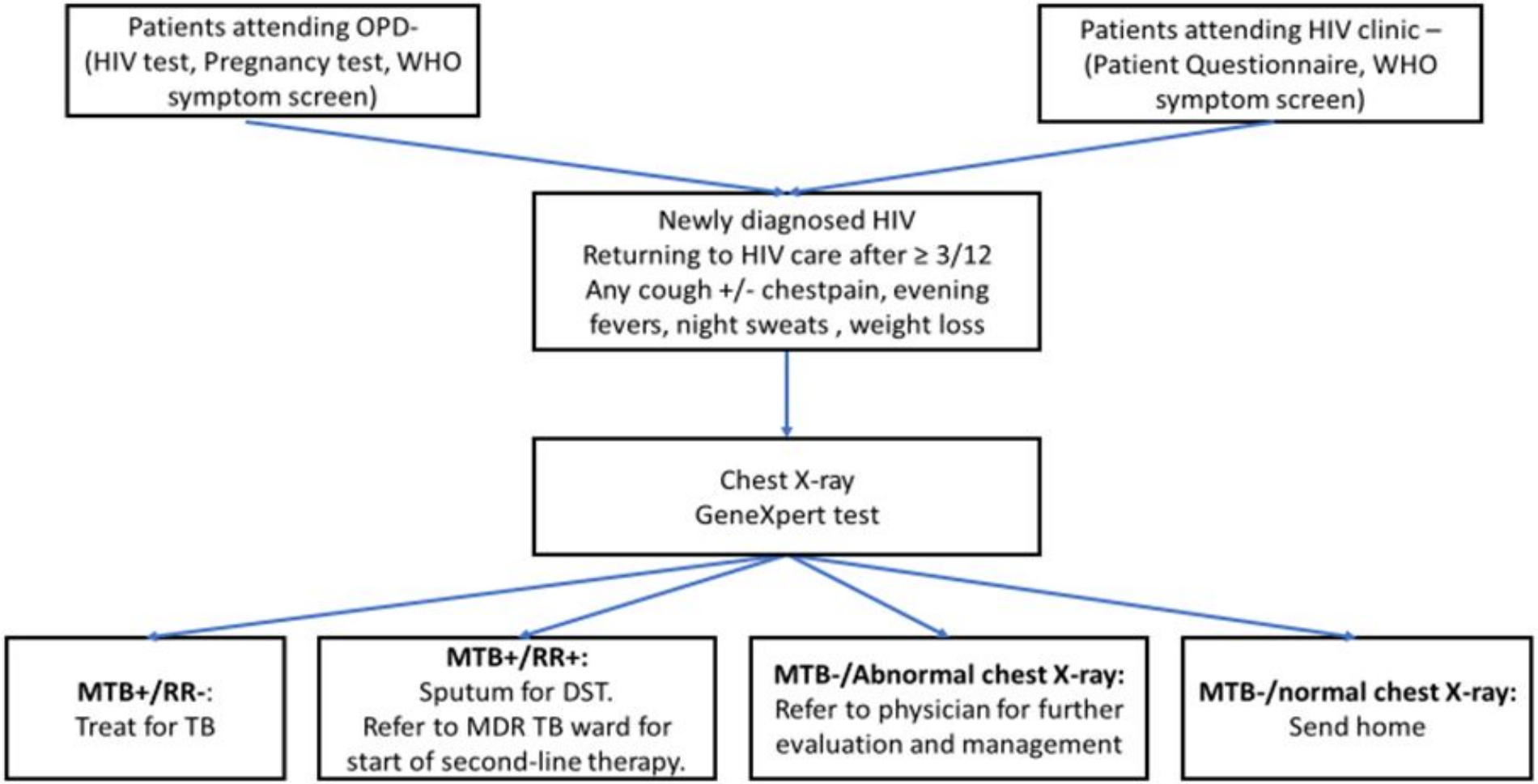
- To determine the sensitivity and specificity of different CAD4TB v7 scores for the detection of bacteriologically confirmed tuberculosis (using Xpert MTB/RIF as the current standard) in the Ugandan population.
- To determine the ideal threshold score to be used for the diagnosis of TB in the Ugandan population



