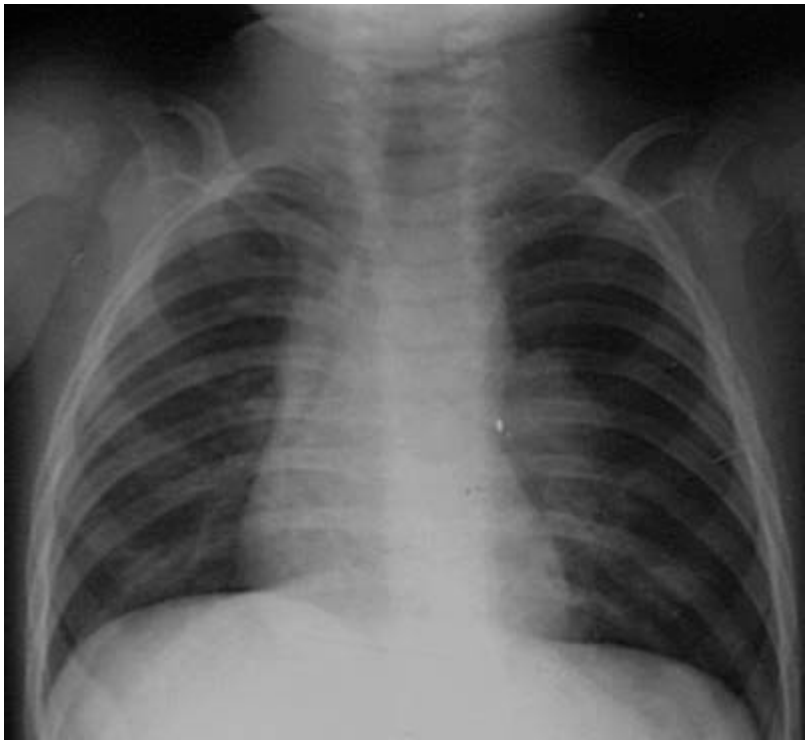
Toward Solving the Diagnostic Dilemma of Tuberculosis



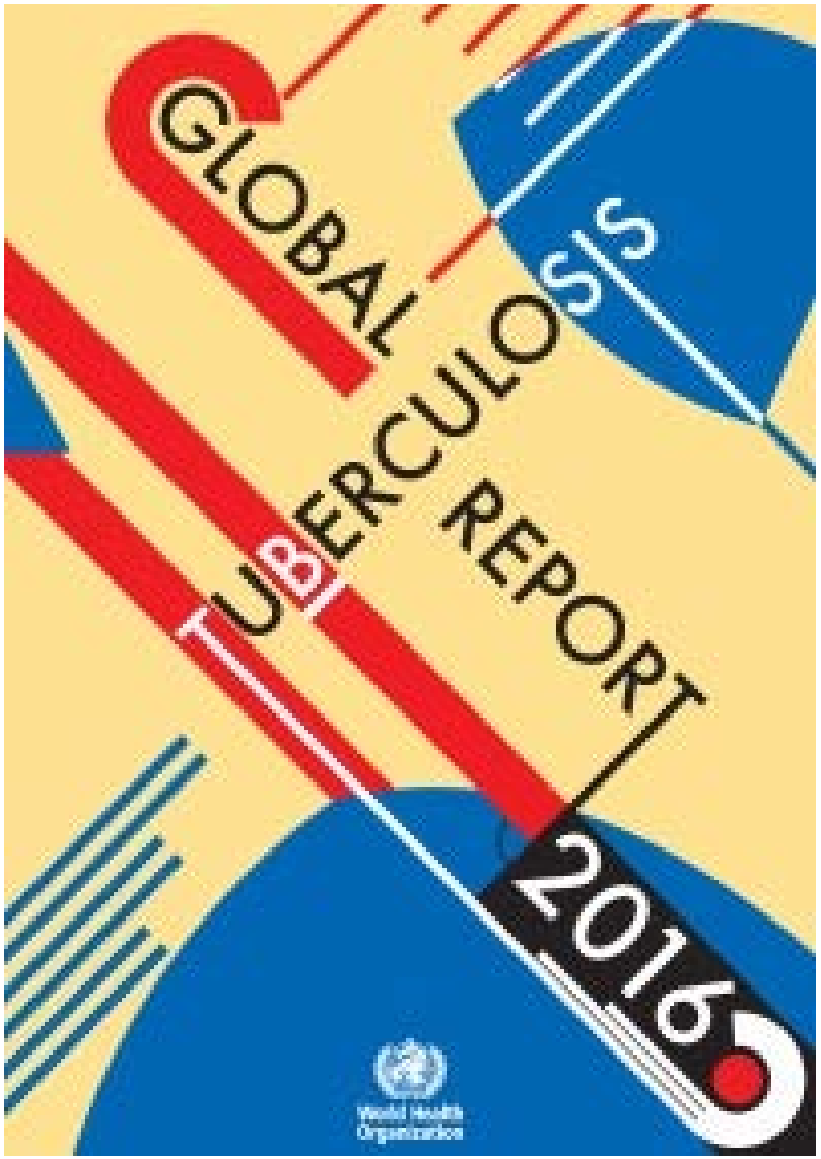
David H. Persing MD, Ph.D.

Executive Vice President, Chief Medical and Technology Officer - Cepheid

Chief Scientific Officer - Danaher

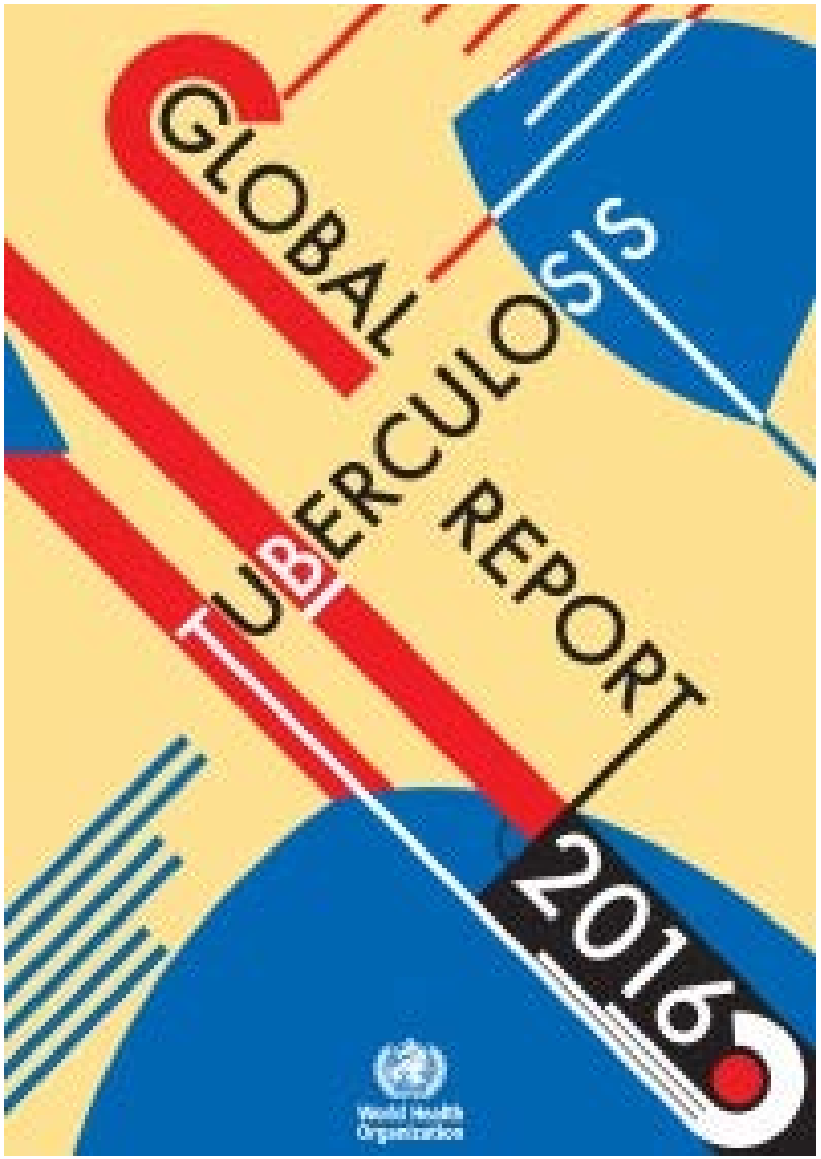
Consulting Professor, Department of Pathology - Stanford University School of Medicine

Global TB Report 2016



1. The Sustainable Development Goals (SDGs) for 2030 were adopted by the United Nations in 2015.
2. One of the targets is to end the global TB epidemic.
3. The WHO End TB Strategy, approved by the World Health Assembly in 2014, calls for a 90% reduction in TB deaths and an 80% reduction in the TB incidence rate by 2030, compared with 2015.
4. This global TB report was the first to be produced in the era of the SDGs and the End TB Strategy.
5. Data were available for 202 countries and territories that account for over 99% of the world's population and TB cases.

Epidemiology of TB



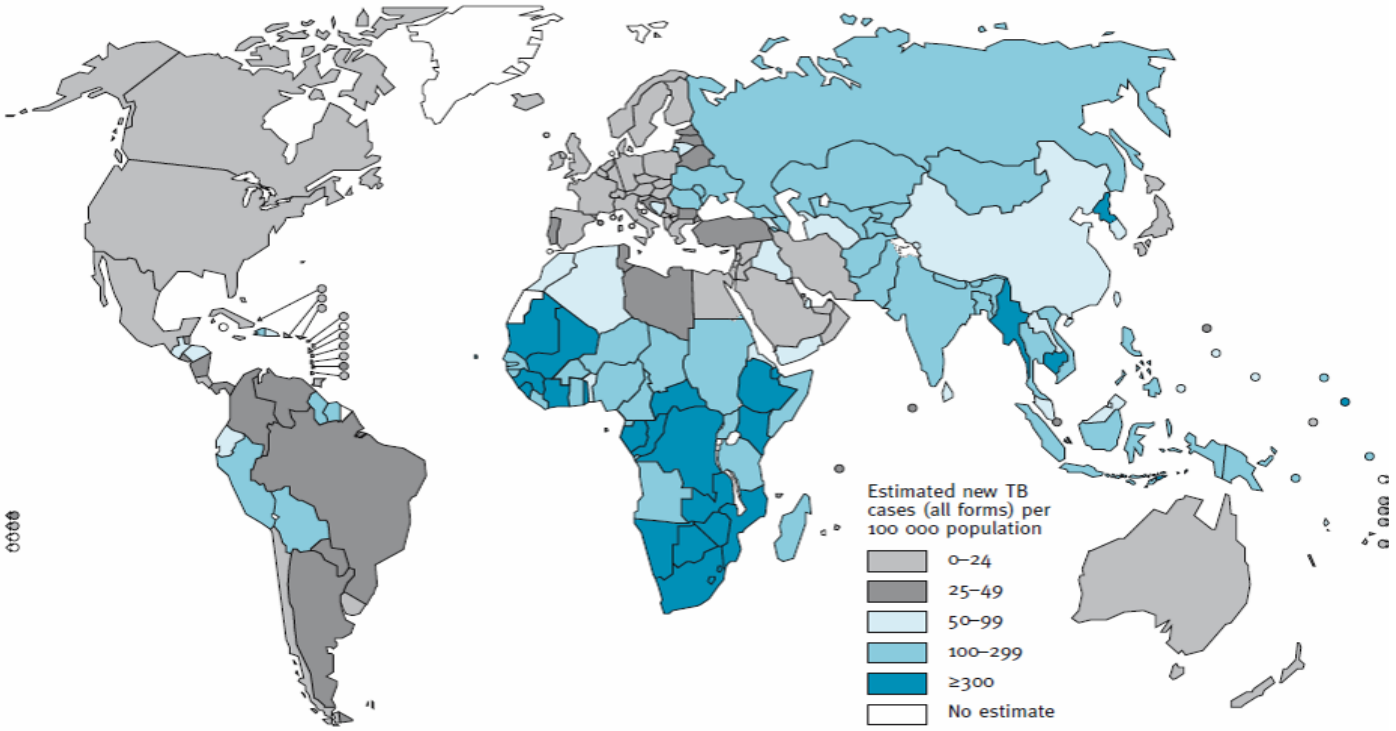
1. Global exposure of TB in 2015: about 1/3 of world population
2. 10.4 million new TB cases in 2015, including 1.2 million cases among people with HIV
3. 5.9 million (56%) were among men, 3.5 million (34%) among women and 1.0 million (10%) among children.
4. Six countries accounted for 60% of the new cases: India,Indonesia, China, Nigeria, Pakistan and South
5. Rate of decline remained at 1.5% from 2014 to 2015.
6. In 2015, there were an estimated 480 000 new cases of multidrug-resistant TB (MDR-TB) and an additional 100 000 people with documented rifampin resistance

High-Burden Countries

- Afghanistan
- Bangladesh[d]
- Brazil
- Cambodia
- China
- DR Congo
- Ethiopia
- India
- Indonesia
- Kenya
- Mozambique
- Myanmar[e]
- Nigeria
- Pakistan
- Philippines
- Russian Federation
- South Africa
- Thailand
- Uganda
- UR Tanzania
- Viet Nam
- Zimbabwe

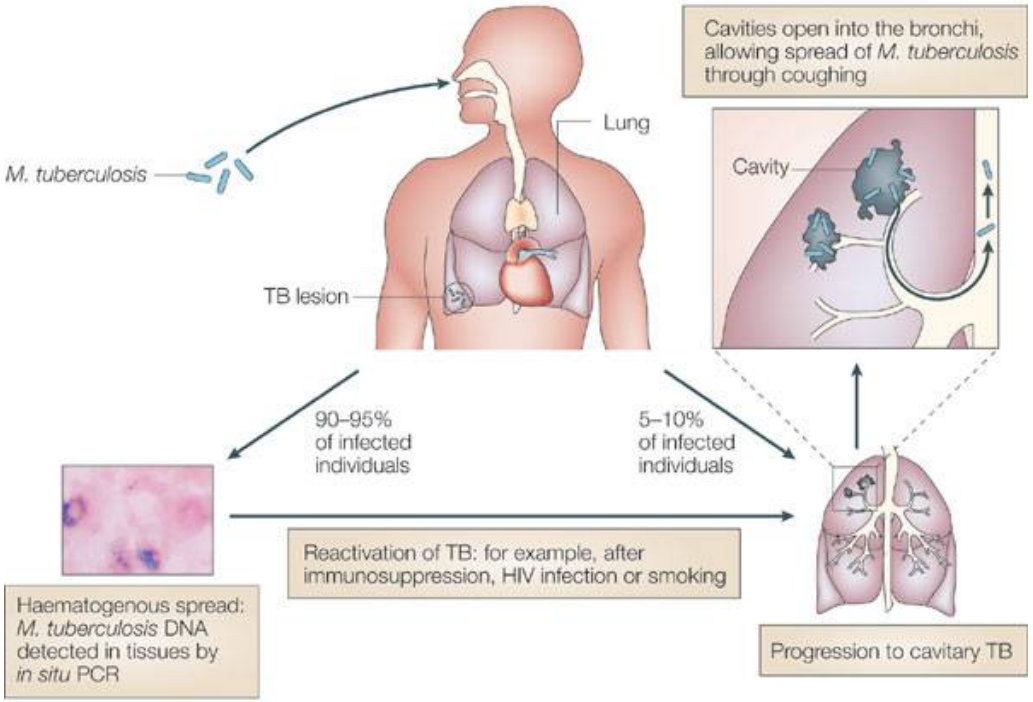
FIGURE 1

Estimated TB incidence rates, by country, 2009



Incidence = rate

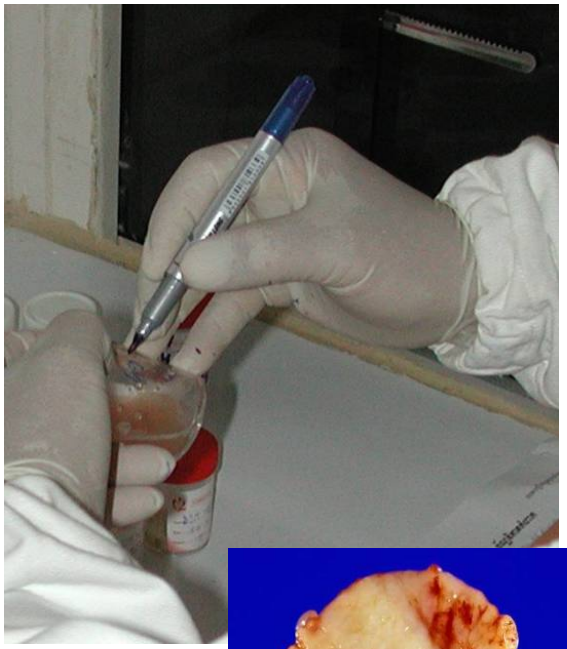
Pathogenesis of TB – kids are different



- **Risk of developing disease after exposure**
  - **43% <1 yr**
  - **25% age 1-5 yr**
- **Children with HIV have 6-fold increased mortality**
- **Often nonspecific presentations**

