Childhood TB in the Americas: challenges, opportunities and steps to be taken

Tuberculose na infancia nas Américas: desafios, e oportunidades e próximos passos

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A clinical case

Pedro, an eight-month old child, weighing nine kilos arrived to the emergency room with a fever and drowsiness. These symptoms were said to have been displayed the last two weeks. Suddenly Pedro presented with meningism and seizures. After an examination and lab test were performed, TB meningitis was confirmed. Pedro underwent surgery for ventricular peritoneal derivation. He survived but remained disabled. 

Background: Six months before the onset of the symptoms, the mother was diagnosed with pulmonary TB. Despite the fact that contact tracing is part of the policy of the TB program, nobody asked the mother about household contacts, in particular those under five years of age. Two months later, a nurse went to the patients' home and found that there was a 4 months old child. Even though the nurse visited the home, the child was eventually only examined two months later, and Isoniazid Preventive Therapy (IPT) was therefore started late. During the first follow up, the child had received one month of IPT. At the request of the family, the pediatrician decided to stop the IPT based on the fact that the mother was smear negative at that moment, and based on the fact that the child was well and previously vaccinated with BCG. The tragedy started one month later.

Evaluation: This case study summarizes a sequence of poor decision making: contact tracing was not implemented as it should; children are often not being considered a priority; a full course of IPT was interrupted. Suffering and disability could have been avoided.

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Burden of childhood TB disease and mortality worldwide and in the Americas

Worldwide, 9.6 million people are estimated to have fallen ill with TB in 2014: 5.4 million men, 3.2 million women; and, 1 million children. In 2014, TB killed 1.5 million people including 136,000 children (81,000 children who were HIV-negative and an additional 55,000 children who were HIV-positive), about 400 childhood TB deaths per day. Worldwide, children represent about 10-11% of all TB cases.

Among the total 208,839 new and relapse TB cases disaggregated by age reported in the Americas in 2014, a total of 10,489 (5%) were cases aged < 15 years. The best estimated number of childhood TB cases in the Americas was 27,000 (with a confidence interval of 25,000 - 29,000). This means that in 2014 at least 16,000 cases were “missed”, either not reported to national TB programmes (and quality of case management unknown) or not diagnosed.

Key risk factors for TB in children include: household or other close contact with a case of pulmonary TB (especially smear-positive or culture-positive pulmonary TB); age less than 5 years; HIV infection; and severe malnutrition. Young children are at an increased risk of severe disease, such as TB of the brain (TB meningitis) or disseminated TB (miliary TB). This is because the immune response in young children is less developed. Children with HIV are at an increased risk of TB.

Challenges in the management of childhood TB

There are usually many missed opportunities for case finding and prevention. Screening for TB is not systematically undertaken among children living in households affected by TB, and recommendations for provision of isoniazid preventive therapy (IPT) for children under 5-years of age and for children and adolescents with HIV-infection are rarely implemented and reported. The current TB vaccine, the Bacillus Calmette-Guérin or BCG vaccine, protects young children against the most severe forms of TB, such as meningitis or disseminated TB, but does not prevent transmission from an infectious contact. There is also a lack of community knowledge and advocacy. Despite the fact that many national TB programmes (NTPs) address the management of childhood TB in their national TB guidelines since multiple years, activities to address childhood TB have not been systematically implemented as childhood TB was not considered a priority (less infectious) and/or because of lack of resources, e.g. for contact tracing. Just recently, countries have started to include activities to scale up the response to childhood TB in national TB strategic plans, budgets of Ministries of Health and donor applications. Childhood TB is a sign of ongoing TB infection in the community and deserves attention within the child health survival agenda.