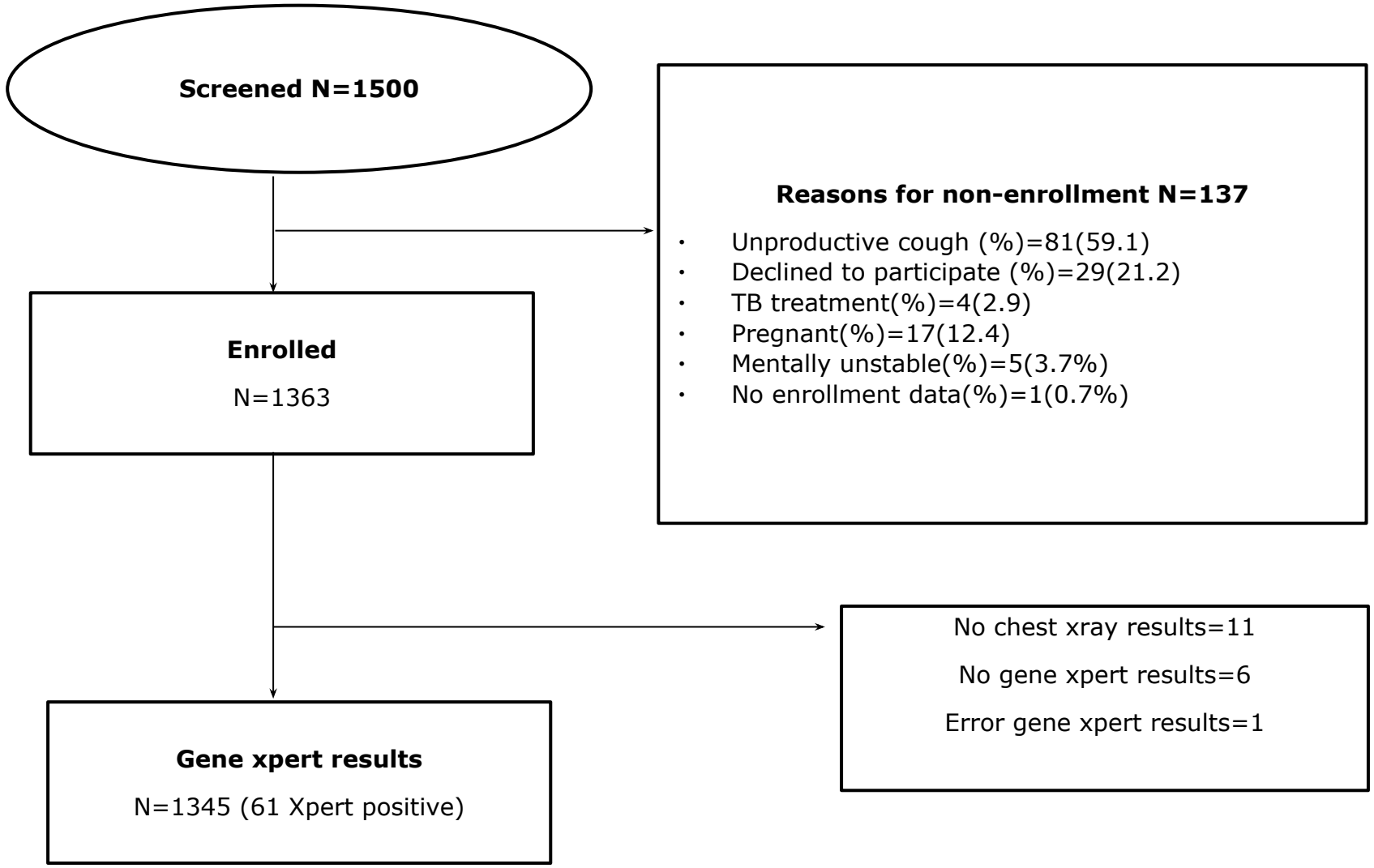
Study Participants

Study Population	Patients ≥15 years presenting to the outpatient department and HIV clinics at the two hospitals
Inclusion Criteria	**HIV+ve patients:** ▪ All patients newly diagnosed with HIV. ▪ All patients returning to HIV care after being lost to follow-up for three months or more. ▪ Patients coming for ART refill visits with cough of any duration. **HIV -ve patients:** ▪ Patients with cough of any duration plus one or more signs and symptoms of TB
Exclusion Criteria	▪ Patients who are unable to provide informed consent ▪ Patients already on TB treatment ▪ Female patients who were pregnant

Patient Flow Chart



Study Results



Results : Patient Characteristics

Characteristic	Overall n=1344†(%)	HIV + N=621(%)	HIV – N=723(%)	P-value
Gender				
Male	449(33.4)	215(34.6)	234(32.4)	0.38
Female	895(66.6)	406(65.4)	489(67.6)	
Age median (iqr)	42(30,52)	40(33,50)	41(27,56)	0.81
Age group† (n=1339)				
15-24 years	196 (14.6)	57(9.2)	139(19.3)	<0.01
25-34 years	257(19.2)	123(19.9)	134(18.6)	
35-44 years	333(24.9)	203(32.9)	130(18.0)	
45-54 years	267(19.9)	139(22.5)	128(17.7)	
>55 years	286(21.4)	95(15.4)	191(26.5)	
BMI mean (sd) (n=945)	22(5)	22(5)	22(5)	0.06
Occupation† (n=1341)				
Student	92(7.0)	14(2.3)	78(10.8)	<0.01
Subsistence Farming	957(71.4)	459(74.2)	498(69.0)	
Informal employment	217(16.2)	118(19.1)	99(13.7)	
Formal employment	75(5.6)	28(4.5)	47(6.5)	

