

T-Cell Marker Based Assays for the Diagnosis of Tuberculosis in Children

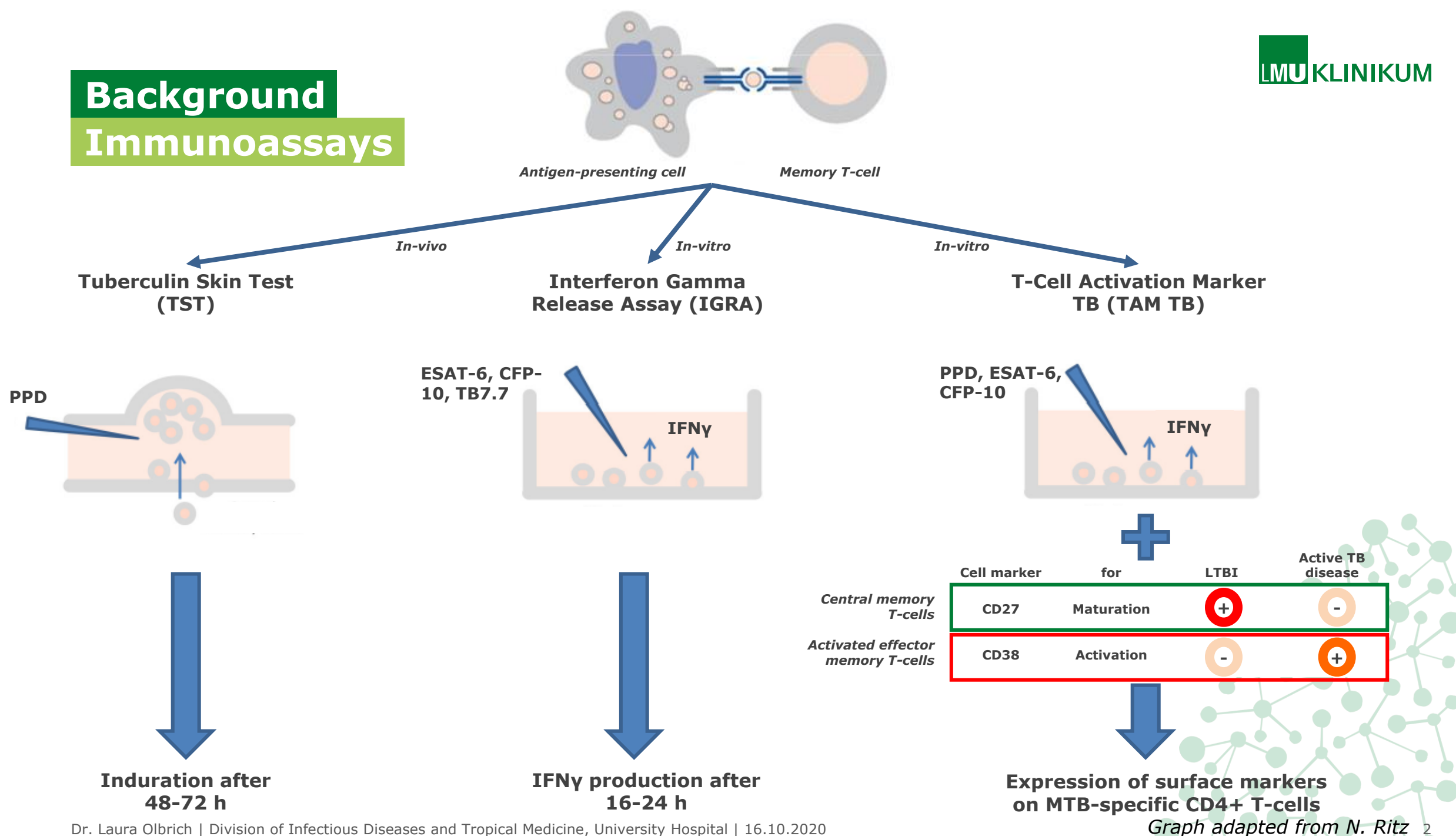
Annual meeting of Child and Adolescent TB Working Group

16.10.2020 | Dr. med. Laura Olbrich

Division of Infectious Diseases and Tropical Medicine, University Hospital, LMU Munich



