TB diagnosis in children

Mark Cotton
Stellenbosch University (SU),
South Africa
What is burden of childhood TB?

• Relatively neglected
  – WHO Stop TB strategy only included reporting in children from 2006

• 6% (490 000) of 8.7 million cases, *Global TB report WHO 2012*
  – South Africa – 16% of total burden

• Childhood TB deaths/year - 64 000
Age-related risk of TB disease after exposure to source case

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Case Fatality Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 1 yrs</td>
<td>7.1 (±1.75)</td>
</tr>
<tr>
<td>1 – 4 yrs</td>
<td>2.8 (±0.6)</td>
</tr>
<tr>
<td>5 – 9 yrs</td>
<td>1.1 (±0.2)</td>
</tr>
<tr>
<td>10 – 14 yrs</td>
<td>1.5 (±0.3)</td>
</tr>
</tbody>
</table>

Peter Donald
TB & HIV in children

• more rapid immune decline, HIV replication
• more severe disease - disseminated, miliary disease
• higher mortality
• risk of disease all ages
• pill burden, interactions ART, side effects
• adherence
• higher exposure in HIV households
BUT diagnosing childhood TB can be difficult...

- Clinical symptoms/signs non-specific
- TB in children often paucibacillary
- HIV co-infection
- False –ve Tuberculin skin tests (TST)
  - HIV
  - Malnutrition
  - Advanced TB disease
- CXR interpretation
More epidemiology
Know your populations

Western Cape 2009

Women and TB

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**Fig. 1.** TB notifications in 2009 for the City of Cape Town stratified by 5-year age groups and by provider-initiated HIV testing results. The denominators for age strata derived from National Department of Health/Health Information System Programme by disaggregating StatsSA district estimates (November 2009) using data from the ‘Small Area Layer’ (StatsSA, 2004).

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**FIGURE 1.** Total TB case detection rates among women by age in selected African countries.\(^\text{10}\)

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Wood SAMJ 2011

Deluca JAIDS 2009
Screening of 70 neonates according to TB exposure:
(4 sets of twins) 2009 – 2010 TBH

confirmed maternal TB
n=41 (59%)
TB prophylaxis n=32
TB treatment n= 5
No TB treatment n=4
7 TB Cases
3 deaths

unconfirmed maternal TB
n= 9 (13%)
TB prophylaxis n=4
TB treatment n=0
No TB treatment n=5
1 TB case
1 death

household contact with
TB n=5 (7%)
TB prophylaxis n=1
TB treatment n=0
No TB treatment n=4
0 TB cases

suggestive TB illness
(no known maternal TB)
n=15 (21%)
TB prophylaxis n=0
TB treatment n=0
No TB treatment n=15
0 TB cases
3 deaths
### Neonates

<table>
<thead>
<tr>
<th></th>
<th>All Neonates n=70</th>
<th>HIV – exposed n=41 (60%)</th>
<th>HIV-unexposed n=28 (40%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male(%)</td>
<td>35 (50)</td>
<td>20 (48)</td>
<td>14 (50)</td>
</tr>
<tr>
<td>Gestation (weeks)</td>
<td>35.5 (33-38)</td>
<td>35.5 (33-38)</td>
<td>35.5 (32-38)</td>
</tr>
<tr>
<td>Birth weight</td>
<td>2000g (1530-2484)</td>
<td>2000g (1555-2310)</td>
<td>2055g (1488-2685)</td>
</tr>
<tr>
<td>PMTCT received</td>
<td></td>
<td>35/36 (97) ²</td>
<td></td>
</tr>
<tr>
<td>PCR positive</td>
<td></td>
<td>5/19 (26) ³</td>
<td></td>
</tr>
<tr>
<td>Mortality in hospital</td>
<td>7 (10)</td>
<td>5 (12)</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