Results: Patient Characteristics

Characteristic	Overall n=1344†	Positive N=621	Negative N=723	P-value
Previous TB history†(n=1339)				
Yes	159(11.9)	97(15.7)	61(8.5)	<0.01
	20(4.6)	18(6.8)	2(1.2)	
	429(95.6)	250(93.3)	179(98.9)	
	893(66.4)	352(56.7)	541(74.8)	<0.01
Concomitant illness				
Diabetes	18(1.3)	6(1.0)	12(1.7)	0.27
Hypertension	73(5.4)	15(2.4)	58(8.0)	<0.01
Alcohol intake (n=1343)				
Yes	291(21.7)	135(21.8)	156(21.6)	0.93
Tobacco use(n=1342)				
Yes	98(7.0)	49(7.9)	49(6.8)	0.43

Results : Patient Characteristics (Xpert positives)

Characteristic	Overall n=1344†(%)	HIV + N=621(%)	HIV – N=723(%)	P-value
Gender				
Male	48(80.0)	21(80.8)	27(79.4)	0.89
Age median (iqr)	42(32,58)	37(31,50)	45(35,62)	0.36
Age group				
15-24 years	5 (8.3)	1(3.9)	4(11.8)	
25-34 years	12(20.0)	8(30.8)	4(11.8)	
35-44 years	17(28.3)	8(30.8)	9(26.5)	
45-54 years	8(13.3)	3(11.5)	5(14.7)	
>55 years	18(30.0)	6(23.1)	12(30.0)	0.32
BMI mean (sd)	19(4)	20(4)	19(4)	0.19
Occupation				
Subsistence farming				
Informal employment	42(70.0)	17(65.4)	25(73.5)	
Formal employment	11(18.3)	7(26.9)	4(11.8)	
Student	3(5.0)	2(7.7)	1(2.9)	
	4(6.7)	0(0.0)	4*11.8)	0.13
Previous TB history				
Yes	15(25.0)	7(27.9)	8(23.4)	0.77

Results: Patient Characteristics (Xpert positives)

Characteristic	Overall n=1344†	Positive N=621	Negative N=723	P-value
	5(8.3) 55(91.7)	3(11.5) 23(88.4)	2(5.9) 32(94.1)	0.43
Alcohol intake Yes	25(41.7)	11(42.3)	14(42.3)	0.93
Tobacco use Yes	13(21.7)	8(30.8)	5(14.7)	0.43
Other Substance use **Yes**	2(3.3)	1(3.9)	1(2.9)	0.54
CAD4TB AI prediction score Median(iqr)	74(59,90)	73(48,88)	75(69,91)	0.14
ART Yes Newly diagnosed Missing		21(32.4) 3(11.5) 2(7.7)		
CD4 Count median(iqr)		264(46,496)		

CAD4TB scores by HIV status and TB status

CAD4TB score	HIV+ ve N=39		HIV-ve N=59	
	MTB+ n=26	MTB- n=13	MTB+ n=34	MTB- n=25
≥0	0	0	1	0
≥5	1	0	0	0
≥10	2	0	0	0
≥15	3	0	0	1
≥20	0	1	1	0
≥25	0	1	0	0
≥30	0	0	1	0
≥35	0	0	0	1
≥40	0	0	1	2
≥45	2	0	0	2
≥50	0	1	1	0
≥55	0	0	0	2
≥57	0	0	1	0
≥60	1	0	0	1
≥65	1	2	1	5
≥70	6	4	8	6
≥75	1	1	1	2
≥80	2	2	1	2
≥85	1	1	2	0
≥90	4	1	5	2
≥95	1	0	4	0

