

## **MORE RESEARCH NEEDED ON TB DIAGNOSTIC TESTS IN CHILDREN: HIGH-QUALITY STUDIES CAN PAVE THE WAY**

A group of experts met at a meeting organized by the Special Programme for Research and Training in Tropical Diseases (TDR) Geneva in May 2010 to discuss the challenges faced when diagnosing tuberculosis (TB) in children. Participants included clinicians, researchers, scientists, biostatisticians and epidemiologists from different parts of the world.

A number of different factors hinder the accurate diagnosis of TB. The disease has a wide clinical presentation ranging from respiratory illness undistinguishable from other respiratory infections, to an invasion of the organs or nervous system. TB occurs as a spectrum, with a continuum from an asymptomatic infection to active disease. Malnutrition, young age and HIV further increase the risk of progressing to active and severe forms of TB disease.

Only a few of the cases occurring in children are confirmed using standard laboratory tests since children often struggle to produce sufficient good quality sputum to confirm the presence of the bacilli. Also, the burden of organisms (bacterial load) is generally lower in young children. Thus, the culture of sputum, which is considered the reference standard for diagnosis in adults, can only diagnose 30-40% of cases and only about 10-15% of children are smear-positive (which helps establish an immediate diagnosis). The diagnosis of TB in children thus often relies on the clinical history and examination plus tests such as the tuberculin skin test and x-rays, which are less reliable.

New and improved diagnostic tests for TB have been developed in recent years and several of these have been endorsed by the World Health Organization (WHO) with the result that a number of national TB control programmes are considering implementation of these tests.

While these new tests are very welcomed and could make a real difference to diagnosing TB in adults, very few have been evaluated in children. Ironically, the fact that childhood TB is difficult to diagnose often inhibits researchers from including children in the evaluation of new diagnostic tools. Children are thus traditionally underserved in research on TB diagnostics. Further, a lack of diagnostics that can be used to confirm diagnosis also makes the evaluation of new drugs for treatment of TB in children more challenging.

In the light of these considerations, the panel of experts reached consensus on the following principles:

- The evidence available on the utility of new diagnostic tools for childhood TB is inadequate, since most of these tests have been evaluated using adult sputum specimens.
- The lack of adequately tested and reliable paediatric diagnostic tests limits the capacity to ascertain the worldwide burden of childhood TB and the appropriate management of TB in children.
- The definitions used by researchers for the diagnosis of TB need to be standardized to enable the comparison of studies in different countries and age groups. It is also necessary to make a distinction between the diagnostic approaches currently used by health professionals to routinely decide the appropriate management of the child (clinical case definition) and those required for research purposes.

- Bacteriological confirmation by culture should be required as a reference standard for research purposes in children, especially for early evaluation of new diagnostics. This may imply that only a small proportion of cases are confirmed with this method.
- For subsequent larger studies (i.e. clinical validation and demonstration studies), a composite reference standard could be developed by using clear disease definitions and a combination of laboratory tests. This approach could be used to make up for the poor sensitivity of culture in children, but would need to be carefully evaluated.
- Current research on childhood TB diagnostics is characterized by a lack of standardization of study designs, entry points to the studies and case definitions, clinical measurements, and standard operating procedures for collection, processing and storage of samples. This makes the interpretation of currently available information very difficult.
- Standard operating procedures should be used for all aspects of study implementation, including sample collection and processing, laboratory procedures, clinical evaluation, chest radiograph reading and reporting.
- Studies evaluating new TB diagnostics need to consider the wide range of clinical presentations of the disease, specify the characteristics of the participants and the treatment outcome. In order to be representative, such studies should also include children from all ages, including young infants and older children. Adult TB diagnostic studies should be encouraged to include children older than 10 years of age, who can be encouraged to provide good quality sputum specimens
- There is an urgent need for the development and evaluation of diagnostic tests for TB in children. High- quality paediatric TB diagnostic studies using standard approaches could improve access to appropriate funding streams. Such studies may lead to the more representative inclusion of children in diagnostic studies for TB.
- Evidence generated by high-quality TB diagnostic studies in children may mean that in future, children may also have better access to research on treatment and prevention studies.

The following specific recommendations were made at the meeting:

- Diagnostic TB studies in children should adhere to the Standards for the Reporting of Diagnostic Accuracy Studies (STARD) and other guidelines for reporting.
- A public-domain standard operating procedure inventory for the evaluation of TB diagnostics in children should be developed.
- New diagnostic tests in early phase studies should use culture for their validation.
- Standardized research case definitions should be developed to enable subsequent evaluation of the clinical validity (reliability) and utility (use) of new TB diagnostic tests in children
- Standard protocols for evaluating TB diagnostic tests in children should be developed. These protocols should include the key methodological aspects around which consensus was achieved
- The expert group should disseminate their findings through formal publication of consensus statement and methodological aspects emanating from this meeting and ongoing consultation.

In summary, there is a clear need for high quality research studies on new diagnostics for childhood TB using standard approaches and reference standards. Both existing and new

diagnostics tests for TB need to be assessed in children, one of the most vulnerable populations. The unique aspects of childhood TB need to be taken into account at every stage from the development of the diagnostic tools through their testing in the field.

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