Tests to Diagnose Pulmonary TB Today

1. Sample types for organism detection
   a. Sputum and surrogates (Induced sputum; gastric aspirate; np aspirate; string sample; stool)
   b. Tissue biopsy material
2. Sample types for antigen, antibody, or reactivity detection
   a. Urine
   b. Serum
   c. Whole blood
   d. Breath
3. Types of tests
   a. Smear and culture
   b. Molecular assays
   c. Interferon-G release assays (IGRAs)



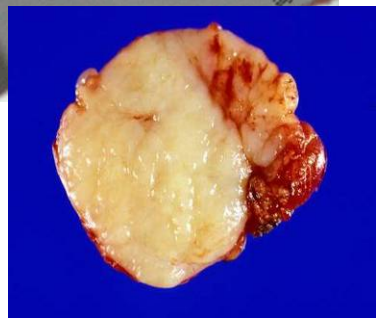
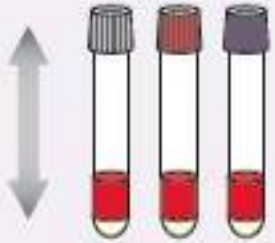
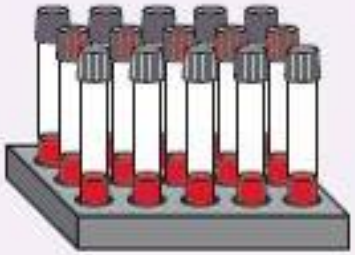


Figure 1. QuantiFERON-TB Gold In Tube (QFT-IT) Technology

Part 1. Blood Incubation

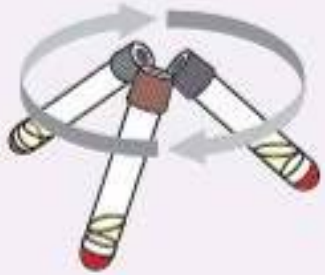


After blood collection, mix QFT tubes thoroughly by shaking vigorously for 5 seconds.



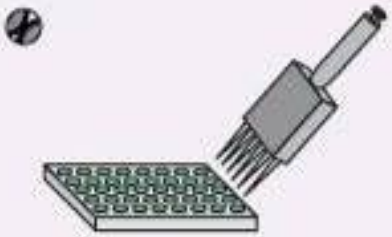
As soon as possible, and within 16 hours of collection, incubate tubes upright at 37°C for 16–24 hours.

Incubated tubes are stable for up to 3 days at room temperature, enabling shipment to laboratory.

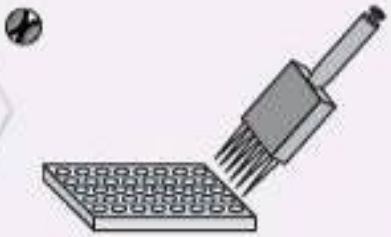


Centrifuge tubes at 2000–3000 g (RCF) for 15 minutes.

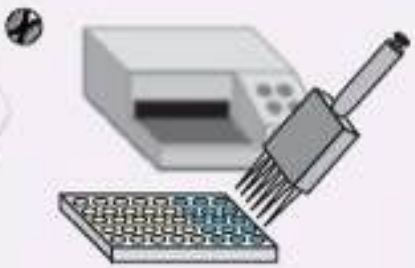
Part 2. IFN-gamma ELISA



Add 50 µL of working conjugate to each well. Add 50 µL of plasma or standard. Incubate for 120 minutes at room temperature.



Wash plate ≥ 6 times. Add 100 µL of substrate. Incubate 30 minutes at room temperature.



Add 50 µL of stop solution. Read absorbance at 450 nm (620–650 nm ref).

Calculate results using QuantiFERON-TB Gold In-Tube Analysis Software, or similar.

Interferon γ release assay for the diagnosis of latent tuberculosis infection and tuberculosis disease in children.

Mendez-Echevarria et al. Arch Dis Child. 2011 May 4

- 459 tests: 4.3% indeterminate
- 318 noninfected
- 73 Latent TB Infection
- 68 TB Disease (only 54% had culture confirmation)
- 87% concordance with skin test overall; only 47% in BCG-vaccinated children

Table 2 Results of the QuantiFERON-TB GOLD In Tube (QTF) test based on final diagnosis

	QTF		
	Positive	**Negative**	**Indeterminate**
TBD	61	1	6
LTBI	32	38	3
Uninfected	3	304	11
Total	96	343	20

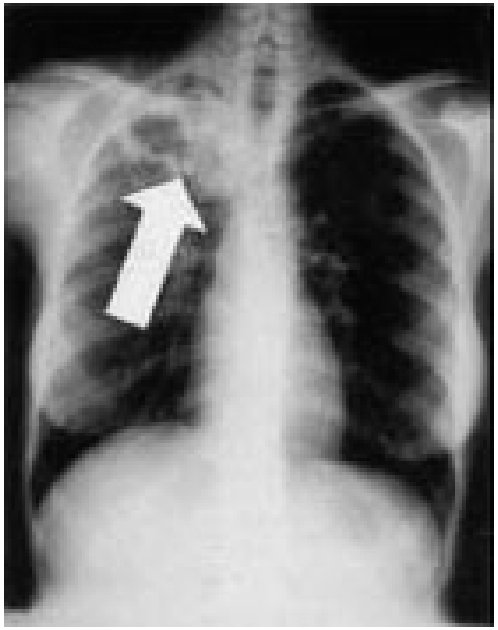
LTBI, latent tuberculosis infection; TBD, tuberculosis disease.

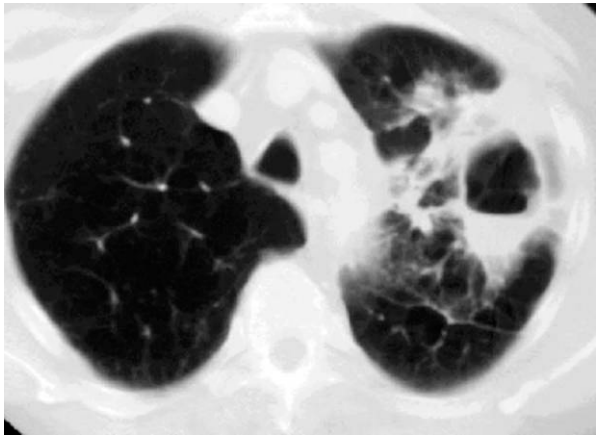
Difficulties Diagnosing Pediatric TB

1. Cavitary disease usually not present; organisms often absent in respiratory secretions (negative smears)
2. Infants and children cannot cough into a container
3. Other sample types (gastric aspirate, induced sputum) hard to obtain
4. Culture yield from intra-thoracic TB = 62%

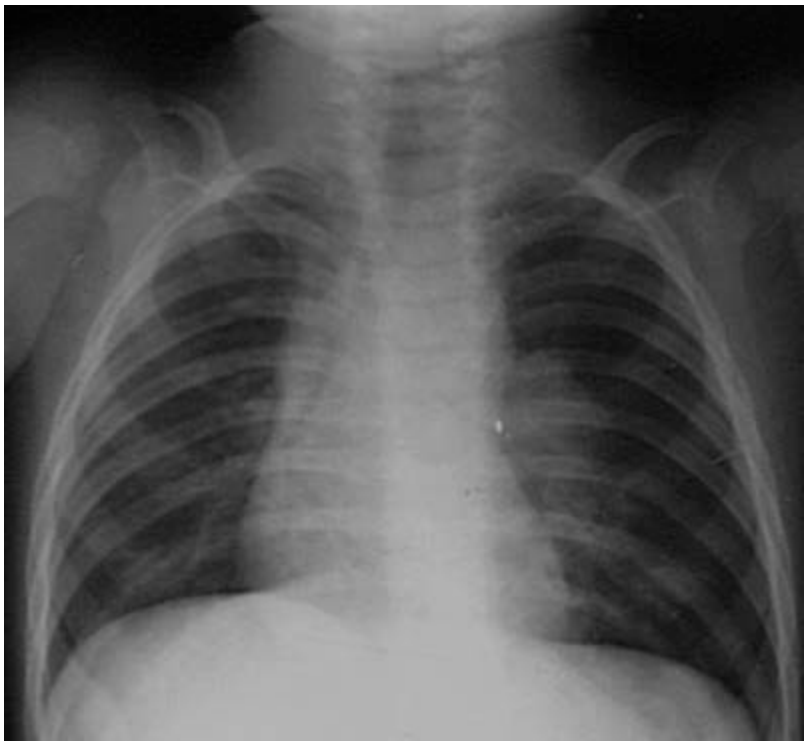
(Culture-confirmed childhood tuberculosis in Cape Town, South Africa: a review of 596 cases. Schaaf HS, et al. BMC Infect Dis. 2007)

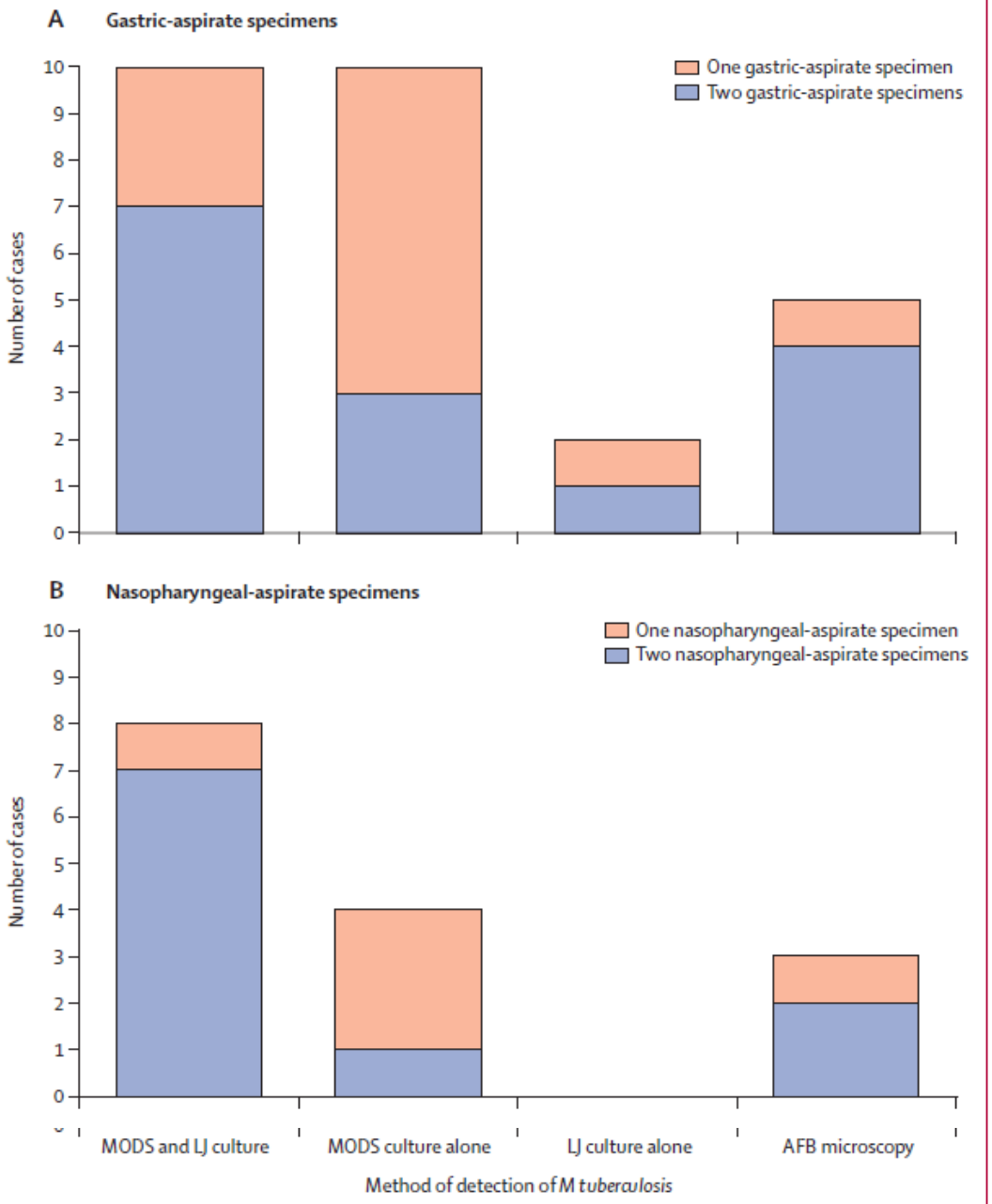
Cavitary TB





Pediatric TB

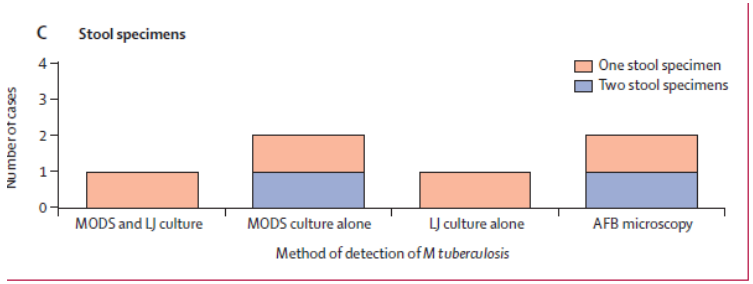




Diagnostic approaches for pediatric tuberculosis by use of different specimen types, culture methods, and PCR: a prospective case-control study.

Oberhelman et al. *Lancet Infect Dis* 2010; 10: 612–20

- 218 cases
- 10% positive cultures



re 2: Number of cases of tuberculosis detected by culture and microscopy, by specimen
DS=microscopic-observation drug-susceptibility. LJ= Lowenstein-Jensen agar. AFB=acid-fast bacilli.