CAD4TB scores : Overall

Criterion	Sensitivity	95% CI	Specificity	95% CI	#above cut off point	# TB cases diagnosed	Proportion of TB cases diagnosed	Xpert positivity rate	# Xpert tests saved.
≥0	100	94.1 - 100.0	0	0.0 - 0.3	1345	61	100	4.5	0
>5	96.7	88.7 - 99.6	51.0	48.2 - 53.7	720	59	96.7	8.2	625
>10	96.7	88.7 - 99.6	65.2	62.5 - 67.8	521	59	96.7	11.3	824
>15	93.4	84.1 - 98.2	70.9	68.4 - 73.4	436	57	93.4	13.1	909
>20	86.9	75.8 - 94.2	75.4	72.9 - 77.7	372	53	86.9	14.2	973
>25	85.3	73.8 - 93.0	78.3	75.9 - 80.5	341	52	85.2	15.2	1004
>30	85.3	73.8 - 93.0	82.8	80.6 - 84.8	277	52	85.2	18.8	1068
>35	83.6	71.9 - 91.8	85.2	83.1 - 87.1	247	51	83.6	20.6	1098
>40	83.6	71.9 - 91.8	87.9	86.0 - 89.7	212	51	83.6	24.1	1133
>45	82.0	70.0 - 90.6	89.7	87.9 - 91.3	186	50	81.9	26.9	1159
>50	78.7	66.3 - 88.1	91.9	90.3 - 93.3	156	48	78.7	30.8	1189
>55	77.1	64.5 - 86.8	93.0	91.4 - 94.3	140	47	77	33.6	1205
>60	75.4	62.7 - 85.5	93.9	92.5 - 95.2	125	46	75.4	36.8	1220
>65	73.8	60.9 - 84.2	95.2	93.8 - 96.3	111	45	73.8	40.5	1234
>70	62.3	49.0 - 74.4	97.1	96.0 - 98.0	81	40	65.6	49.4	1264
>75	44.3	31.5 - 57.6	98.8	98.0 - 99.3	46	27	44.3	58.7	1299
>80	41.0	28.6 - 54.3	99.1	98.4 - 99.5	38	25	40.9	65.8	1307
>87	36.1	24.2 - 49.4	99.5	99.0 - 99.8	31	23	37.7	74.2	1314
>90	24.6	14.5 - 37.3	99.5	99.0 - 99.8	25	18	29.5	72.0	1320
>95	8.2	2.7 - 18.1	99.9	99.6 - 100.0	8	6	9.8	75.0	1337
>98	0	0.0 - 5.9	100	99.7 - 100.0	1	0	0		1344

