LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN

Abteilung für Infektions- und Tropenmedizin
Klinik und Poliklinik IV
Campus innenstadt

PAST LESSONS AND IMPLICATIONS FOR FUTURE TESTING STRATEGIES FOR CHILDREN

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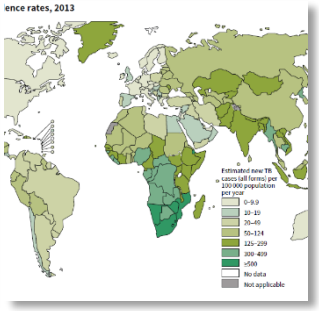

aida_TB
New diagnostics to end tuberculosis

EDCTP

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.

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

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

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.

CHILDHOOD TB - DIAGNOSIS

Proportion of children treated for pulmonary TB with bacteriological confirmation:

- samples not easy to obtain:
- sputum inducution
- 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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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.

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)

	Xpert Positive		Xpert Non Evaluable[a]		Xpert Negative			
Samples	Tuberculosis[b] n	Not Tuberculosis[c] n	Tuberculosis[b] n	Not Tuberculosis[c] n	Tuberculosis[b] n	Not Tuberculosis[c] n	Sensitivity % (95% CI)	Specificity % (95% CI)
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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- 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

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

ildhood Tuberculosis
Expression in Africa

M.R.C.P.C.H., Myrsini Kaforou, M.Phil.,
oria J. Wright, Ph.D., Claire M. Banwell, Ph.D.,
Crampin, F.F.P.H.M., Hazel M. Dockrell, Ph.D.,
S. Hamilton, Ph.D., Martin L. Hibberd, Ph.D.,
ford, Ph.D., F.S.B., Ling Ling, M.B., B.S.,
(SA), Tom H.M. Ottenhoff, M.D., Ph.D.,
, M.B., Ch.B., J. Anthony G. Scott, F.R.C.P.,

Articles

ment of the novel T-cell activation marker–tuberculosis
or diagnosis of active tuberculosis in children:
ective proof-of-concept study

Felicien Moukambi, Petra Clowes, Asli Bauer, Mkunde Chachage, Nyanda E Ntinginya, Elirehema Mfinanga, Khadija Said,
Andrea Rachow, Elmar Saathoff, Maximilian Mpina, Levan Jughefi, Fred Lwilla, Ben J Marais, Michael Hoelscher,
erger, Klaus Reither*, Christof Geldmacher*

The diagnosis of paediatric tuberculosis is complicated by non-specific symptoms, difficult specimen
d the paucibacillary nature of the disease. We assessed the accuracy of a novel immunodiagnost
rker–tuberculosis (TAM-TB) assay in a proof-of-concept study to identify children with active tuber

dren with symptoms that suggested tuberculosis were prospectively recruited at the NIMR
arch Center in Mbeya, and the Ifakara Health Institute in Bagamoyo, Tanzania, between May 1
2012. Sputum and peripheral blood mononuclear cells were obtained for *Mycobacterium tuberculosis*
erformance assessment of the TAM-TB assay. The children were assigned to standardised clinical case
based on microbiological and clinical findings.

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

Lancet Infect Dis 2014

S1473-3099(14)70898-9
*Contributed equally
Swiss Tropical and Public Health Institute, Basel, Switzerland
(D Portevin PhD, L Jugheli PhD, Prof C Daubenberger DVM,

Articles

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

Daniel E Zak*, Adam Penn-Nicholson*, Thomas J Scriba*, Ethan Thompson†, Sara Suliman†, Lynn M Amon, Hassan Mahomed, Mzwandile Erasmus, Wendy Whatney, Gregory D Hussey, Deborah Abrahams, Fazlin Kafaar, Tony Hawkridge, Suzanne Verver, E Jane Hughes, Martin Ota, Jayne Sutherland, Rawleigh Howe, Hazel M Dockrell, W Henry Boom, Bonnie Thiel, Tom H M Ottenhoff, Harriet Mayanja-Kizza, Amelia C Crampin, Katrina Downing, Mark Hatherill, Joe Valvo, Smitha Shankar, Shreemanta K Parida, Stefan H E Kaufmann, Gerhard Walzl, Alan Aderem, Willem A Hanekom, for the ACS and GC6-74 cohort study groups‡

