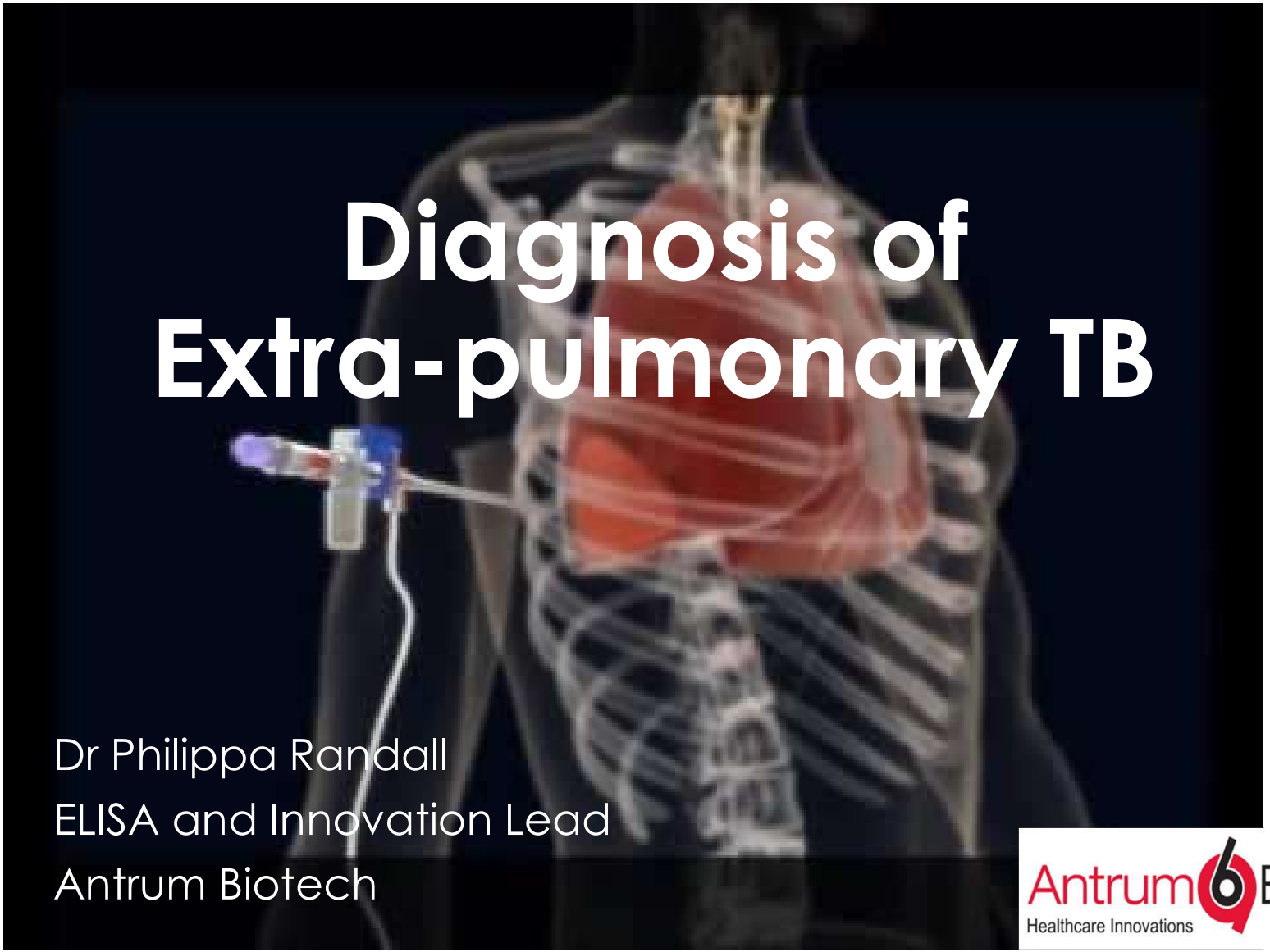

Diagnosis of Extra-pulmonary TB

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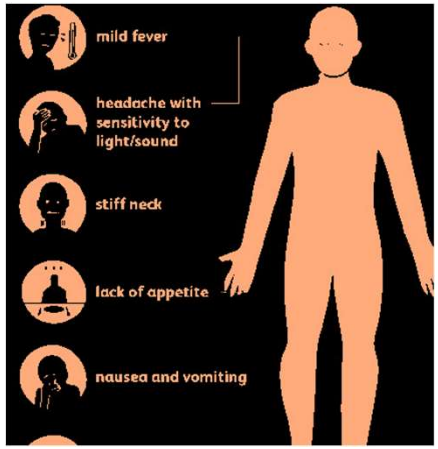
Healthcare Innovations