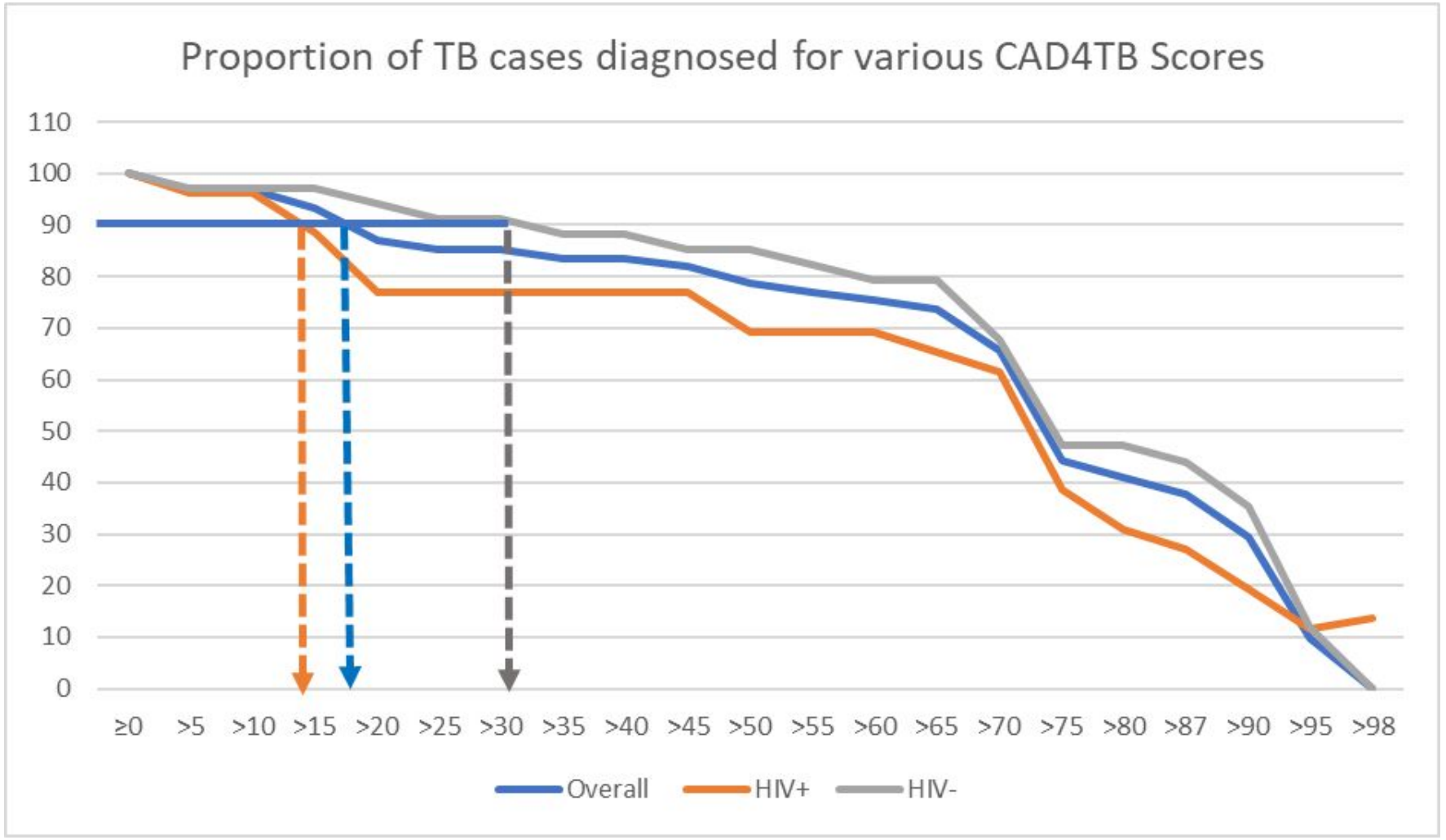
CAD4TB scores: HIV+

Criterion	Sensitivity	95% CI	Specificity	95% CI	# above cutoff point	# of TB cases diagnosed	Proportion of TB cases diagnosed	Xpert positivity rate	# Xpert tests saved
≥0	100	86.8 - 100.0	0	0.0 - 0.6	621	26	100	4.2	0
>5	96.2	80.4 - 99.9	47.9	43.8 - 52.0	352	25	96.2	7.1	269
>10	96.2	80.4 - 99.9	62.2	58.2 - 66.1	257	25	96.2	9.7	364
>15	88.5	69.8 - 97.6	68.7	64.8 - 72.4	210	23	88.4	11.0	411
>20	76.9	56.4 - 91.0	73.8	70.1 - 77.3	177	20	76.9	11.3	444
>25	76.9	56.4 - 91.0	77.3	73.7 - 80.6	158	20	76.9	12.7	463
>30	76.9	56.4 - 91.0	82.2	78.9 - 85.2	128	20	76.9	15.6	493
>35	76.9	56.4 - 91.0	84.9	81.7 - 87.7	111	20	76.9	18.0	510
>40	76.9	56.4 - 91.0	87.6	84.6 - 90.1	95	20	76.9	21.1	526
>45	76.9	56.4 - 91.0	89.2	86.5 - 91.6	86	20	76.9	23.3	535
>50	69.2	48.2 - 85.7	90.9	88.3 - 93.1	73	18	69.2	24.7	548
>55	69.2	48.2 - 85.7	92.8	90.4 - 94.7	63	18	69.2	28.6	558
>61	65.4	44.3 - 82.8	93.5	91.1 - 95.3	57	18	69.2	31.6	564
>65	65.4	44.3 - 82.8	95.1	93.1 - 96.7	49	17	65.4	34.7	572
>70	57.7	36.9 - 76.6	96.6	94.9 - 97.9	37	16	61.5	43.2	584
>75	38.5	20.2 - 59.4	98.7	97.4 - 99.4	18	10	38.5	55.6	603
>80	30.8	14.3 - 51.8	98.7	97.4 - 99.4	16	8	30.8	50.0	605
>87	26.9	11.6 - 47.8	99.5	98.5 - 99.9	11	7	26.9	63.6	610
>91	11.5	2.4 - 30.2	99.7	98.8 - 100.0	7	5	19.2	71.4	614
>94	3.9	0.10 - 19.6	100	99.4 - 100.0	3	3	11.5	100.0	618
>97	0.0	0.0 - 13.2	100	99.4 - 100.0	1	1	13.8	100.0	620

