

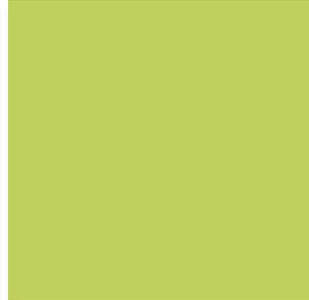
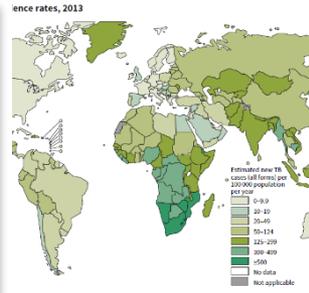
PAST LESSONS AND IMPLICATIONS FOR FUTURE TESTING STRATEGIES FOR CHILDREN

Dr. Norbert Heinrich, MD

Paediatric Specialist

Senior Scientist, Group Leader: Tuberculosis

Division for Infectious Diseases and Tropical Medicine, University of Munich (LMU)



CONTENTS OF THIS TALK

- Particulars of paediatric TB
- Challenges in diagnostics
- Epidemiology
- Improved sampling strategies – will they do the trick?
- New child-friendly tests



CHILDHOOD TB

WHO definition: children = people ≤ 14 yrs



CHILDHOOD TB

- Probability of disease after infection is age-dependent
- Child TB takes different forms

Age (yrs)	<1	1-2	2-5	5-10	>10
No disease (%)	50	70-80	95	98	80-90
Pulmonary (%)	30-40	10-20	5	2	10-20
TBM/Miliary (%)	10-20	2-5	0.5	<0.5	<0.5

Marais B, Int J Tuberc Lung Dis. 2004 Apr;8(4):392-402.

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CHILDHOOD TB

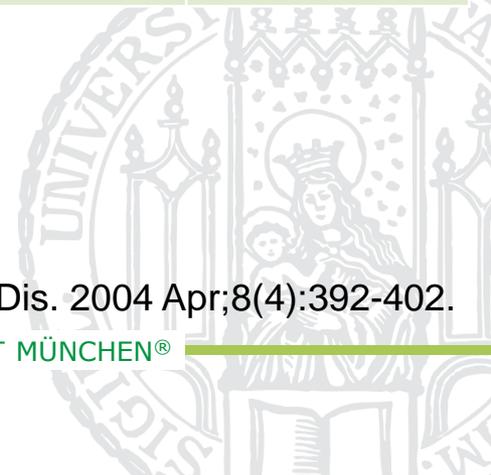
- Probability of disease after infection is age-dependent
- Child TB takes different forms

Age (yrs)	<1	1-2	2-5	5-10	>10
Form of Pulmon. TB	Ghon, Lymph node, bronchial	Ghon, Lymph node, bronchial	Lymph node, bronchial	Lymph node, effusion adult type	Effusion, adult type

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CHILDHOOD TB - DIAGNOSIS

Proportion of children treated for pulmonary TB with bacteriological confirmation in Western Cape:

Disease manifestation	No. (%) of children	Proportion (%) with bacteriologic confirmation ^a
Ghon focus	4 (1.3)	4/4 (100)
Primary (Ghon) complex	15 (3.6)	5/9 (55.6)
Lymph node disease		
Uncomplicated	147 (47.9)	24/69 (34.7)
Complicated		
Airway compression	25 (8.1)	10/18 (55.6)
Parenchymal consolidation	62 (20.6)	40/49 (81.6)
Pleurisy	24 (7.8)	10/17 (58.8)
Pericarditis	1 (0.3)	1/1 (100)
Disseminated (miliary) disease	15 (4.9)	14/15 (93.3)
Adult-type disease	14 (4.6)	14/14 (100) ^b
All	307 (100)	122/196 (62.2)

Marais B, Clin Infect Dis. 2006 Apr 15;42(8):e69-71.