Summary

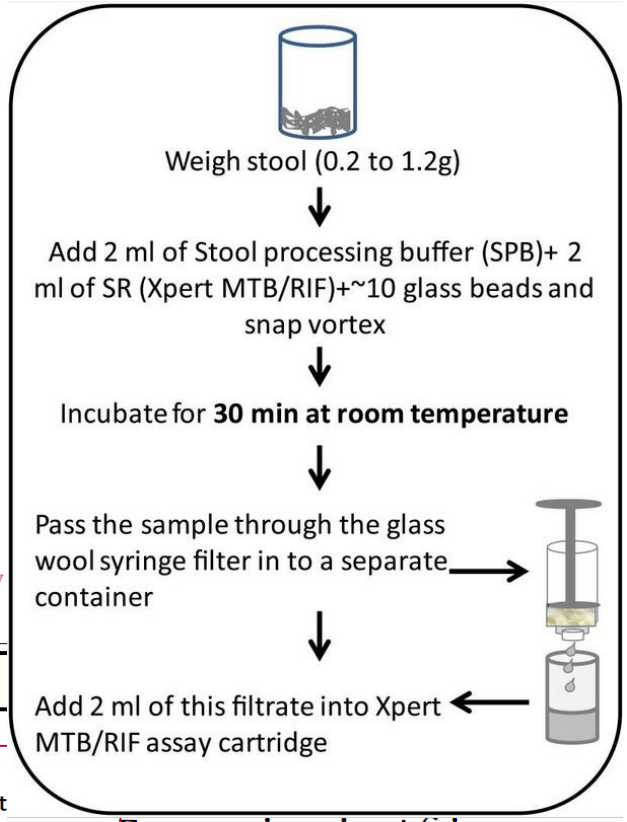
Lancet 2016; 387: 2312–22
Published Online March 23, 2016
http://dx.doi.org/10.1016/S0140-6736(15)01316-1

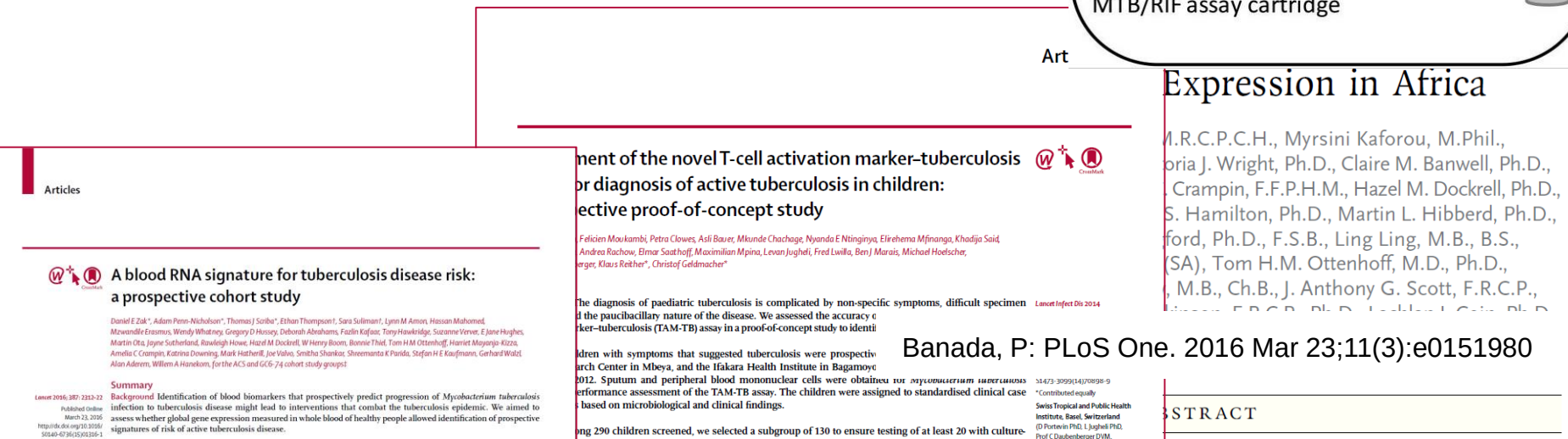
Background Identification of blood biomarkers that prospectively predict progression of *Mycobacterium tuberculosis* infection to tuberculosis disease might lead to interventions that combat the tuberculosis epidemic. We aimed to assess whether global gene expression measured in whole blood of healthy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