### Mothers

<table>
<thead>
<tr>
<th></th>
<th>All Mothers n=66</th>
<th>HIV positive n=38 (58%)</th>
<th>HIV negative N=27 (42%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27 (24-32)</td>
<td>27 (26-32)</td>
<td>27 (23-33)</td>
</tr>
<tr>
<td>Absolute CD₄ count</td>
<td>176 (90-328) ⁴</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAART/PMTCT</td>
<td></td>
<td>23/33 (69) ⁵</td>
<td></td>
</tr>
<tr>
<td>Mortality in hospital</td>
<td>3 (5)</td>
<td>1 (3)</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>
Countries with the highest numbers of estimated MDR-TB cases, 2007. Horizontal lines denote 95% confidence intervals. The source of estimates is drug resistance surveillance or surveys (DRS, in red) or modelling (in grey).
Culture-confirmed Drug Resistant (DR) M.tb in children – W Cape, RSA

Diagnostic methods for TB in children

• Clinical
• Radiological
• Immune response
  – Skin testing, IGRAs, serology
• Microbiologic confirmation
  – Smear and culture, improved culture methods
  – Molecular diagnosis
  – Antigen detection
Why do we need better & more rapid TB diagnosis in children?

Role of *S. pneumoniae* in Acute Community-acquired Pneumonia & Culture-confirmed *M. tb* in Children: a PCV probe study

*DP Moore, KP Klugman, SA Madhi*

*Pediatr Infect Dis J* 2010; 29: 1099-1104

<table>
<thead>
<tr>
<th></th>
<th>PCV-9 19 922</th>
<th>Placebo 19 914</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture-confirmed TB</td>
<td>33</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Per 100 000</td>
<td>166</td>
<td>286</td>
<td>0.013</td>
</tr>
</tbody>
</table>
BUT: 44 (48%) children with culture-+ve TB & with acute pneumonia not treated in hospital

• 4 died during the hospitalization
• 12 began TB Rx 40 days after discharge
• 28 children ????
• Median duration of cough: 4 (IQR: 2-7) days in 38 children
TB in infants with acute pneumonia not responding to abx in 48hrs

Effect of age, polymicrobial disease, & maternal HIV status on Rx response & cause of severe pneumonia
McNally L et al Lancet 2007; 369: 1440-51
Clinical diagnosis

- NIH workshop June 2011 - *Critical issues in Pediatric diagnostic research*
  - consensus clinical case definitions
  - standardise methodological approaches to new diagnostics in children

*Graham et al JID 2012*
Clinical case definitions for PTB

- **Confirmed**
  - 1 sign/symptom + culture confirmation
- **Probable**
  - 1 sign/symptom + CXR consistent + exposure/ response to therapy/ immune evidence of infxn
- **Possible**
  - 1 sign/symptom + CXR consistent/exposure/ response to therapy/immune evidence of infxn
- **Unlikely** – symptomatic but no criteria
- **NOT TB** – alternative Dx

Graham et al JID 2012
Clinical signs/ symptoms

• Persistent (x 2 weeks) cough
• Weight loss / FTT
• Persistent (1 week) unexplained fever
• Persistent, unexplained lethargy
• History of exposure – household/ close contact within 24 months
• Response to treatment – 2 month f/up (also 2 weeks and 6 months) – assess clinical features

Graham et al JID 2012
How well does it work?

Retrospective application

- 1445 children < 2 yrs with suspected PTB in BCG study followed for 2 yrs
- 12% culture positive; 2% HIV pos
- Associated with +ve culture
  - wheeze
  - lower chest retractions
  - PPD pos
  - CXR suggestive
- Not associated
  - Fever
  - Persistent cough
  - Wt loss / FTT

Luabeya KKA et al PIDJ 2012; 31: 42-46
Possible causes of Failure to Thrive

- TB
- Food insecurity (new)
- ARV failure or poor adherence in HIV+
- Depression in mother
- HIV disease
Radiological diagnosis

- Non-specific
- Hilar adenopathy – wide inter/intra-observer variation
  - inter-observer agreement 30%
  - accuracy not improved with lateral CXR
Chest X ray & PTB pathogenesis

Chronic lung disease common in HIV-infected children

- Bronchiectasis
- Gastro-esophageal reflux disease
- Recurrent pneumonia
- Lymphoid Interstitial Pneumonitis
- Cor pulmonale