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CHILDHOOD TB - DIAGNOSIS

Proportion of children treated for pulmonary TB with bacteriological confirmation:

- samples not easy to obtain:
- sputum induction
- gastric aspirate
- low volumes, low bacterial burden
- GeneXpert suboptimally sensitive - 62%

Disease manifestation	No. (%) of children	Proportion (%) with bacteriologic confirmation ^a
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Marais B, Clin Infect Dis. 2006 Apr 15;42(8):e69-71.
 Detjen A, Lancet Respir Med. 2015 Jun;3(6):451-61

CHILDHOOD TB - EPIDEMIOLOGY

- WHO: 1 million new child TB cases every year
- 239,000 child TB deaths per year
- Likely one of the top ten causes of under five deaths

Why:

masks as other diseases:

children with severe pneumonia: 7.5% have confirmed TB

- diagnosis is often missed or not attempted

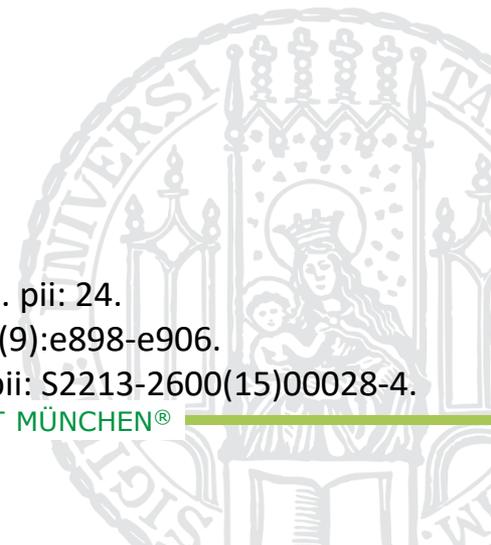
Jenkins HE: Pneumonia (Nathan). 2016;8. pii: 24.

Dodd PJ: Lancet Glob Health. 2017 Sep;5(9):e898-e906.

Oliwa, Lancet Respir Med. 2015 Jan 28. pii: S2213-2600(15)00028-4.

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NEW SAMPLING STRATEGIES

„Child-friendly“ samples using Xpert MTB/RIF:

Table 3. Diagnostic Accuracy of Xpert MTB/RIF for Culture-Confirmed Tuberculosis: Intention-to-Diagnose Population (n = 272)

Samples	Xpert Positive		Xpert Non Evaluable ^a		Xpert Negative		Sensitivity % (95% CI)	Specificity % (95% CI)
	Tuberculosis ^b n	Not Tuberculosis ^c n	Tuberculosis ^b n	Not Tuberculosis ^c n	Tuberculosis ^b n	Not Tuberculosis ^c n		
All	23	6	3	79	3	158	79.3 (60.3–92.0)	97.5 (94.7–99.1)
Standard samples	21	4	5	32	3	207	72.4 (52.8–87.3)	98.4 (95.8–99.5)
Alternative samples	22	3	1	62	6	178	75.9 (56.5–89.7)	98.8 (96.4–99.7)
NPA only	20	1	1	12	8	230	69.0 (49.2–84.7)	99.6 (97.7–100)
String test only ^d	9	2	9	46	7	132	36.0 (18.0–57.5)	98.9 (96.0–99.9)
Stool only	18	1	2	19	9	223	62.1 (42.3–79.3)	99.6 (97.7–100)
NPA and stool	22	2	1	23	6	218	75.9 (56.5–89.7)	99.2 (91.7–99.9)
NPA and string test ^d	18	2	1	54	6	124	72.0 (50.6–87.9)	98.9 (96.0–99.9)
String tests and stool ^d	16	2	2	53	7	125	64.0 (42.5–82.0)	98.9 (96.0–99.9)

