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Use of Xpert MTB/RIF for the diagnosis of tuberculosis in children

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Fumbling in the dark...

- Quandaries in diagnosing TB in children
 - Based on clinical diagnosis, we think that
 - culture is a poor reference standard (20-50%)
 - microscopy is infrequently helpful (<10%)
 - However, clinical diagnosis is probably even worse
 - chest radiography interpretation is variable
 - clinical scoring systems seldom concur
- Problem when evaluating novel diagnostics

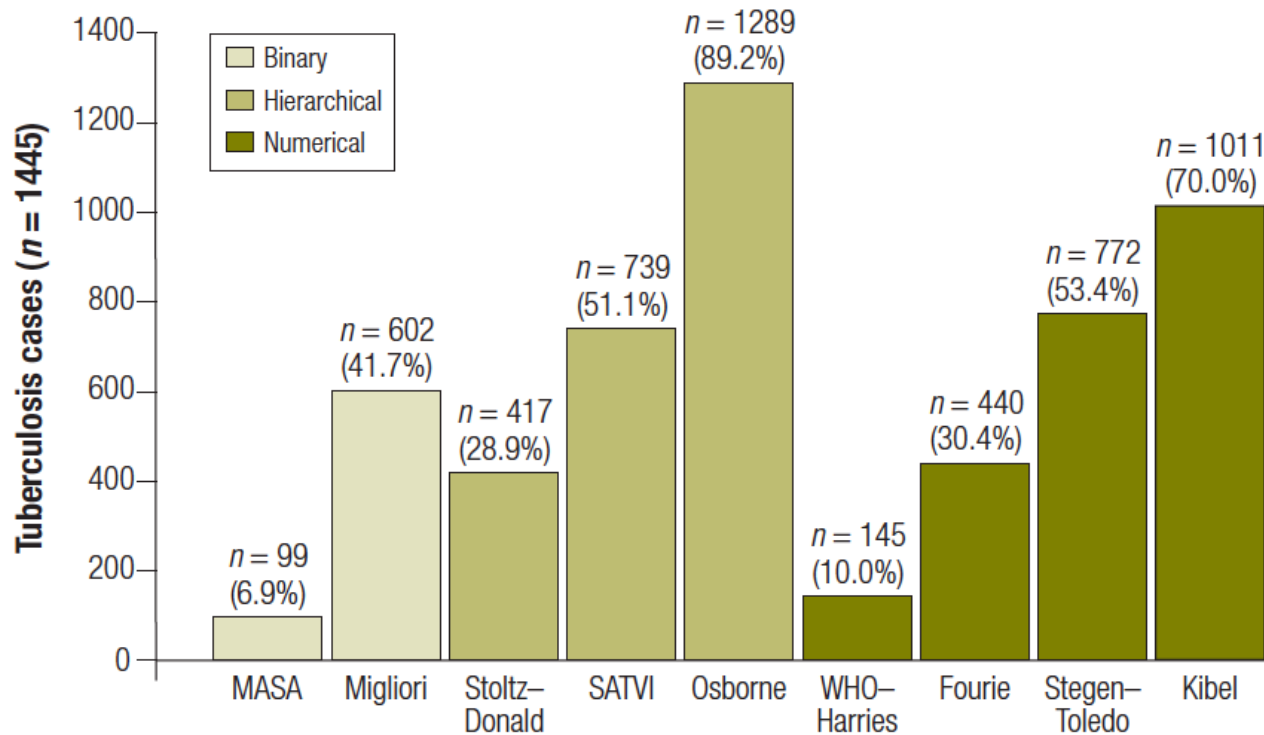
Interpretation of CXR is highly inconsistent

Table 1. Results of chest radiograph assessment by three independent paediatric reviewers, grouped by certainty of tuberculosis diagnosis, South Africa, 2001–2006

Diagnostic certainty ^a	Reviewer 1		Reviewer 2		Reviewer 3		Final classification	
	No.	%	No.	%	No.	%	No.	%
Highly likely to have tuberculosis	16	1.1	29	2.0	171	11.8		
Likely to have tuberculosis	20	1.4	38	2.6	323	22.4		
Suspected of having tuberculosis	124	8.6	145	10.0	242	16.7		
Positive	160	11.1	212	14.6	736	50.9	271	18.8
Inconclusive	45	3.1	35	2.4	82	5.7		
Abnormal but not tuberculosis	102	7.1	139	9.6	312	21.6		
Normal	1038	71.8	778	53.9	59	4.1		
Negative	1185	82.0	952	65.9	453	31.4	1174	81.2
Not read	100	6.9	281	19.5	256	17.7		
Total	1445	100	1445	100	1445	100	1445	100

Structured scoring systems?