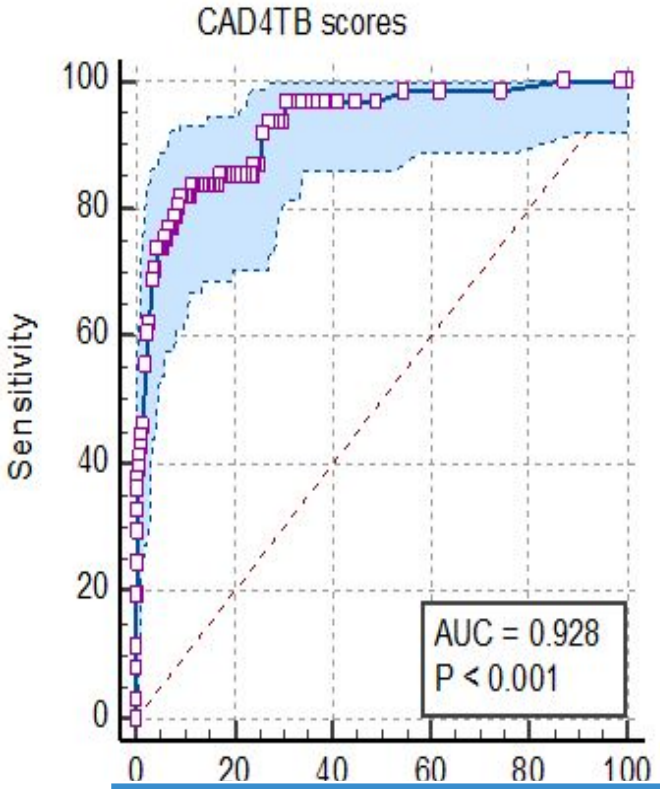
CAD4TB scores: HIV-

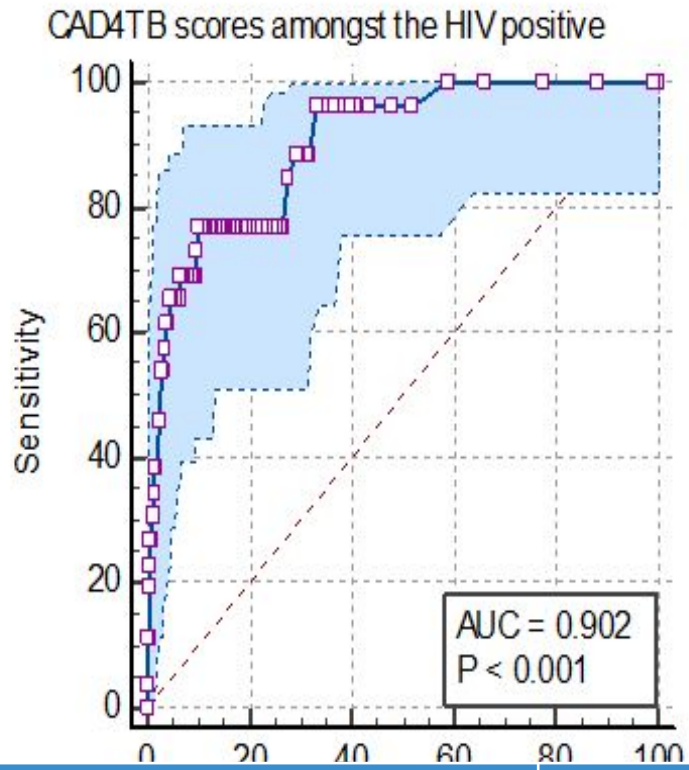
Criterion	Sensitivity	95% CI	Specificity	95% CI	# above cutoff point	# TB cases diagnosed	Proportion of TB cases diagnosed	Xpert positivity rate	Number of Xpert tests saved.
≥0	100.0	89.7 - 100.0	0.0	0.0 - 0.5	723	34	100	4.7	0
>5	97.1	84.7 - 99.9	53.6	49.8 - 57.4	367	33	97	9.0	356
>10	97.1	84.7 - 99.9	67.7	64.1 - 71.2	263	33	97.1	12.5	460
>15	97.1	84.7 - 99.9	72.8	69.3 - 76.1	225	33	97.1	14.7	498
>20	94.1	80.3 - 99.3	76.7	73.4 - 79.9	194	32	94.1	16.5	529
>25	91.2	76.3 - 98.1	79.1	75.8 - 82.1	182	31	91.2	17.0	541
>30	91.2	76.3 - 98.1	83.3	80.3 - 86.0	148	31	91.2	20.9	575
>35	88.2	72.5 - 96.7	85.5	82.6 - 88.0	135	30	88.2	22.2	588
>40	88.2	72.5 - 96.7	88.2	85.6 - 90.5	116	30	88.2	25.9	607
>45	85.3	68.9 - 95.0	90.1	87.6 - 92.2	99	29	85.3	29.3	624
>50	85.3	68.9 - 95.0	92.7	90.5 - 94.6	82	29	85.3	35.4	641
>55	82.4	65.5 - 93.2	93.2	91.0 - 94.9	76	28	82.4	36.8	647
>60	79.4	62.1 - 91.3	94.3	92.3 - 95.9	67	27	79.4	40.3	656
>65	79.4	62.1 - 91.3	95.2	93.3 - 96.7	61	27	79.4	44.3	662
>70	64.7	46.5 - 80.3	97.5	96.1 - 98.6	43	23	67.6	53.5	680
>75	47.1	29.8 - 64.9	98.8	97.7 - 99.5	27	16	47.1	59.3	696
>80	47.1	29.8 - 64.9	99.4	98.5 - 99.8	21	16	47.1	76.2	702
>87	41.2	24.6 - 59.3	99.6	98.7 - 99.9	19	15	44.1	78.9	704
>90	26.5	12.9 - 44.4	99.6	98.7 - 99.9	16	12	35.3	75.0	707
>95	8.8	1.9 - 23.7	99.9	99.2 - 100.0	6	4	11.8	66.7	717
>98	0.0	0.0 - 10.3	100	99.5 - 100.0	1	0	0	0.0	722