Examples of Molecular Tests for Detection of TB (not all FDA-cleared)

Assay	Notes
Amplicor (Roche)	16S rRNA gene; smear +
MTD (GenProbe)	16S rRNA gene
Probe-Tec (BD)	16S rRNA & IS*6110*; smear +
Xpert Mtb/RIF (Cepheid)	rpoB gene
LAMP (Eiken; ?Meridian)	gyrA gene
GTMD (HAIN)	23S rRNA gene; smear +
Gold nanoparticle probe (Taiwan)	IS*6110* & Rv*3618*

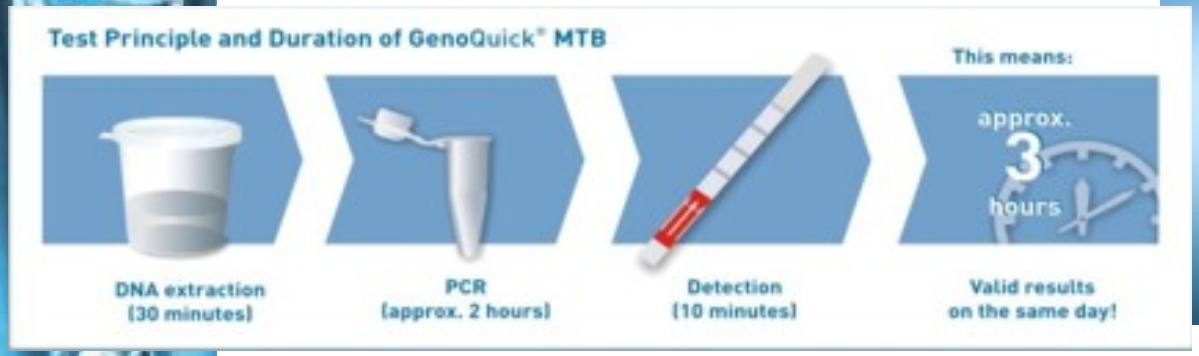
Most still require specimen decontamination & concentration

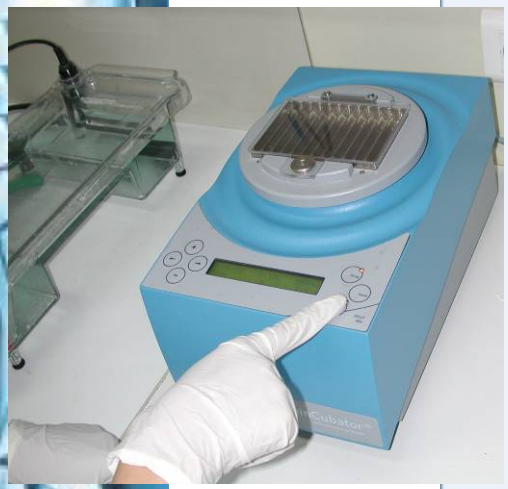
Evaluation of reverse transcription loop-mediated isothermal amplification in conjunction with ELISA-hybridization assay for molecular detection of Mycobacterium tuberculosis
Lee et al. 2009. J. Microbiol. Methods 76:174-

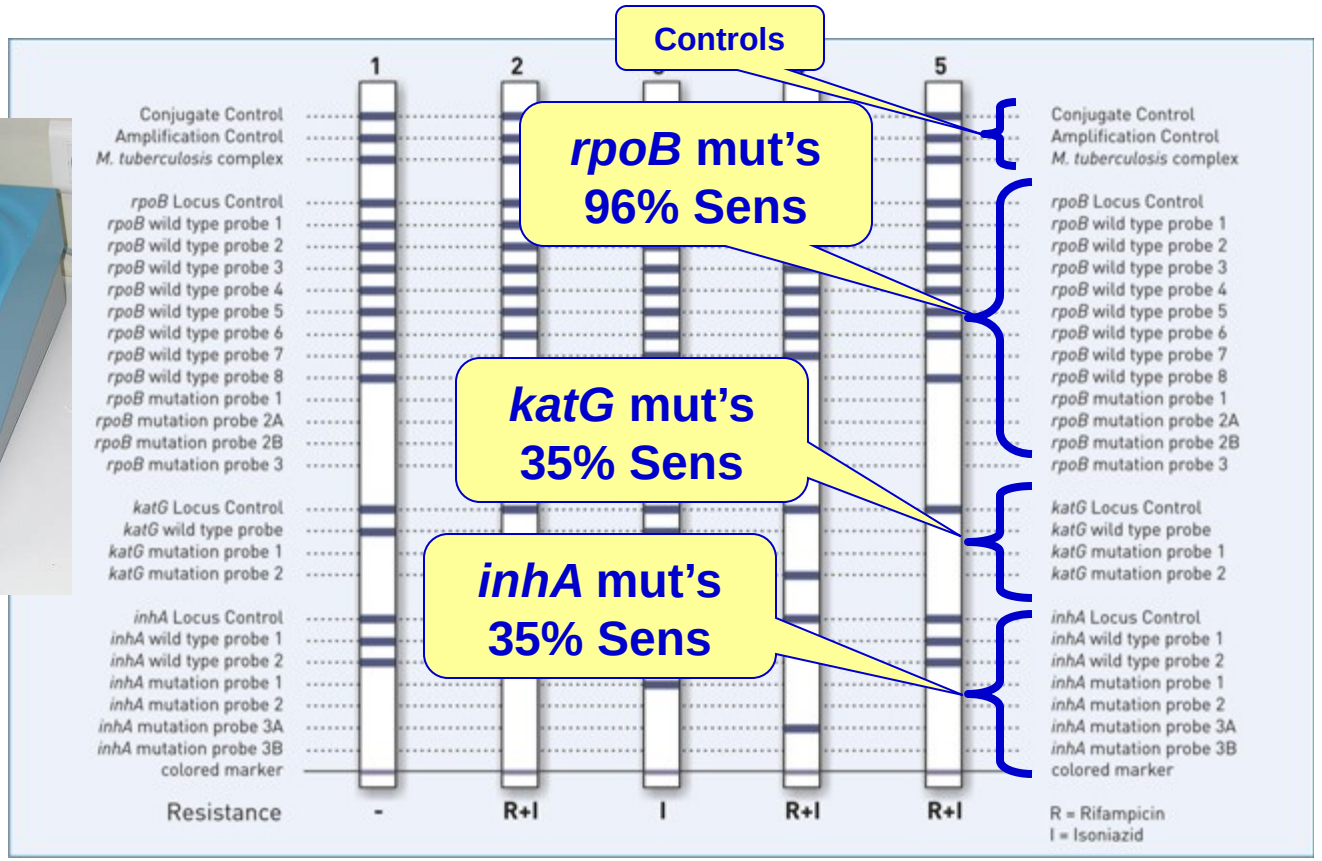
Operational Feasibility of Using Loop-Mediated Isothermal Amplification for Diagnosis of Pulmonary Tuberculosis in Microscopy Centers of Developing Countries
Boehme et al. 2007. J. Clin. Microbiol. 1936-

Results vs Sputum Culture	SENS	SPEC
Lee	94%	83%
Boehme		
Smear +	98%	99%
Smear neg	49%	

HAIN GTMD (~5 hr TAT)







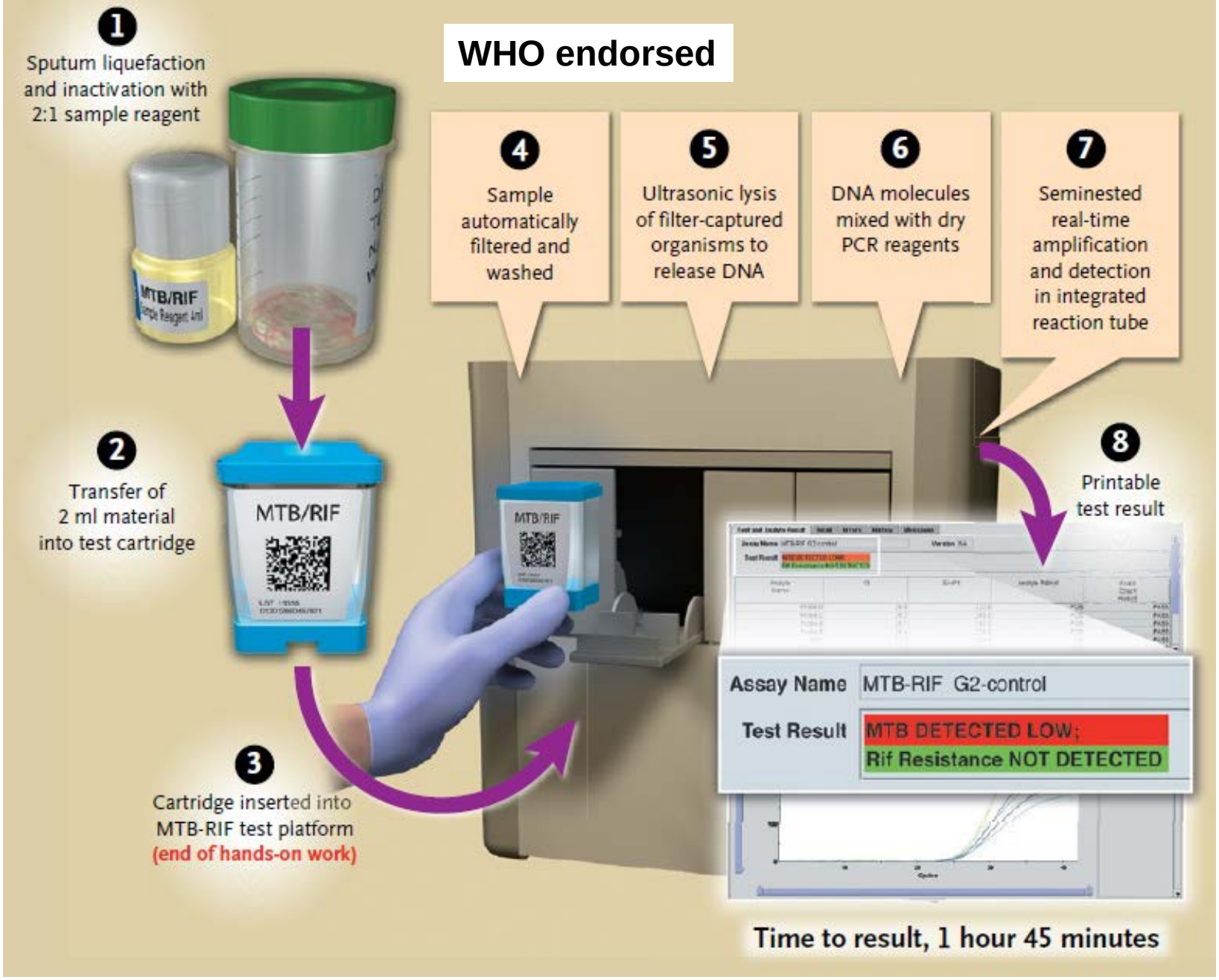
The NEW ENGLAND JOURNAL of MEDICINE

Rapid Molecular Detection of Tuberculosis and Rifampin Resistance

September 1, 2010

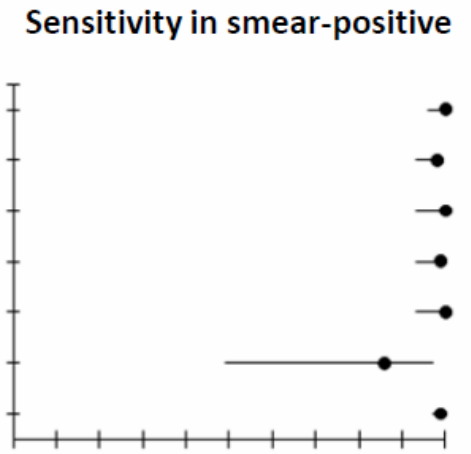
Catharina C. Boehme, M.D., Pamela Nabeta, M.D., Doris Hillemann, Ph.D., Mark Nicol, Ph.D., Shubhada Shenai, Ph.D., Fiorella Krapp, M.D., Jenny Allen, B.Tech., Rasim Tahirli, M.D., Robert Blakemore, B.S., Roxana Rustomjee, M.D., Ph.D., Ana Milovic, M.S., Martin Jones, Ph.D., Sean M. O'Brien, Ph.D., David H. Persing, M.D., Ph.D., Sabine Ruesch-Gerdes, M.D., Eduardo Gotuzzo, M.D., Camilla Rodrigues, M.D., David Alland, M.D., and Mark D. Perkins, M.D.

Cepheid GeneXpert assay

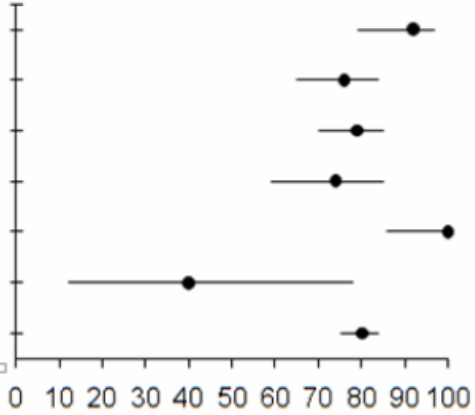

WHO endorsed
1
Sputum liquefaction and inactivation with 2:1 sample reagent
MTB/RIF
2
Transfer of 2 ml material into test cartridge
MTB/RIF
3
Cartridge inserted into MTB-RIF test platform
(end of hands-on work)
4
Sample automatically filtered and washed
5
Ultrasonic lysis of filter-captured organisms to release DNA
6
DNA molecules mixed with dry PCR reagents
7
Seminested real-time amplification and detection in integrated reaction tube
8
Printable test result
Assay Name
MTB-RIF G2-control
Test Result
MTB DETECTED LOW;
Rif Resistance NOT DETECTED
Time to result, 1 hour 45 minutes

Sensitivity of a single, direct Xpert in S+C+ and S-C+

Site	TP	FN	Sensitivity (95 CI)
Lima, Peru	88	0	100 (96-100)
Baku, Azerbaijan	99	2	98 (93-99)
Cape Town, SA	49	0	100 (93-100)
Kampala, Uganda	79	1	99 (93-100)
Vellore, India	49	0	100 (93-100)
Manila, Philippines	6	1	86 (49-97)
Total	370	4	99 (97-100)



Site	TP	FN	Sensitivity (95 CI)
Lima, Peru	35	3	92 (79-97)
Baku, Azerbaijan	59	19	76 (65-84)
Cape Town, SA	81	22	79 (70-85)
Kampala, Uganda	29	10	74 (59-85)
Vellore, India	24	0	100 (86-100)
Manila, Philippines	2	3	40 (12-78)
Total	230	57	80 (75-84)



(RUO* in U.S.; CE-IVD marked)

Boehme et al. 2011. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study
www.thelancet.com April 19

Non-Pulmonary Samples..