Marcy, O. Clin Infect Dis. 2016 May 1;62(9):1161-8

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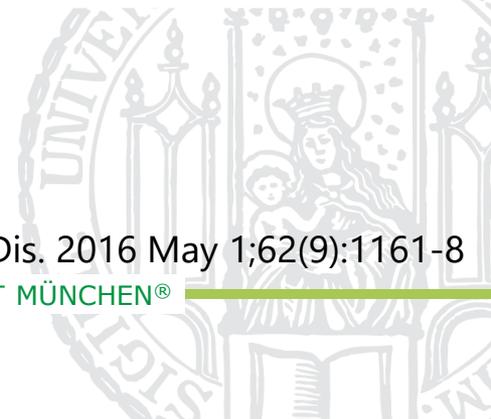
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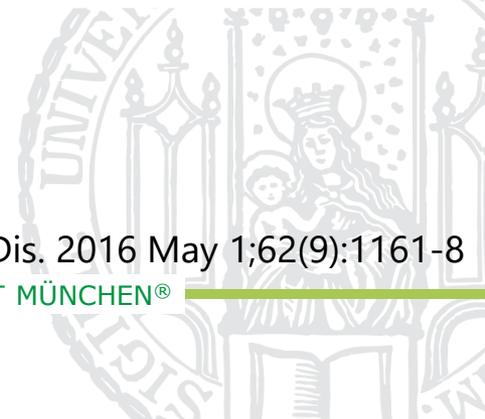
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	n	n	n	n	n	n		
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- Total N:
- 29 with culture - confirmed TB
- *in 116 children TB was probable but not confirmed by either method.*

Marcy, O. Clin Infect Dis. 2016 May 1;62(9):1161-8

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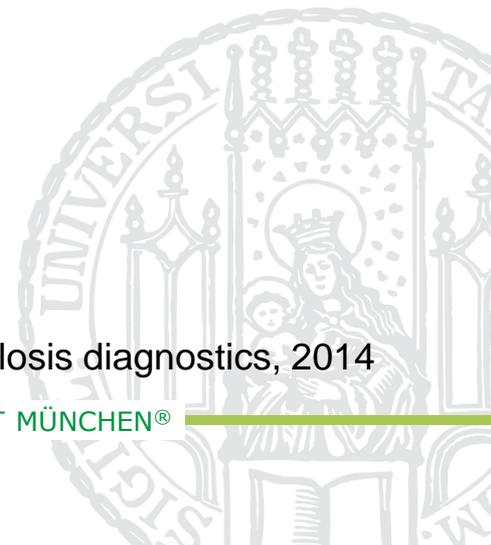


NEW TESTS ARE NEEDED

High-Priority Target product profiles - WHO

- a rapid point-of-care biomarker (non-sputum) test: child TB, EPTB
- a point-of-care triage test
- a point-of-care sputum-based test to replace smear microscopy
- a rapid drug-susceptibility test at the microscopy-centre level
- (a test to predict incipient TB)

WHO: High priority target product profiles for new tuberculosis diagnostics, 2014



CURRENT APPROACHES AT NEW TESTS

- GeneXpert Ultra[®] - sputum – rapid PCR;
- higher sensitivity in induced sputum: (63.2% vs 73.7% , culture 82.9 %) / 17% over MTB/RIF

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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Richard Ford, Ph.D., F.S.B., Ling Ling, M.B., B.S.,
Gerrit van Marrewijk, M.B., Ch.B., J. Anthony G. Scott, F.R.C.P.,
Christoph Denkinger, Ph.D., Leifert G. Coetzee, Ph.D.

Nicol, M.: *Pediatr Infect Dis J.* 2018 Feb 22

Articles



A blood RNA signature for tuberculosis disease risk: a prospective cohort study

Daniel E Zak¹, Adam Penn-Nicholson¹, Thomas J Sorba¹, Ethan Thompson¹, Sara Sulimani¹, Lynn M Amorn, Hassan Mahomed, Mawardi Erasmus, Wendy Whitmore, Gregory D Hanson, Deborah Abrahams, Faizil Kalfaje, Tony Hawke, Suzanne Verwo, E Jane Hughes, Martin Ota, Joyce Sutherland, Bawlegh Howd, Hafid M Dockrell, W Henry Bloom, Bonnie Thiel, Tom H M Ottenhoff, Harriet Mayanja-Rizzo, Amelia C Crampin, Katrina Downing, Mark Hattherll, Joe Valvo, Smitho Shanka, Sheemanta K Purida, Stefan H E Kaufmann, Gerhard Walz, Alan Adere, Willem A Hanekom, for the ACS and GCG-74 cohort study groups†

