Received: 16 June 2021 | Revised: 28 July 2021 | Accepted: 6 August 2021

DOI: 10.1111/pai.13637

SUPPLEMENT ARTICLE

WILEY

Diagnostic accuracy of Xpert ultra for childhood tuberculosis: A preliminary systematic review and meta-analysis

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Editor: Amelia Licari

Abstract

Diagnosis of childhood tuberculosis (TB) is challenging. Xpert MTB/RIF and the new version Xpert MTB/RIF Ultra (Ultra) are molecular tests currently used to rapidly identify the infection. We reviewed the literature for the accuracy of Ultra assay in the diagnosis of tuberculosis and rifampicin resistance in children. We conducted a full search in PubMed, Web of Science (WOS), Embase, and Scopus, up to April 2021. A bivariate random-effects model was used to determine the pooled sensitivity and specificity of Ultra, with a 95% confidence interval (CI), compared with culturing and the composite reference standard (CRS). In the ten included studies (2,427 participants), the pooled Ultra sensitivity and specificity, in diagnosing pulmonary tuberculosis (PTB), were 78% (95% CI, 73–82) and 92% (95% CI, 91–94), respectively, against culture. Since a high heterogeneity was found between studies, we created subgroups based on different samples and ages. Ultra-pooled sensitivity was consistently lower against CRS (95% CI, 35%, 32–38). Compared to Xpert MTB/RIF, Ultra sensitivity tended toward higher values (Ultra: 73%, 67%–78% vs. Xpert MTB/RIF: 66%, 60%–72%), but specificity was lower (Ultra: 95%, 94%–96% vs. Xpert MTB/RIF: 99%, 98%–99%). Ultra has improved the definitive diagnosis of PTB, particularly in subjects with paucibacillary TB, including children. The lower specificity could be due to the fact that culture is an imperfect reference standard. Further studies are needed to evaluate the accuracy of Ultra in the diagnosis of childhood TB.

KEYWORDS
children, diagnosis, *Mycobacterium tuberculosis*, Xpert MTB/RIF ultra

1 | BACKGROUND

Microbiological diagnosis of tuberculosis in children can be challenging since they often have a paucibacillary disease and difficulty producing respiratory secretions.[1] In 2013, the WHO recommended Xpert MTB/RIF, a real-time polymerase chain reaction–based system, detecting *Mycobacterium tuberculosis* DNA and rifampicin resistance, as the initial diagnostic test for children with presumptive tuberculosis.[2] In 2017, Cepheid launched the second-generation GeneXpert MTB/RIF Ultra assay to increase sensitivity. Ultra reduces detection limits from 112 to 16 organisms per milliliters, adding two amplification targets (IS6110 and IS1081).[3]

This meta-analysis aims to assess the diagnostic accuracy of Ultra for the diagnosis of tuberculosis and rifampicin resistance in the pediatric population.

2 | METHODS

Search strategy, study selection, reference standards, data extraction, and statistical analysis are available in the Online Repository.

3 | RESULTS

Ten studies have been included for a total of 2,427 samples.[4–13] Quality assessment is reported in the Online Repository (Figure S1).

Table S1 summarizes the characteristics of the included studies. Regarding PTB, we calculated Ultra-pooled sensitivity and specificity of all specimens (95% CI) against culture were 78% (73%–82%) and 92% (91%–94%), respectively (Figure S2).[4–13] A high heterogeneity emerged. Therefore, we created subgroups based on different samples and ages to assign statistical significance to the data. In three studies, we could not separate the different types of respiratory samples, and we included them as "respiratory tract samples (RTS)."

Ultra-pooled sensitivity and specificity (95% CI) were 74% (66%–81%) and 97% (95%–98%) in the sputum group[4–6,10]; 46% (29%–63%) and 97% (94%–99%) in the nasopharyngeal aspirate (NPA) group[6]; 87% (76%–94%) and 85% (81%–89%) in the GA group[8,13]; 73% (59%–85%) and 87% (84%–90%) in the stool group[10,11]; 74% (65%–82%) and 92% (90%–95%) in the RTS group[9,11,12]; 91% (76%–98%) and 80% (74%–86%) in the BAL group (Figure S3).[7] However, a remarkable heterogeneity was still observed for sensitivity and specificity in the RTS subgroup and only for specificity, in the sputum subgroup. Concerning age subgroup analysis, Ultra sensitivity (95% CI) was 79% (62%–91%) in children 0 to 4 years of age and 70% (35%–93%) in children 5–18 years of age.[11,13] The difference was not statistically significant. Ultra-pooled sensitivity against CRS was considerably lower (95% CI, 35%, 32–38), but specificity was higher (95% CI, 99%, 99–100) (Figure S4A).[4–13]