BACKGROUND

- **~10 million** new TB cases per annum (WHO, 2018)
- In South Africa TB is the **no.1 leading cause of death**
- 73% of adult TB cases are HIV co-infected (SA DoH)
- Sputum scarce (25%), smear negative (50%) and **extra-pulmonary disease (25%)** (Peter & Dheda, Lancet Resp. Dis., 2014)

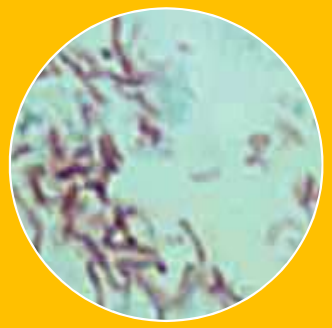
WHAT IS EXTRA-PULMONARY TB

~1,5 million
TB cases **extra-pulmonary (EPTB)**
(occurs outside of the lung)



- **TB serositis**
  - **Pleural**
  - **Pericardial**
  - **Peritoneal**
- **TB meningitis**

CURRENT DIAGNOSTIC LANDSCAPE



Culture:
50% sensitive
and
95% specific

Smear:
5% sensitive and
95% specific

ADA: 80 – 85%
sensitive and
60 – 85% specific

Variable cut-offs

Xpert Ultra/
MTB RIF:
30 – 70%
sensitive and
95% specific

Available diagnostics work poorly and

DO NOT solve the problem

AN URGENT NEED

- Both a sensitive and specific diagnostic
- Effective across all EPTB sub-types
- Not bacilli or nucleic acid dependent

One such biomarker is unstimulated IFNγ

THE CASE FOR IFNγ

	Sensitivity	Specificity
Pleural TB	94.8	98%
Pericardial TB	95.7%	96%
TB peritonitis	97%	97%
TB meningitis	92%	100%

Eur Respir J 2009; 34: 1118–1126
DOI: 10.1183/09031936.00005309

Utility of quantitative T-cell responses *versus* unstimulated interferon-γ for the diagnosis of pleural tuberculosis

K. Dheda*,#,*, R.N. van Zyl-Smit*, L.A. Sechi+, M. Badri*, R. Meldau*, S. Meldau*, G. Symons*, P.L. Semple*, A. Maredza*, R. Dawson*, H. Wainwright§, A. Whitelaw/, Y. Vallie*, P. Raubenheimer*, E.D. Bateman* and A. Zumla*

Comparison of same day diagnostic tools including Gene Xpert and unstimulated IFN-γ for the evaluation of pleural tuberculosis: a prospective cohort study

Richard Meldau[1], Jonny Peter[1], Grant Theron[1], Greg Calligaro[1], Brian Allwood[1], Greg Symons[1], Hoosain Khalfey[1], Gina Ntombenhle[1], Ureshnie Govender[1], Anke Binder[1], Richard van Zyl-Smit[1] and Keertan Dheda[1,2*]

RESEARCH ARTICLE Open Access

Diagnostic accuracy of quantitative PCR (Xpert MTB/RIF) for tuberculous pericarditis compared to adenosine deaminase and unstimulated interferon-γ in a high burden setting: a prospective study

Shaheen Pandie[1†], Jonathan G Peter[2,3†], Zita S Kerbelker[1], Richard Meldau[2], Grant Theron[2], Ureshnie Govender[2], Mpiko Ntsekhe[1], Keertan Dheda[2,4†] and Bongani M Mayosi[1,4*†]

Diagnostic Accuracy of Ascitic Fluid IFN-γ and Adenosine Deaminase Assays in the Diagnosis of Tuberculous Ascites

S.K. SHARMA,[1] MOHAMMAD TAHIR,[1] ALLADI MOHAN,[2] DUNCAN SMITH-ROHRBERG,[3] HEMANT K. MISHRA,[1] and R.M. PANDEY[4]