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Of 290 children screened, we selected a subgroup of 130 to ensure testing of at least 20 with culture-



Lancet Infect Dis 2014

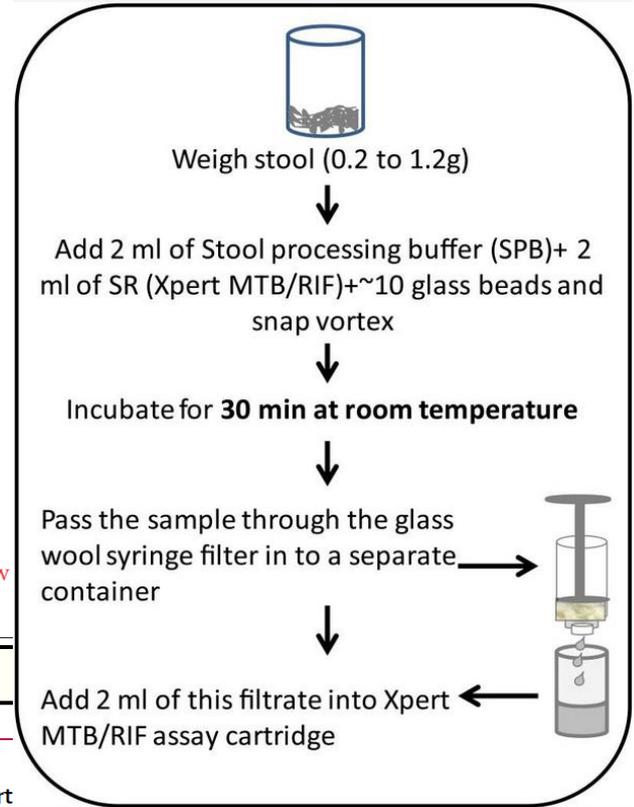
1473-3099(14)70898-9

*Contributed equally
Swiss Tropical and Public Health Institute, Basel, Switzerland
(D) Professor in Paediatrics, Justus Liebig University, Giessen, Germany

ABSTRACT

CURRENT APPROACHES AT NEW TESTS

- GeneXpert stool kit: new processing method
- LOD: 1,000 CFU/g stool
- Sensitivity in 20 paed TB patients: 85% (95% CI 0.6–0.9) for 0.6g stool samples



The NEW

Art

Expression in Africa

M.R.C.P.C.H., Myrsini Kaforou, M.Phil.,
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 FRCO, Ph.D., Leifert, G.D., Ph.D.

Banada, P: PLoS One. 2016 Mar 23;11(3):e0151980

STRACT

Articles



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In a cohort of 290 children screened, we selected a subgroup of 130 to ensure testing of at least 20 with culture-



Lancet Infect Dis 2014

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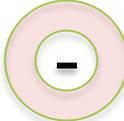
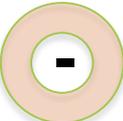
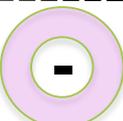
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Swiss Tropical and Public Health

Institute, Basel, Switzerland

ID Professor PhD, U Jugheli PhD, Prof, Co-lead author, DVM

"TAM-TB ASSAY" BASED DIAGNOSIS OF MTB INFECTION AND DISEASE

Cell marker	for	<i>LTBI</i>	Active TB disease
CD27	maturation		
CD38	activation		
HLA DR	activation		
Ki67	cell cycle		

CURRENT APPROACHES AT NEW TESTS

- Immunological, blood based tests – TAM –TB
(83% sens., 96% spec.)

	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

Portevin, D.: Lancet Infect Dis. 2014 Oct;14(10):931-8.