Eight studies compared Ultra and Xpert MTB/RIF.[4–10,12] Ultra-pooled sensitivity (95% CI) tended toward higher values (73%, 67%–78%) compared with Xpert MTB/RIF (66%, 60%–72%), but Ultra-pooled specificity was lower (Ultra: 95%, 94%–96% vs. Xpert MTB/RIF: 99%, 98%–99%) (Figure S4b,C). Eight studies focused on Ultra for the detection of rifampicin resistance,[4,6–9,11–13] but we exclusively included three of them,[6,11,13] because the others had no cases of rifampicin resistance or did not report data relating to the reference standard. Ultra-pooled sensitivity and specificity (95% CI) were 100% (40%–100%) and 100% (95%–100%) (Figure S5).

4 | DISCUSSION

This meta-analysis is the first to focus exclusively on the performance of Ultra for diagnosing pediatric PTB, based on the currently available literature.

Overall, Ultra sensitivity tended toward higher values (78%, 73%–82% vs. 73%, 65%–80%), but specificity was lower, even if still good (92%, 91%–94% vs. 97%, 96%–98%). However, Ultra sensitivity and specificity varied according to the different samples. In particular, sensitivity would be higher in BAL and GA specimens usually collected in hospitalized patients, probably with advanced disease and a higher microbiological load.[1]

On the stool, it is noteworthy that Ultra sensitivity (73%, 59%–85%) was almost comparable to that on the sputum (74%, 66%–81%), as already emerged for Xpert MTB/RIF. Stools may be a good specimen for children since they are non-invasive and easily collectible.[1]

Regarding age, Ultra sensitivity tended toward higher values in children up to 4 years (79%, 62%–91%), compared with older children (70%, 35%–93%). If confirmed in extensive studies, this result could improve the more difficult diagnosis in young children, also affected by a worse tuberculosis outcome.[13]

In line with the Cochrane review,[1] in a head-to-head comparison, Ultra sensitivity tended to be higher than Xpert MTB/RIF (73% vs. 66%), but specificity was lower (95% vs. 99%). One of the reasons could be the inclusion of the trace-positive category in the semi-quantitative analysis, which does not exist for Xpert MTB/RIF. Many studies included in this review had a consistent proportion of Ultra results evaluated as "trace."[4–6,8–10] Nevertheless, in children, owing to the paucibacillary specimens, "trace calls" should be considered to be true-positive results for clinical decisions.[3]

Our meta-analysis has several limitations: the number of studies and participants is small, and this restricts our confidence in the precision of the estimates; many of the included studies used frozen samples and were conducted in high TB burden countries, both aspects that can affect the diagnostic accuracy of the test.

Key Message

Thanks to its significant sensitivity, Ultra has improved the definitive diagnosis of pulmonary tuberculosis in children, typically with a low number of bacilli.

5 | CONCLUSIONS

Ultra is a sensitive test that has improved the definitive diagnosis of PTB, mainly in the paucibacillary forms. The lower specificity could be since culture is an imperfect reference standard.[3] Further studies are needed to evaluate the accuracy of Ultra assay, particularly in culture-negative children. Ideally, these studies would be prospective, conducted in high-income countries, and evaluate fresh, non-invasive, and even extrapulmonary specimens.

ACKNOWLEDGEMENTS

Open Access funding provided by Universita degli Studi di Firenze within the CRUI-CARE Agreement. [Correction added on

11-May-2022, after first online publication: CRUI-CARE funding statement has been added.]

CONFLICT OF INTEREST

The authors declare that they do not have a conflict of interests related to the contents of this article.

AUTHOR CONTRIBUTIONS

Claudia Signorino: Methodology (equal); writing—review and editing (equal). **Elena Chiappini** and **Luisa Galli**: Conceptualization (equal); supervision (lead); writing—review and editing (equal). **Martina Votto** and **Maria De Filippo**: Writing—review (supporting). **Gian Luigi Marseglia**: Supervision (lead).

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SUPPORTING INFORMATION

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How to cite this article: Signorino C, Votto M, De Filippo M, Marseglia GL, Galli L, Chiappini E. Diagnostic accuracy of Xpert ultra for childhood tuberculosis: A preliminary systematic review and meta-analysis. *Pediatr Allergy Immunol*. 2022;33(Suppl. 1):80–82. doi:10.1111/pai.13637