Background Immunoassays



Background

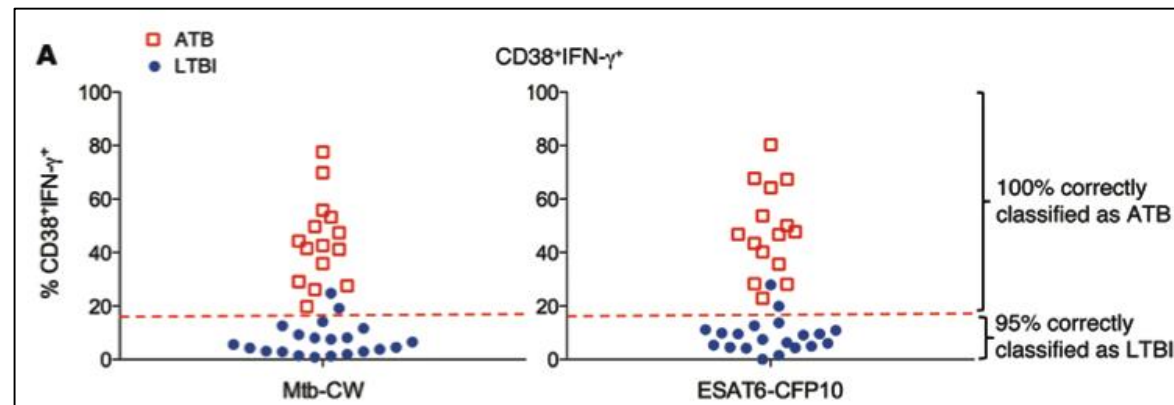
TAM TB Results from Endemic Settings

Paediatric TB suspects, Tanzania, CD27

	Culture-confirmed tuberculosis (n=18)	Highly probable tuberculosis (n=8)	Probable tuberculosis (n=12)	Not tuberculosis (n=63)	Indeterminate (n=12)
Assay-positive cases	15 (83%)	3 (38%)	2 (17%)	2 (3%)	1 (8%)
Assay-negative cases	3 (17%)	5 (63%)	10 (83%)	61 (97%)	11 (92%)

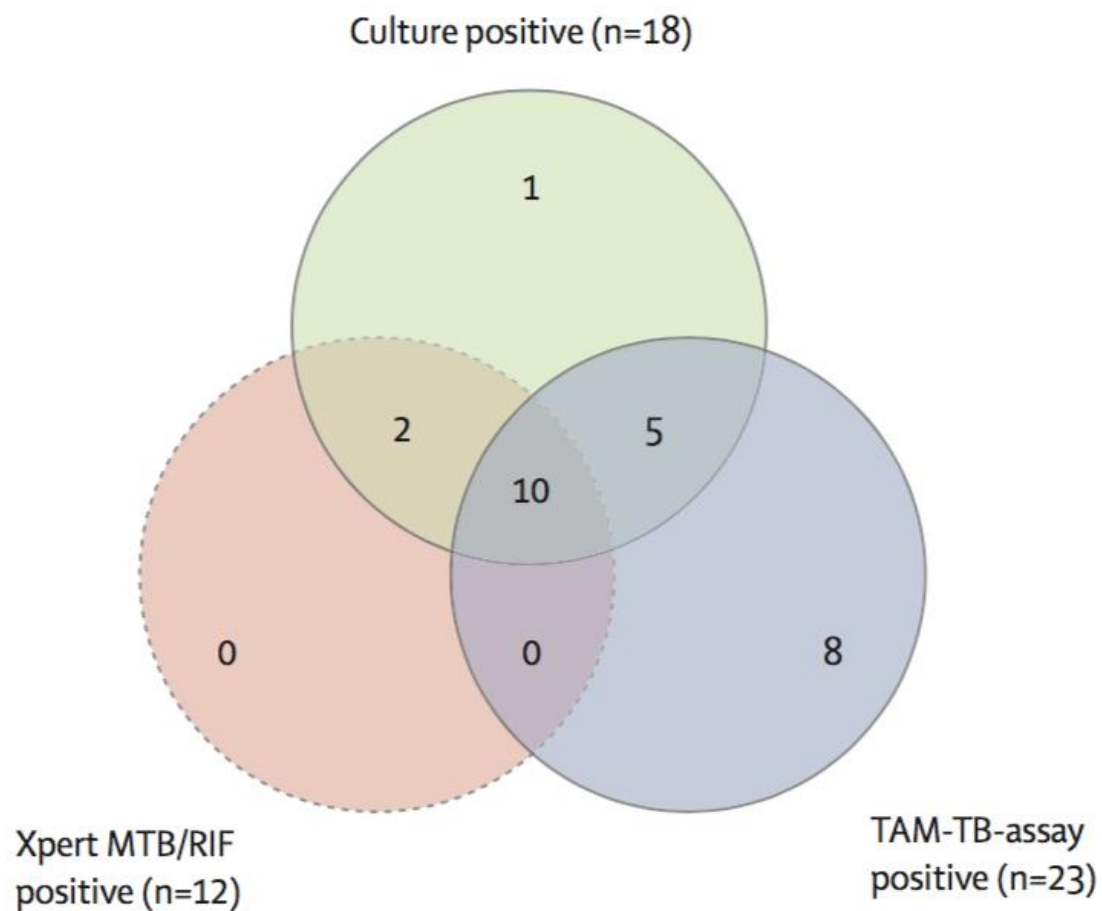
Table 2: T-cell activation marker-tuberculosis assay results by classification groups

