# Performing TB Research in Children – Issues to Consider

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Tuberculosis (TB) control programs place an almost exclusive emphasis on adults with sputum smear-positive disease, as they represent the most infectious cases that sustain the TB epidemic. However, although pre-adolescent children contribute little to TB transmission, they contribute significantly to the global TB caseload and experience considerable TB-related morbidity and mortality, especially in high burden settings(1-4). Despite TB being an easily treatable disease few children in these settings have access to TB treatment, as evidenced by the absence of child friendly drug formulations in many high burden countries. Luckily this is changing and there is increased awareness and commitment at an international level to reduce the TB disease burden in children. The World Health Organization (WHO) recently published guidelines for national TB programs on the management of TB in children(5), and for the first time the Global Drug Facility (GDF) has made child friendly drug formulations available to poor countries. These positive developments focus the attention on the tenacious problem of establishing an accurate TB diagnosis in children, particularly in TB-endemic settings with limited resources that carry the brunt of the disease burden.

The diagnosis of TB in children is complicated by the absence of a practical "gold standard" test, as sputum smears, the "gold standard" used in adults, are positive in less than 10-15% of children diagnosed with TB(6). For research purposes accurate case definition is essential and revolves mainly around the ability to differentiate primary infection from active disease. Primary infection occurs when a previously uninfected child inhales an infectious aerosol droplet and a localized pneumonic process, referred to as the Ghon focus, results at the site of organism deposition. Initially unrestrained organism multiplication occurs within the Ghon focus and bacilli drain via local lymphatics to the regional lymph nodes to form the classic Ghon complex, represented by the Ghon focus, with or without some overlying pleural reaction, and affected regional lymph nodes(7).

Spread of bacilli beyond the regional lymph nodes (occult dissemination) is not uncommon during this early phase before cell-mediated immunity is fully activated and positive *M. tuberculosis* cultures may be found in the absence of active disease eg. following culture collection in otherwise asymptomatic children with a history of recent TB exposure(4,8). This demonstrates the uncomfortable overlap that exists between recent infection and active disease. It is important to consider this overlap when case definitions are formulated for research purposes, particularly in the contact setting. It is less relevant in everyday clinical practice where there is no reason to obtain cultures from a completely asymptomatic child.

Culture-based case definitions remain the most definitive outcome measure available, but it is important to be aware of its limitations. Firstly, despite being far more sensitive than smear microscopy, culture yields remain low in children with less advanced disease. Secondly, transient *M. tuberculosis* excretion may occur after recent primary infection (probably also after re-infection) in the absence of symptoms or signs indicative of active disease(4,8). Unfortunately, there is no novel test on the immediate horizon that promises

improved sensitivity and specificity. A recent review of novel diagnostic tests demonstrated inadequate test validation in children and persistent difficulty to differentiate *M. tuberculosis* infection (recent primary infection, re-infection or latent infection) from active disease(6).

Chest radiography is often used as a practical alternative; although it has well recognized limitations and interpretation is highly subjective(6). Uncomplicated hilar adenopathy remains the most common disease manifestation in children and is usually regarded as the hallmark of primary tuberculosis(9). By convention, asymptomatic hilar adenopathy is currently treated as active disease, but in terms of pathophysiology, microbiology and natural history, asymptomatic hilar adenopathy is more indicative of recent primary infection and particular caution is required when interpreting the relevance of these radiologic signs in the absence of clinical data.

During protocol development it is essential to carefully consider the point of entry (to prevent/ reduce selection bias), to develop clear definitions for the symptoms and signs that will be evaluated and to define the outcome measure (case definition) that will be used. The most accurate case definitions are provided by a combination of symptomatic presentation and either bacteriologic confirmation or radiographic certainty. In our experience, the majority of symptomatic children diagnosed with intra-thoracic TB have unequivocal *X*-ray chest (CXR) signs(9). The following measures were identified to try and optimize radiographic diagnosis as a study endpoint; 1) only perform chest radiographs on symptomatic children, 2) antero-posterior and lateral views should be taken, 3) all chest radiographs should be read by two independent blinded experts with sufficient clinical experience, 4) the quality of the CXR should be assessed first and poor quality radiographs rejected/ repeated, 5) observations must be documented on a standard report form, and 6) expert readers must have the option to indicate uncertainty.

When reporting results, it is important to reflect the demographics of the study population with special emphasis on risk stratification(4). The natural history of disease demonstrates that age and immune status are the most important variables that determine the risk to progress to active disease following primary *M. tuberculosis* infection. Immune competent children older than 3 years of age are at low risk, but as the vast majority of children only become infected after 2-3 years of age, they still contribute a significant percentage of the total disease burden. In settings where HIV is prevalent, it is important to report the HIV status, as this has a dramatic influence on the child's risk to develop TB and the type of disease manifestations that may occur(10).

It is also important to reflect the disease diversity observed. Childhood tuberculosis represents a diverse spectrum of pathology and one of the obstacles to progress has been the lack of standard descriptive terminology. Accurate disease classification is important to provide the reader with a clear overview. If intra- and extra-thoracic disease entities are not separated, it becomes extremely difficult to evaluate the relevance of the CXR findings *e.g.,* cervical adenitis, the most common extra-thoracic disease manifestation of TB in children, is frequently associated with a normal CXR(11,12). Consistent and standardized terminology should also be used to describe CXR findings to facilitate comparison and scientific communication(7).

This edition of the journal contains results from an observational study on child TB that demonstrates some of the issues outlined above. Doing research on children with TB remains a daunting task and studies conducted in high burden settings add valuable new data. In order to improve understanding and facilitate progress, we need to develop consistent methodology that takes some of the issues discussed into consideration.

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## Long-Term Prognosis of Neonatal Seizures – Where are We?

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Neonatal seizures are a relatively common marker of brain dysfunction in the newborn. Population based studies from Western countries(1) suggest a relatively low incidence of 2.6/1000. The incidence in outborn babies admitted to Indian NICUs is close to 12%, and reflects the actual reality in our country where babies are born in small hospitals and nursing homes(2).

The recurring question uppermost in both parents and pediatrician's mind is what will be the long term neurological outcome in a baby with neonatal seizures. For many decades, it has been clear that the etiology of neonatal seizures is one factor critical in determining outcome. Newborns with transient correctible metabolic abnormalities, focal ischemia and without clear etiology do well, while those with hypoxic-ischemic encephalopathy (HIE), CNS infections and cerebral dysgenesis regularly do poorly(1,3). In India, where perinatal care is uneven, transient metabolic disturbances like hypocalcemia and hypoglycemia still account for about a fifth of the neonatal morbidity(2). Also, the outcome of hypoglycemia is not necessarily