Norton et al AJR 2001; 176: 1553
- 1990-1997
- 32.8% had chronic CXR findings by 4y
  - Nodules >3m – 26%
  - Parenchymal consolidation >3m – 24%
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

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

Hatherill et al. Bull WHO2010
Case: Infant commenced ART at 9w of age
Baseline CD4 3226 per mm$^3$; HIV RNA 218,000 copies/ml

3w later:

Mother reported that grandmother started treatment for TB

- TST 2mm
- Gastric aspirate X2 –ve
- LPV/r + RTV super-boosting
  - mg:mg
- INH, Rif & PZA X 2m
- INH & Rif X 4m

At 16 m of age – new respiratory illness

Had visited Father in separate town
• Father suspected to have TB

Patient:
• Small area consolidation Lt Base
• Mild RDS
• TST –ve
• IV abx X1 day, ➔ much improvement; given oral abx
• Dx: intercurrent pneumonia
• INH post exposure prophylaxis
TB Contacts:

- Cousin at mother’s house – DS TB
- Father diagnosed with TB when Pt was 9m of age
  - Smear & culture +ve
  - No sensitivities
  - 4 drug Rx
  - Defaulted
Unexpected death 5m later (21m old)

• Post Mortem – TB bronchopneumonia and miliary spread
• Molecular Analysis
  – M tb complex
  – High level INH Resistance
  – Ethambutol and Rifampicin resistance
• 1m later, father again presented for treatment
  • Smear & culture +ve (NO DST)
  • 2\textsuperscript{nd} line TB Rx
  • Deteriorated
  • Could not tolerate MDR treatment
TB in infant on ART from 2m- Limited disease & value of serial CXR’s

8m

14m

Culture +ve
How good are we at identifying source TB cases?

- Is there a TB contact in the home?
- Is anyone coughing a lot? (present/past)
- Do you know anyone with TB?
- Is the source case receiving injections
- How many times has he/she been treated for TB?
- Is he/she adherent?
- Crowded poorly ventilated settings?
  - Taxi
  - Church
  - Family gatherings
When is source case (contact) identified in HIV-exposed children diagnosed with TB? (P1041)

19 month HIV+ infant

- 3 week history of otorrhoea, ge
Also failure to thrive
Mother

- Cough & wt loss for 3 weeks
- Did not volunteer this info
TB Diagnostic tests

Microbiology
- Organism
  - smear
  - culture
- DNA
- Histology
- Tuberculin skin test (TST)

Immunology
- Host response
  - antigen-specific production of IFNγ
- Production of IFNγ
Tuberculin Skin Test (TST)

• +ve test helps
  – 44/78 (56%) +ve in culture-confirmed cases pre ART
    Hesseling et al Arch Dis Child 2005; 90; 1171-4

• -ve test does not help

• HIV ≥5mm
  – Adults no difference 5 vs 10mm Cobelens FC CID 2006; 43: 634-9

• Can repeat later (once on TB Rx & on ART)
Interferron $\gamma$ release assays (IGRA)

- Specific for TB antigens
- Useful in low prevalence settings
- Little advantage over TST
TB Microbiological diagnosis in children

- NOT standard
- Perceptions:
  - not feasible / possible / practical
  - not useful - paucibacillary disease
  - not possible in infants or young children
  - no place in primary care settings
Unusual sites

- Otorrhoea: 3 of 12 culture-confirmed cases
  Schaaf HS PIDJ 1998; 17: 599
- Parotitis
Value of ANY positive TB test

Treat for TB

Value of a TB culture

Treat appropriately for TB
What specimen?

- Gastric lavage was standard for diagnosis
  - 3 sequential GLs
- Overnight starve
- Unpleasant for child and person doing GL
- Hospitalization
- Yield low - positive in 10-20% children with PTB
Other (? improved) specimens?