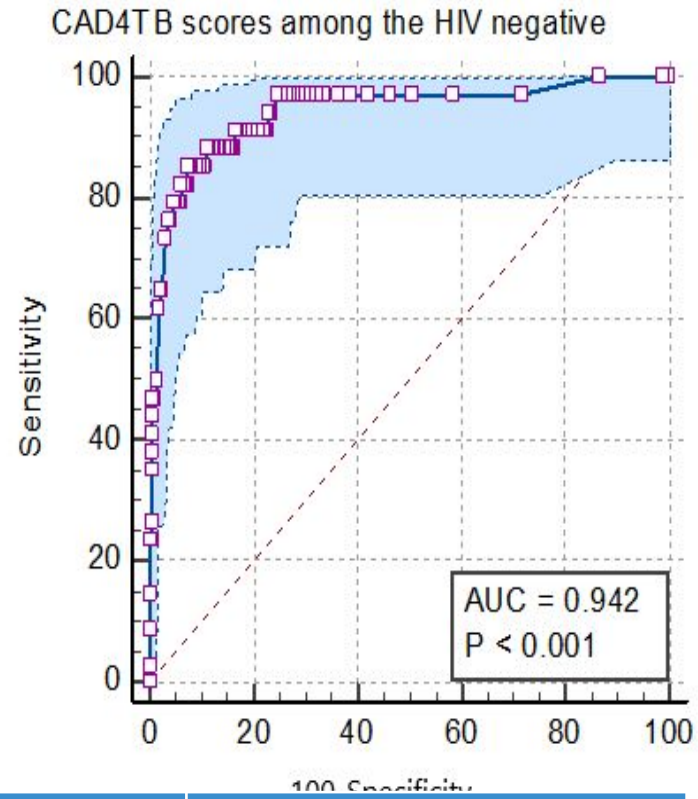
WHO Criteria for Diagnostics (90% Sens)



