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Item Type	Article
Authors	Zar, H.J.;Nicol, M.P
Citation	Zar HJ, Nicol MP. Strengthening Diagnosis of Pulmonary Tuberculosis in Children: The Role of Xpert MTB/RIF Ultra. Pediatrics. 2019 Nov;144(5):e20192944. doi: 10.1542/peds.2019-2944
DOI	10.1542/peds.2019-2944
Publisher	American Academy of Pediatrics
Journal	Pediatrics
Rights	Attribution 3.0 United States
Download date	2025-05-14 21:54:29
Item License	http://creativecommons.org/licenses/by/3.0/us/
Link to Item	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6855810/

Strengthening Diagnosis of Pulmonary Tuberculosis in Children: The Role of Xpert MTB/RIF Ultra

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Pediatric tuberculosis is a global concern, with children estimated to account for 10% to 15% of the overall case load, representing almost 1 million cases annually. However, modeling estimates indicate that only 30% of childhood tuberculosis cases are diagnosed and notified.¹ Diagnosis of pulmonary tuberculosis (PTB) in children may be challenging because of nonspecific clinical or radiologic signs, paucibacillary disease, and low sensitivity of microbiologic diagnosis.² However, microbiologic confirmation is needed for accurately defining the burden of disease, effective treatment (particularly for drug-resistant tuberculosis), and limiting unnecessary use of tuberculosis medication.

Recent advances in specimen collection with the development of rapid molecular diagnostics have improved the ability to obtain a rapid microbiologic diagnosis. In this edition of *Pediatrics*, Sun et al³ report the accuracy of Xpert *Mycobacterium tuberculosis* and rifampicin (MTB/RIF) Ultra (Ultra), a next-generation assay on the GeneXpert platform,⁴ using bronchoalveolar lavage (BAL) samples. Ultra had a high sensitivity (91%) against a microbiologic reference standard of a positive culture result or smear-on-BAL result. Ultra had a nonsignificantly higher sensitivity than GeneXpert (80% vs 67%). Most strikingly, Ultra was positive in the majority (34 of 59; 58%) of children clinically diagnosed with PTB in whom a culture result was negative. These

may be true-positive cases because they were symptomatic, implying an additional role for Ultra in detecting culture-negative cases.

However, a high proportion of cases (71%) remained Ultra-positive after 2 months of tuberculosis treatment, and there were 3 case patients with nontuberculosis lower respiratory tract infection in whom Ultra results were positive. Ultra may be positive with a corresponding negative culture if there are operational issues in transporting, processing or culture of samples in the laboratory. No details were provided on the type of culture testing (solid versus automated liquid) or decontamination procedures, which may influence the sensitivity of the culture.⁵ False-positive Ultra results have been reported in adults, particularly those previously treated for tuberculosis,⁶ and it is evident from the current study that Ultra results remained persistently positive through 2 months of treatment in most children. No data were provided on previous tuberculosis treatment in the current study, which would also be important in interpreting positive Ultra results. An additional consideration may be contamination of bronchoscopy equipment that may lead to false-positive Ultra results.⁷ Quantitative Ultra results were not specifically reported in the current study but may have been useful in interpreting results from culture-negative children. However, many children who are culture-positive have low or trace Ultra



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Opinions expressed in these commentaries are those of the authors and not necessarily those of the American Academy of Pediatrics or its Committees.

DOI: <https://doi.org/10.1542/peds.2019-2944>

Accepted for publication Sep 10, 2019

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Funded by the Regional Prospective Observational Research in Tuberculosis and cofunded by the South African Medical Research Council and the National Institutes of Health (R01HD058971). Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2019-0262.

To cite: Zar HJ and Nicol MP. Strengthening Diagnosis of Pulmonary Tuberculosis in Children: The Role of Xpert MTB/RIF Ultra. *Pediatrics*. 2019;144(5):e20192944

results, reflecting the low bacillary load⁸; the World Health Organization has therefore recommended that low or trace levels in children be regarded as true-positive results.⁹ Further study of children with positive Ultra but negative culture results is needed to determine if these are cases missed by culture testing or are false-positive results by Ultra. Caution may therefore be needed in interpreting Ultra-positive results in children.

The high sensitivity of Ultra for *Mycobacterium tuberculosis* and rifampicin resistance on BAL is an important advance for diagnosis in children. Unfortunately, BAL is rarely available in high-burden tuberculosis areas because it requires considerable resources and expertise, which make it unsuitable for a point-of-care diagnostic specimen. Alternative respiratory specimens that are more easily obtainable include nasopharyngeal aspirate (NPAs), induced sputum (IS), or gastric lavage. Importantly, in children, repeated specimens significantly improve diagnostic sensitivity.^{8,10,11} Ultra on IS was recently reported to have high sensitivity, with an incremental yield for repeated specimens observed in low- and middle-income countries.⁸ A single NPA Ultra had a sensitivity of up to 46%, Ultra tests on 2 sequential NPAs increased this to 54%, whereas a single Ultra on IS had a sensitivity of 74%, and a single IS and NPA further increased this to 80%. The highest sensitivity (87%) was obtained by testing 2 NPAs and a single IS compared with culture-confirmed cases.⁹ Importantly, in the current study, no comparison in yield by using Ultra on repeated IS samples compared with BAL was performed, so it is unknown how many children may have been diagnosed on IS, or other less invasive specimens, sparing them a bronchoscopy and BAL.

The high yield of Ultra on BAL indicates that this should be a first-line investigation, together with culture testing, in children undergoing bronchoscopy when PTB is suspected. However, for most children with suspected PTB, BAL should not and will not be performed; the current evidence indicates that repeated IS specimens or a combination of IS and NPAs provide a high yield for testing with Ultra. However, there remains a large group of children who are clinically diagnosed with negative culture results, highlighting the pressing need for a better diagnostic test to distinguish those children who truly have tuberculosis among the unconfirmed tuberculosis cases. Because most cases of childhood tuberculosis occur in low- and middle-income countries, a better, rapid, accurate, point-of-care diagnostic for use in these settings is a priority.

ABBREVIATIONS

BAL: bronchoalveolar lavage
 IS: induced sputum
 NPA: nasopharyngeal aspirate
 PTB: pulmonary tuberculosis

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Pediatrics originally published online October 25, 2019;

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