International Journal of Infectious Diseases 140 (2024) 86–91

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Diagnostic accuracy of Xpert MTB/RIF Ultra for childhood tuberculosis in West Africa – a multicenter pragmatic study

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ARTICLE INFO

Article history:
Received 6 October 2023
Revised 2 January 2024
Accepted 3 January 2024

Keywords:
Diagnostic accuracy
GeneXpert
Children
Tuberculosis

ABSTRACT

Objective: To evaluate the performance of Xpert Mycobacterium Tuberculosis/rifampicin (MTB/RIF) Ultra (Ultra) for diagnosis of childhood tuberculosis (TB) within public health systems.
Methods: In this cross-sectional study, children aged <15 years with presumptive pulmonary TB were consecutively recruited and evaluated for TB at tertiary-level hospitals in Benin, Mali, and Ghana. Bivariate random-effects models were used to determine the pooled sensitivity and specificity of Ultra against culture. We also estimated its diagnostic yield against a composite microbiological reference standard (cMRS) of positive culture or Ultra.
Results: Overall, 193 children were included in the analyses with a median (interquartile range) age of 4.0 (1.1-9.2) years, 88 (45.6%) were female, and 36 (18.7%) were HIV-positive. Thirty-one (16.1%) children had confirmed TB, 39 (20.2%) had unconfirmed TB, and 123 (63.7%) had unlikely TB. The pooled sensitivity and specificity of Ultra verified by culture were 55.0% (95% confidence interval [CI]: 28.0–79.0%) and 95.0% (95% CI: 88.0–98.0%), respectively. Against the cMRS, the diagnostic yield of Ultra and culture were 67.7% (95% CI: 48.6–83.3%) and 70.9% (95% CI: 51.9–85.8%), respectively.
Conclusion: Ultra has suboptimal sensitivity in children with TB that were investigated under routine conditions in tertiary-level hospitals in three West African countries.

Introduction

Globally in 2021, there were an estimated 10.6 million incident cases of tuberculosis (TB) including 1.2 million cases in children younger than 15 years of age, while as many as 240,000 children died of TB [1]. Recent reports show that children aged <15 years constitute 11% and 14% of global TB morbidity and mortality, respectively, although National TB programs often notify less than half of all estimated childhood TB cases [1]. The paucibacillary nature of TB in children and difficulties with obtaining good-quality respiratory samples constitute major obstacles to microbiological confirmation of TB in children [2], which is only achieved in less than 40% of all children starting TB therapy [3,4]. Diagnosis of childhood TB is, therefore, most often made presumptively, based

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https://doi.org/10.1016/j.ijid.2024.01.003

on non-specific clinical, epidemiological, and radiological features [5].

The Xpert Mycobacterium TB/rifampicin (MTB/RIF) Ultra (Ultra; Cepheid, Sunnyvale, CA, USA) is an advanced version of the first-generation Xpert MTB/RIF, and it was designed to have improved sensitivity for the detection of *Mycobacterium tuberculosis (M.tb)* DNA by incorporating a relatively wider reaction chamber and two different multi-copy amplification targets (IS6110 and IS1081) [6]. In a systematic review and meta-analysis of the performances of Xpert MTB/RIF and Ultra for detection of TB in children, Xpert MTB/RIF demonstrated sensitivity and specificity of 64.6% and 99.0%, respectively, relative to the Ultra that demonstrated sensitivity and specificity of 72.8% and 97.5%, respectively [7]. Although the relatively higher sensitivity of Ultra for diagnosis of childhood TB as reported from various research studies looks promising, very few studies have evaluated the diagnostic accuracy of the Ultra within public health systems in resource-limited settings where operational conditions may be sub-optimal [8].

Therefore, we conducted a multicenter evaluation of the performance of Ultra for diagnosis of childhood TB under routine clinical and laboratory conditions at tertiary-level hospitals in three West African countries.

Methods

Settings, patients and samples, and laboratory procedures

Children (aged <15 years) with presumptive pulmonary TB were consecutively recruited from March 2020 to February 2022 at the dedicated outpatient childhood TB clinics of three tertiary hospitals, which are part of the West African Networks of Excellence for TB, AIDS, and Malaria (WANETAM). The WANETAM consortium is funded by the European and Developing Countries Clinical Trials Partnership (EDCTP), and it aims to build on previous achievements to develop expertise for clinical research, including the implementation of clinical trials, for the control of poverty-related diseases in West Africa [9].