Hillemann et al. 2011 JCM 49:1202-5. (FIND Study)

Sample	#	Cult +
Tissues	245	30
CSF	0	0
Gastric	30	8
Pleural fluid	113	0
Stool	23	2
Urine	91	5

TABLE 2. Sensitivity and specificity of Xpert assay with culture method as reference standard

Specimen type	Sensitivity (%)	Specificity (%)
Tissue	69.0	98.4
CSF	Not calculable	100.0
Gastric fluid	87.5	100.0
Pleural fluid	Not calculable	98.1
Stool	100.0	91.7
Urine	100.0	98.6
Total	77.3	98.2

Contaminated cultures = 26

Non-TB mycobacteria = 17

Requires Lab Validation for non-pulmonary samples

Study on TB Prevalence in Cambodian Children

Dr. Rinn Song
Instructor Pediatrics
Harvard Medical School

Currently collaborating with FIND on pediatric TB issues

Dr. Anne Goldfeld
President and Co-Founder, Cambodian Health Committee

Professor of Medicine at Harvard Medical School and Professor of Immunology and Infectious Disease at the Harvard School of Public Health

Cambodian Health Committee
Global Health Committee

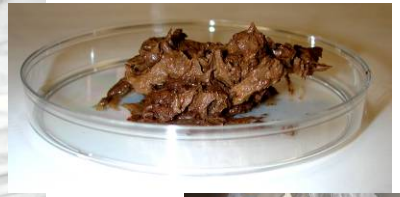
AERAS
Global TB Vaccine Foundation

Developing New Tuberculosis Vaccines for the World

Stop TB
Save Lives

Study Design

- Clinical criteria assessed (X-ray, skin test, IGRA, etc.)
- Samples collected over 3 days: 2 gastrics; 1 induced sputum; 1 stool
- Gastrics and sputum sent to Pasteur Instit. Lab in Phnom Penh for conventional culture, identification and susceptibilities of isolates (GenProbe; HAIN) and split and sent to Cambodian National TB Lab for Xpert® Mtb/Rif
- Stool frozen for later testing in Xpert ® Mtb/Rif

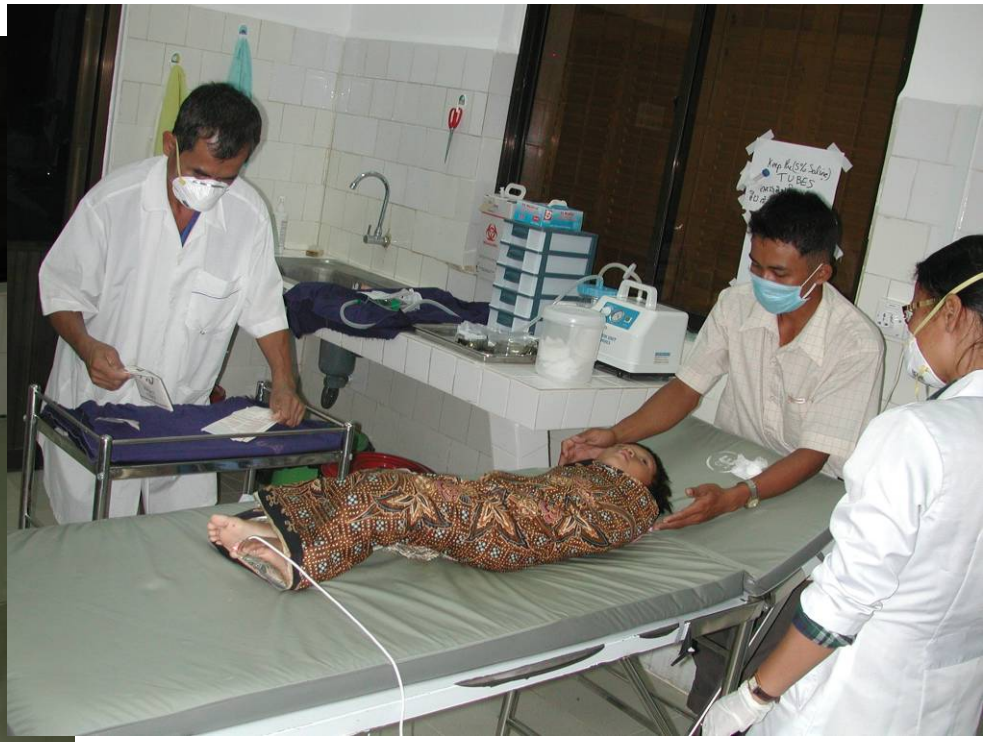


Sample Collection in Cambodia: Aerosol Induction

Albuterol pulse to open airways

15 min breathing saline mist

Aerosol Induction: Step 2

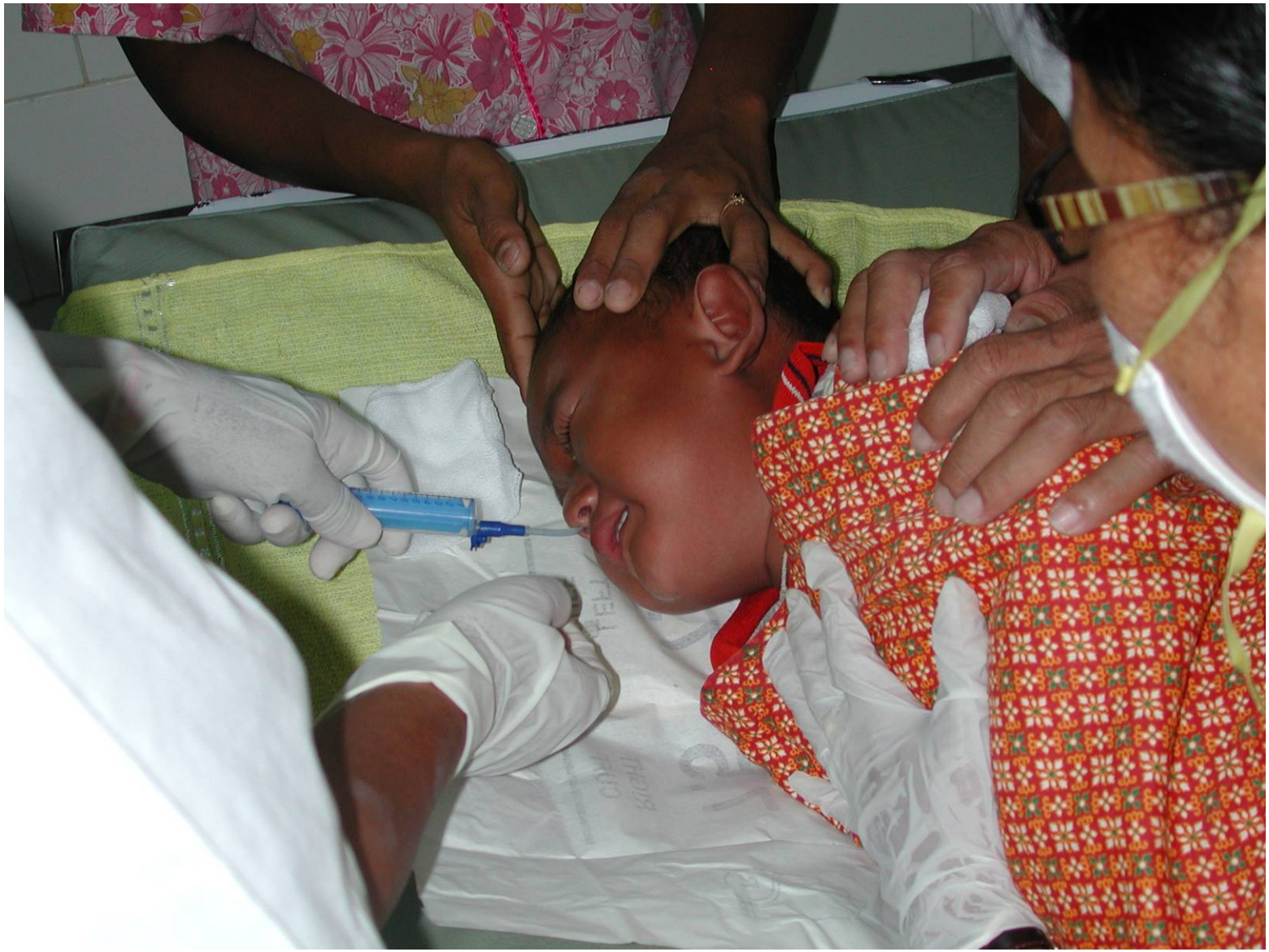


Aerosol Induction: Step 2

Gastric Aspirate

Gastric Aspirate

Gastric Aspirate



Gastric Aspirate

After the Procedures

OPEN ACCESS Freely available online

PLOS ONE

Enhancing TB Case Detection: Experience in Offering Upfront Xpert MTB/RIF Testing to Pediatric Presumptive TB and DR TB Cases for Early Rapid Diagnosis of Drug Sensitive and Drug Resistant TB

Neeraj Raizada[1]*, Kuldeep Singh Sachdeva[2], Sreenivas Achuthan Nair[3], Shubhangi Kulsange[1], Radhey Shayam Gupta[2], Rahul Thakur[1], Malik Parmar[3], Christen Gray[4], Ranjani Ramachandran[3], Bhavin Vadera[1], Shobha Ekka[1], Shikha Dhawan[2], Ameet Babre[1], Mayank Ghedia[3], Umesh Alavadi[1], Puneet Dewan[3], Mini Khetrapal[5], Ashwini Khanna[6], Catharina Boehme[4], Chinnambedu Nainarappan Paramsivan[1]

1 Foundation for Innovative New Diagnostics, New Delhi, India, **2** Central TB Division, Government of India, New Delhi, India, **3** World Health Organization, Country Office for India, New Delhi, India, **4** Foundation for Innovative New Diagnostics, Geneva, Switzerland, **5** District Tuberculosis Center, Mumbai, India, **6** District Tuberculosis Center, New Delhi, India

Accelerating access to quality TB care for paediatric TB suspects in 4 cities of India, though improved diagnostic strategies

Dr. Neeraj Raizada
Project Leader, FIND India

Xpert MTB/RIF & Smear Microscopy Performance

Specimen Type	Specimen Tested	Xpert Positive (%)	Smear Positive (%)	Rif Resistance (%)
Sputum/IS	10280	769 (7.5%)	334 (3.2%)	86 (11.2%)
Gastric Asp./Lavage	10026	603 (6.0%)	136 (1.4%)	56 (9.3%)
CSF	1808	127 (7.0%)	1 (0.1%)	16 (12.6%)
Pleural Fluid	733	29 (4.0%)	7 (1.0%)	4(13.8%)
BAL	647	96 (14.8%)	16 (2.5%)	8 (8.3%)
Pus	303	123 (40.6%)	29 (9.6%)	11 (8.9%)
Lymph Node/ FNAC	281	101 (35.9%)	13 (4.6%)	14(13.9%)
Ascetic Fluid	149	4 (2.7%)	1 (0.7%)	0 (0.0%)
Others*	272	40 (14.7%)	11 (4.0%)	7 (17.5%)
Total	**24,499**	**1,892(7.7%)**	**548 (2.2%)**	**202 (10.7%)**

Others= Tissue, Pericardial Fluid, Urine, Cervical Aspirate, Peritoneal Fluid, Tracheal aspirate, Abscess, Synovial Fluid, Serum Bone, Chyle fluid, Nasal Aspirate, Pleural Biopsy, Thoracic swab

Xpert MTB/Rif not validated for non-respiratory specimen types

Raizada et al.

Rifampicin Resistant Pediatric Cases

	Total Suspects	Total Xpert Positives	Total Rif Resistant	Proportion (%)
Total	**22079**	**1,735 (7.9%)**	**156 (9.0%)**	**100.0%**
Smear Status				
NA	1,057	60 (5.7%)		1.9%
Smear Negative	20,474	[illegible]		60.3%
Smear Positive	548	533 (97.3%)		37.8%
Past History of TB Rx				
Unknown	1,256	57 (4.5%)	0 (0.0%)	0.0%
Negative History	18,253	[illegible]	[illegible]	59.0%
Positive History	811	[illegible]	64 (21.3%)	41.0%
H/O contact with TB Patient				
Positive History		[illegible]	[illegible]	57.1%
Negative History		[illegible]	[illegible]	32.1%
Unknown		[illegible]	17	10.9%
Age Group (in years)				
<5	7419	376 (5.1%)	30 (8.0%)	19.2%
5 to 9	7362	405 (5.5%)	39 (9.6%)	25.0%
10 to 14	7298	954 (13.1%)	87 (9.1%)	55.8%

60% of rif resistant cases were smear negative

59% of rif resistant cases had no prior history of anti TB treatment

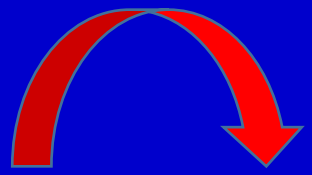
32% of rif resistant cases had no history of contact

Same level of rif resistance observed in all three age groups

Rif resistance detected in all age grps; Better correlation with H/O contact as compared to H/O past RX; >50% of cases- smear negative

MTB/Rif Ultra: Next Generation Test

- Current test is smear replacement
  - More sensitive than smear, but not as sensitive as culture
- No great reason for culture to be more sensitive than a nested PCR assay
- Multi-copy target provides 10-15 fold boost in sensitivity
- High resolution melt: improve accuracy for drug resistance
- ~30 minutes faster



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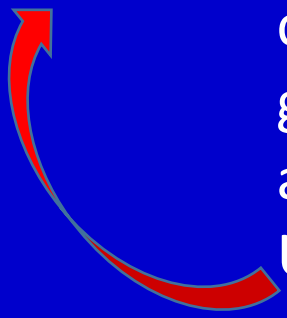
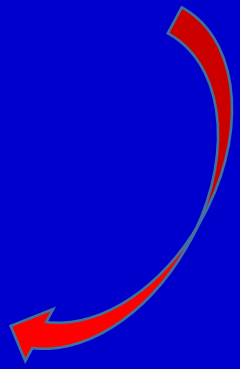
RUTGERS

Cepheid®

Early in 2014 our collaborative team met to create a TB test with the goal of being as sensitive as culture: The Xpert MTB Ultra





FIND
foundation
for innovative new diagnostics

Xpert Ultra: Increased performance with new fluidics and thermal cycling

New Multicopy target

Fully nested amplification – extra sensitivity.

Enhanced sample processing fluidics.

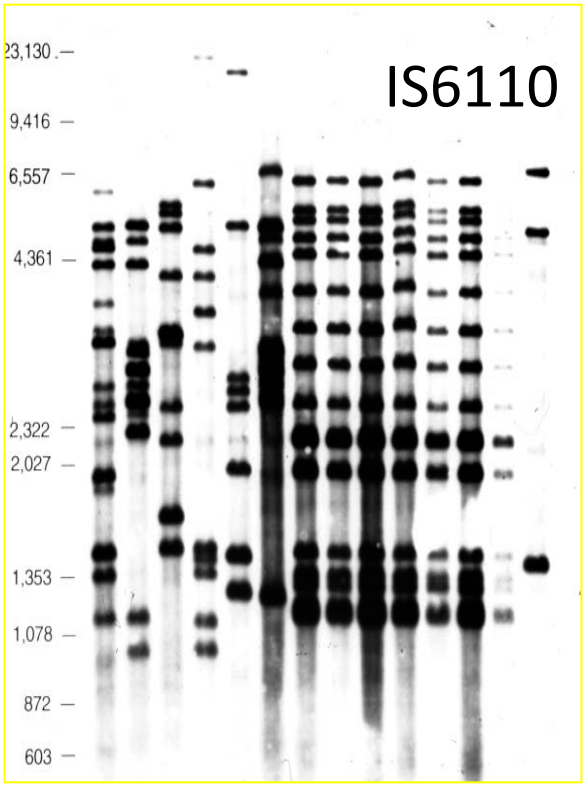
More rapid and better use of thermal cycling.

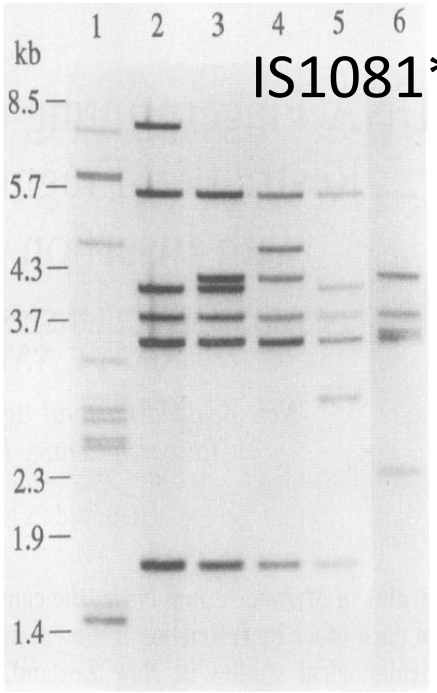
Time to result Xpert MTB/RIF = 110 min
Time to positive result Xpert Ultra = 80 min (estimated).
Time to negative result = 66 min (estimated).

