Emerging experiences with diagnostic approaches in children with HIV, severe pneumonia and malnutrition

Feasibility of NPA, stool collection, and Ultra testing for microbiological diagnosis

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Annual meeting of the Child and Adolescent TB working group
16 October 2020
TB-Speed project

- **Goal (impact)**
  - Contribute to the reduction in childhood mortality from TB

- **Outcome**
  - Feasible and cost-effective strategy using innovative diagnosis tools and decentralized approaches improving childhood TB diagnosis in high TB-burden settings

- **Research project implemented in 7 countries**
  - Cambodia, Cameroon, Côte d’Ivoire, Mozambique, Sierra Leone, Uganda, Zambia
Microbiological diagnosis approach

Nasopharyngeal aspirates (NPA) & Stool samples
High feasibility and good Dx performance with Xpert MTB/RIF
Now recommended by WHO (2020)

Molecular testing using Xpert MTB/RIF Ultra
GeneXpert G4
Battery-operated G1 Edge
Highly vulnerable children in TB speed

- Children with HIV-infection, severe acute malnutrition (SAM), severe pneumonia
  - High risk of TB disease
  - High risk of death
  - High risk of under-diagnosis

- 3 studies targeting specifically these 3 groups in TB-Speed
  - TB-Speed Pneumonia: children <5 years hospitalized with WHO-defined severe pneumonia
  - TB-Speed SAM: children <5 years hospitalized for severe acute malnutrition
  - TB-Speed HIV: HIV-infected children <15 years with presumptive TB

Preliminary results focusing on the feasibility of NPA and stool sample collection and Xpert Ultra testing for TB diagnosis in vulnerable children
TB-Speed Pneumonia: study design

- **Primary objective**: to evaluate the impact on all-cause mortality at 12 weeks of adding the systematic early detection of TB with Xpert Ultra, performed on one NPA and one stool sample (followed by immediate TB Tx if positive, to the WHO SOC in young children with severe pneumonia, as compared to the SOC alone.
- **Cluster-randomized trial, stepped wedge design**
- **15 tertiary level hospitals, 6 high TB incidence countries** (CI, CM, MZ, UG, ZM, and KH)
- **3780 children**
  - Aged 2 to 59 months
  - Newly hospitalized for severe pneumonia defined using WHO criteria
- **Control arm**: the WHO standard of care (SOC)
- **Intervention**: in addition to the SOC,
  - Xpert Ultra performed immediately upon admission on 1 NPA and 1 stool sample
  - Immediate TB treatment initiation if Ultra positive
## TB-Speed Pneumonia: Baseline characteristics – Comorbidities

<table>
<thead>
<tr>
<th></th>
<th>Overall (N = 1940)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n(%) or median [IQR]</td>
</tr>
<tr>
<td>Gender (F)</td>
<td>830 (42.8%)</td>
</tr>
<tr>
<td>Age (months)</td>
<td>11 [5, 20]</td>
</tr>
<tr>
<td>Tachypnea*</td>
<td>1068 (55.1%)</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>48 [38, 58]</td>
</tr>
<tr>
<td>Peripheral O₂ saturation</td>
<td>93 [88, 97]</td>
</tr>
<tr>
<td>Positive HIV test</td>
<td>103 (5.3%)</td>
</tr>
<tr>
<td>Malaria test</td>
<td>158 (8.1%)</td>
</tr>
<tr>
<td>Severe Acute Malnutrition**</td>
<td>383 (19.7%)</td>
</tr>
</tbody>
</table>

* Defined by children aged 0-11 with RR > 50 ; children aged 12-35 with RR > 40 ; children aged 36-60 with RR > 30

* WHZ < -3SD and/or MUAC < 115 and/or Presence of edema
NPA – collection and Xpert testing feasibility

- **619 Children included in Intervention arm**
  - Not attempted N = 14

- **605 (97.7%) Children with NPA attempted**
  - Not successful N = 5

- **600 (96.9%) Children with NPA successful**
  - No XPERT N = 5

- **595 (96.1%) Children with ULTRA done on NPA**
  - Invalid/error result + No retest N = 7
  - Retest – Invalid result N = 2

- **586 (94.7%) Children with a valid result**
Stool – collection and Xpert testing feasibility

- 619 Children included in Intervention arm
  - Not collected N = 100
- 519 (83.8%) Children with collected stool
  - No XPERT N = 36
- 483 (78.0%) Children with XPERT test done
  - Invalid/error result + No retest N = 7
- 476 (76.9%) Children with a valid result
TB-Speed HIV: study design

- **Primary objective**: To evaluate the proportion of missed TB cases (i.e. false negative) in HIV-infected children with presumptive TB not initiated on treatment as per the PAANTHER TB treatment decision algorithm.

- **External validation study**: prospective, multicenter management study evaluating the safety and feasibility of the PAANTHER TB treatment decision algorithm for HIV-infected children with presumptive TB.

- **7 hospitals, 4 countries** (CI, UG, MZ, ZM) that did not participate in the PAANTHER study.

- **550 HIV-infected children**
  - Aged 1 month to 14 years
  - With presumptive TB based on the PAANTHER inclusion criteria.

The PAANTHER TB treatment decision algorithm

At any level of the decision algorithm, a score of 100 points is enough to start a TB-treatment.