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

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





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

Cell marker	for	*LTBI*	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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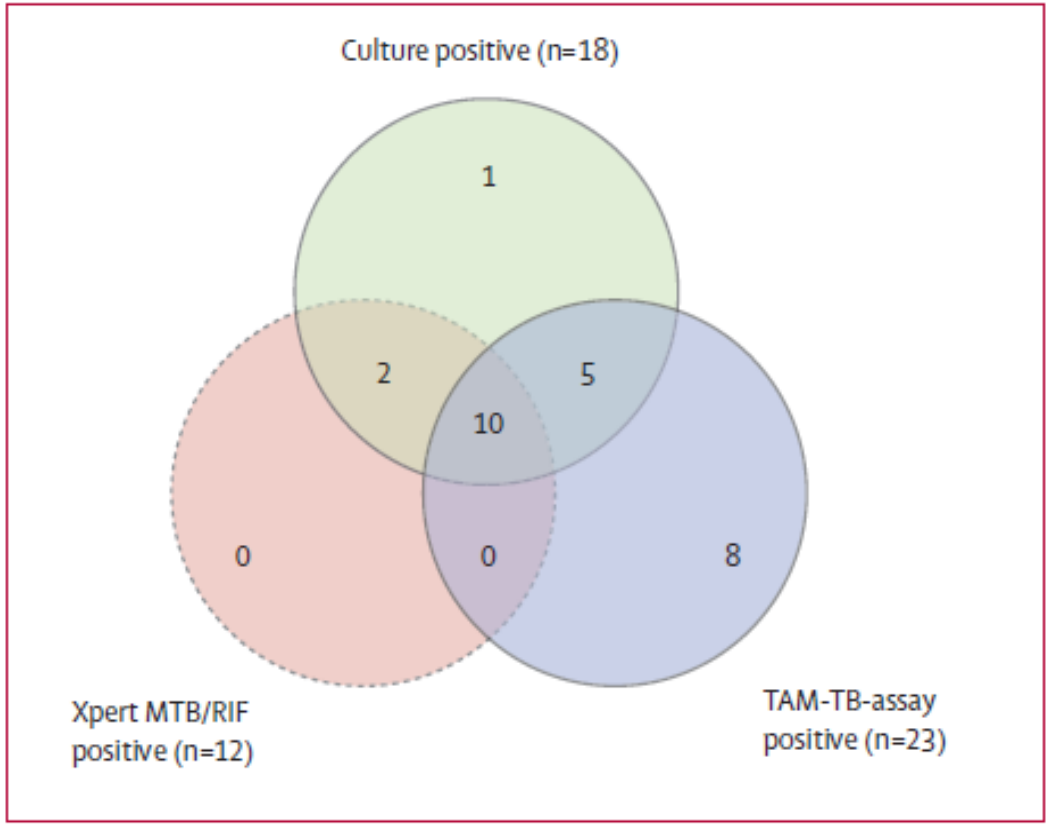
CURRENT APPROACHES AT NEW TESTS

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

	Culture-confirmed tuberculosis (n=18)	High prob tube (n=8
Assay-positive cases	15 (83%)	3 (3
Assay-negative cases	3 (17%)	5 (6

Table 2: T-cell activation marker–tuberculosis a



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

CURRENT APPROACHES AT NEW TESTS

- Biomarker signatures - diverse
- Host (4 gene) transcription signatures as diagnostic test[2]
- Prediction of TB through host transcription signatures[3]:

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

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 possible[2]
- prediction of TB through host transcription signatures:
  71% sens at 80% spec. – best at 6 months before disease[3].

1.Anderson ST: N Engl J Med. 2014 May 1;370(18):1712-23.
2. Roe J: JCI Insight. 2016 Oct 6;1(16):e87238.
3. Zak D: Lancet. 2016 Jun 4;387(10035):2312-2322.