Xpert Ultra: Increased sensitivity for TB detection

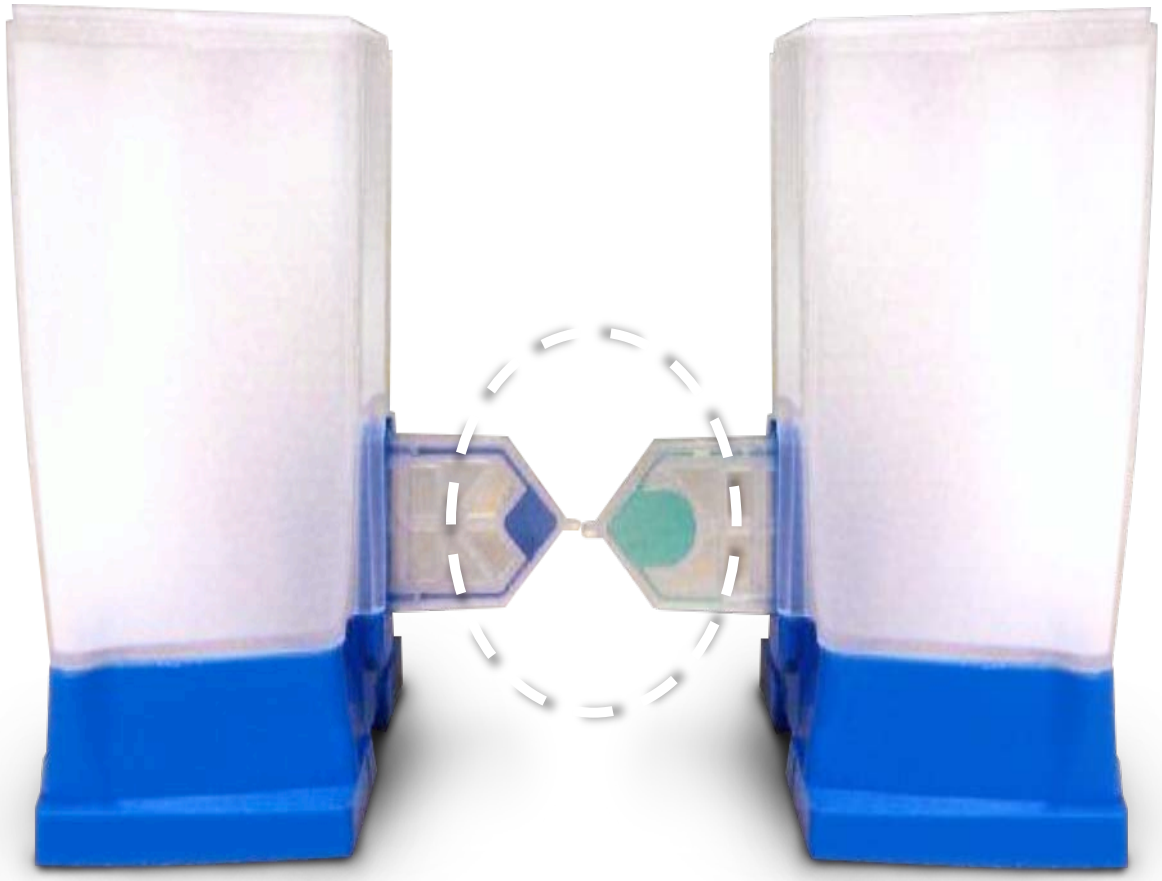
•Xpert MTB/RIF: Detects TB with a single copy target (*rpoB* gene)

•Ultra: Detects two different multi-copy targets (IS6110 & IS1081)





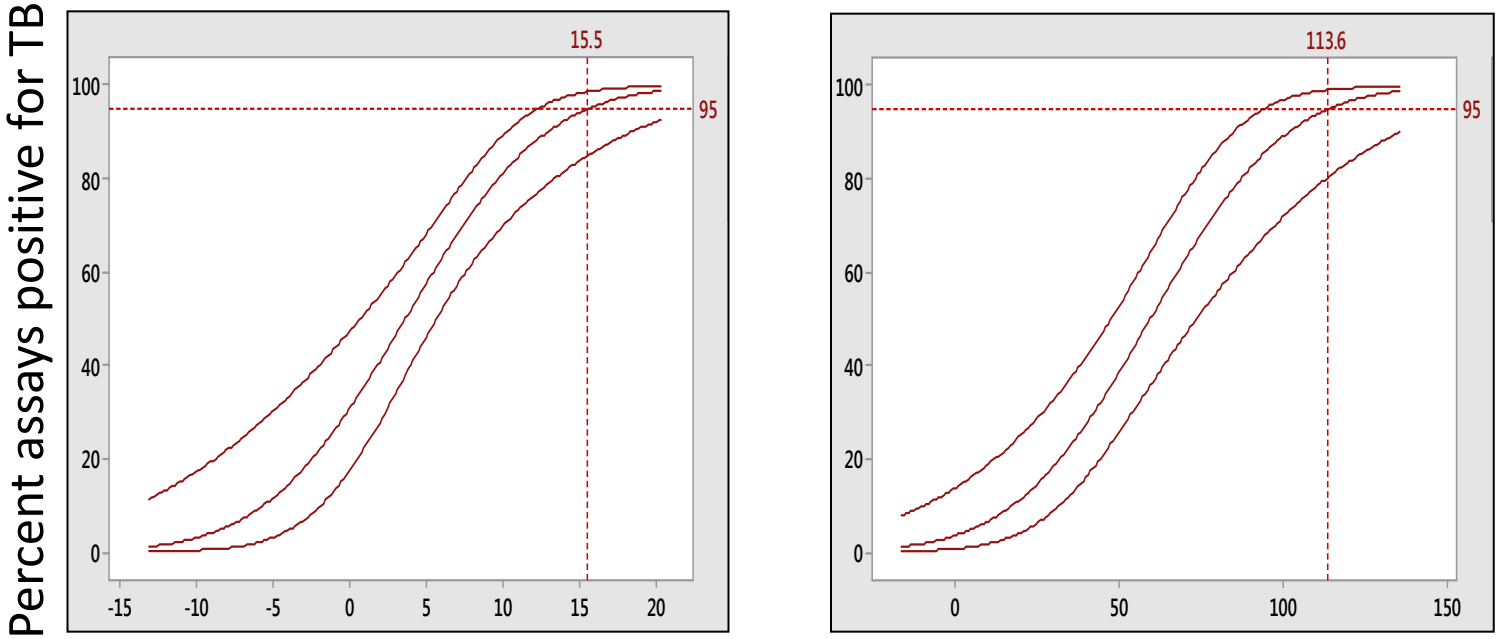
Xpert MTB/Rif Ultra: PCR Tube Size Matters



Limit of detection (LOD) of Ultra versus Xpert in spiked sputum samples

Ultra

Xpert

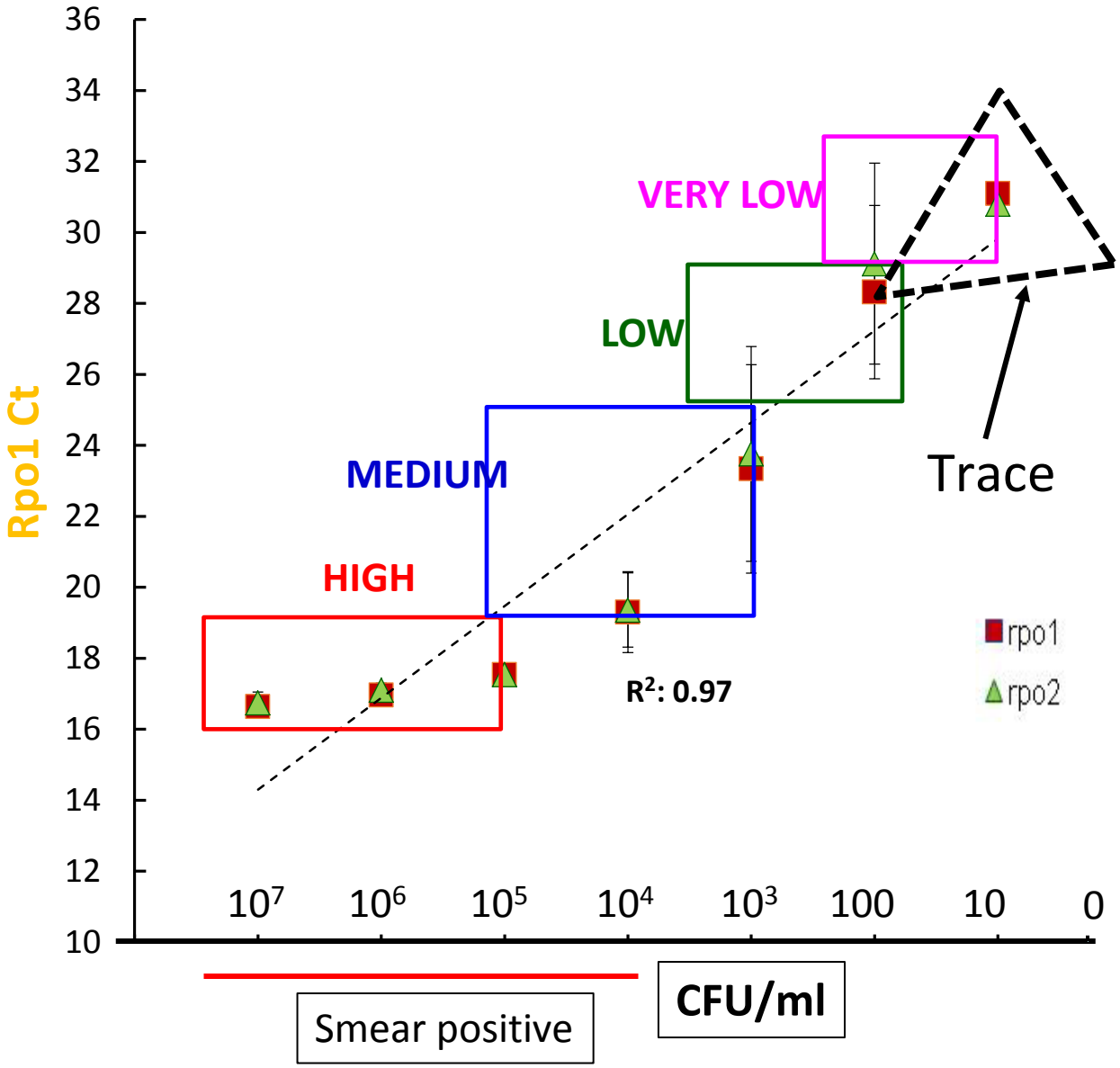


Assay limit of detection

Ultra: 15.5 CFU/ml

Xpert 113.6 CFU/ml

Dynamic range and semi-quantitation using first rpoB real-time signal (average Ct from 10 replicates).



Rifampin resistance testing by Xpert 98% sensitivity/specificity might not be good enough!

Mixed *Mycobacterium tuberculosis* Complex Infections and False-Negative Results for Rifampin Resistance by GeneXpert MTB/RIF Are Associated with Poor Clinical Outcomes

Nicola M. Zetola,[a,c,d] Sanghyuk S. Shin,[h] Kefentse A. Tumedi,[a] Keletso Moeti,[b] Ronald Ncube,[e] Mark Nicol,[f] Ronald G. Collman,[g] Jeffrey D. Klausner,[h] Chawangwa Modongo[a,c]

Limited ability to detect mixtures of susceptible and resistant TB

Comparison of Xpert MTB/RIF with Line Probe Assay for Detection of Rifampin-Monoresistant *Mycobacterium tuberculosis*

Syed Beenish Rufai, Parveen Kumar, Amit Singh, Suneel Prajapati, Veena Balooni, Sarman Singh

Potential difficulty detecting *rpoB* 533 C to G mutations (especially in mixtures) could lead to false susceptible results

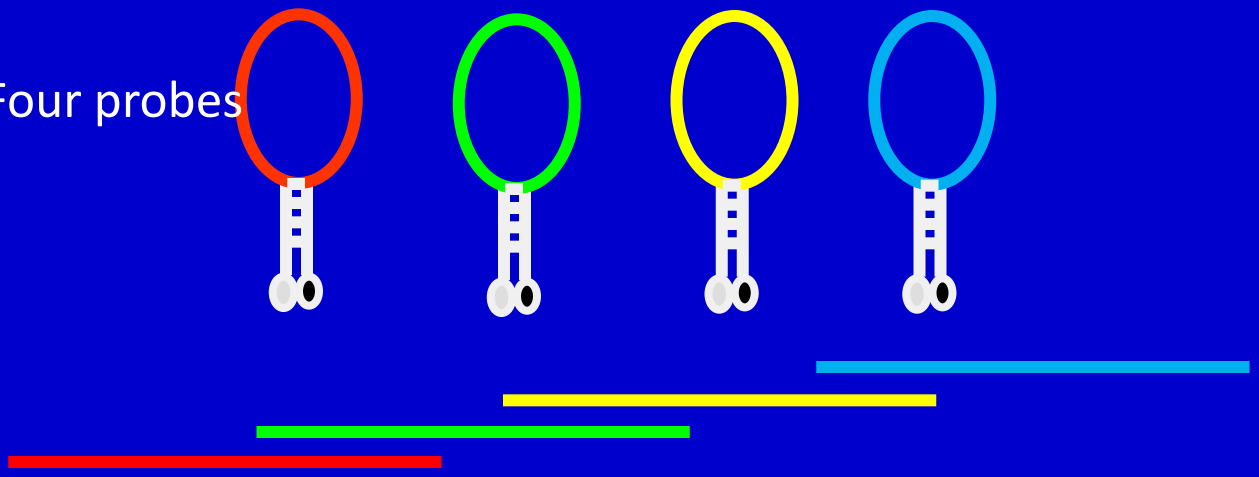
An evaluation of the Xpert MTB/RIF assay and detection of false-positive rifampicin resistance in *Mycobacterium tuberculosis*☆,☆☆

Deborah A. Williamson*, Indira Basu, James Bower, Joshua T. Freeman, Gillian Henderson, Sally A. Roberts

Occasional false positive for Rifampin resistance in samples with low bacterial loads due to delay of probe D or E!!!!

4 probes identify rifampin-R mutations in *rpoB* by shifting their Tm away from a wild type reference value.