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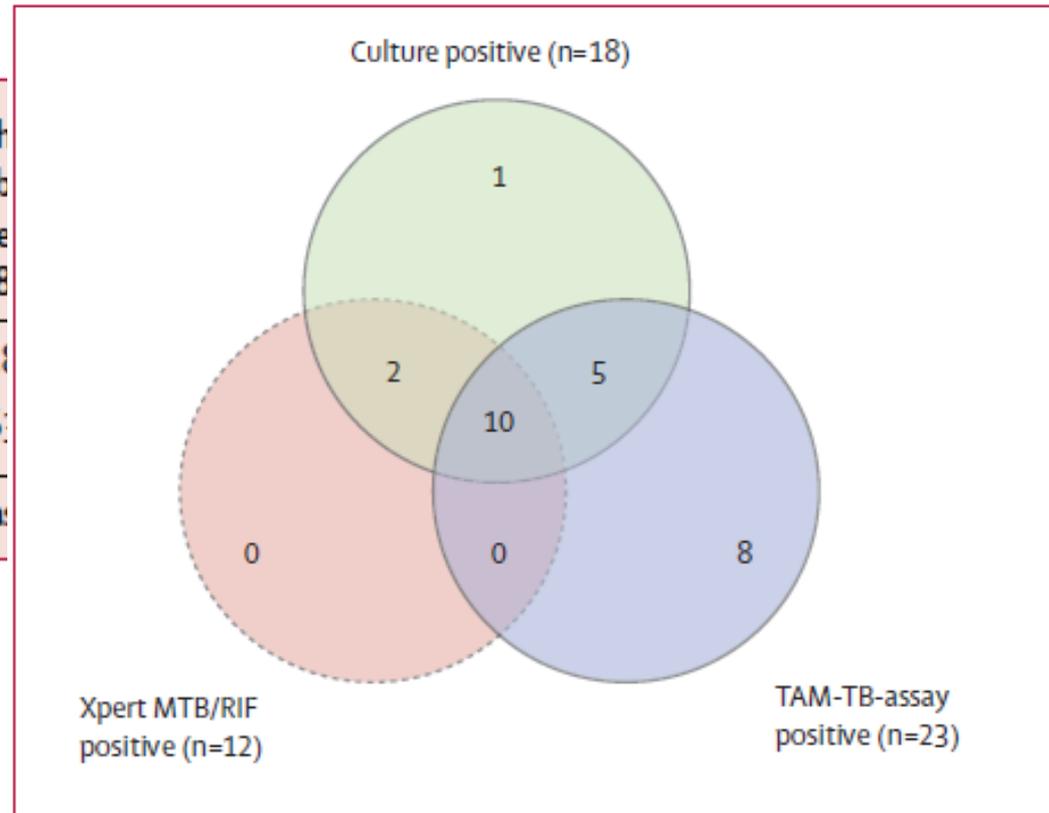
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CURRENT APPROACHES AT NEW TESTS

- Biomarker signatures - diverse
- Host (4 gene) transcription signatures as diagnostic test²
- Prediction of TB through host transcription signatures³:

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Prof C. Odenbreit, DM, DM.

Lancet 2016; 387: 2213-22

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CURRENT APPROACHES AT NEW TESTS

- Host transcription signatures as diagnostic tests:
- Sensitivity 82.9% (68.6 – 94.3), Specificity 83.6% (74.6 – 92.7)¹
- 4- gene signature possible²
- prediction of TB through host transcription signatures: 71% sens at 80% spec. – best at 6 months before disease³.

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a prospective proof-of-concept study

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Andrea Rachow, Elma Soathoff, Maximilian Mpina, Levan Jughdhi, Fred Lwilla, Benj Marais, Michael Hoetscher,
Georg Knaus Röhler*, Christof Geldmacher*

The diagnosis of paediatric tuber-
culosis is challenging because of the
paucibacillary nature of the
disease. We evaluated the
diagnostic performance of the
TAM-TB assay in children with
symptoms that suggest tuber-
culosis.

Children with symptoms that suggest
tuberculosis were screened at the
National Reference Laboratory
Center in Mbeya, and the
National Reference Laboratory
Center in Dar es Salaam. The
diagnostic performance of the
TAM-TB assay was compared
with that of the GeneXpert
MTB/RIF assay. The
diagnostic performance of the
TAM-TB assay was compared
with that of the GeneXpert
MTB/RIF assay.

