The “Titi” study
Transmission Investiguée de la Tuberculose Infantile

Valérie Schwoebel
Childhood TB working group meeting
Liverpool, 26 October 2016
Background

- A workshop was organized by The Union in January 2014 in Benin with NTP (managers/childhood TB focal points) and paediatricians from 8 countries in francophone Africa: Benin, Burkina Faso, Cameroon, Central African Republic, Côte d'Ivoire, DRC, Madagascar, Niger.

- The objective of the workshop was to identify key actions to improve the control of childhood TB.

- Among the major conclusions of the workshop: systematic investigation and preventive therapy for children <5 years who are contacts of contagious TB cases, although internationally and nationally recommended, remain partially implemented and are not fully documented.
Workshop recommendations

On operational research:

- To conduct a study on how to implement and document systematic investigation and preventive therapy for contact children < 5 years within the NTP framework.
- To conduct a study on how to implement a shorter RH regimen for preventive therapy in children < 5 years.

The Union together with 4 country teams (Benin, Burkina Faso, Cameroon, CAR) decided to write a protocol of an implementation research study combining these 2 objectives and to submit it to Expertise-France for funding. Research grant obtained in 2015.
National research teams

• 1 PI and 1 co-investigator
  – 1 NTP
  – 1 pediatrician or pneumologist
• 1 research assistant (social worker or anthropologist)
• Nurses
• Data managers
Study objectives

• Primary objective is to demonstrate the feasibility of conducting contact investigation and preventive therapy within the framework of the NTP

• Specific objectives
  – Estimate the number of children < 5 years who are close contacts of sputum smear positive (SS+) cases
  – Determine the prevalence and analyse risk factors for active TB among contact children (at inclusion)
  – Determine the incidence of active TB in children during and after preventive therapy using 6H or 3 RH75/50
  – Assess children adherence to preventive therapy
  – Develop standardised simple recording & reporting tools
Sites - Population

• Study sites
  – Major city of each country: Cotonou, Ouagadougou, Douala, Bangui,
  – 13 Basic Management Units (BMUs)

• Study population
  – 2 000 children : 500 per country
  – Recruitment : screening of all adult SS+TB cases diagnosed in each BMU
    • Residence > 3 months
    • Home < 5 km of BMU
    • With children < 5 years living at home
    • Accepting to participate
Inclusion (1)

- **Step 1 : Basic Management Unit (BMU)**
  - As part of consultation of each new SS+ adult TB case
  - Questionnaire : minimal information – eligibility criteria
  - Informed consent signed by parents of children

- **Step 2 : Home visit**
  - Performed < 3 days of initial adult consultation
  - Nurse and social worker/anthropologist
  - Questionnaire on family structure and contacts
  - Questionnaire for each child < 5 : contacts, symptoms & physical examination
  - (Tuberculin Skin Test in some countries)
  - BMU appointment
Inclusion (2)

- **Step 3**: clinical evaluation of child at BMU (nurse)
  - TST (read 48 - 72 h)
  - Chest X-ray: all read by a doctor using a standard form
  - Physical examination (height, weight, $T\degree$, RR)
  - Child referred to pediatrician if signs/symptoms suggestive of TB (cough, fever, weight loss, reduced playfulness) and/or abnormal X-Ray
  - If child not referred, or later found free of TB by pediatrician, preventive chemotherapy is initiated
    - RH 75/50 mg during 3 months (CAR, BF, CMR)
    - H 100 mg during 6 months in BEN
# Dosages

**Table 4a.** *H50 or H100 tablets daily for 6 months duration (IPT – 6H)*

<table>
<thead>
<tr>
<th>Weight bands</th>
<th>Isoniazid (mgs)</th>
<th>H50 tablet</th>
<th>H100 tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-7 kg</td>
<td>50</td>
<td>1</td>
<td>1/2</td>
</tr>
<tr>
<td>8-11 kg</td>
<td>100</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>12-15 kg</td>
<td>150</td>
<td>3</td>
<td>1 1/2</td>
</tr>
<tr>
<td>16-24 kg</td>
<td>200</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

**Table 4b.** *RH 75/50 FDC daily for 3 months (3RH)*

<table>
<thead>
<tr>
<th>Weight bands</th>
<th>RH 75/50 tabs</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-7 kg</td>
<td>1</td>
</tr>
<tr>
<td>8-11 kg</td>
<td>2</td>
</tr>
<tr>
<td>12-15 kg</td>
<td>3</td>
</tr>
<tr>
<td>16-24 kg</td>
<td>4</td>
</tr>
</tbody>
</table>

For children that are 25 kg and above, use adult preparations: one tablet of H300mg or two RH150/75.
Follow-up

• **Monthly during preventive chemotherapy**
  – 4 TB symptoms
  – Physical examination
  – Adherence to treatment
  – Adverse reactions (AR)

• **Quarterly after preventive chemotherapy**
  – Up to 12 months after termination of therapy
  – 4 TB symptoms
  – Physical examination

• If any sign/symptom suggestive of TB or suspected AR, nurse refers the child to the pediatrician
Chest X-Ray form

- Based on the « template chest X-Ray review tool » (Graham S et al. JID 2012)
  1. Airway compression or tracheal displacement
  2. Image suggestive of lymphadenopathy
  3. Air space opacification
  4. Nodular picture
  5. Pleural effusion
  6. Cavity
  7. Calcified parenchyma
  8. Vertebral spondylitis

- Conclusion: normal/abnormal suggestive of TB/abnormal suggestive of other disorder
## Register for preventive Tt

<table>
<thead>
<tr>
<th>Month 0 Date</th>
<th>Month 1 Date</th>
<th>Month 2 Date</th>
<th>Month 3 Date</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poids</td>
<td>Dose</td>
<td>Poids</td>
<td>Dose</td>
<td>Poids</td>
</tr>
</tbody>
</table>

TT (Treatment completed, A (Treatment stopped for adverse reaction), PDV (lost to follow-up), DCD (death), F (transferred out), TB (tuberculosis)
Progress

- The study has started successfully
  - Authorizations from the ethical committees (national, The Union) were obtained at the end of 2015
  - Inclusion started 01/04/16 and will last ~18 months.
  - Already > 500 children started on preventive therapy.

- No major problem encountered in conducting home visits, BMU visits, doctor visits and monthly follow-up

- Good participation of families, children happy to take RH75/50 (good taste!)

- Tools appear useful
Challenges and perspectives

- Procurement of tuberculin has been a headache

- Quality and interpretation of chest X-rays appear heterogeneous between countries: NTPs lack experience in doing chest X-rays in young children

- The study highlights the needs for training NTP staff in children clinical evaluation and in obtaining specimen (gastric aspiration) for TB diagnosis

- Final results expected for end-2018, but lessons could be learned from preliminary results next year
Thank you for your attention