CURRENT APPROACHES AT NEW TESTS

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

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

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

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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

aida_TB
New diagnostics to end tuberculosis

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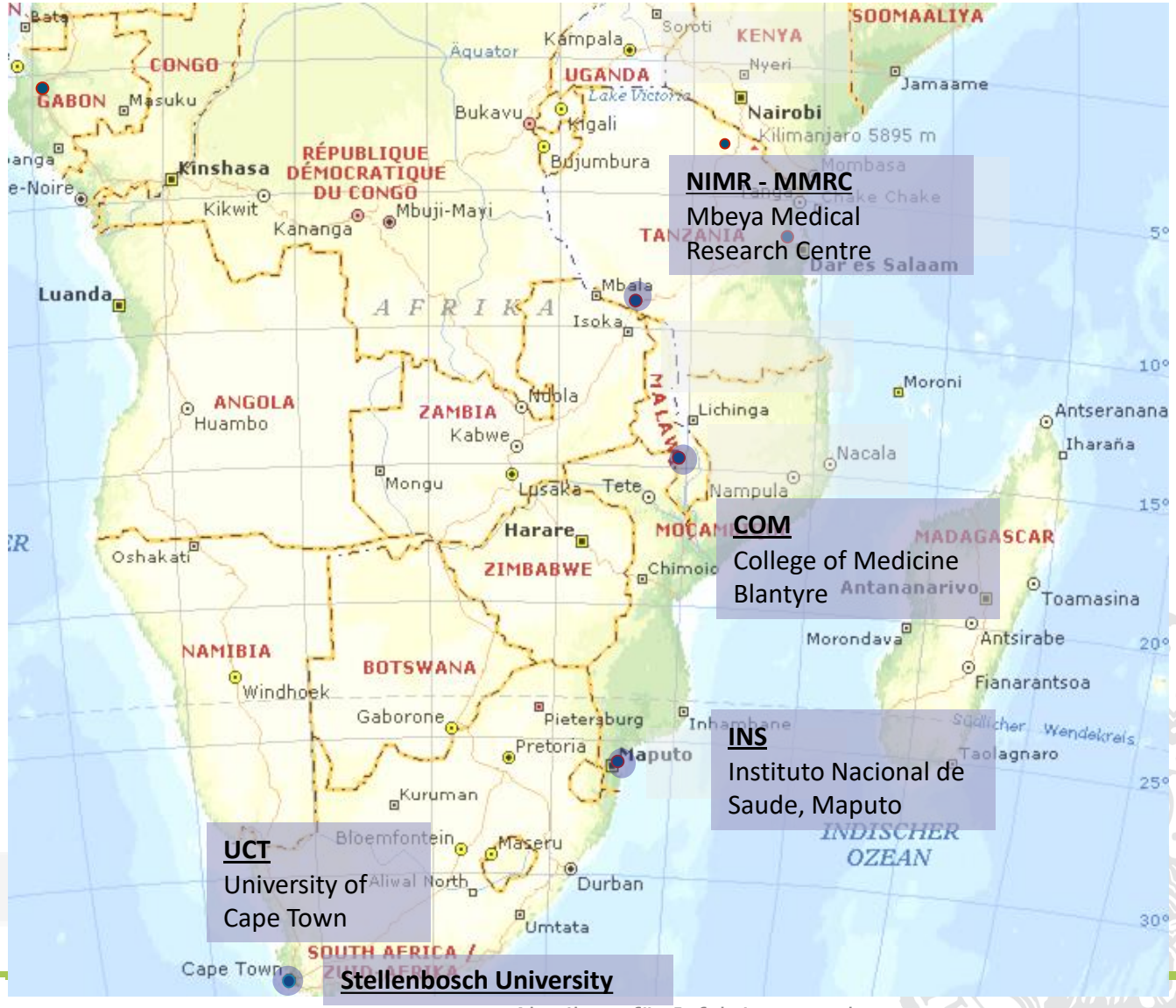
THE *RAPAED-TB* CONSORTIUM



ACKNOWLEDGEMENTS

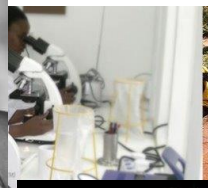
- Michael Hoelscher
- Laura Olbrich
- Christof Geldmacher
- Craig Dalgarno

The RaPaed TB consortium:

- Heather Zar
- Steve Graham
- Claudia Denkinger
- Liz Corbett
- Nyanda Ntinginya
- Nilesh Bhatt
- Rinn Song

Our funders:

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



THANK YOU FOR YOUR ATTENTION!