Diagnostic Accuracy of CAD4TB

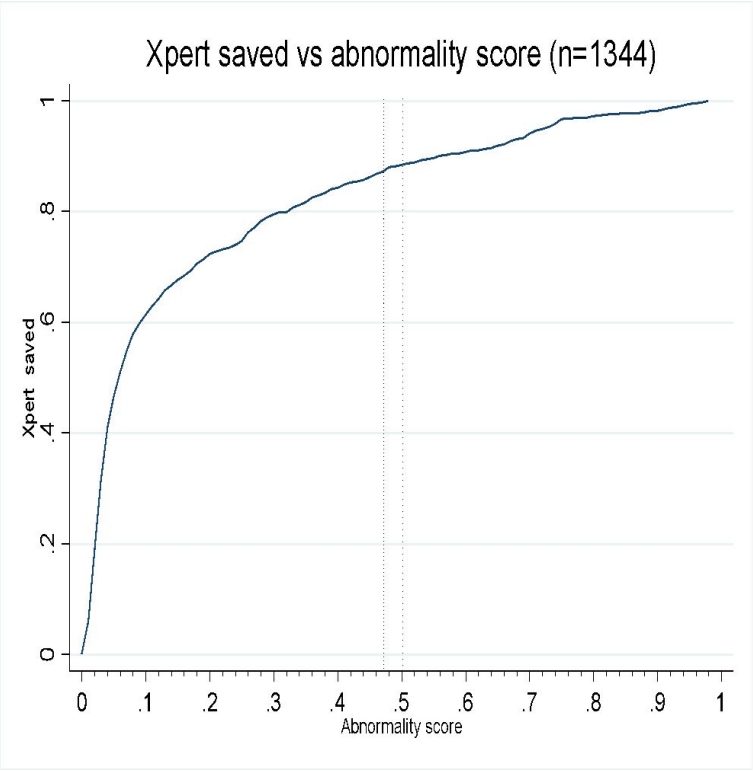


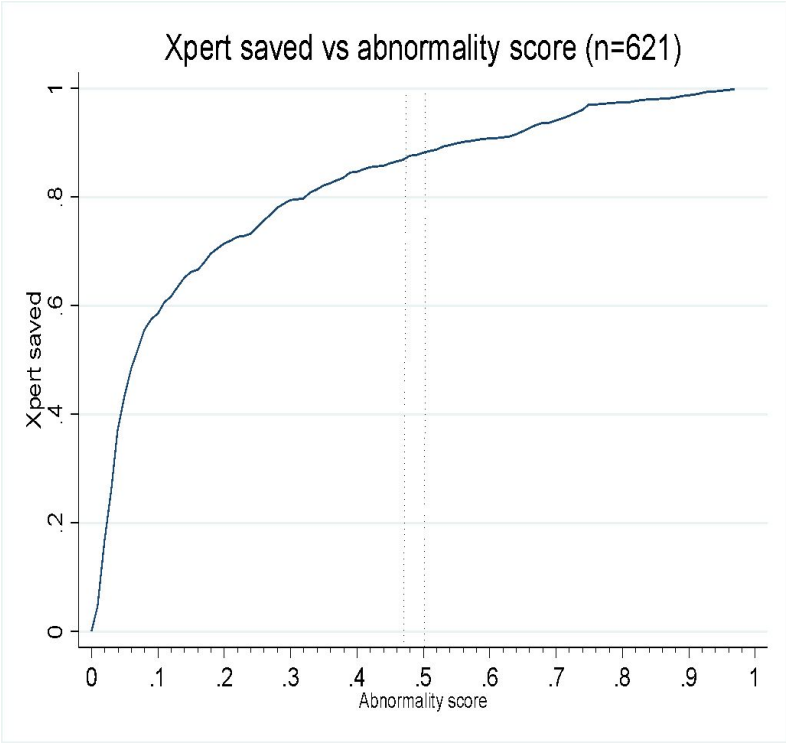




	Overall (Value CI)	HIV positive (Value CI)	HIV Negative (Value CI)
Youden index	0.73(0.63-0.81)	0.67(0.52-0.78)	0.78(0.64-0.86)
Associated threshold score	>47 (>13 - >60)	>47 (>13 - >66)	>50 (>18 - >68)
Associated sensitivity	81.97(70.0 - 90.6)	76.92(56.4 – 91.0)	85.29(68.9– 95.0)
Associated specificity	91.04(89.3-92.5)	90.08(87.4-92.4)	92.73(90.5-94.6)

Number of Xpert tests saved





Using a threshold score of 47% saves about 80% of all GeneXpert tests.

Considerations during threshold score selection.

CAD calibration analysis should be carefully interpreted in the context of the intended TB screening program.

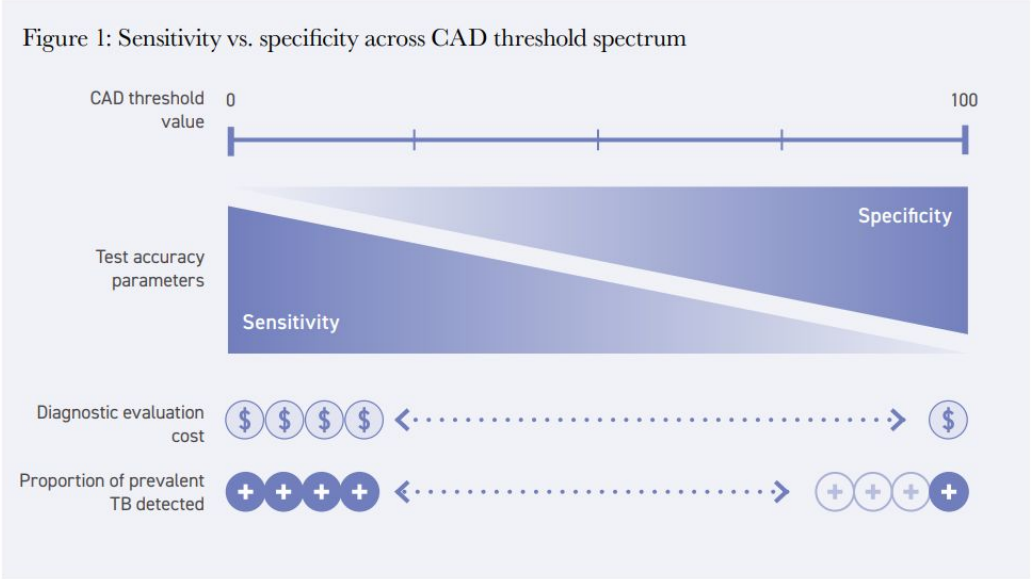
Considerations for the most appropriate CAD threshold include:

- The prevalence of TB and of other relevant comorbidities in the population CAD is going to be used.
- Where CAD will be placed in the screening algorithm

- The goal of CAD use e.g.

a) If CAD is being used to maximize case detection. In this case it should be used as an early screening tool

b) If CAD is used to improve efficiency of a triage system? In this case, CAD should be preceded by earlier screening steps e.g. symptom screen.



- Finally, costs of over and under diagnosis at different CAD threshold scores should be calculated and taken into consideration when determining an appropriate threshold.

Implications

- Uganda uses about 700,000 Xpert tests annually
- Adding CXR with CAD4TB to the screening algorithm could significantly reduce the no. of Xpert tests needed with minimal reduction in the no. of TB cases diagnosed
- Follow on benefits may include

a) reduced sputum results TAT,
b) reductions in pretreatment LFU and ultimately
c) reduction in mortality

- However, this has to be balanced against the cost of CAD, CXR maintenance and personnel to operate the CXR

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THE REPUBLIC OF UGANDA
MINISTRY OF HEALTH

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Thank you for listening.

For further questions or comments, please contact:
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