Diagnosis of childhood TB can be challenging. TB in children is often missed or overlooked due to non-specific signs and symptoms (cough, fever and weight loss). Children with TB or child contacts usually enter the health system at the lower levels of the health system and outside the national TB programme where health personnel do not have the skills and capacity to diagnose TB in children. Young children are unable to produce sputum and health workers are usually not trained in sputum aspiration and sputum induction. Due to the paucibacillary nature of the disease, the majority of children will have negative results by using any of the available bacteriological tests. A negative test result does not exclude TB. In the absence of affordable and sensitive diagnostic tests that are not based on sputum specimens, a diagnosis can reliably be made on careful history of exposure (including history of TB contact and symptoms consistent with TB), clinical examination (including growth assessment), other investigations relevant for suspected pulmonary TB and suspected extrapulmonary TB, and HIV testing.

The development of affordable diagnostic tests for TB in children in low-resource settings should be a priority for researchers and policy makers. In the meantime, health personnel would benefit from training to make a reliable diagnosis based on careful history of exposure and clinical examination. Bacteriological confirmation should be sought whenever possible. TB in older children and adolescents is often similar to adult-type disease (and not so paucibacillary). In this group, sputum is often readily available and TB can be confirmed through the use of bacteriological or molecular methods (e.g. GeneXpert MTB/Rif). TB in children can be treated and most children tolerate treatment very well. In December 2015, appropriate child-friendly fixed-dose combinations have become available (see more information below). Prior to this, treatment was challenging and involved practices of crushing and cutting of old childhood TB formulations or adult formulations often resulting in incorrect dosages. Treatment was often mixed with food to mask the bitter taste. Interaction between food and medication remains unknown. DR-TB is treated based on expert opinion. There are currently no child TB formulations of second line TB drugs as children are not often part of clinical trials. We are currently observing an expansion of clinical trials with the inclusion of children (both prevention and treatment of drug susceptible and drug-resistant TB). It is expected that results will be able inform the development of global policy recommendations in the near future.

Progress in addressing TB in children over the past 5 years and opportunities to scale up the response

In March 2011, during a meeting in Stockholm, Sweden, global partners launched a Call for Action on childhood TB. Later in 2011, the Global TB Symposium in Lille, France, focused on addressing the unmet needs of women and children. This was followed by the World TB Day 2012 on childhood TB and the Global TB Report 2012 including for the first time childhood TB disease burden and mortality estimates. Since 2012, countries have improved reporting by age and sex and methods to estimate the burden of TB have been refined.
We now have an improved understanding of the burden of TB among children. In October 2013, partners united in the in the Stop TB Partnership Childhood TB Subgroup produced the Childhood TB Roadmap: Towards Zero Deaths, a first-ever targeted roadmap with key steps to scale up the response to childhood TB and end childhood TB deaths1.

The Roadmap shows that the goal of reaching zero TB deaths among children worldwide is within our grasp. It requires sustained advocacy, greater commitment, mobilization of increased resources and a joint effort by all stakeholders involved in providing health care for children and in TB control. The Roadmap advocates for a shift from the many challenges we face towards immediate actions that we can take to accelerate progress. It calls for the following immediate actions to be taken: we need to get the many tools that exist to find and prevent TB in the hands of frontline health workers; childhood TB cannot and should not be the sole responsibility of NTPs; especially in high-burden countries, we must use every opportunity to identify children at risk; TB screening needs to be integrated with existing maternal and child care services - not just in health facilities, but throughout the community using a community- and family-centered approach; and, we must strengthen routine health surveillance and reporting systems. There is stronger global political commitment to tackle childhood TB in all countries.

Information is essential to understand the epidemiological situation of TB among young patients. Since 2006, almost all countries in the Region of the Americas report on TB disaggregated by sex and age (0 to 4 and 5 to 14 years). In addition, the WHO/PAHO Regional Office for the Americas is collecting data on contact investigation, IPT and treatment outcomes which they propose to be reflected in future Global TB Reports.

