The future of diagnostics for paediatric TB

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TB in children

- Statistics unreliable
  - Historical emphasis on reporting smear-positive patients
  - Difficult to confirm the diagnosis
  - Different clinical presentation
Up to 25% of cases in some high TB burden settings occur in children.
1-1.4 million cases
Children

- Paucibacillary
- Less cavitations
- More disseminated disease
  - miliary TB,
  - EPTB,
  - bone,
  - abdominal,
  - glandular,
  - TBM

- Unable to expectorate
- Dependent on adults to attend a clinic
Non-sputum specimens

- Nasopharyngeal aspirate (NPA)
- Sputum induction (IS)
- Throat swabs
- Gastric aspirates (GA)
- Urine
- Stools
- Blood
- Fine needle aspiration biopsy

- Low volume
- Most test optimised for sputum
- Diagnosis is difficult
- Perception that children
  - Respond well to treatment
  - Treatment has fewer side effects
- Confirmation of diagnosis considered less necessary
Typically 5%-15% of cases confirmed
Clinicians do not bother confirming cases
Low numbers reported
Child-friendly TB diagnostics receive low priority by
- control programmes
- researchers
- test developers
Without proper diagnostics

- Difficult to define outcomes to assess
  - The magnitude of the problem
  - Prevalence of drug resistance
  - New drugs
  - New vaccines
  - Efficacy of control measures

"A high risk area for investment"
## Current diagnostics

<table>
<thead>
<tr>
<th>Year</th>
<th>Method</th>
<th>Results</th>
<th>Sensitivity</th>
</tr>
</thead>
</table>
| Before 2007 | ZN microscopy  
     Solid Culture | 2-3 days  
     30-60 days |                    |
| 2007 | Liquid Culture / DST  
     Rapid speciation | 8-30 days | +10% than LJ |
| 2008 | Line Probe Assay (1st line, Rif & INH) | 2-4 days | For SM+ |
| 2009 | LED - FM | 1-2 days | +10% than ZN |
| 2009 | MODS, CRI, NRA | 8-30 days | +10% than LJ |
| 2010 | Xpert | 90 minutes | +40% than ZN |
Have you heard of these tests?
What we hardly hear:

How do these tests perform in children?
<table>
<thead>
<tr>
<th>Test</th>
<th>Publications</th>
<th>Performance in children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fine needle aspiration</td>
<td>&gt; 6000</td>
<td>Potentially good. Most promising when combined with culture or NAAT</td>
</tr>
<tr>
<td>Fluorescence Microscopy (FM)</td>
<td>299</td>
<td>No data for LED-FM</td>
</tr>
<tr>
<td>LED-FM</td>
<td>33</td>
<td>More sensitive than LJ. Duplicate GA for MODS was the best diagnostic test in one study</td>
</tr>
<tr>
<td>MODS</td>
<td>31</td>
<td>Anecdotic data suggest performance in children's sputum similar to adults</td>
</tr>
<tr>
<td>BACTEC 960</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Fully automated BACTEC</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Line Probe assays</td>
<td>113</td>
<td></td>
</tr>
<tr>
<td>LAMP</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Automated NAAT (Xpert)</td>
<td>32</td>
<td></td>
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</table>
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

- 452 children
- Comparison with culture
- 70 (16%) positive culture
- 58 (13%) Xpert positive (2 x tests)
- (75% of culture confirmed)
1459 children screened

967 excluded
- 612 not eligible
- 345 discharged
- 10 withdrew consent

492 children enrolled

40 excluded
- 33 without at least one valid induced sputum culture and MTB/RIF result
- 7 with positive culture from another site

452 children with one induced sputum specimen
- 385 children with two induced sputum specimens

70 children with definite tuberculosis
- 52 MTB/RIF positive
- 27 smear positive

216 with possible tuberculosis
- 6 MTB/RIF positive
- 0 smear positive

166 without tuberculosis
- 0 MTB/RIF positive
- 0 smear positive
It is possible to do good quality research, but our house has been a bit messy.
Different entry criteria

Poor diagnostics

Diagnosis rarely confirmed

Data difficult to interpret

Many algorithms

Studies not comparable

Different entry criteria
How to break this circle?

- Increase advocacy
- Consensus standard methods
  - Entry
  - Categories for diagnosis
  - Reporting
Advocacy

International Childhood Tuberculosis Meeting 2011
Stockholm, 17-18 March 2011
CALL TO ACTION for CHILDHOOD TB

Read the Call in French, Read the Call in Russian

Sign the Call to Action

We, participants gathered at the ‘International Childhood Tuberculosis Meeting’ held March 17-18, 2011 in Stockholm, Sweden recognize that:

Signed by more than 1000 individuals/organisations
Building consensus

- Stop TB Partnership – DEWG – Child TB
- NDWG
- NIH
- TDR
- Many individual researchers
Research methods

Evaluation of TB diagnostics in children:


Consensus from an Expert Panel*
- Standard analysis and reporting
- Explore alternative methods
  - whether the famous LCA could be applied.
Funding or research

- Conditional of using consensus case definitions
- Demonstrate high quality research is possible to stimulate funding and test evaluations in children.
The future – what is needed?

- Further evaluate new diagnostics - such as Xpert
  - A few studies underway

- Optimise tests to improve Mtb identification in non-sputum specimens

- Develop mechanisms to bring non POC tests to the child and feedback
  - Active case finding (e.g. TB Reach)
  - Contact tracing
Biomarkers

- Distinguish infection and disease
- Identify children at risk of disease progression after infection
- Methods to deliver these biomarkers to the POC
We are ready to start running. Are you?

- Special thanks to
  - Steve Graham, Anneka Hesseling, Patrick Jean-Phillippe