- Induced sputum
- Nasopharyngeal specimen
- Ear secretions
- String test
- Fine needle aspiration of node
- Bronchoalveolar lavage (BAL)
Induced Sputum

- nebulised hypertonic (3-5%) saline interstitial fluid drawn into airways
- mobilises lower respiratory secretions
- stimulates cough
- lower respiratory tract secretions moved up and expectorated or suctioned
Method sputum induction

- Pretreat with bronchodilator (asthma pump and spacer)
- Nebulise with 3-5mls 5% hypertonic saline
- Suction through nose using mucus trap
- Older children can expectorate
Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study

Heather J Zar, David Hanslo, Patricia Apolles, George Swingler, Gregory Hussey

Summary

Background For microbiological confirmation of diagnosis of pulmonary tuberculosis in young children, sequential gastric lavages are recommended; sputum induction has not been regarded as feasible or useful. We aimed to compare the yield of Mycobacterium tuberculosis from repeated induced sputum with that from gastric lavage in young children from an area with a high rate of HIV and tuberculosis.

Methods We studied 250 children aged 1 month to 5 years who were admitted for suspected pulmonary tuberculosis in Cape Town, South Africa. Sputum induction and gastric lavage were done on three consecutive days according to a standard procedure. Specimens were stained for acid-fast bacilli; each sample was cultured singly for M tuberculosis.

Findings Median age of children was 13 months (IQR 6–24). A positive smear or culture for M tuberculosis was obtained from 62 (25%) children; of these, 58 (94%) were positive by culture, whereas almost half (29 [47%]) were smear positive. Samples from induced sputum and gastric lavage were positive in 54 (87%) and 40 (65%) children, respectively (difference in yield 5–6% [1.4–9.8%], p=0.018). The yield from one sample from induced sputum was similar to that from three gastric lavages (p=1.0). Microbiological yield did not differ between HIV-infected and HIV-uninfected children (p=0.17, odds ratio 0.7 [95% CI 0.3–1.3]). All sputum induction procedures were well tolerated; minor side-effects were increased coughing, epistaxis, vomiting, or wheezing.

Interpretation Sputum induction is safe and useful for microbiological confirmation of tuberculosis in young children. This technique is preferable to gastric lavage for diagnosis of pulmonary tuberculosis in both HIV-infected and HIV-uninfected infants and children.
Induced sputum (IS) vs gastric lavage (GL)

- 250 children with suspected PTB
  - median age 13 (6-24) months
- 3 IS vs 3 GLs
- +ve smear or culture in 62 (25%)
  - yield IS (54, 87%) 3X HIGHER than GL (40, 65%) – OR 2.8
  - single IS (41, 66%) equivalent to 3 GLs (40, 65%), OR 1.1

Zar et al, Lancet 2005
Induced Sputum (IS)

- Youngest - 1 month
  - with +ve culture - 3 months
- 48% younger than 1 year
- 2nd IS increased yield by 15%
- 3rd IS increased yield by 7%

Zar et al, Lancet 2005
Sputum collection routine in adults: Why not for children?

Kuyasa Clinic – (Community setting)

- 270 children with suspected PTB
- Median age 38 months
- 2 IS specimens on sequential days
  - Smear, liquid culture
- IS in 269 (99%)
- 29 (10.7%) positive for *M. tb*
  - 7 (24%) HIV-infected

Moore et al Int J Tuber Lung Dis 2011

- 18 children not clinically diagnosed had positive microbiology and treated
- IS improved diagnostic yield from 65 (clinically Dx) to 83 cases
  - 22% increase
- IS well tolerated, no severe adverse events
TB diagnostic studies in children: Gastric aspirate / Induced sputum

- 31 studies
- Insufficient rigor in documenting:
  - Time of sample
  - Sample volume
  - Buffers
  - Gastric aspirate versus Lavage – Dilution factor
The Diagnostic Triangle for TB diagnosis in children
Elisabetta Walters, DTTC, SU
Sample Quality
Elisabetta Walters, DTTC, SU

