



TB suspects





# EPTB

- Worldwide: 25% of all TB (even higher in HIV and paediatrics)
  - Limited diagnostics tests
  - No gold standard
  - Culture based methods not adequate
  - No standardized processing e.g. concentration
- Composite reference standard is often used (radiological and histological evidence)
- Sample collection: invasive procedures

### Vadwai et al. J Clin Microbiol 2011, 40(7):2540 - 2545

Method compared to CRS <sup>a</sup>	Biopsy specimens		Pus		Body fluids		CSF		Total (pooled)	
	% positive specimens (no. of positive specimens/total no. of specimens)	95% CI	% positive specimens (no. of positive specimens/total no. of specimens)	95% CI	% positive specimens (no. of positive specimens/total no. of specimens)	95% CI	% positive specimens (no. of positive specimens/total no. of specimens)	95% CI	% positive specimens (no. of positive specimens/total no. of specimens)	95% CI
Culture sensitivity	50 (70/139)	42-59	64 (56/103)	45-64	62 (21/34)	45-76	43 (3/7)	16-75	53 (150/283)	47-59
Xpert sensitivity All CRS positive	75 (105/139)	68-82	95 (98/103)	8998	71 (24/34)	54-83	29 (2/7)	8-65	81 (228/283)	76-85
S-CRS+	62 (48/78)	50-72	90 (26/29)	73-97	57 (13/23)	37-74	29 (2/7)	8-65	64 (89/138)	56-72

- Low numbers especially for CSF
- Low culture sensitivity (many patients on anti-TB therapy, decontamination methods)
- Pooled sensitivity smear neg 64%, smear pos 96% and specificity 99.6%







Denkinger et al. ERJ Express 2014 published 2 April					
18 studies (44	61 samples)				
Sample proces studies	ssing varied grea	tly among the			
Xpert sensitivi sample types	ty differed subst	antially between			
Xpert sensitivi sample types <sup>Site</sup>	ty differed subst	Pooled Specificity (vs.			
Xpert sensitivi sample types Site Lymph node (tissue or aspirate)	ty differed subst Pooled Sensitivity (vs. Culture) 83.1%	Pooled Specificity (vs. CRS) 81.2%			
Xpert sensitivi sample types Site Lymph node (tissue or aspirate) CSF	ty differed subst Pooled Sensitivity (vs. Culture) 83.1% 80.5	Pooled Specificity (vs. CRS) 81.2%			

### WHO Policy update in 2013

Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance:

Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children

- 22 studies (7 unpublished), 5922 samples
- 59% in high burden settings

Specimen type	Comparison (No. of studies, No. of samples)	Median (%) pooled sensitivity (pooled 95% Crl)	Median (%) poolec specificity (pooled 95% Crl)
	Xpert MTB/RIF compared against culture	84.9 (72–92)	92.5 (80–97)
Lymph node tissue	(14 studies, 849 samples)		
and aspirate	Xpert MTB/RIF compared against a composite reference standard (5 studies, 1 unpublished)	83.7 (74–90)	99.2 (88–100)
Cerebrospinal fluid	Xpert MTB/RIF compared against culture (16 studies, ZO9 samples)	79.5 (62–90)	98.6 (96–100)
	Xpert MTB/RIF compared against a composite reference standard (6 studies, 512 samples)	55.5 (51–81)	98.8 (95–100)

	Xpert MTB/RIF compared against	43.7	98.1
	culture	(25-65)	(95-99)
	(17 studies, 1385 samples)		
leural fluia	Xpert MTB/RIF compared against	17	99.9
	a composite reference standard	(8-34)	(94-100)
	(7 studies, 698 samples)		•
	Xpert MTB/RIF compared against	83.8	98.1
Gastric lavage	culture	(66-93)	(92-100)
and aspirate	(12 studies, 1258 samples)		
od in	Xpert MTB/RIF compared against	81.2	98.1
Other fissue	culture	(68–90)	(87-100)
samples	(12 studies, 699 samples)		

Box	<ol> <li>Using Xpert MTB/RIF to diagnose extrapulmonary TB and rifampicin resistance in adults and children</li> </ol>
Thes	se recommendations should be read in conjunction with the remarks in section 5.2.
•	Xpert MTB/RIF should be used in preference to conventional microscopy and culture as the initial diagnostic test for CSF specimens from patients suspected of having TB meningtits (strong recommendation given the urgency for rapid diagnosis, very low-quality evidence).
	Xpert MTB/RIF may be used as a replacement test for usual practice (including conventional microscopy, culture or histopathology) for testing specific nonrespiratory specimens (lymph nodes and other tissues) from patients suspected of having extrapulmonary TB (conditional recommendation, very lowquality evidence).