Of 290 children screened, we selected a subgroup of 130 to ensure testing of at least 20 with culture-

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Articles



A blood RNA signature for tuberculosis disease risk: a prospective cohort study

Daniel Ezek*, Adam Penn-Nicholson*, Thomas J Soriba*, Ethan Thompson†, Sara Sulimani†, Lynn M Amon, Hassan Mahomed,
Mwambili Erasmus, Wendy Whitmore, Gregory D Hanson, Deborah Abrahams, Fazlul Karim, Tony Hwalekijigye, Suzanne Verwo, E Jane Hughes,
Martin Ota, Joyce Sutherland, Rowleigh Howie, Hazel M Dockrell, W Henry Boom, Bonnie Thiel, Tom H M Ottenhoff, Harriet Mayanja Kizza,
Amelia C Crampin, Katrina Downing, Mark Hatherill, Joe Valvo, Smitho Shankar, Sheemunta K Pirida, Stefan H E Kaufmann, Gerhard Walz,
Alan Adere, Willem A Hanekom, for the ACS and GCG-74 cohort study groups†

Summary

Background Identification of blood biomarkers that prospectively predict progression of *Mycobacterium tuberculosis* infection to tuberculosis disease might lead to interventions that combat the tuberculosis epidemic. We aimed to assess whether global gene expression measured in whole blood of healthy people allowed identification of prospective signatures of risk of active tuberculosis disease.

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STRUCT

CURRENT APPROACHES AT NEW TESTS

- New Urinary LAM (Karolinska):
Sensitivity in HIV-negative TB patients (n=17): 82%
healthy controls (n=22) specificity 100%

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ORIGINAL ARTICLE

Articles

Childhood Tuberculosis Expression in Africa

M.R.C.P.C.H., Myrsini Kaforou, M.Phil.,
Aria J. Wright, Ph.D., Claire M. Banwell, Ph.D.,
L. Crampin, F.F.P.H.M., Hazel M. Dockrell, Ph.D.,
S. Hamilton, Ph.D., Martin L. Hibberd, Ph.D.,
L. Ford, Ph.D., F.S.B., Ling Ling, M.B., B.S.,
M.Sc., Tom H.M. Ottenhoff, M.D., Ph.D.

Hamasur B: LoS One. 2015 Apr 23;10(4):e0123457.

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Validation of the novel T-cell activation marker-tuberculosis for diagnosis of active tuberculosis in children: a prospective proof-of-concept study

Felicien Moukambi, Petra Clowes, Asil Bauer, Mkuunde Chachage, Nyanda E Ntinginya, Eirehema Mfinanga, Khadija Said, Andrea Rachow, Elma Soathoff, Maximilian Mpina, Levan Jughdji, Fred Lwilla, Ben J Marais, Michael Hoetscher, Ingrid Geiger, Klaus Reither*, Christof Goldmacher*

The diagnosis of paediatric tuberculosis: validation of the paucibacillary nature of the interferon-γ-tuberculosis (TAM-TB) assay in a

children with symptoms that suggested tuberculosis in the arch Center in Mbeya, and the Ifakara Health Research Center in Morogoro, Tanzania, 2012. Sputum and peripheral blood interferon-γ performance assessment of the TAM-TB assay based on microbiological and clinical

Among 290 children screened, we selected a subgroup of 130 to ensure testing of at least 20 with culture-



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CONCLUSION

- Child TB has inherent disease characteristics different from adults
- Detection with „adult-type“ assays/samples difficult
- New sampling strategies may be more feasible, BUT substantial gains in child TB case detection questionable
- New tests provide opportunity to improve case detection