- Gastric Aspirate
  - improving volume
    • Performing GA when child is still asleep
    • Place NGT previous night, so child need not be awakened
    • Child must be recumbent
    • Aspirate in 3 positions (supine, left and right lateral);
  - improving quality
    • Aspiration is better than lavage (lavage results in dilution)
    • check GA pH and add NaHCO3 to optimal pH (6.5) for \textit{M.} \textit{tb} growth
    • Rapid delivery to lab.
    • Adequate preceding time nil per os to avoid food contamination

- Induced Sputum (IS)
  - Hypertonic saline
  - Chest physiotherapy
Specimen handling

• 4°C storage until reaches lab
  – Get to lab quickly
• Rapid processing in lab
• Bacterial contamination
Laboratory Processing

- Use entire sample volume – concentrate and reconstitute rather than discard
- Use milder decontamination for culture
  - Avoids killing viable *M.tb*
  - But increased risk of contamination with other bacteria
  - Prevent cross-contamination of TB specimens
Decontamination of pediatric samples – how low can you go?

NaOH 1.5% (standard)
Versus
NaOH 1%

Andrew Whitelaw (NHLS, UCT)
Keithea Mentoor (NHLS)
Heather Zar (RCWMCH, UCT)
Mark Nicol (UCT)
Contamination Rates: 1.5 vs 1% NaOH

- All samples: 9% vs 9%
- Resp tract: 8% vs 7%
- Gastric aspirates: 10% vs 10%
- NPA: 8% vs 8%

NS\textsuperscript{a}, NS\textsuperscript{b}

\textsuperscript{a} OR 1.3 (0.8-2.2)
\textsuperscript{b} OR 1.8 (0.5-6.9)
Culture Positivity Rate
1.5 vs 1% NaOH

p = 0.003
Culture Positivity Rate
1.5 vs 1% NaOH

p=0.003\(^a\)
p=0.01\(^b\)

a: OR 1.7 (1.2-2.4)
b: OR 5.3 (1.5-19.3)
Culture

- Still gold standard
- Limitations
  - Expense
  - Time
  - Contamination
Microscopy

Ziehl-Nielsen (acid-fast)  Auramine
GeneXpert

Concentrates bacilli and removes inhibitors

Sample is automatically filtered and washed

Ultrasonic lysis of filter captured organisms to release DNA

DNA molecules are mixed with dry PCR reagents

Semi-nested real-time amplification and detection in integrated reaction tube

Printable test result

End of hands-on work

Time-to-result: 1 h 45 min

Transfer of 2 ml after 15 min

Sputum liquefaction and inactivation with 2:1 SR

Lawn, Nicol. Future Microbiol 2001; 6(9): 1067-8

- Rapid diagnosis
- Rifampin -clinically relevant Rifampicin resistance inducing mutations in the RNA polymerase beta (rpoB) gene
Mycobacterium tuberculosis complex detected by GeneXpert: Closely related species that can cause TB

- *Mycobacterium tuberculosis*
- *Mycobacterium africanum*
- *Mycobacterium bovis*
- *Mycobacterium bovis BCG*
- *Mycobacterium microti*
- *Mycobacterium canettii*
- *Mycobacterium pinnipedii*
- *Mycobacterium mungi*
GeneXpert

- Adult data
  - 88% sensitivity PTB
  - 98% smear positive
  - 68% for smear negative
  - specificity 99%, Steingart et al, Cochrane 2013
- WHO recommended 2011 [www.who.int/tb/laboratory/](http://www.who.int/tb/laboratory/)
  - Xpert replace smear for PTB as initial diagnostic test in areas of high HIV or drug resistant TB
  - consider as a follow-on test to smear in other areas
Accuracy of the Xpert MTB/RIF test for the diagnosis of pulmonary tuberculosis in children admitted to hospital in Cape Town, South Africa: a descriptive study

Mark P Nicol, Lesley Workman, Washiefa Isaacs, Jacinta Munro, Faye Black, Brian Eley, Catharina C Boehme, Widaad Zemanay, Heather J Zar

Summary

Background WHO recommends that Xpert MTB/RIF replaces smear microscopy for initial diagnosis of suspected HIV-associated tuberculosis or multidrug-resistant pulmonary tuberculosis, but no data exist for its use in children. We aimed to assess the accuracy of the test for the diagnosis of pulmonary tuberculosis in children in an area with high tuberculosis and HIV prevalences.