Comparative Utility of Cytokine Levels and Quantitative RD-1-Specific T Cell Responses for Rapid Immunodiagnosis of Tuberculous Meningitis[▽]

Vinod B. Patel,[1] Ravesh Singh,[2] Cathy Connolly,[3] Victoria Kasprowicz,[2] Thumbi Ndung'u,[2] and Keertan Dheda[4,5,6]*

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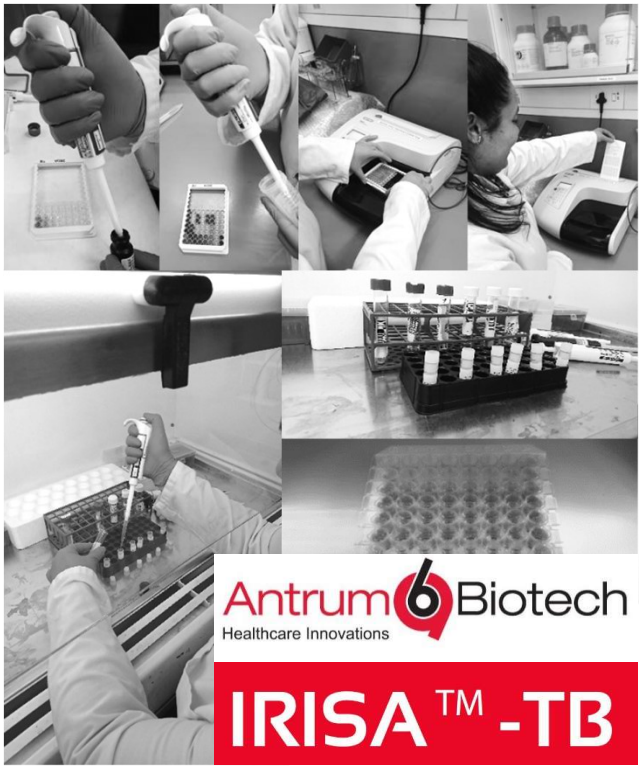


IRISA-TB™

Ultra-sensitive and rapid detection of unstimulated human interferon-gamma for the diagnosis of pleural TB, pericardial TB, TB peritonitis and TB meningitis

IRISA™ -TB

RECENT VALIDATION STUDIES

- Retrospective study: TB meningitis (Zambia)
- Prospective study: TB meningitis (Malawi and Zimbabwe)
- Rule-out cohort: TB meningitis (South Africa)
- Prospective study: Pleural TB (South Africa)

CENTRE FOR LUNG INFECTION AND IMMUNITY

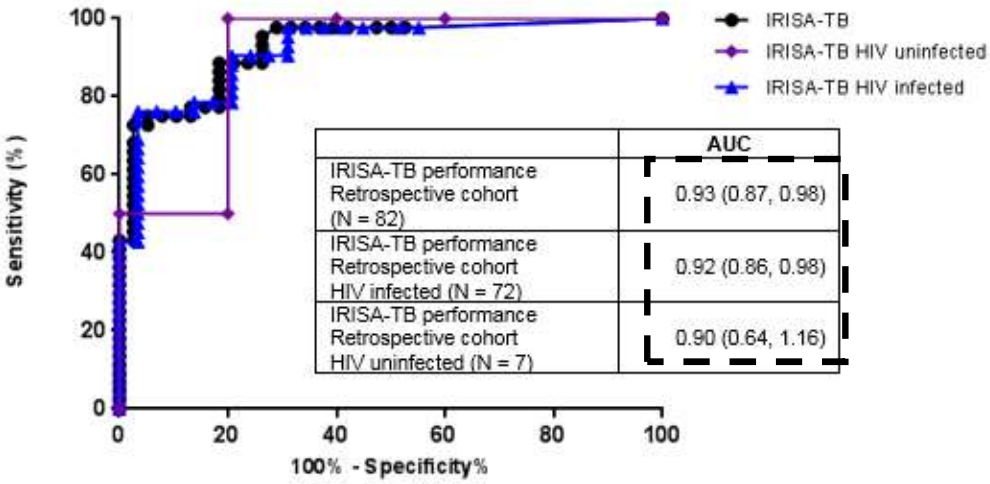
University of Cape Town • iYunivesithi yaseKapa • Universiteit van Kaapstad