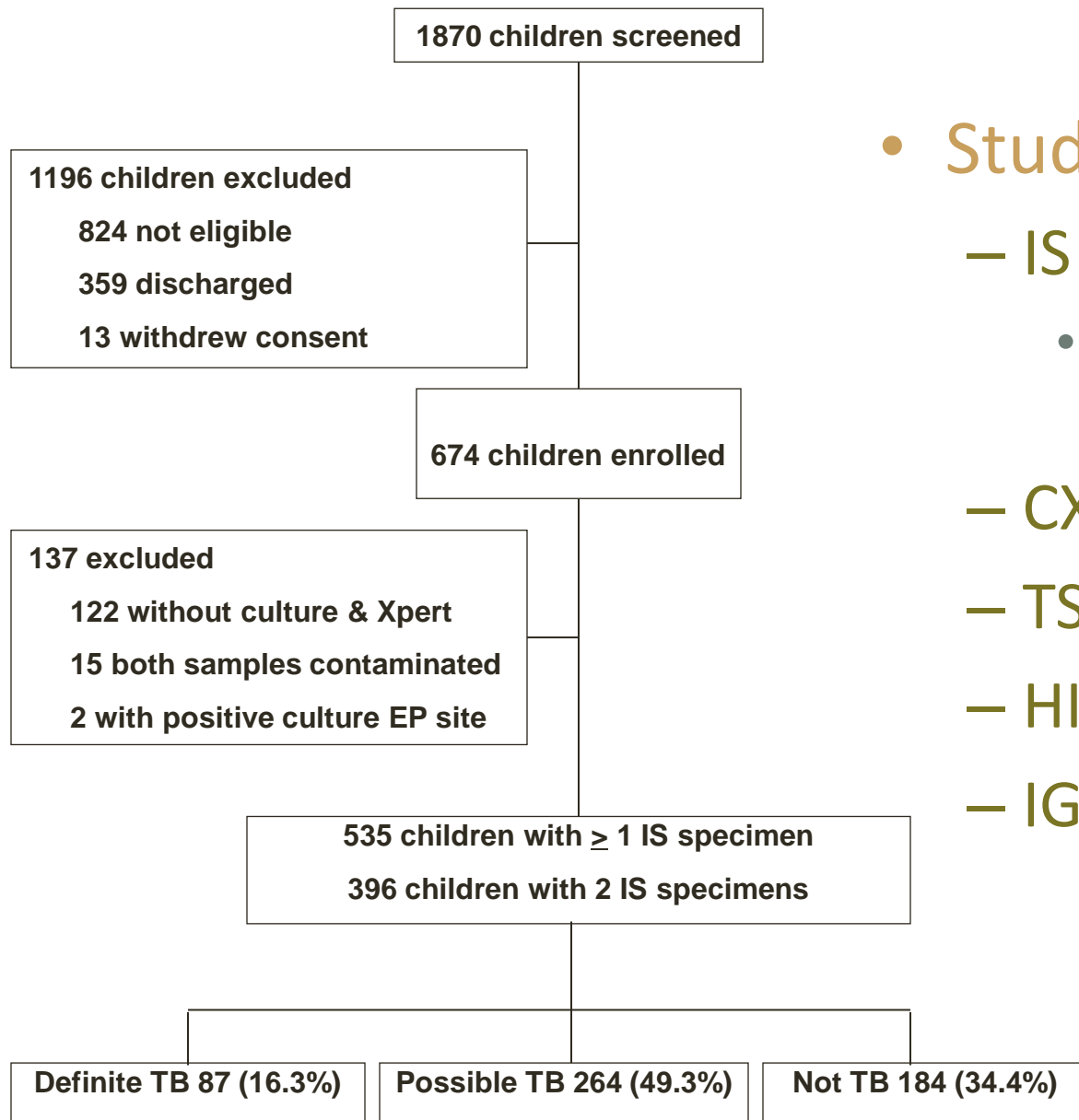
Fig. 1. Frequency of cases classified as tuberculosis with various scoring systems, with hierarchical and numerical outcomes condensed to a binary “tuberculosis/not tuberculosis” output, South Africa, 2001–2006



MASA, Medical Association of South Africa; SATVI, South African Tuberculosis Vaccine Initiative; WHO, World Health Organization.