Methods In this prospective, descriptive study, we enrolled children aged 15 years or younger who had been admitted to one of two hospitals in Cape Town, South Africa, with suspected pulmonary tuberculosis between Feb 19, 2009, and Nov 30, 2010. We compared the diagnostic accuracy of MTB/RIF and concentrated, fluorescent acid-fast smear with a reference standard of liquid culture from two sequential induced sputum specimens (primary analysis).

Results 452 children (median age 19·4 months, IQR 11·1–46·2) had at least one induced sputum specimen; 108 children (24%) had HIV infection. 27 children (6%) had a positive smear result, 70 (16%) had a positive culture result, and 58 (13%) had a positive MTB/RIF test result. With mycobacterial culture as the reference standard, MTB/RIF tests when done on two induced sputum samples detected twice as many cases (75·9%, 95% CI 64·5–87·2) as did smear microscopy (37·9%, 25·1–50·8), detecting all of 22 smear-positive cases and 22 of 36 (61·1%, 44·4–77·8) smear-negative cases. For smear-negative cases, the incremental increase in sensitivity from testing a second specimen was 27·8% for MTB/RIF, compared with 13·8% for culture. The specificity of MTB/RIF was 98·8% (97·6–99·9). MTB/RIF results were available in median 1 day (IQR 0–4) compared with median 12 days (9–17) for culture (p<0·0001).

Interpretation MTB/RIF testing of two induced sputum specimens is warranted as the first-line diagnostic test for children with suspected pulmonary tuberculosis.
Xpert in children

- Children (median 19m) hospitalised with suspected PTB
- 2 IS for smear, liquid culture, Xpert
- 492 children enrolled
  - 452 (92%) had 1 IS, 385 (78%) had 2 IS
- 70 (16%) culture +ve TB
  - Xpert detected 52/70 (74%) overall

Nicol et al Lancet ID 2011
Xpert vs culture-confirmed PTB

- 2 Xpert on 2 IS detected 76% cases
  - Xpert 100% sensitive smear pos; 61% smear neg
- 28% incremental yield with 2\textsuperscript{nd} Xpert test (14% for 2\textsuperscript{nd} culture)
- Specificity 99%
- Rifampicin resistance - 99% sensitive
- Results faster than culture (1 vs 12 days)

Nicol et al Lancet ID 2011
Detection threshold:

*M. tb* CFU/ml required for a positive test

CFU = Culture-forming Units
Specimens for TB diagnosis:

More specimens better than fewer
The worse the CXR, the better the yield

• Gastric aspirates - Traditional
• Induced sputum - Better
• Nasopharyngeal aspirates – Easier

Rising incidence of MDR and XDR TB
How best to use GeneXpert in children?

• Good
  – Rapid result (4hrs)
  – Rifampicin resistance
  – Rapid therapy
  – Correlates with + smear

• Less good
  – Not as sensitive as culture
  – Rif resistance readout not reliable enough
    • 4th Generation awaited
Novel use of GeneXpert

The new “GOLD”

Stool for TB diagnosis - % culture positive cases identified in stool

• 47% Nicol M. Clin Infect Dis J 2013
• 50% Walters E. Pediatr Infect Dis J 2012
Urine dipstix

Urinary LAMM (lipoarabinomannan)

Benefits
• Rapid
• Not sensitive
• Very useful in adults with advanced HIV

Data in children awaited
E Walters Union Mtng 2013
Culture-confirmed unmasking TB
Immune Reconstitution Inflammatory Syndrome (IRIS)

Basic principles for TB diagnosis in children

- High index of suspicion
- Very good contact history
- Variety of specimens from as many sources as possible over 1 or 2 days
- Follow-up & review
Acknowledgements

• Elisabetta Walters – DTTC, SU
• Steve Innes – KID-CRU, SU
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