BIOMEDICAL RESEARCH & TRAINING INSTITUTE

RETROSPECTIVE STUDY: TB MENINGITIS

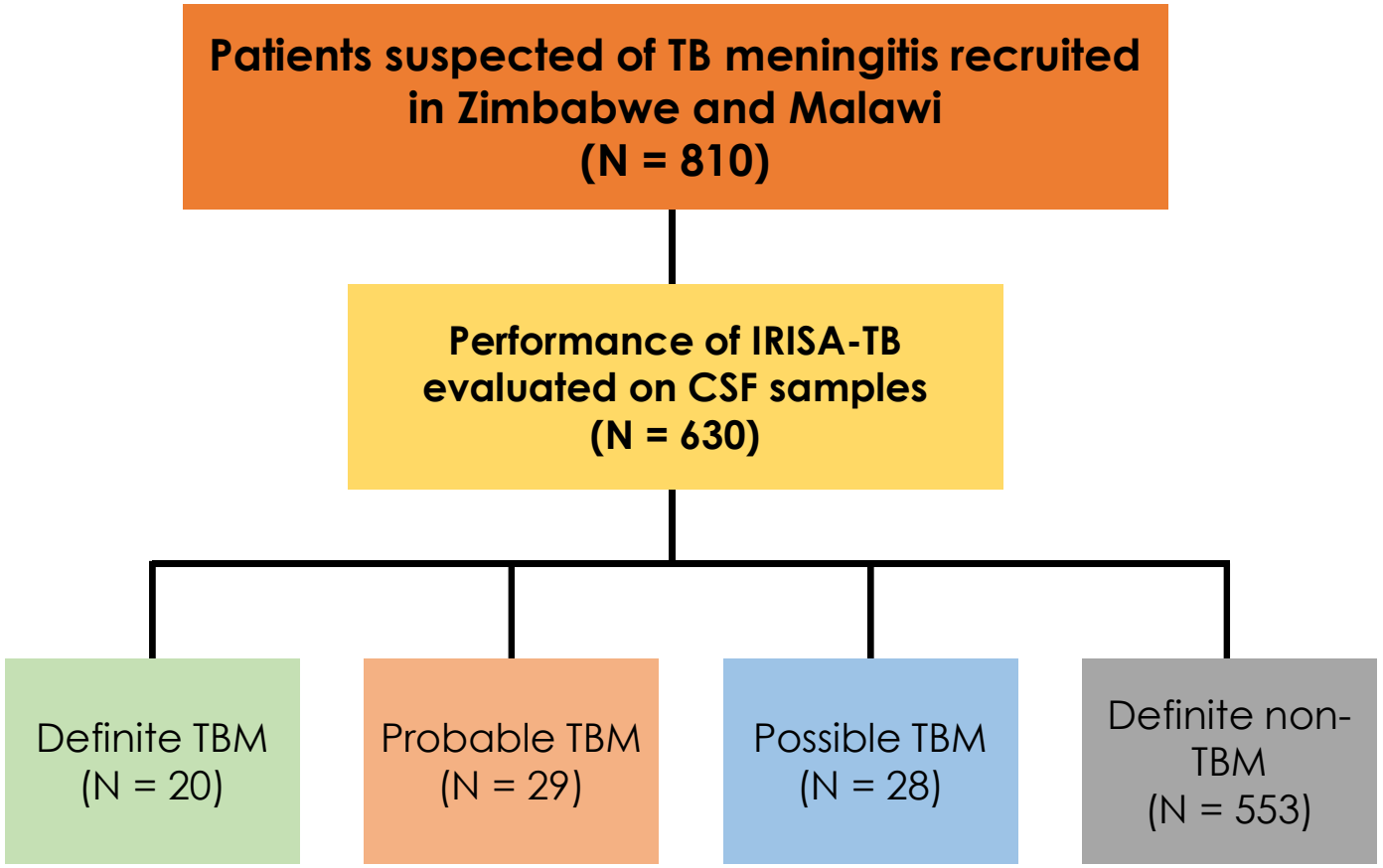
Bio-banked CSF samples (N = 82) were applied to IRISA-TB
(Definite TBM = 44 and Definite non-TBM = 38)