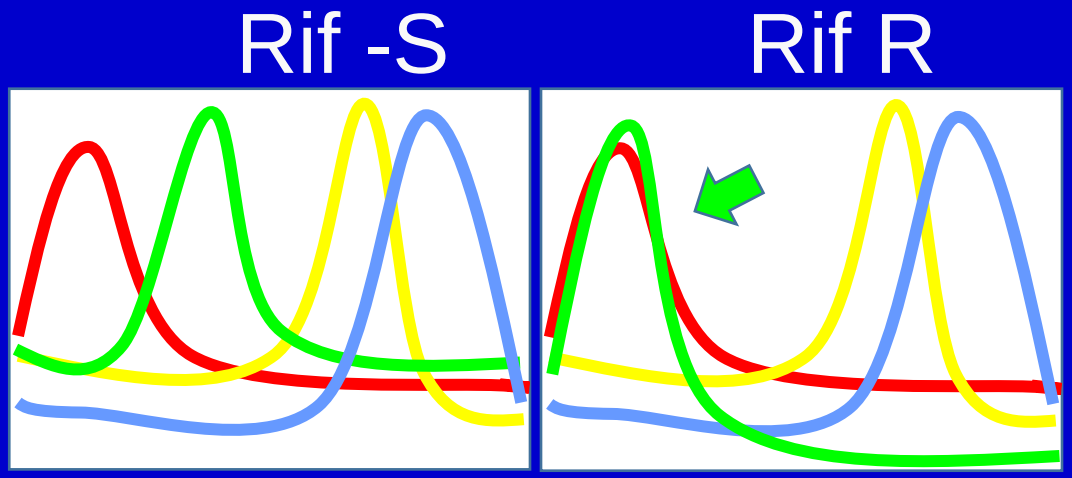
Four probes



rpoB core region. Any mutation = Rifampin resistance

Probes over lap *rpoB* sequence

<u>A clear change</u> in Tm distinguishes wild type from resistant mutant



Preliminary report from the first prospective clinical trial of the Ultra assay

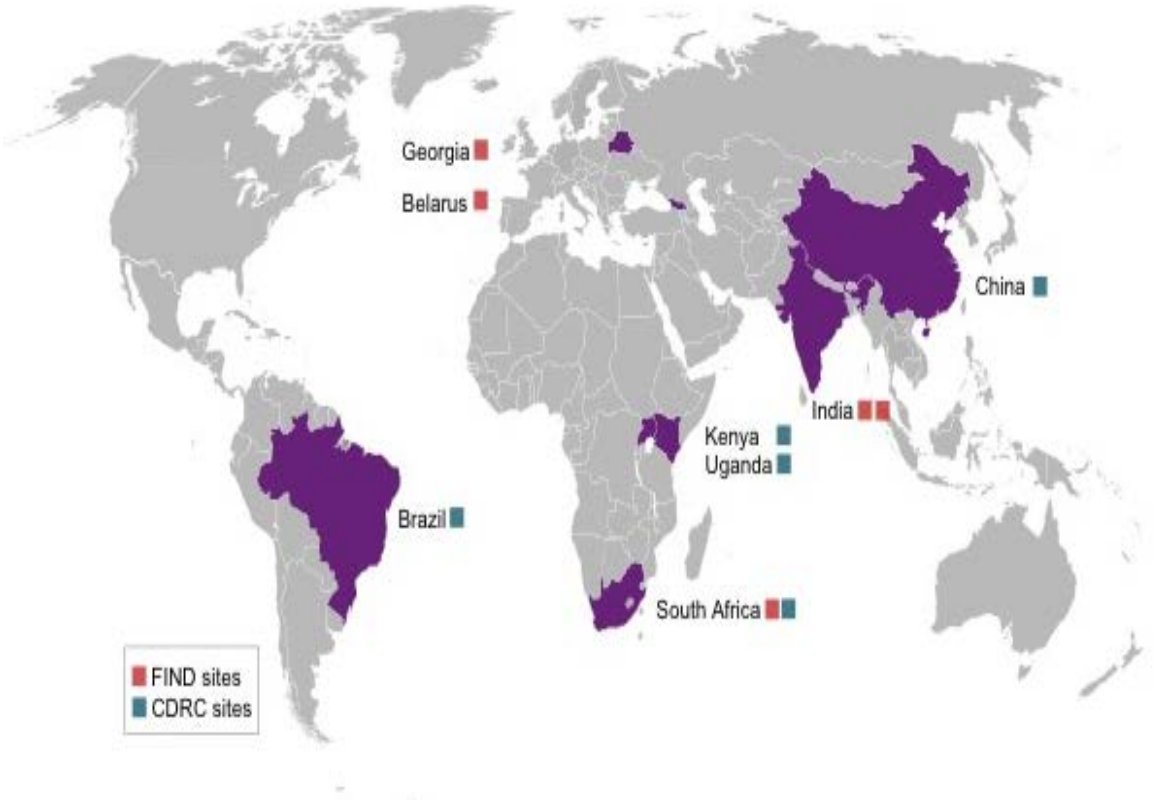
A Multicenter Diagnostic Accuracy Study Of The Xpert Ultra For Tuberculosis Diagnosis

Presenter: David Alland, MD.

Authors: Samuel G Schumacher[1], Pamela Nabeta[1], Catharina C Boehme[1], Jerrold Ellner[2], David Alland[3], Susan E Dorman[4], Claudia M Denkinger[1], for the TB Clinical Diagnostics Research Consortium and FIND Trial Consortium

Affiliations: [1]FIND, Geneva, Switzerland, [2]Boston Medical Center, Boston, MA, [3]Division of Infectious Diseases, Rutgers-New Jersey Medical School, Newark, [4]Johns Hopkins University, Baltimore, MD

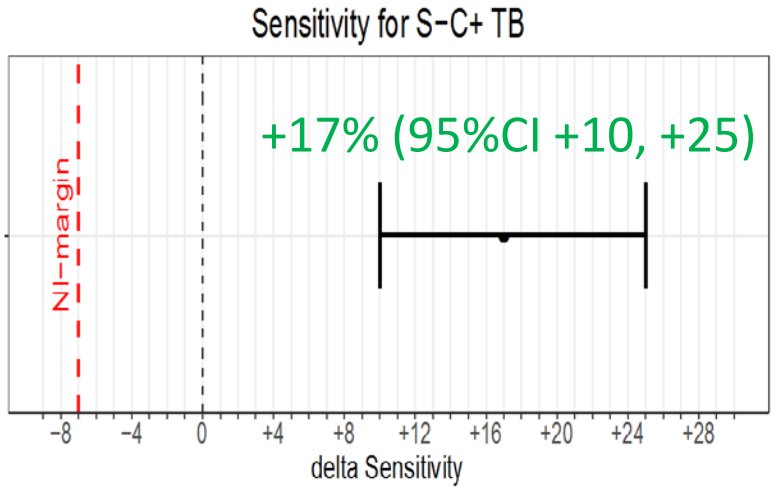
Study Design: Multicenter - 10 sites in 8 countries

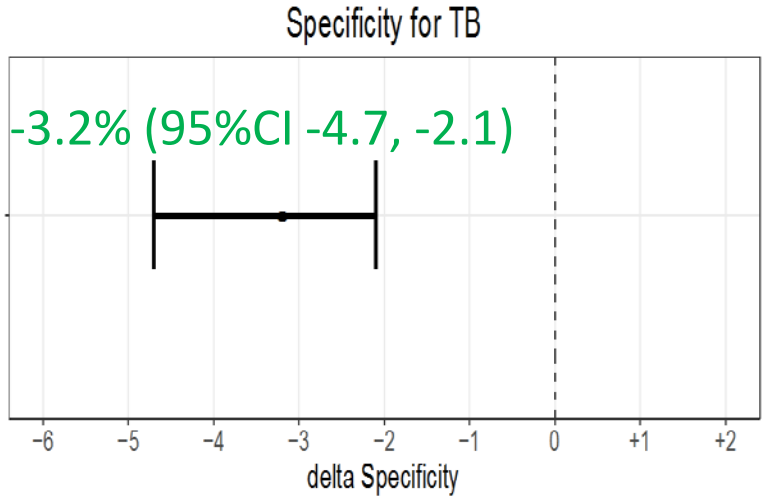


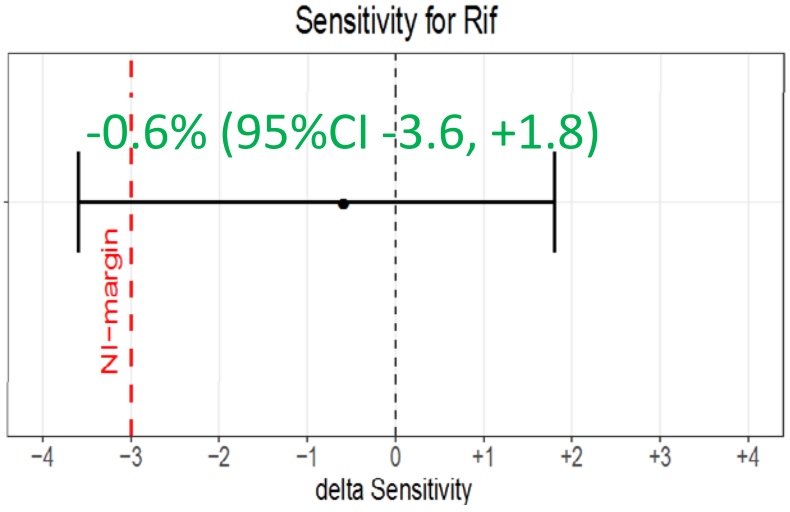
- Non-inferiority: Ultra versus Xpert
  - Reference standard culture/DST (4x)
  - Primary endpoint: Δ in sensitivity and specificity between Xpert Ultra and Xpert for detection of MTB and RIF
  - Both assays performed on same specimen
- Enrollment
  - Case detection group: patients under evaluation for TB (no TB treatment in past 6 months)
  - MDR risk group: patients under evaluation for TB/MDR-TB (may already be on TB treatment)
- Analyses
  - MTB detection analysis: limited to case detection group
  - RIF detection analysis: done in all participants (Case detection group & MDR risk group)

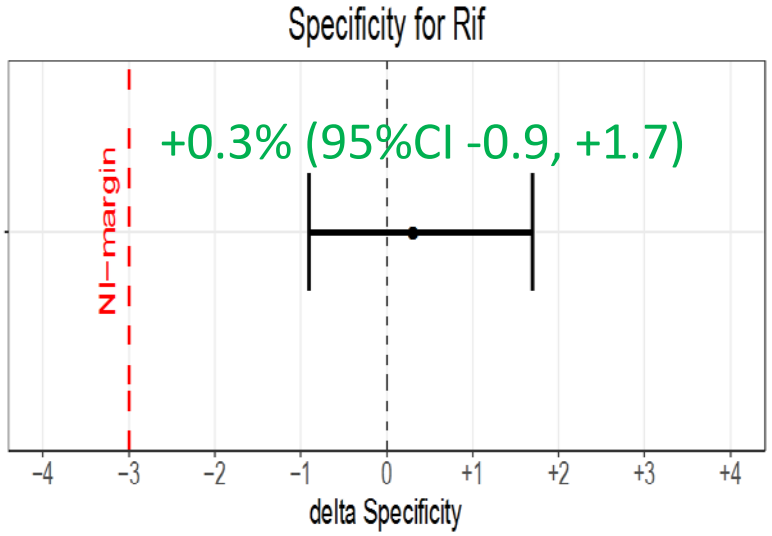
- Total 1,520 participants met eligibility criteria Feb – Oct 2016
  - 1,243 participants in ‘Case Detection Group’
  - 277 participants in ’MDR-risk Group’
- Case Detection Group
  - 403 (32.4%) were culture-positive - 119 (29.5%) were smear-negative
  - 840 (67.6%) were culture-negative – ie not TB
- Among all 1,520 participants
  - 187 (**12.3%**) were rifampin-resistant
  - 416 (**27.4%**) were rifampin-sensitive
- 25% were HIV-infected and 21% had a history of prior TB

Results: Non-inferiority analysis









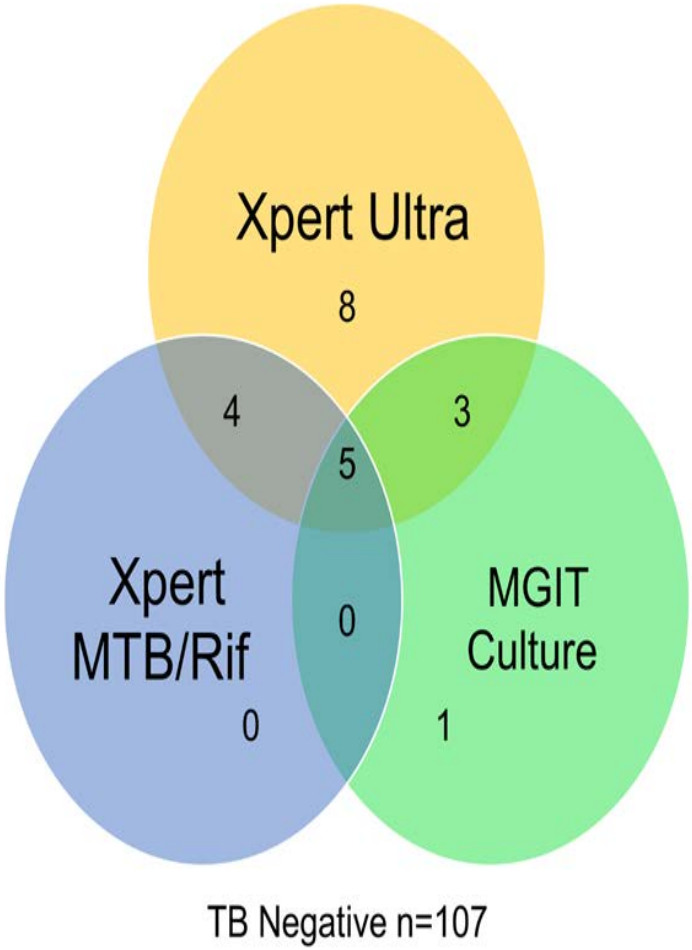
Δ sensitivity for HIV-infected: +12% (95%CI +4.9, +21)

Conclusions- MTB/Rif Ultra Studies

- Ultra has superior sensitivity compared to Xpert in smear-negative (+17%) and HIV-infected patients (+12%)
- Ultra also detects TB DNA in some patients with prior TB disease, possibly due to persistence of non-viable bacilli, leading to reduced specificity.
- Improved Rif R accuracy
- Whether *M. tuberculosis* culture-negative but Ultra test-positive patients represent a high risk group for relapse remains to be determined.
- Despite these questions, WHO endorsed Ultra on March 24, 2017.

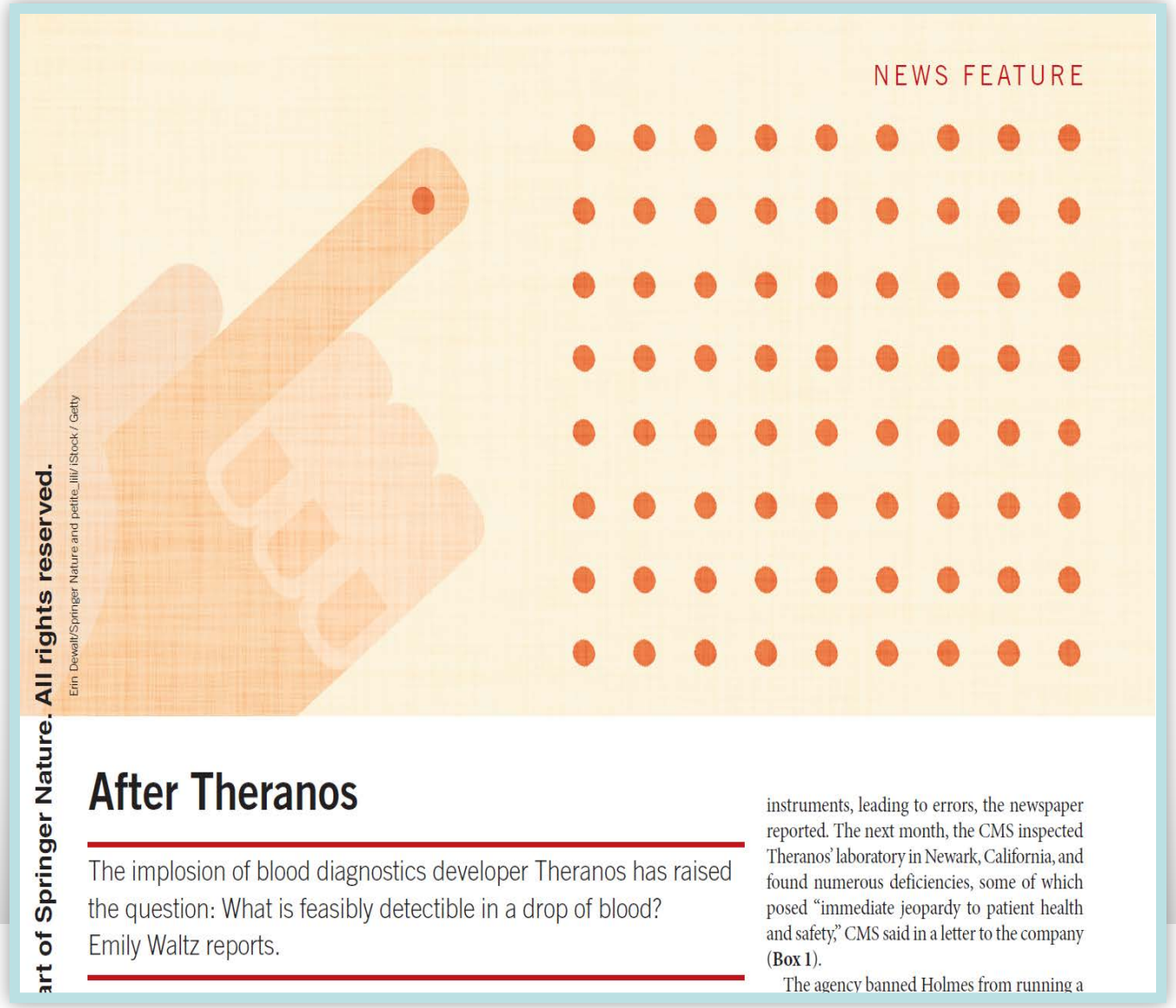
MTB/RIF Ultra: More Sensitive for Extrapulmonary TB

- **TB meningitis is a life-threatening condition and difficult to diagnose**
- **128 HIV infected adults tested in Mbarara, Uganda**
- **Sensitivity of culture: 43% for clinically and microbiologically-proven definite TB meningitis**
- **Sensitivity of G4: 43% (9/21; P=0.002)**
- **Sensitivity of Ultra: 95% (20/21)**



Quote from David Boulware, MD (PI):
"This is a game changer"

After Theranos: What?