Guidelines and training materials for health workers and national TB programmes on the management of TB in children have been developed. In 2013, the Union developed a Desk Guide for diagnosis and management of TB in children for health workers at the district or more peripheral level of care4. In 2014, WHO published the second edition of the Guidance for NTPs on the management of TB in children5. In 2014, WHO also developed a Framework for conducting reviews of NTPs with an annex on childhood TB including questions for assessing childhood TB during a TB Programme review: the place of childhood TB in the national TB policy; Appropriateness of the procedures used to identify TB in children; Quality of the case-management of children with TB; Appropriateness of the data collected on childhood TB; and, Actions that need to be taken to improve approaches to childhood TB6.

The KNCV Tuberculosis Foundation has recently developed a Benchmarking tool for Childhood TB policies and practice, a self-assessment tool, which should assist countries in assessing the current situation and in planning activities for scaling up childhood TB6. WHO and the Union have developed the following training materials: (1) a Childhood TB training toolkit (2014) for NTPs and health workers who manage sick children and/or TB cases of any age in the community or at the more peripheral level of health care - primary health care facilities and district hospitals7. The training can be added onto another TB training (does not have to be stand-alone training); and, (2) an Online training course on childhood TB for health workers (2015)8.

The six-module curriculum covers how to diagnose, treat and prevent childhood TB, including how to perform contact screening. The modules are interactive and ask participants to make decisions about patient care in various settings through case examples. The self-paced course of which the content is based on the WHO’s 2014 Guidance for NTPs on the management of TB in children, as well as The Union’s Desk guide for diagnosis and management of TB in children, is available on the Union’s Childhood TB Learning Portal. The Learning Portal will offer a variety of resources aimed to support countries’ efforts to address the 10-step plan outlined in The Roadmap for Childhood TB, published in 2013. Currently, an online course on the management of MDR-TB among children is being developed. Some of the guidelines, tools and training materials are already (or will soon be) available in Spanish and/or Portuguese.

At the 46th Union World Conference on Lung Health in Cape Town, South Africa, in 2015 the Global Alliance for TB Drug Development (TB Alliance) and Partners announced the availability of appropriate child-friendly TB fixed-dose combinations (child TB FDCs) in line with the WHO dosing recommendations: (Chart 1.)

The following dosing table provides information on the number of daily tablets needed to reach proper dosing, based on the child’s weight: (Table 1)

<table>
<thead>
<tr>
<th>Weight band</th>
<th>Number of tablets</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>
<tr>
<td>25+ kg</td>
<td>Adult dosages recommended</td>
</tr>
</tbody>
</table>

* Ethambutol should be added in the intensive phase for children with extensive disease or living in settings where the prevalence of HIV or of isoniazid resistance is high.
The child-friendly formulations are dispersible with a pleasant flavour which will improve adherence and contribute to child survival. Following approval by a WHO Expert Review Panel in June 2015, countries can access the new formulations through the Global TB Drug Facility (GDF).

Other products that are currently under development and likely to become available in 2016 are: 100 mg Ethambutol dispersible tablets and 100mg isoniazid dispersible tables (recommended for preventive therapy).

**The End TB Strategy 2016-2035 and the UN Sustainable Development Goals 2030**

The End TB Strategy 2016-2035 and the UN Sustainable Development Goals 2030 provide major opportunities to further scale up the response to childhood TB. The End TB Strategy envisions a world free of tuberculosis - zero deaths, disease and suffering. The goal is to end the TB epidemic by 2035. Targets for 2035 compared to 2015 include: a 95% reduction of number of TB deaths; a 90% reduction in TB incidence by 2035; and, zero TB affected families facing catastrophic costs due to TB as of 2020. Achievements of these targets will require: Expanding the scope and reach of interventions for TB care and prevention, with a focus on high-impact, integrated and patient-centered approaches; Eliciting full benefits of health and development policies and systems through engaging a much wider set of collaborators across government, communities and the private sector; and, pursuing new scientific knowledge and innovations that can dramatically change TB prevention and care. To reach the targets set out in the End TB Strategy, the annual decline in global TB incidence rates must accelerate from 2% per year in 2015 to 10% per year by 2025. The targets for declines in incidence and deaths by 2025 are ambitious yet feasible with existing tools and complemented by universal health coverage and social protection. To sustain progress beyond 2025 and achieve the SDG 2030 and End TB 2035 targets, additional tools must be available by 2025. In particular, a new vaccine that is effective pre- and post-exposure and a safer and more effective treatment for latent TB infection are needed to reduce the number of new TB cases arising from approximately 2 billion people worldwide who are infected with M. Tuberculosis, as well as better diagnostics and safer and easier treatment including shorter drug regimens for TB disease.