	sensitivity	specificity	PPV	NPV
Test performance IRISA-TB (CIs; n/N)	**75% (60.6, 85.5) 33/44**	**86.9% (72.7, 94.3) 33/38**	86.9% (72.7, 94.3) 33/38	75% (60.6, 85.5) 33/44
Test performance IRISA-TB HIV infected (CIs; n/N)	76.2% (61.5, 86.6) 32/42	86.3% (69.5, 94.6) 25/29	88.9% (74.7, 95.6) 32/36	71.5% (55, 83.7) 25/35
Test performance IRISA-TB HIV uninfected (CIs; n/N)	50% (9.5, 90.6) 1/2	80% (37.6, 96.4) 4/5	50% (9.5, 90.6) 1/2	80% (37.6, 96.4) 4/5



At a cut-off of 13pg/ml IRISA-TB's showed superior performance over current diagnostics

PROSPECTIVE STUDY: TB MENINGITIS



	sensitivity	specificity	PPV	NPV	AUC	Likelihood Ratio	DOR
Test performance prospective cohort (N = 573) (CIs; n/N)	**75% (53.2, 88.9) 15/20**	**90.3% (87.5, 92.5) 499/553**	21.8% (13.7, 32.9) 15/69	**99.1% (97.7, 99.6) 499/504**	0.91 (0.85, 0.97)	7.68	27.72 (9.695, 79.27)
Test performance prospective cohort HIV infected individuals (N = 374) (CIs; n/N)	**92.4%* (66.7, 98.7) 12/13**	88.1% (84.4, 91.1) 318/361	21.9% (13, 34.4) 12/55	**99.7% (98.3, 100) 318/319**	0.93 (0.86, 1.01)	7.75	88.74 (11.25, 699.9)
Test performance prospective cohort HIV uninfected individuals (N = 150) (CIs; n/N)	**50%* (18.8, 81.3) 3/6**	93.8% (88.6, 96.7) 135/144	25% (8.9, 53.3) 3/12	**97.9% (93.9, 99.3) 135/138**	0.91 (0.844, 0.98)	8.00	15 (2.640, 85.22)
	*p value = 0.04						

At a cut-off of 13pg/ml IRISA-TB's sensitivity was higher in HIV infected individuals

The NPV is a major draw card

RULE-OUT COHORT: TB MENINGITIS

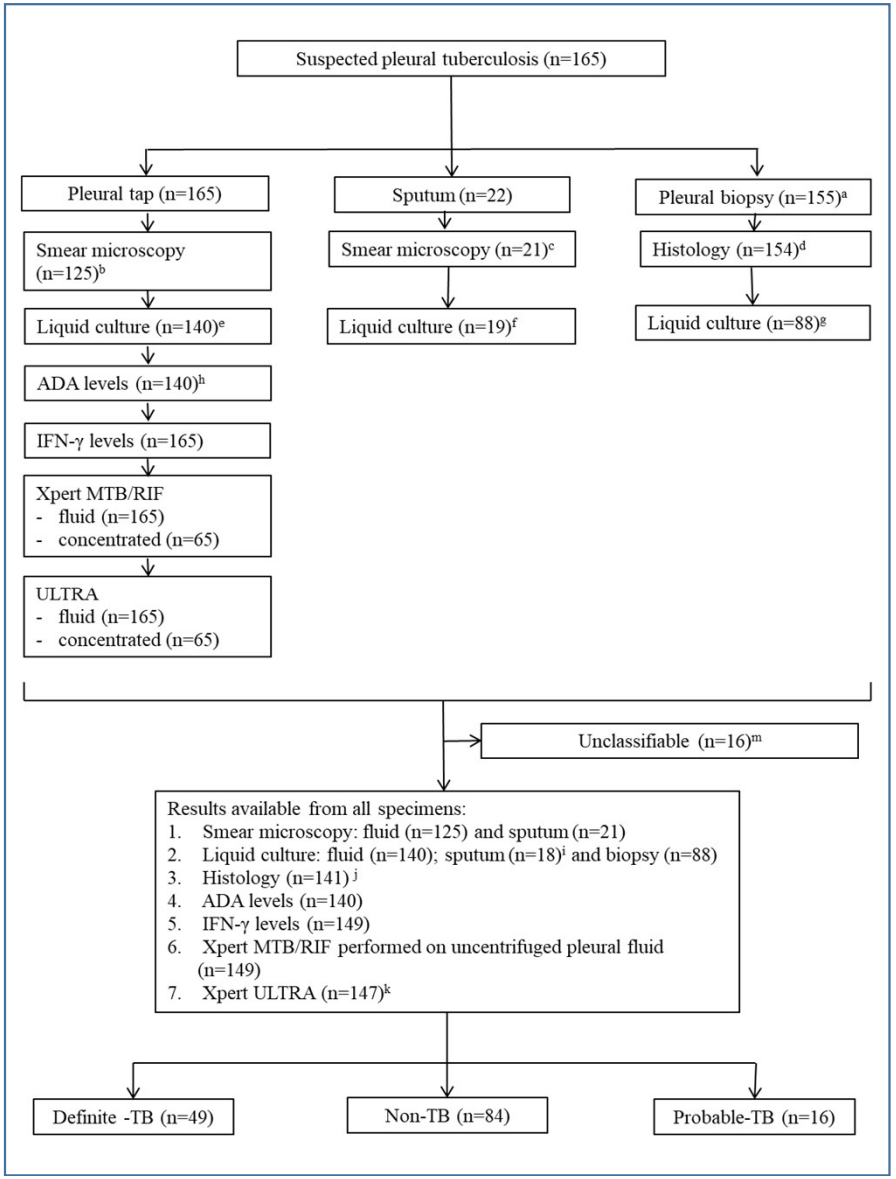
- Patients suspected of meningitis (not TBM) were recruited (N = 173)
- Embedded evaluation on those with normal CSF results (N = 122)