Erin Dewalt/Springer Nature and petite_lili/iStock / Getty

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The agency banned Holmes from running a

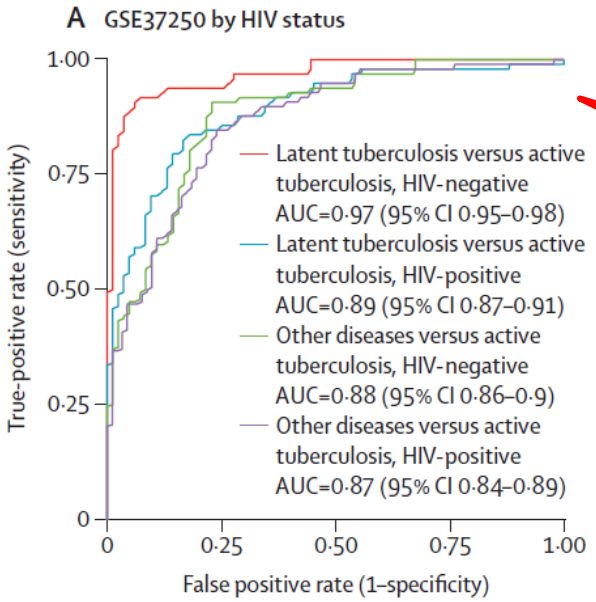
Blood-Based Tuberculosis Biomarkers

Genome-wide expression for diagnosis of pulmonary tuberculosis: a multicohort analysis

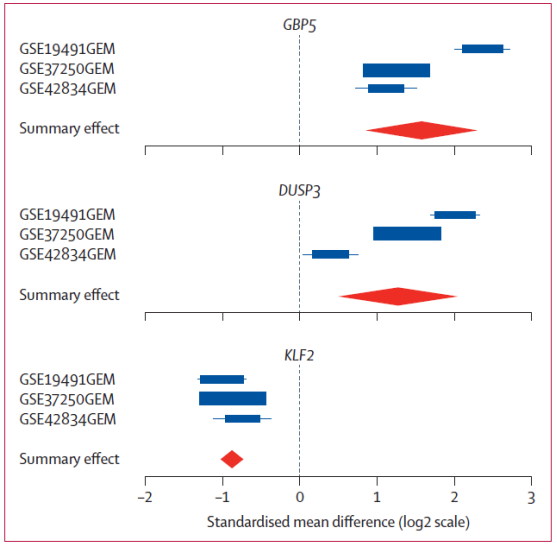
Lancet Respir Med 2016; 4: 213–224

Timothy E Sweeney, Lindsay Braviak, Cristina M Tato, Purvesh Khatri

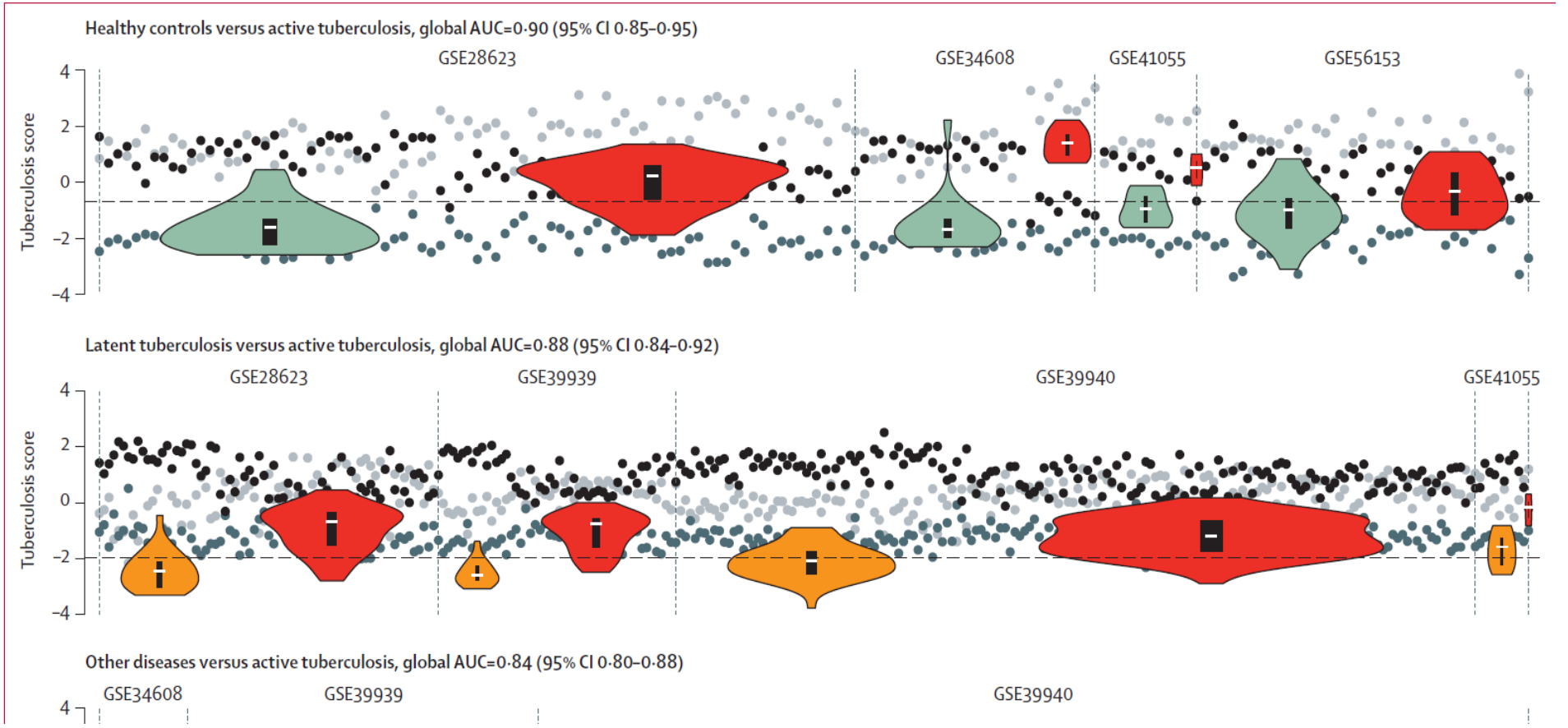
- **14 data sets, 2572 samples from 10 countries, adult and pediatric patients**
- **Only whole blood data included**
- **266 genes (158 over-expressed; 108 under-expressed)**
- **Narrowed down to 3 genes**
- **Robert Wallis, now with Aurum Institute, already developing a test**



No effect of HIV status



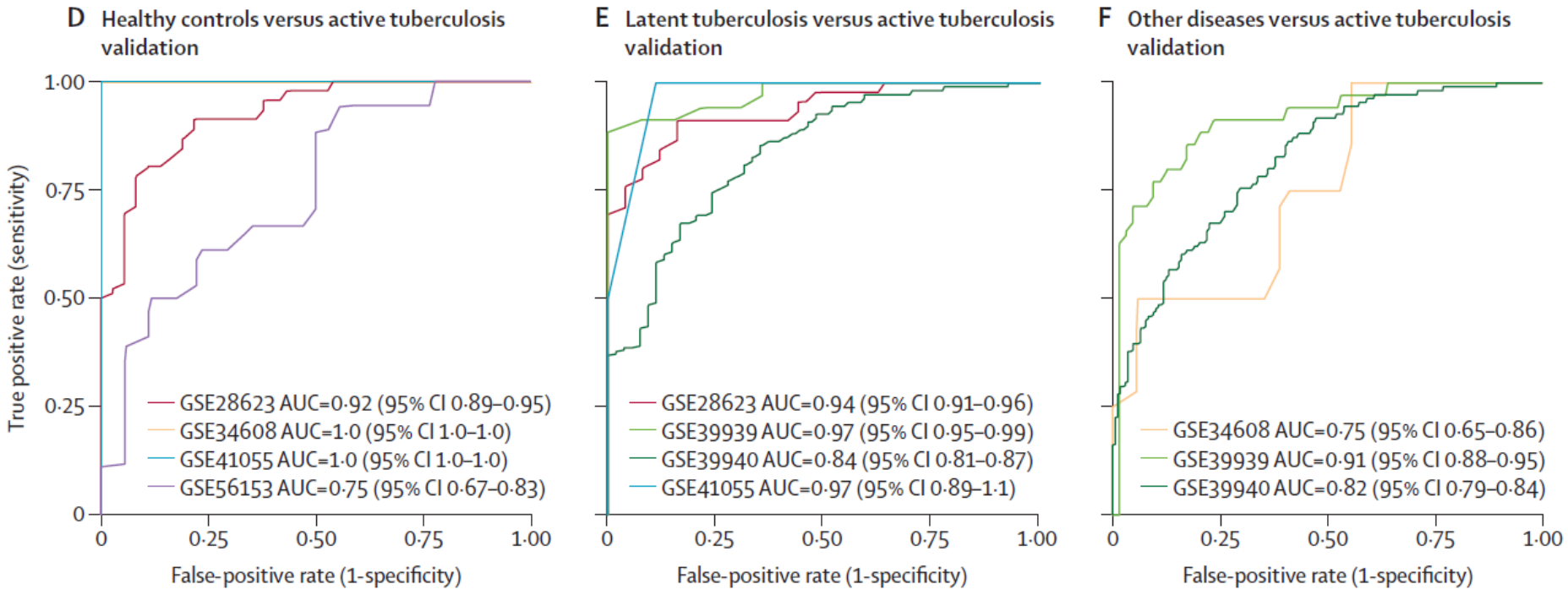
Violin Plots of Different Data Sets (need different cutoff scores)



3 most informative genes from peripheral blood:

(DUSP3, GBP5, KLF2)

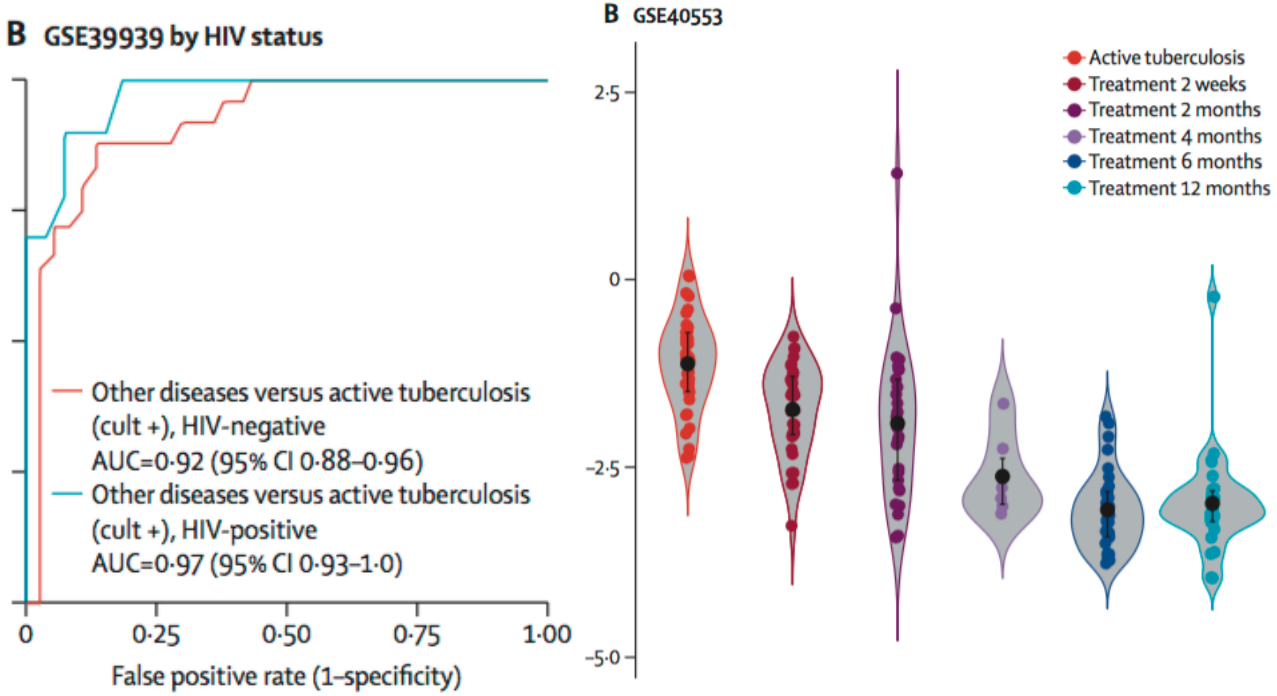
Validation ROCs



ATB Diagnosis vs healthy, LTB and other diseases
sensitivity = 86%; specificity = 86%; NPV = 99% @ 10% prevalence