IGRA+ Adults from Western Cape, RSA, CD38



Background

Detection of Culture-Negative TB Cases in Paediatric TB Suspects



15 years	Highly probable tuberculosis by radiograph
7 years	Highly probable tuberculosis by sputum smear
9 years	Highly probable tuberculosis by lymph node cytology
11 years	Probable tuberculosis by symptoms, resolution after treatment
1 year	Probable tuberculosis by symptoms, resolution after treatment

RefuScreen-AIDA-TB

TAM TB Evaluation in Adults and Children

- Study Design: Prospective TB diagnostic multi-site cohort study in Munich, Germany
- Analysis dataset: Patients suspected to have TB n=338
incl. <18yrs n=47
- TAM TB assay: Whole blood assay, CD38
Antigens: ESAT6/CFP10 and PPD

	Ref test +	Ref test -	
TAM TB +	63 (80.8%)	1 (1.8%)	64
TAM TB -	15 (19.2%)	55 (98.2%)	70
	78 (100%)	56 (100%)	134

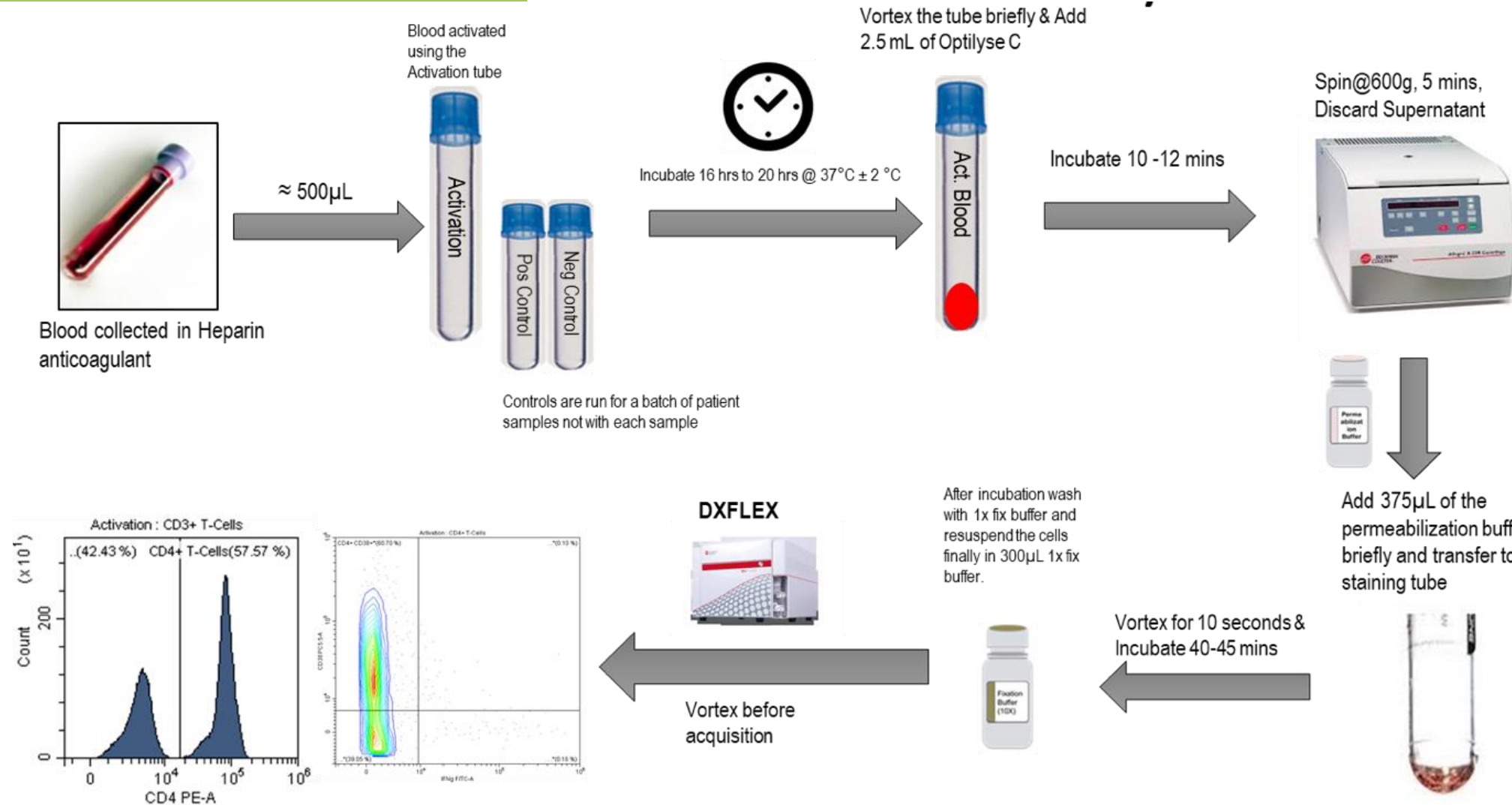
Sensitivity 80.8% (95% CI 70.3 – 88.8%)