	Rule-out value	HIV infected	HIV uninfected	Children (≤ 16 years old)	Adults (> 16 years old)
Test performance specificity rule-out cohort (N = 173) (CIs; n/N)	98.3% (95.1, 99.5) 170/173	100% (92, 100) 44/44	95.7% (88, 98.6) 66/69	97.1% (89.9, 99.2) 66/68	99.1% (94.9, 99.9) 104/105
Test performance specificity CSF normal (N = 122) (CIs; n/N)	100% (97, 100) 122/122	100% (86.7, 100) 25/25	100% (92.8, 100) 49/49	100% (92.9, 100) 50/50	100% (95, 100) 72/72

At a cut-off of 13pg/ml IRISA-TB's NPV was above 95% irrespective of age and HIV status

PROSPECTIVE STUDY: PLEURAL TB

- 165 patients suspected of pleural TB were recruited
- Comparison of same-day diagnostics tools was performed
- Samples were run on Xpert MTB/RIF, Xpert Ultra, ADA and IRISA-TB



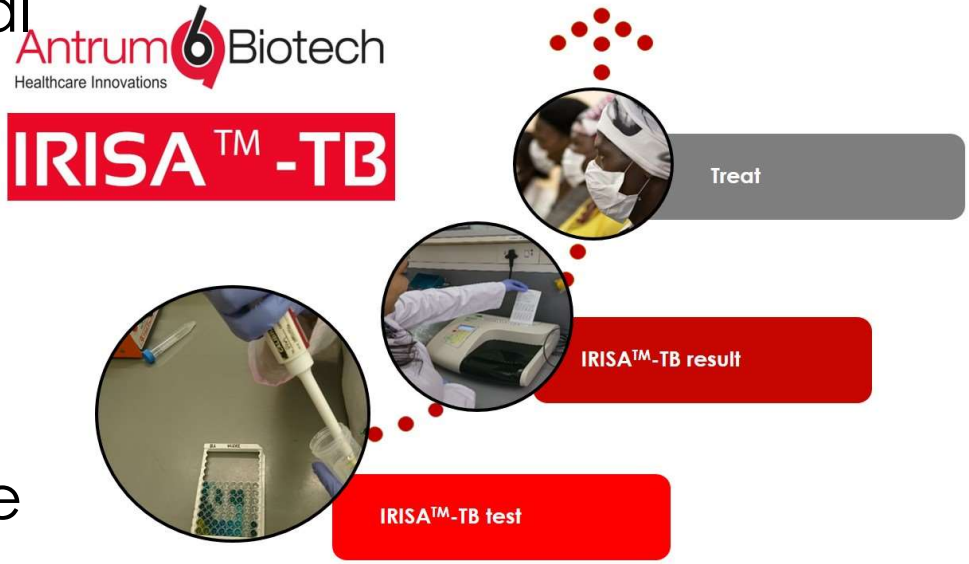
Submitted to JCM –
R. Meldau, P. Randall et al., 2019

