# Minding (and Reducing) the Detection Gap: An Algorithm to Diagnose TB With HIV Infection

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Globally, an estimated 239 000 children younger than 15 years, including 39 000 with HIV infection, die of tuberculosis each year. More than 95% of these deaths occur in children who did not receive tuberculosis treatment.[1] Children treated for tuberculosis have low mortality rates.[2] Therefore, it is likely that the number of childhood tuberculosis deaths would decline dramatically if the case-detection ratio were improved from its current proportion of ~1 in 3. Multiple factors contribute to this dismal case-detection rate, including the health care barriers faced by the poor and marginalized populations most affected by tuberculosis, the inability of most children to expectorate sputum for sample collection, and the paucibacillary nature of childhood tuberculosis, which leads to infrequent microbiologic confirmation. The most sensitive microbiologic test (culture) identifies *Mycobacterium tuberculosis* in just 25% of cases.[3]

Health officials in countries with high tuberculosis burden have prioritized contagious adult cases as the drivers of the tuberculosis epidemic. Consequently, front-line providers often lack adequate training to evaluate children for tuberculosis.[4] Because their clinical training emphasizes tuberculosis in adults, which has a much higher rate of microbiologic confirmation, providers may be reluctant to start antituberculosis therapy without identification of *M tuberculosis* or may have false confidence in negative testing results. This confluence of factors results in children with tuberculosis experiencing diagnostic delays or never receiving a diagnosis at all. Children who do not receive a diagnosis are not reported as having tuberculosis, resulting in a vicious cycle of childhood cases not being counted and thus not being a perceived public health problem.

Diagnostic challenges as well as the consequences of missing a tuberculosis diagnosis are exacerbated in the estimated 1.8 million children living with HIV around the world.[5] Children with HIV have a risk of progression from tuberculosis infection to disease that is estimated to be at least 8 times higher than that for children without HIV.[6] Children with HIV infection are also 8 to 14 times more likely to die of tuberculosis disease compared with children without HIV.[2]

Previous clinical-decision scores developed for diagnosing childhood pulmonary tuberculosis have suboptimal sensitivity and specificity in children with HIV,[7] in part because of atypical symptomatology and radiographic findings and because of overlapping findings with other opportunistic infections. In this issue of *Pediatrics*, Marcy et al[8] describe the development and internal validation of a treatment-decision score for pulmonary tuberculosis in children <14 years old infected with HIV in 4 countries in sub-Saharan Africa and Southeast Asia. This score integrated symptoms, chest radiography,

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abdominal ultrasonography, and Xpert MTB/RIF (a real-time molecular assay widely available in high-burden countries). The authors also assessed the added value of tuberculin skin tests and interferon-γ release assays (IGRAs). The authors evaluated the sensitivity and specificity of several models, including those integrating all components of the tool, as well as models that did not include IGRAs and abdominal ultrasonography, which may not be available in all settings. The sensitivity and specificity of the optimal tool (which did not incorporate IGRAs) were 89% and 61%, respectively. Importantly, the tool can be scaled to the available resources of different settings.

Considering the limitations of the current diagnostic armamentarium for childhood tuberculosis, particularly in the context of HIV co-infection, these results are promising. The authors' findings require validation in other settings because the inclusion and exclusion criteria and the study clinicians' high index of suspicion for tuberculosis may have impacted the performance of the diagnostic tool. Additionally, almost 40% of the subjects in this trial had mild to nonsignificant immunosuppression, and the model may perform differently in settings where children have less well-controlled HIV infection. Moreover, pediatric radiographic quality and interpretation skills vary widely between settings, and studies have revealed poor interrater agreement on the presence of hilar lymphadenopathy.[9] Finally, the impact of this clinical-decision score should be evaluated with respect to key clinical outcomes, including the case-detection ratio of childhood tuberculosis, time to treatment initiation, and treatment outcomes.

Compared with microbiologic assays, this decision tool may improve diagnostic sensitivity by >60%. Given the high mortality risk associated with missing tuberculosis diagnosis in children with HIV infection, as well as the safety and tolerability of first-line and many second-line antituberculous drugs in children,[10] the sensitivity and specificity of this tool represent a reasonable risk/benefit ratio. Notably, the authors mention that their treatment-decision tool did not perform as well as expert clinicians, which is unsurprising given the nuanced clinical diagnosis of tuberculosis. Nonetheless, when used at the primary care level by front-line providers, this tool may facilitate the diagnosis and timely treatment of tuberculosis in children co-infected with HIV and tuberculosis and, in doing so, may save lives.

**ABBREVIATION**

IGRA: interferon γ release assay

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