Specificity 98,2% (95% CI 90.4 – 100.0%)

ROC AUC: 0.89 (95% CI: 0.85 – 0.94)

Preliminary Results - Data cleaning still ongoing

Development of TAM TB Commercialized Kit



BEC-CMC Pilot Study

- Study Design: Prospective evaluation of TAM TB compared to microbiological reference standard (culture, Xpert®)
- Analysis dataset: 90 children recruited at Christian Medical College, Vellore, India
Age 0.5 – 15 yrs
- Diagnostic classifications: Microbiologically confirmed TB 30 (33%)
Unconfirmed/Probable TB 23 (26%)
Unlikely TB 37 (41%)
- TAM TB assay: Whole blood assay, CD38
Antigens: ESAT6/CFP10



	Ref test +	Ref test -	
TAM TB +	24 (80%)	6 (16%)	30
TAM TB -	6 (20%)	31 (84%)	37
	30 (100%)	37 (100%)	67

Sensitivity 80%

Specificity 84%

→ **Higher Specificity with more stringent unlikely TB classification**

RaPaed-AIDA-TB Consortium

Study Design:

- Diagnostic validation study
- 8 new diagnostic tests incl. TAM TB
- 1,000 symptomatic children
- 20-25% target confirmation rate

Consortium & Partners:

- NIMR – MMRC, Mbeya, Tanzania
- INS, Maputo, Mozambique
- CoM, Blantyre, Malawi
- UCTLI, Cape Town, South Africa
- CMC, Vellore, India
- LMU, Munich, Germany
- FIND, Switzerland
- University of Melbourne, Australia
- Stellenbosch University, South Africa
- Karolinska Institute, Sweden
- Research Center Borstel, Germany
- NTP Tanzania, NTP Mozambique
- MoH, Malawi
- OVG, Oxford University, UK



RaPaed-AIDA-TB

TAM TB Performance

- Analysis dataset:

571 children	
4,6 years median age	IQR 1.7 - 8.2
91 HIV pos	20.0%
TAM TB result available for analysis	n=171

- Diagnostic classifications:

Microbiologically confirmed TB	129 (26.0%)
Unconfirmed TB	202 (40.7%)
Unlikely TB	165 (33.3%)

Defined by investigators and NO TB Rx – Endpoint review pending

- TAM TB assay:

Whole blood assay, CD38
Antigens: ESAT6/CFP10

Preliminary Results - Data entry & Data cleaning still ongoing

Results

TAM TB Performance

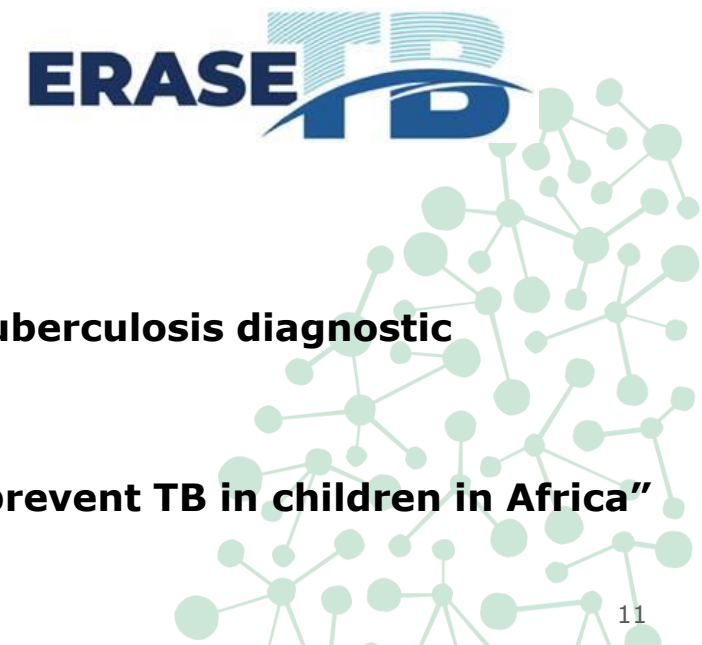
	Sensitivity – all pos		Sensitivity – without single Xpert trace cases		Specificity		ROC area
All	56.5% (41.1% - 71.1%)	26/46	75.8% (57.7% - 88.9%)	25/33	91.7% (77.5% - 98.2%)	33/36	0.74 (0.66 – 0.83)
0 -1 yr	66.7% (34.9% - 90.1%)	8/12	88.9% (51.8% - 99.7%)	8/9	100.0% (29.2% - 100.0%)	3/3	0.82 (0.67 – 0.97)
1-5 yr	50.0% (24.7% - 75.3%)	8/16	77.8% (40.0% - 97.2%)	7/9	88.9% (65.3% - 98.6%)	16/18	0.71 (0.57 – 0.85)
5-10 yr	60.0% (26.2% - 87.8%)	6/10	66.7% (29.9% - 92.5%)	6/9	90.9% (58.7% - 99.8%)	10/11	0.75 (0.57 – 0.94)
10-14 yr	50.0% (15.7% - 84.3%)	4/8	66.7% (22.3% - 95.7%)	4/6	100.0% (39.8% - 100.0%)	4/4	0.75 (0.56 – 0.94)

Preliminary Results - Data entry & Data cleaning still ongoing

TAM TB for the Diagnosis of Paediatric TB

Conclusion

- TAM TB shows promising performance in a variety of settings, in both children and adults
- Simplified and standardized assay kit developed
- RaPaed-AIDA-TB promising test performance, particularly for infants
- Requires laboratory infrastructure, incl. incubation and flow cytometry
- Ongoing evaluation
 - RaPaed-AIDA-TB, Endpoint Review is being conducted
 - ERASE TB (incipient TB, household contacts, initiation of recruitment Q1 2021)
- More RaPaed-AIDA-TB at the Union:
 - **„Performance of new screening and diagnostic tests in potential pediatric tuberculosis diagnostic algorithms: interim results from the RaPaed study“**
 - **Friday, 23rd Oct, 13:05-13:15h (CET)**
Symposium „Towards a TB-free childhood: best practices to find, cure and prevent TB in children in Africa“



Acknowledgements

LMU: C. Geldmacher, M. Ibraheem, K. Held, C. Dalgarno, E. Saathoff, S. Mutuku, F. Rieß, M. Hoelscher, N. Heinrich

RaPaed Consortium: H. Zar, N. Ntinginya, I. Sabi, A. Mfinanga, C. Khosa, D. Banze, M. Nliwasa, E.L. Corbett, R. Semphere, M. J. Sarojini, V. Verghese, S. Graham, R. Song, P. Nabeta

RefuScreen: L. Kübler, M. Saar, F. Gültekin, C. Bräu-Heberger, K. Avsar, U.v. Both, M. Steinhauser, U. Behrends, M. Seilmaier, B. Witzler, H. Hoffmann

Funders: German Center for Infection Research (DZIF); European and Developing Countries Clinical Trials Partnership (EDCTP; RIA2016MC -1623)

Beckman Coulter Inc.: M. Adelman, N. Girish, S. Chawla, S. Pattabhiraman, A. Jarare



**NO MORE
CRYING,
NO MORE
DYING.
TOWARDS
ZERO TB
DEATHS IN
CHILDREN.**



E-Mail: Olbrich@lrz.uni-muenchen.de Tel.: +49 89 4400-5980