Diagnosis of tuberculosis is very difficult in children resulting in high proportion of children started on TB treatment empirically and potential missed cases. We investigated a cohort of children for active TB in a regional reference hospital in Mbarara, South-Western Uganda.

Objectives
- To compare characteristics between children started or not on TB treatment
- To assess the proportion of confirmed and probable TB after the retrospective cases review by 2 independent paediatricians (Graham et al. JID 2012)
- To assess the performance of Xpert in sputum (spontaneous or induced) for diagnosis of TB as compared to culture and to retrospective case review
- To document the diagnostic yield of Xpert in stool

METHODS

Eligibility criteria
- Between 1 month and 14 years AND
- At least 1 symptom suggestive of TB: unexplained weight loss or documented failure to thrive over the past 3 months; cough, wheeze or chest pain > 2 weeks; night sweats > 2 weeks; fever > 7 days after common causes excluded; unexplained weakness, lethargy or reduced playfulness > 2 weeks; painless superficial lymph node mass; recent gibbus, OR
- Child referred with a chest X-ray suggestive of TB, OR
- Asymptomatic child with recent TB contact history and abnormal chest X-ray

Study design and procedures

- Clinical assessment
  - Contact history in the past 12 months
  - Tuberculin Skin Test
  - Antero-posterior and lateral chest X-ray

- 2 sputum or induced sputum: LED-FM, Xpert, culture (MGIT and LJ)
- Further tests for extra-pulmonary TB

- No treatment
- TB treatment
- Collection of stool for Xpert
- 3 months follow-up
- Monthly follow-up for 6 months

Retrospective case review by 2 independent paediatricians

Double reading of chest X-rays: clinician on site and external radiologist
- Confirmed TB: Xpert or MTB culture positive in sputum
- Probable TB: clinical signs and CKR suggestive of TB + TB contact history or positive TST or response to TB treatment, OR certain extra-pulmonary TB
- Possible TB: clinical signs suggestive of TB but not CKR + TB contact history or positive TST or response to TB treatment, OR clinical signs and CKR suggestive of TB without TB contact history or positive TST
- Unlikely TB: clinical signs suggestive of TB + not fitting above definition + no alternative diagnosis
- Non TB: clinical signs suggestive of TB + not fitting above definition + alternative diagnosis, OR clinical signs suggestive of TB + not fitting above definition + response without TB treatment

RESULTS

392 included children between April 2012 and January 2014
Median age: 4.1 months (IQR 1.4, 7.6)
144 started on TB treatment

Comparison of children characteristics at baseline

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall</th>
<th>TB treatment</th>
<th>No TB treatment</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>178 (45.4)</td>
<td>63 (43.8)</td>
<td>115 (46.4)</td>
<td>0.615</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2 years</td>
<td>125 (31.9)</td>
<td>64 (44.4)</td>
<td>61 (24.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2-5 years</td>
<td>103 (26.3)</td>
<td>42 (29.2)</td>
<td>61 (24.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5-10 years</td>
<td>112 (28.6)</td>
<td>23 (16.0)</td>
<td>89 (35.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>52 (13.3)</td>
<td>15 (10.4)</td>
<td>37 (14.9)</td>
<td></td>
</tr>
<tr>
<td>HIV infected</td>
<td>121 (30.9)</td>
<td>48 (33.3)</td>
<td>73 (29.4)</td>
<td>&lt;0.393</td>
</tr>
<tr>
<td>TB contact history</td>
<td>76 (19.4)</td>
<td>54 (36.4)</td>
<td>24 (9.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight for height z score &lt; -2SD</td>
<td>79 (20.2)</td>
<td>48 (33.3)</td>
<td>31 (12.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TST positive</td>
<td>99 (25.3)</td>
<td>69 (47.9)</td>
<td>30 (12.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥ 1 grade 3 (severe) clinical sign</td>
<td>80 (20.6)</td>
<td>48 (33.6)</td>
<td>32 (13.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥ 3 clinical signs</td>
<td>161 (41.1)</td>
<td>72 (50.0)</td>
<td>89 (35.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CXR suggestive of TB</td>
<td>138 (35.2)</td>
<td>113 (78.5)</td>
<td>25 (10.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positive sputum smear, Xpert or culture</td>
<td>20 (5.4)</td>
<td>18 (13.2)</td>
<td>2 (0.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Retrospective case review</td>
<td>373</td>
<td>135</td>
<td>238</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Confirmed TB</td>
<td>19* (5.1)</td>
<td>18 (13.3)</td>
<td>1 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Probable TB</td>
<td>39 (10.5)</td>
<td>38 (28.1)</td>
<td>1 (0.4)</td>
<td></td>
</tr>
</tbody>
</table>

* 1 case with sputum Xpert negative, culture negative and scanty smear classified as not TB

Probable or confirmed TB:
- 16.1% in children < 5 years vs 14.7% in children ≥ 5 years, p=0.77
- 22.0% in HIV infected children vs 12.3% in non-infected children, p = 0.01
- 24.3 % in moderate to severe malnourished children vs 13.6% in mild to normal, p = 0.02

Microbiological investigations

Sputum or induced sputum investigations
- 358 (91.3%) children with respiratory specimen collected
- 20 with positive sputum result: 17 by Xpert, 13 by culture, 5 by microscopy
- 347 children with both Xpert and culture results on sputum (or induced sputum)
  - Sensitivity of Xpert: 10/11, 90.9%
  - Specificity of Xpert: 332/336, 98.8%

Accuracy of Xpert in stool in children started on TB treatment

<table>
<thead>
<tr>
<th>Stool Xpert or culture</th>
<th>Confirmed or probable TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool</td>
<td>Yes</td>
</tr>
<tr>
<td>Positive</td>
<td>7</td>
</tr>
<tr>
<td>Negative</td>
<td>20</td>
</tr>
</tbody>
</table>

Sensitivity: 7/27 (25.9%)
Specificity: 54/54 (100%)

CONCLUSION & RECOMMENDATIONS

- High prevalence of HIV infection and malnutrition
- Very low proportion of confirmed TB
  - Low pre-test probability of TB (based on only one sign or symptom suggestive of TB)
  - High proportion of TB empirical treatment
- Only 41% of children started on TB treatment classified as confirmed or probable TB
- High sensitivity and specificity of Xpert in sputum as compared to culture
- Xpert in stool can detect more than half of cases confirmed in sputum

- Recommendations:
  - HIV and malnutrition should raise a high level of suspicion for TB
  - Xpert should be a front line investigation for diagnosis of TB
  - Stool might be a promising alternative specimen that requires further investigation
  - More robust diagnostic tests are required to increase the proportion of children treated on the basis of confirmed TB

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