	Sensitivity % (CI) n/N	Specificity % (CI) n/N	Positive Predictive Value % (CI) n/N	Negative Predictive Value % (CI) n/N	Positive Likelihood Ratio (CI)	Negative Likelihood Ratio (CI)	Diagnostic odds Ratio (CI)
Xpert ULTRA	37.5[bd] (23.8 – 51.2) 18/48	98.8[f] (96.5 - 100) 83/84	94.7[j] (84.7 – 100) 18/19	73.5[nk] (65.3 – 81.6) 83/113	31.5 (4.3 – 228.6)	0.6[qt] (0.5 - 0.8)	49.8 (6.4 – 389.4)
Xpert MTB/RIF	28.6[ac] (15.9 – 41.2) 14/49	98.8[e] (96.4 - 100) 83/84	93.3[i] (80.7 - 100) 14/15	70.3[ml] (62.1 – 78.6) 83/118	24.0 (3.2 – 177.0)	0.7[sr] (0.6 - 0.9)	33.2 (4.2 – 262.3)
IRISA-TB - Cut point 20.5 pg/ml	**89.8[ab] (81.3 – 98.3) 44/49**	**96.4[g] (92.4 – 100) 81/84**	**93.6 [h] (86.6 – 100) 44/47**	**94.2[kl] (89.2 – 99.1) 81/86**	25.1[p] (8.2 – 76.7)	0.1[qs] (0.0 - 0.2)	237.6 (54.2 – 1041.3)
ADA - Cut point 30 IU/ml	84.4[cd] (73.9 – 95.0) 38/45	87.5[feg] (79.9 – 95.1) 63/72	80.9 [hij] (69.6 - 92.1) 38/47	90.0[mn] (83.0 - 97.0) 63/70	6.8[p] (3.6 – 12.6)	0.2[rt] (0.1 - 0.4)	38.0 (13.1 – 110.4)
P-value	[a]; [b]; [c] and [d]: p < 0.0001	[e]: p=0.004 [f]: p=0.005 [g]: p = 0.034	[h]: p = 0.028 [i]: p = 0.071 [j]: p = 0.032	[k]; [l] and [m]: p < 0.0001 [n]: p = 0.00013	[p]: p = 0.032	[q]; [r] and [s]: p < 0.0001 [t]: p = 0.0006	

IRISA-TB's sensitivity and NPV significantly higher than Xpert (Ultra & MTB/RIF) and its specificity and PPV is superior to ADA

SUMMARY

- Current diagnostics are sub-optimal
- IRISA-TB is a rapid, effective test that is able to rule-in and rule-out EPTB sub-types
- Validated across multiple studies
- Its NPV is a major advantage
- Out competes all diagnostics in the diagnosis of pleural TB



ACKNOWLEDGEMENTS

OUR TEAM

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University of Zambia

OUR FUNDERS

DTI
IDC
UCT
SANBio
SA MRC

	sensitivity	specificity	PPV	NPV	Likelihood ratio	DOR
IRISA-TB cut-off 13pg/ml						
Test performance IRISA-TB (CIs; n/N)	50% (9.5, 90.6) 1/2	97%*# (84.7, 99.5) 32/33	50% (9.5, 90.6) 1/2	97% (84.7, 99.5) 32/33	11	16 (0.71, 362)
Without trace calls included						
Test performance Xpert Ultra (CIs; n/N)	50% (9.5, 90.6) 1/2	72.8%*@ (55.8, 85) 24/33	10% (1.8, 40.5) 1/10	96% (80.5, 99.3) 24/25	1.83	2.67 (0.15; 47.34)
With trace calls included						
Test performance Xpert Ultra (CIs; n/N)	100% (34.3, 100) 2/2	48.5%#& (32.6, 64.8) 16/33	10.6% (3, 31.4) 2/19	100% (80.7, 100) 16/16	1.94	4.71 (0.21, 105.8)
		*p-value = 0.0064 #p-value = < 0.0001 @p- value = 0.0014 &p-value = < 0.0001				