



E Kumbakumba (1), M Nasumba (2), M Bastard (3), J Kiwanuka (1), D Nansera (1), P Orikiriza (2), Y Boum (1,2), M Bonnet (2,4)

1 Mbarara University of Science and Technology and Mbarara Regional Reference Hospital, Mbarara, Uganda; 2 Epicentre, Mbarara, Uganda; 3 Epicentre, Paris; 4 IRD UMI 233 TransVIHMI - UM – INSERM U1175, Montpellier, France



BACKGROUND AND OBJECTIVES

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

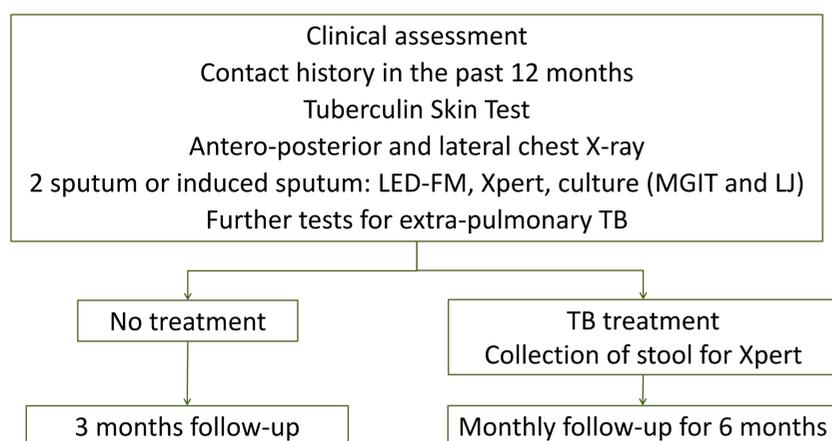
- To compare characteristics between children started or not on TB treatment
- To assess the proportion of confirmed and probable TB after the retrospective cases review by 2 independent paediatricians (*Graham et al. JID 2012*)
- To assess the performance of Xpert in sputum (spontaneous or induced) 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



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 CXR 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 CXR + TB contact history or positive TST or response to TB treatment, OR clinical signs and CXR 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

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

* 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

| Stool | Sputum Xpert or culture | | Stool | Confirmed or probable TB | |
|--|-------------------------|----------|--|--------------------------|----|
| | Positive | Negative | | Yes | No |
| Positive | 4 | 1 | Positive | 7 | 0 |
| Negative | 3 | 56 | Negative | 20 | 54 |
| Sensitivity: 4/7 (57.1%) Specificity: 56/57 (98.2%) | | | 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 empiric 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

Acknowledgements: patients; Médecins Sans Frontières; Epicentre Mbarara Research centre; University of Science and Technology; Mbarara Regional Reference Hospital; vRAD (<http://www.vrad.com/>)