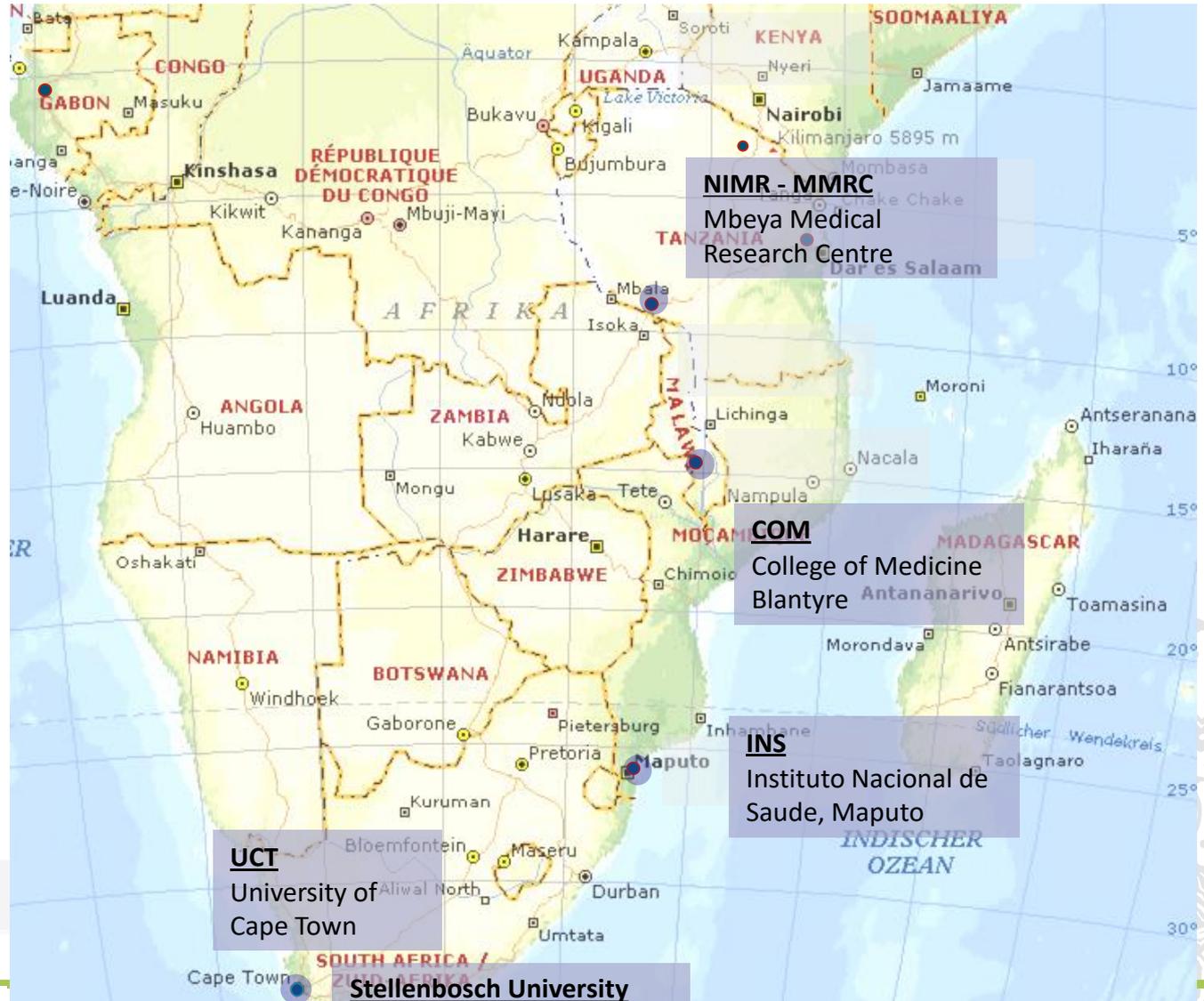
THE *RAPAED TB* PROJECT – VALIDATING NEW CHILD-FRIENDLY TESTS



- 10 new diagnostic assays, independent of sputum
- Planned cohort size: 800 children
- Design: single-gate, multiple diagnostic study
- Performance of single tests and potential testing algorithms
- On diagnostic study platform AIDA



THE RAPAED-TB CONSORTIUM



Abteilung für Infektions- und Tropenmedizin

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- European and Developing Countries Clinical Trials Partnership (EDCTP)
- German Center for Infection Research (DZIF)



THANK YOU FOR YOUR
ATTENTION!

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