Xpert MTB/RIF for the diagnosis of TB in children

- Prospective study enrolling children with suspected TB at two hospitals in Cape Town
 - Cough >2 weeks plus one of:
 - Household contact with TB
 - Loss of weight or failure to gain weight
 - Positive TST
 - Suggestive CXR
- Definitions:
 - Definite TB = culture positive
 - Not TB = no TB treatment plus symptoms/signs resolve
 - Possible TB = all others



- **Study investigations**

- IS x2, NPA x2

- Xpert, smear, MGIT, (MODS)

- CXR

- TST

- HIV (plus CD4)

- IGRA

Xpert for the diagnosis of TB in children

Characteristics of subjects (n=535)

	All	Definite TB	Possible TB	Not TB
Age (months)	19.0 (11.2-38.3)	21.1 (11.9-45.7)	18.3 (11.2-34.8)	18.4 (11.0-38.7)
Male (%)	294 (55.0)	51 (58.6)	142 (53.8)	101 (54.9)
HIV infection (%)	117 (21.9)	15 (17.2)	65 (24.6)	37 (20.1)
Prior TB (%)	56 (10.4)	6 (6.9)	28 (10.6)	22 (12.0)
CXR suggests TB (%)	333 (67.4)	55 (73.3)	167 (69.0)	111 (63.4)
TB treatment (%)	273 (51.4)	87 (100)	185 (70.1)	0 (0)
WAZ score < -2 (%)	68 (15.6)	17 (29.3)	33 (15.5)	18 (10.9)
TST positive (%)	191 (39.2)	62 (74.7)	111 (47.2)	18 (10.7)

Performance of Xpert and smear microscopy

	Sensitivity	Specificity	PPV	NPV	Sensitivity in smear-positive	Sensitivity in smear-negative
<i>All children with complete results from at least one specimen (n=535)</i>						
Xpert						
All	64/87	443/448	92.8	95.1	29/30	35/57
	73.6 (64.1-83.0)	98.9 (97.9-99.9)			96.7 (89.9-100)	61.4 (48.4-74.4)

Specificity calculated using only children with 2 culture results available

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HIV infected	14/15 93.3 (79.0-100)	102/102 100 (96.4-100)	100	99.0	9/9 100 (66.4-100)	5/6 83.3 (40.5-100)
HIV uninfected	50/72 69.4 (58.5-80.3)	340/345 98.6 (97.3-99.8)	90.9	93.9	20/21 95.2 (85.3-100)	30/51 58.8 (44.8-72.8)

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Smear	28/87 32.2 (22.2-42.2)	448/448 100 (99.2-100)	100	88.4		

Specificity calculated using only children with 2 culture results available

Performance of Xpert and smear microscopy

	Sensitivity	Specificity	PPV	NPV	Sensitivity in smear-positive	Sensitivity in smear-negative
<i>Children with complete results from two specimens (n=396)</i>						
Xpert x 1	36/63	332/333	97.3	92.5	21/21	15/42
	57.1 (44.6-69.7)	99.7 (99.1-100)			100 (83.9-100)	35.7 (20.6-50.8)

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HIV infected	7/8 87.5 (57.9-100)	72/72 100 (95.0-100)	100	98.6	6/6 100 (54.1-100)	1/2 50 (-5.9 – 6.9)
HIV uninfected	38/55 69.1 (56.5-81.7)	257/260 98.8 (97.6-100)	92.7	93.8	15/15 100 (78.2-100)	23/40 57.5 (41.5-73.5)

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Specificity calculated using only children with 2 culture results available

Zar, Nicol. Unpublished

Summary of performance for TB detection

- Sensitivity twice that of smear microscopy (33%)
 - 1 Xpert 57% (smear negative: 36%)
 - 2 Xpert 71% (smear negative: 57%)
- Specificity excellent
 - 99% for children with 2 negative cultures
 - 1/184 in “not TB” group false positive (99.5%)