- Additional 124 specimen results that were contaminated by MGIT
- Proposed routine testing, setting up SOPs for SA



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Evaluation of GeneXpert MTB/RIF for Diagnosis of Tuberculous Meningitis

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- Vietnam study, 379 suspected TB meningitis
- Sensitivities: Xpert (59.3%), ZN smear (78.6%) and MGIT culture (66.5%)
- Recommended meticulous examination via smear, although not always practical
- Xpert can be an advance



### Overview

- 500 000 1 000 000 new childhood cases (yet true burden unknown)
- Majority: Smear and culture negative
- Dx: Clinical
- Overdiagnosis  $\rightarrow$  inappropriate treatment
- Underdiagnosis  $\rightarrow$  poor outcome
- HIV (co-infection 5 50%)
- · Limitations of the tuberculin skin test and IGRAs
- Investigation: usually hospital admission for gastric lavages or induced sputum

# Vs. Adults?

- Children are at much higher risk of progression to active disease
- This risk is greatest for infants and children under 2
- Majority of children develop radiological abnormalities however they control the disease by the host immune response (difficult to diagnose active disease)
- Risk of disease is highest among infants and in late teens (lowest risk between 5 and 10), in the first year following infection
- Disease in young children reflects recent infection (vs. secondary reactivation) → the paediatric disease burden potentially provides a useful measure of current transmission within a community



### Jenkins et al. Lancet 2014 published 24 March

- Estimates unknown
- Systematic review
- Setting-specific risk of multidrug-resistant tuberculosis was nearly identical in children and treatment-naive adults
- Identified similar risk for transmission of MDR-TB
- 999 792 children developed tuberculosis disease in 2010
- 31 948 MDR
- Highlighted the need for detection

#### Jenkins et al. Lancet 2014 published 24 March

	Estimated number of child tuberculosis cases (95% Cl)	Estimated number of child multidrug-resistant tuberculosis cases (95% CI)
frican region	279 825 (250 187-308 717)	4736 (2829-6848)
astern Mediterranean region	71162 (60 320-83 193)	2417 (339-5087)
uropean region	43 224 (39 572-47 242)	5645 (4206-7463)
egion of the Americas	27199 (24935-29635)	606 (374-854)
outh-East Asia region	397 040 (350 615-447 474)	10 000 (4993-15 568)
lestern Pacific region	179 515 (159 246-202 626)	8349 (5639-11610)
otal	999792 (937 877-1055 414)	31948 (25594-38663)
ese regions correspond to those define	d by WHO.	

#### The NEW ENGLAND JOURNAL of MEDICINE

#### ORIGINAL ARTICLE

### Diagnosis of Childhood Tuberculosis and Host RNA Expression in Africa

Suzanne T. Anderson, Ph.D., M.R.C.P.C.H., Myrsini Kaforou, M.Phil, Andrew J. Brent, Ph.D., M.R.C.P., Victoria J. Wright, Ph.D., Claire M. Banwell, Ph.D., George Chagulua, M.B., B.S., Amelia C. Crampin, F.F.P.H.M., Hazel M. Dockrell, Ph.D., Neil French, F.R.C.P., Ph.D., Melissa S. Hamilton, Ph.D., Martin L. Hibberd, Ph.D., Florian Kern, M.D., Paul R. Langford, Ph.D., F.S.B., Ling Ling, M.B., B.S., Rachel Moltah, F.C.P. (Paeds) (SA), Torn H.M. Ottenhoff, M.D., Ph.D., Sandy Pienaar, M.S.C., Vashini Pillay, M.B., Ch.B., J. Anthony G. Scott, F.R.C.P., Hemed Twahir, M.Med, Robert J., Wilkinson, F.R.C.P., Ph.D., Lachlan J. Coin, Ph.D., Robert S. Heyderman, F.R.C.P., Ph.D., Michael Levin, Ph.D., and Brian Eley, F.C.P. (Paeds) (SA), for the ILULU Consortium and KIDS TB Study Group\*



**RESULT** We identified a 51-transcript signature distinguishing tuberculosis from other discases in the South African and Malawian children (the discovery cohord). In the Keymen children the validation cohord, a risk score based on the signature for traberculosis and for diseases other than tuberculosis showed a sensitivity of 23/W (9% confidence interval [CL], 68.6 vol 93.1 and a specificity of 83.3 W (9% C, 17.4 for Validation 10.4 for a strain transcription of the validation cohord a tuberculosis. Among patients with fullers negative was C2.5 to 23.2 A c1 0.8 J0.8, and 35.3 to 70.6 K, respectively, for different estimates of attual tuberculosis was 54.3 to 73.6 V, respectively, for different estimates of attual tuberculosis was 54.3% (9% C, 17.4 to 48.6), and the sensitivity in highly probable, probable, or possible cases was an estimated Z5.0 to 35.7 K, 53 to 13.3%, and 0%, respectively, the specificity of the assay was 10%. Concursoons

CONCLUSIONS RNA expression signatures provided data that helped distinguish tuberculosis from other diseases in African children with and those without HIV infection. (Funded by the European Union Action for Diseases of Poverty Program and others).

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### Xpert MTB/Rif and children

- Prior to 2011, one study
- 16 studies (4 unpublished)
- Pooled sensitivity was similar on expectorated sputum and gastric lavage/aspiration (66%), specificity (98%)
- Poor performance on smear negative (4-15%)
- Rif resistance (86%)

# Using Xpert MTB/Rif to diagnose pulmonary TB and rifampicin resistance in children

- Initial diagnostic test (rather than smear, culture or DST) for suspected MDR and HIV associated TB (Strong recommendation, <u>very</u> <u>low quality evidence</u>)
- All suspected of having TB (conditional recommendation acknowledging resource implications, very low quality evidence)