Sweeney *et al. Lancet Resp Med* 2016

Other Important Findings



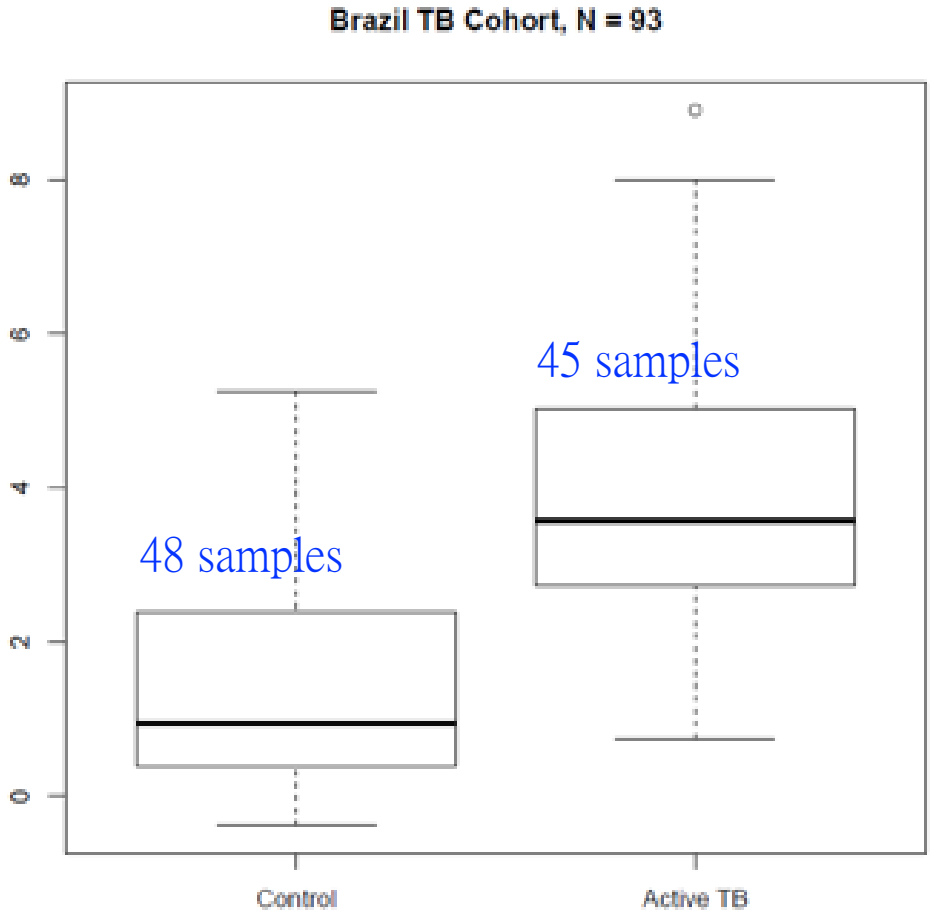
Not confounded by HIV co-infection

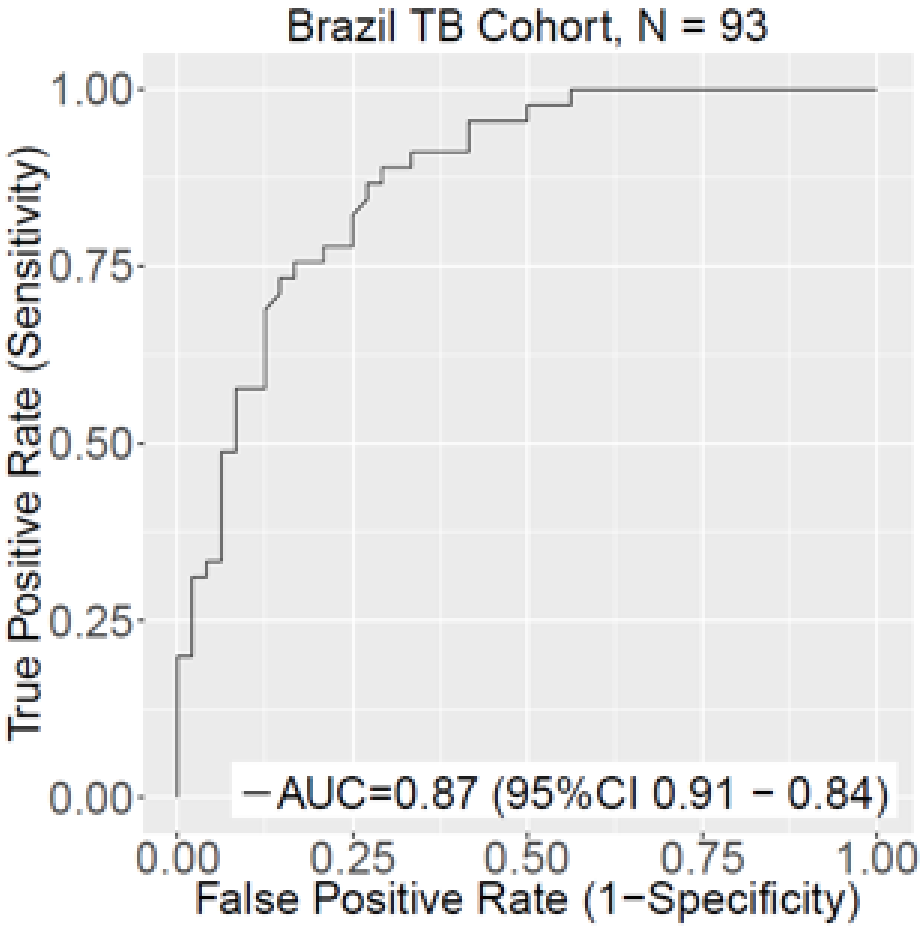
May allow monitoring treatment response

Not confounded by BCG vaccination

Sweeney *et al. Lancet Resp Med* 2016

Real Data: 3-Gene Signature Maintains Accuracy in Active Case Finding Screen



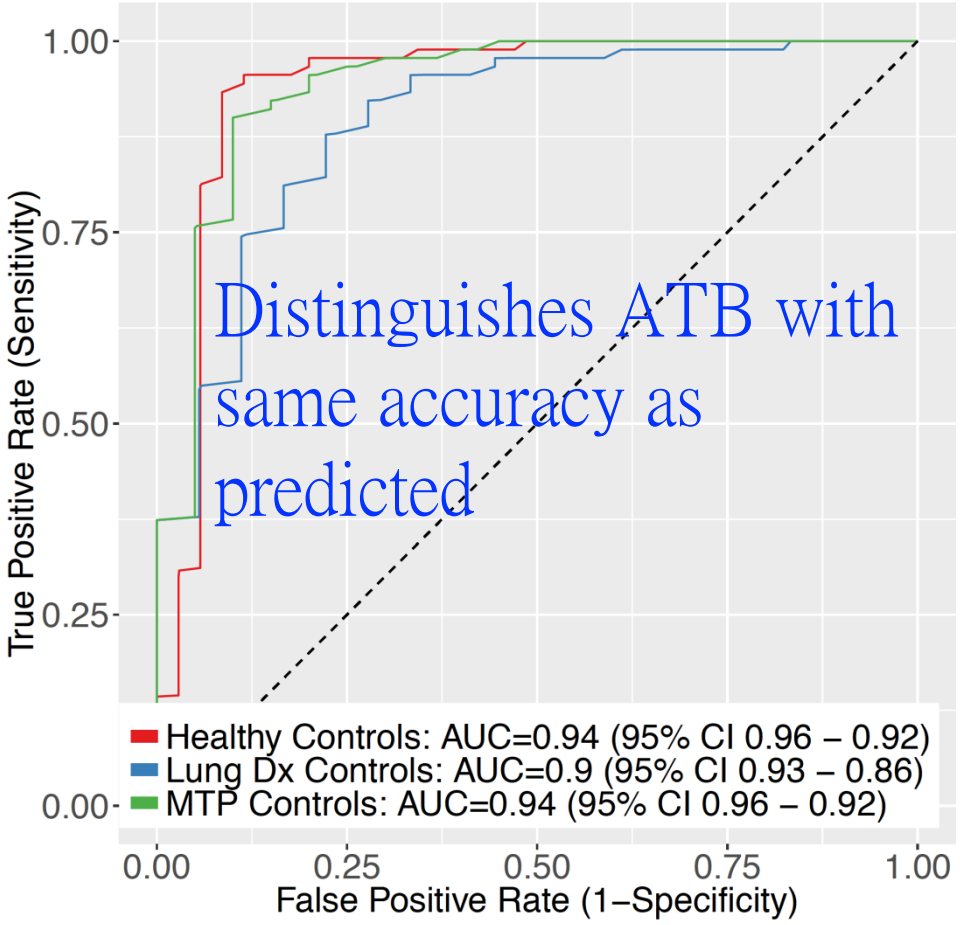


- Prospectively enrolled in Brazil (Julio Croda and Jason Andrews)
- Active case-finding (low severity patients)
- PCR and culture-defined positivity

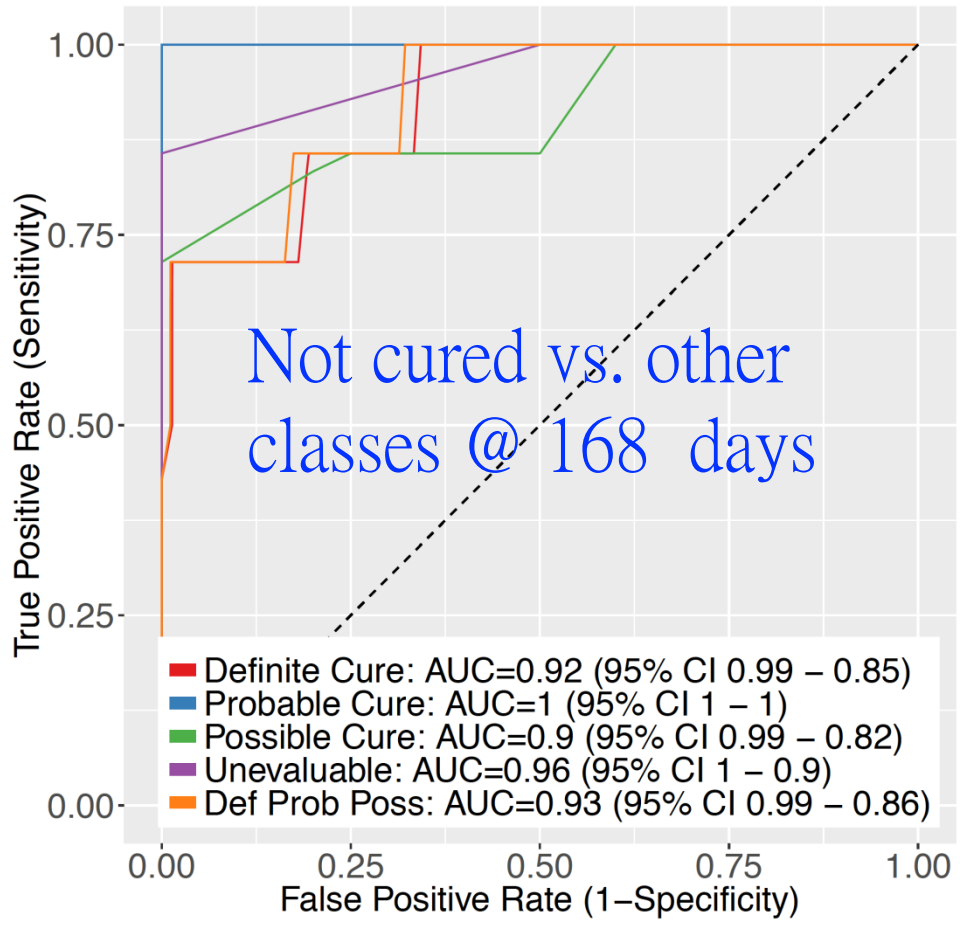
Persisting positron emission tomography lesion activity and *Mycobacterium tuberculosis* mRNA after tuberculosis cure

Stephanus T Malherbe[1,2], Shubhada Shenai[3], Katharina Ronacher[1,2], Andre G Loxton[1,2], Gregory Dolganov[4], Magdalena Kriel[1,2], Tran Van[4], Ray Y Chen[5], James Warwick[6,7], Laura E Via[5,8], Taeksun Song[9], Myungsun Lee[9], Gary Schoolnik[4], Gerard Tromp[1,2], David Alland[3], Clifton E Barry III[1,2,5,8], Jill Winter[10], Gerhard Walzl[1,2], the Catalysis TB–Biomarker Consortium[15]

Nature Medicine 2016



Active TB diagnosis



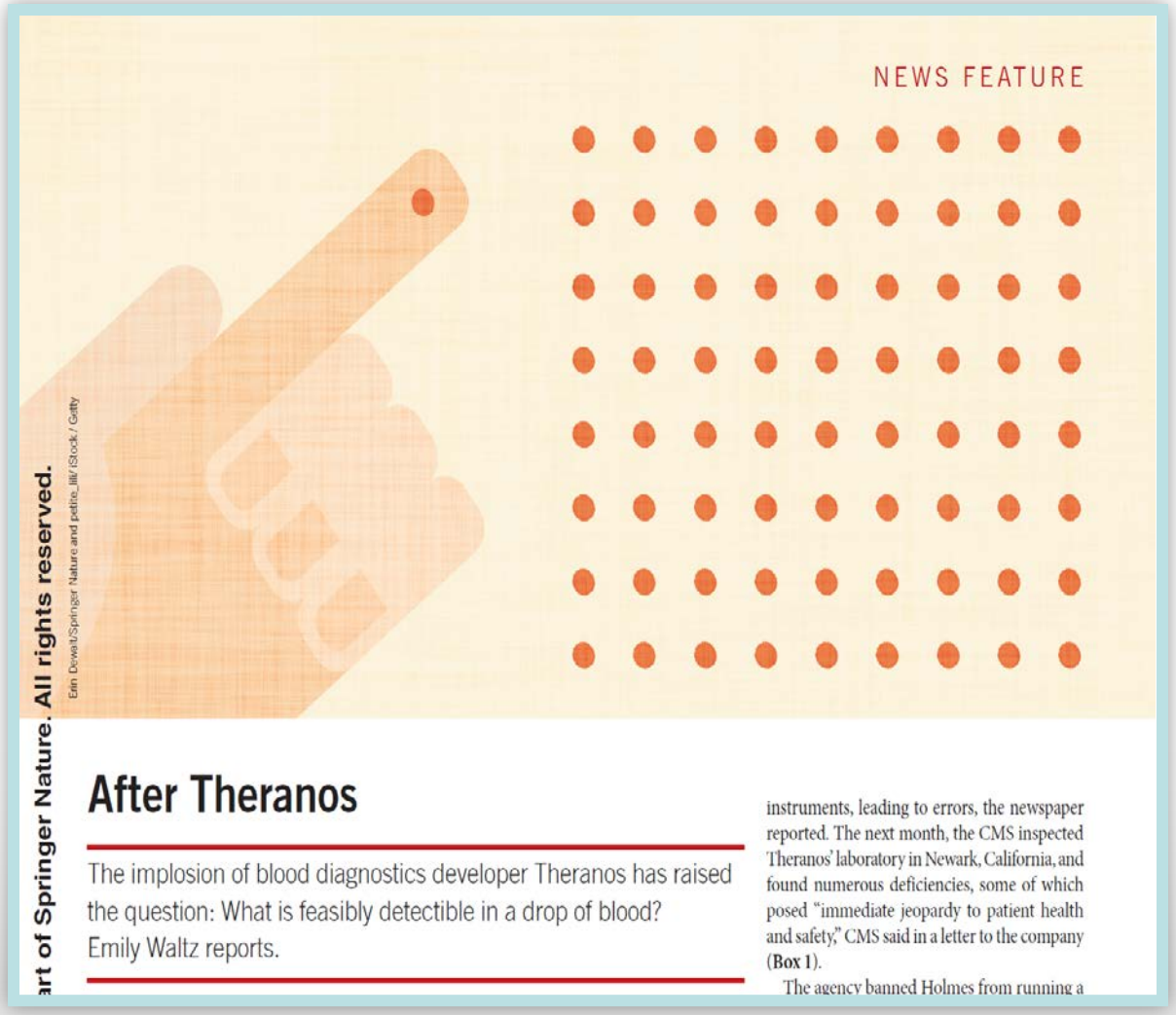
Predicting treatment response

Unpublished data

Summary

- 3-gene whole blood signature
  1. Seems able to distinguish ATB from LTB, other lung diseases and healthy controls
  2. Preliminary but successful validated using PCR in a prospective cohort for active case finding
  3. Can identify treatment non-responders at the end-of-treatment

After Theranos: What?



NEWS FEATURE

Erin Dewalt/Springer Nature and petrie_lili/iStock / Getty

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Potentially a lot:

HIV qual for case detection and EID

HIV quant (Gates project)

Ebola (Gates funded)

HCV quant

Active TB?

Viral versus bacterial

Addressing the Dx Dilemma of TB

- Still very challenging given its nonspecific presentation and paucibacillary nature
- More sensitive detection methods may help
- Validation of non-pulmonary samples, including stool, may help
- Non invasive blood based signatures may hold promise to fill some of the gaps