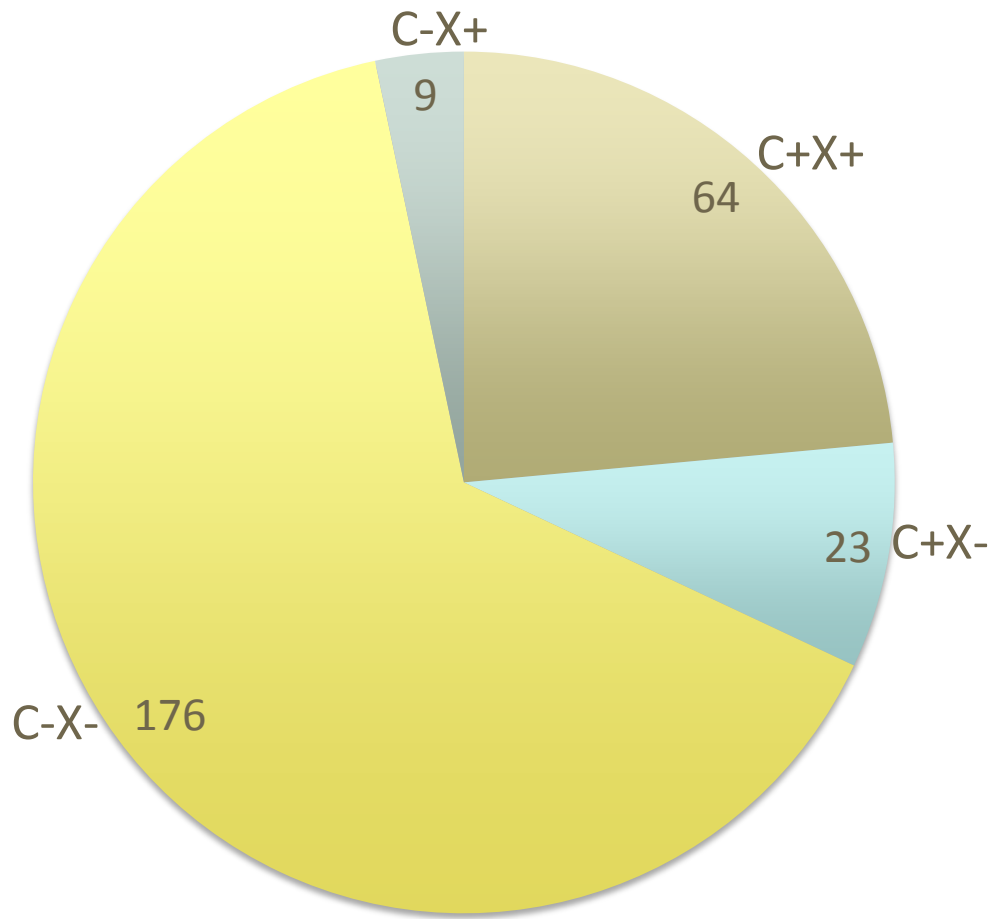
Xpert for detection of RIF resistance

	MTBDR<i>plus</i> resistant	MTBDR<i>plus</i> sensitive	MTBDR<i>plus</i> inconclusive
Xpert resistant	5	1	0
Xpert sensitive	1	114	2
Xpert indeterminate	0	4	0

Sensitivity 83%
Specificity 99%

Has Xpert solved the problem?

Culture and Xpert results in children started on TB treatment
n=272



27% Xpert positive

32% Culture positive

65% Both negative

Difference in yield of Xpert
vs. culture = 14 cases (5%)

Specific questions still to be answered

- Other respiratory samples
 - Gastric washings, NPA...
 - NPA may offer alternative where IS not available
 - Promising early results
- Extra-pulmonary TB
 - FNA looks very promising
 - 97% sensitivity in adult patients
 - (Ligthelm et al. J Clin Microbiol 2001, Epub Aug 31)
- Children with less severe illness (not hospitalized)
 - Studies currently underway in Cape Town
- Performance in larger group of HIV-infected children

Suggested recommendations

- Xpert should not replace culture for the diagnosis of TB in children, however
 - Where culture is available
 - Xpert in combination with culture (on IS samples)
 - Rapid confirmation of diagnosis is possible in more than two-thirds of culture-confirmed cases
 - Particularly useful where MDR-TB is suspected
 - Where culture not available
 - Xpert on IS/sputum should be first-line test
 - Where culture and IS/sputum not available
 - Xpert on NPA (data out shortly)

Acknowledgements

- UCT
 - Heather Zar (co-PI)
 - Lesley Workman
 - Washiefa Issacs
 - Jacinta Munro
 - Faye Black
 - Brian Eley
 - Widaad Zemanay
 - Andrew Whitelaw
- FIND
 - Catharina Boehme
- Children and their caregivers
- NHLS Groote Schuur
- Staff at New Somerset and Red Cross War Memorial Children's Hospital
- Funders:
 - NIH (1R01HD058971-01)
 - NHLS Research Trust
 - MRC (South Africa)
 - The Wellcome Trust (085251/B/08/Z)