Clinical suspicion of TB in a HIV-infected child:
- Cough > 2 weeks
- Fever > 2 weeks
- Deviation in the growth curve or a WAZ <-2SD
- Failure of antibiotics for a pulmonary infection
- Suggestive chest radiography

Consent form signed (YES) → Routine follow up; not enrolled in study (NO)

SAMPLES FOR XPERT MTB/RIF ULTRA

HISTORY OF CONTACT WITH SMEAR+ TB (NO)

DETAILED ASSESSMENT OF SYMPTOMS AND SIGNS
- Score: Fever lasting > 2 wks 66
- Unremitting cough 39
- Hemoptyisis in previous 4 wks 79
- Weight loss in previous 4 wks 24
- Tachycardia 54

YES

Score 118

YES

Score 100

YES

Ultra results
- Score 241
  - Positive Xpert
  - Miliary
  - Alveolar opacity
  - Lymph nodes

Score 100

YES

Initiate TB treatment
TB-Speed HIV: Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (N = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n(%) or median [IQR]</td>
<td></td>
</tr>
<tr>
<td>Gender (F)</td>
<td>28 (43.1%)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>5 [2, 10]</td>
</tr>
<tr>
<td>Previous TB treatment</td>
<td>6 (9.2%)</td>
</tr>
<tr>
<td>Severe Acute Malnutrition</td>
<td>26 (40.0%)</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>9.8 [8.1, 12]</td>
</tr>
<tr>
<td>On ART at inclusion</td>
<td>38 (58.5%)</td>
</tr>
<tr>
<td>CD4 percentage</td>
<td>23 [10, 30]</td>
</tr>
<tr>
<td>Persistent cough for more than 2 weeks</td>
<td>49 (75.4%)</td>
</tr>
<tr>
<td>Persistent fever for more than 2 weeks</td>
<td>18 (27.7%)</td>
</tr>
<tr>
<td>History of contact with TB case and any symptom duration</td>
<td>11 (16.9%)</td>
</tr>
</tbody>
</table>
TB-Speed HIV - NPA collection and Xpert testing feasibility

65 Children included in the study

Not attempted N = 2

63 (96.9%) Children with NPA attempted

Not successful N = 4

59 (90.8%) Children with NPA successful

No XPERT N = 0

59 (90.8%) Children with ULTRA done on NPA

Invalid/error result N = 0

59 (90.8%) Children with a valid result
65 Children included in the study

Not collected N = 5

60 (92.3%) Children with collected stool

No XPERT N = 3

57 (87.7%) Children with XPERT test done

Invalid/error result N = 2

55 (84.6%) Children with a valid result
TB-Speed SAM: study design

- **Primary objective**: To develop a diagnostic prediction score for TB in hospitalized children with SAM
- Prospective diagnostic cohort study
- **3 hospitals, 2 countries** (Uganda, and Zambia)
- **720 children with SAM**
  - Aged 2-59 months
  - Hospitalized per clinician’s decision (medical complication, danger sign)
- **TB diagnosis made according to existing National guidelines.**
- At the end of the study, children will be **retrospectively classified** as confirmed, unconfirmed, or unlikely TB, using the updated Clinical Case Definitions
### TB-Speed SAM: Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (N = 137)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n(%) or median [IQR]</td>
</tr>
<tr>
<td>Gender (F)</td>
<td>54 (39.4%)</td>
</tr>
<tr>
<td>Age (M)</td>
<td>14 [10, 19]</td>
</tr>
<tr>
<td>Weight for height Z score (WHZ) &lt; -3SD</td>
<td>104 (75.9%)</td>
</tr>
<tr>
<td>Mid upper arm circumference (MUAC) &lt; 115mm</td>
<td>89 (65.0%)</td>
</tr>
<tr>
<td>Clinical signs of bilateral pitting edema</td>
<td>67 (48.9%)</td>
</tr>
<tr>
<td>Previous TB treatment</td>
<td>1 (&lt;0.1%)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>8.5 [6.9, 9.7]</td>
</tr>
<tr>
<td>Positive HIV test</td>
<td>20 (14.6%)</td>
</tr>
</tbody>
</table>
137 Children included in the study

Not attempted N = 2

135 (98.5%) Children with NPA attempted

Not successful N = 2

133 (97.1%) Children with NPA successful

No XPERT N = 4

129 (94.2%) Children with ULTRA done on NPA

Invalid/error result + No retest N = 0

129 (94.2%) Children with a valid result
137 Children included in the study

Not collected N = 8

129 (94.2%) Children with collected stool

No XPERT N = 11

116 (84.7%) Children with XPERT test done

Invalid/error result + No retest N = 0

116 (84.7%) Children with a valid result
Conclusion

- High feasibility of NPA sample collection confirmed in highly vulnerable children
  - > 90% of children with valid Ultra result from NPA
- High feasibility of stool sample in HIV infected children with presumptive TB and hospitalized children with SAM
  - Slightly more challenging in children hospitalized with severe pneumonia
- Feasibility of approaches at lower level of care (District Hospital and PHC)
  - Currently assessed in TB-Speed Decentralizations
- Qualitative assessment on feasibility and acceptability starting
  - Interviews with parents and healthcare workers in the Pneumonia study
- Final study results
  - TB-Speed Pneumonia: Q4 2021
  - TB-Speed HIV: Q1 2022
  - TB-Speed SAM: Q3 2021
Role and contribution of algorithm and score for diagnosis of paediatric TB. 23 OCT 12:30 13:50 B1.

  - Overview of challenges in diagnosing TB in children and shortcomings of existing diagnostic algorithms and scores
  - Methodological challenges and alternatives in the evaluation of TB diagnostic algorithms in children
  - *New TB diagnostic algorithm/score for vulnerable children: children with HIV infection and children with severe acute malnutrition*
  - Performance of new screening and diagnostic tests in potential paediatric TB diagnostic algorithms: interim results from the RaPaed study
  - Contribution of chest X-ray in the paediatric diagnostic algorithm?
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Chishala CHABALA
Country Principal Investigator
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