The UN Sustainable Development Goal 3: Ensure healthy lives and promote well-being for all at all ages, target 3.3, calls to end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, waterborne and other communicable diseases. The actions required to achieve the ambitious goals as included in the SDGs and the End TB Strategy provide an unprecedented opportunity to address the needs of children and adolescents with TB.

**Proposed steps to scale up the response to childhood TB**

Participants of the 3rd Regional Meeting on Childhood TB and MDR-TB in the Americas, 21-22 October 2015, Brasilia, Brazil, identified the following challenges and areas where there is room for improvement to scale up the response to childhood TB (similar to challenges in other WHO regions): (Chart.2)

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Proposed strategies and actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Case detection</td>
<td>Health workers need training to suspect and diagnose TB; all tools available for diagnosis need to be used; sample taking and management needs to be improved; rapid tests need to be made available and their use optimized; infection control measures need to be implemented; and staff turn-over needs to be addressed.</td>
</tr>
<tr>
<td>(2) Treatment of Childhood TB Tuberculosis</td>
<td>Appropriate paediatric TB formulations need to be made available without shortages; treatment adherence needs to be improved and challenges related to migration need to be addressed; health care workers need training coupled with supervision; care needs to be patient-centered; and, where recommended, Directly Observed Treatment (DOT) needs to be implemented.</td>
</tr>
<tr>
<td>(3) Contact tracing and management of latent TB infection</td>
<td>Health care workers need to be trained to improve understanding; diagnostics, PPD and IPT need to be available without shortages; monitoring and evaluation mechanisms need to be developed; families need to be counselled about the need for preventive therapy and duration of preventive treatment in order to improve adherence; and, further guidance is needed on preventive treatment for contacts of patients with drug-resistant forms of TB.</td>
</tr>
</tbody>
</table>

In order to address these challenges, and to reach all children with TB or at risk of TB, the participants of the 3rd Regional Meeting on Childhood TB and MDR-TB in the Americas proposed the following strategies and actions for the various stakeholders who all have an important role to play in scaling up the response to childhood TB:

National TB programmes (NTP) to: include childhood TB in the national strategic plan; identify a paediatrician to scale up childhood TB; set up a working group on childhood TB involving various stakeholders across sectors; develop or update childhood TB guidelines; plan for uptake of new rapid diagnostics, universal drug susceptibility testing (DST) and for the procurement of child-friendly TB formulations; facilitate training of health professionals on childhood TB; advocate for universal health coverage for TB patients and implementation of strategies to ensure that no families are facing catastrophic cost related to TB; promote research; consider incentives for implementation of contact tracing; ensure that children who are not (or no longer) infectious remain in school; ensure availability of recording and reporting systems; and, address the needs of adolescents.
Scientific societies to: coordinate with the NTP; implement existing commitments; ensure continuous education; include TB in curricula of medical schools and other health professional education; teach on TB; and, conduct research. Scientific societies could work closely with academic institutions to this extent.

Civil society can help to raise social awareness on childhood TB (it is a significant problem which is preventable and treatable) and request that new childhood TB-friendly formulations be made available as soon as possible.

WHO was requested to provide continued technical guidance; raise and maintain political commitment; guarantee production of PPD and BCG; consider organizing an annual meeting on childhood TB bringing stakeholders together; and, create a virtual network for sharing paediatric TB publications and distribute of information including good practices.

REFERENCES