Specifically, the study sites were the National Teaching Hospital for TB and Respiratory Diseases (CNHU-PPc), Cotonou, Republic of Benin, Gabriel Toure University Teaching Hospital (CHU Gabriel Toure), Bamako, Mali, and Korle Bu Teaching Hospital (KBTH), Accra, Ghana. Recruitment of eligible children was conducted under routine clinical and laboratory conditions at the three study sites. Participants were recruited and investigated for pulmonary TB based on presentation with suggestive symptoms and signs, characterized by persistent or unremitting cough for at least two weeks with any weight loss, failure to thrive, or persistent unexplained fever [10].

Demographic information was obtained at enrollment, and all recruited children had detailed clinical evaluations conducted by site-based pediatricians, including symptom reviews and physical examinations. All recruited children also underwent HIV testing and chest radiography that was interpreted by the pediatricians at each site. One or two sputum samples (spontaneously expectorated or induced) were obtained from children aged ≥7 years while gastric aspirates (GA) were obtained from children aged <7 years, according to the standard operating procedures at each hospital. When two samples of spontaneously expectorated or induced sputum were obtained from a child, the samples were pooled for Ultra and Mycobacterial culture. This approach reflects the practical considerations within the national public health systems including the cost of the laboratory consumables, among others. Depending on the clinical presentation, samples were also collected from the pleural cavity or lymph nodes by fine-needle aspiration and sent for testing by Ultra and Mycobacterial culture.

Samples were processed according to standard laboratory protocols at each hospital. Testing of samples with Ultra was performed in accordance with the manufacturer's recommendations, as previously described [11]. The samples were also inoculated for solid culture on Lowenstein-Jensen medium and/or liquid culture using Mycobacterial Growth Indicator Tube (Becton Dickinson, Franklin Lakes, NJ, USA). The presence of *M.tb* in positive cultures was confirmed using Ziehl-Neelsen or Auramine acid-fast staining and MPT64 antigen detection test (Abbott, Palatine, IL, USA) or MTBDRplus line-probe assays (Hain Life Sciences, Nehren, Germany).

Using findings from the clinical and radiological evaluations and results of the TB diagnostic tests, each study participant was classified according to the revised case definitions for the classification of intrathoracic TB in children, comprising *"confirmed TB"*, *"unconfirmed TB"* and *"unlikely TB"* [10]. All children diagnosed with TB were referred for treatment of either drug-susceptible or drug-resistant TB, as appropriate, according to the national pediatric TB treatment guideline in each country. Children with unlikely TB were treated for other respiratory diseases, with follow-up clinic visits within four weeks to ascertain their well-being.

Statistical analysis

Due to the pragmatic nature of our study, we did not carry out a formal sample size calculation. All eligible consecutively recruited children were included in the analyses. Study data were entered directly into internet-enabled tablets with REDCap software, double-checked, and corrected for data entry errors at each site. Collected data were synchronized with a centralized database hosted at the Medical Research Council Unit The Gambia at the LSHTM (MRCG at LSHTM), Fajara, The Gambia, where the data were extracted for analysis. This study is reported in accordance with the guidelines of the Standards for Reporting of Diagnostic Accuracy Studies (STARD) and a complete STARD checklist is provided as supplementary material [12].

For the primary analysis, we calculated the sensitivity and specificity of Ultra against Mycobacterial culture-confirmed TB disease as the reference standard. However, it is known that culture has sub-optimal sensitivity in childhood TB, which makes it an imperfect reference standard [13]. Therefore, we also estimated the diagnostic yield of Ultra against a composite microbiological reference standard (cMRS) which includes positive results for Mycobacterial culture or Ultra in the sub-group of children with confirmed TB, as was previously described [14]. Using the cMRS, we reported the diagnostic yield separately for culture and Ultra irrespective of the respiratory sample type or country and also stratified by type of respiratory sample (i.e. sputum or GA) and country. We determined the point estimates for the sensitivity and specificity, with the respective 95% confidence interval (CI), by performing the bivariate random-effects meta-analysis using STATA command '*metadta*' to account for the possible heterogeneity across the three study sites [15]. Statistical analyses were performed using STATA statistical software (version 17.0, StataCorp, College Station, Texas).

Results

Characteristics of study participants

A total of 200 children with presumptive pulmonary TB were recruited, out of which seven children were subsequently excluded from the analyses due to missing Ultra or Mycobacterial culture results, contaminated Mycobacterial culture, and/or missing clinical or demographic data. Of the 193 children included in the analysis, 22 (11.4%) were *M.tb* culture positive, and 171 (88.6%) were found to be culture-negative. Twelve children had positive Ultra results

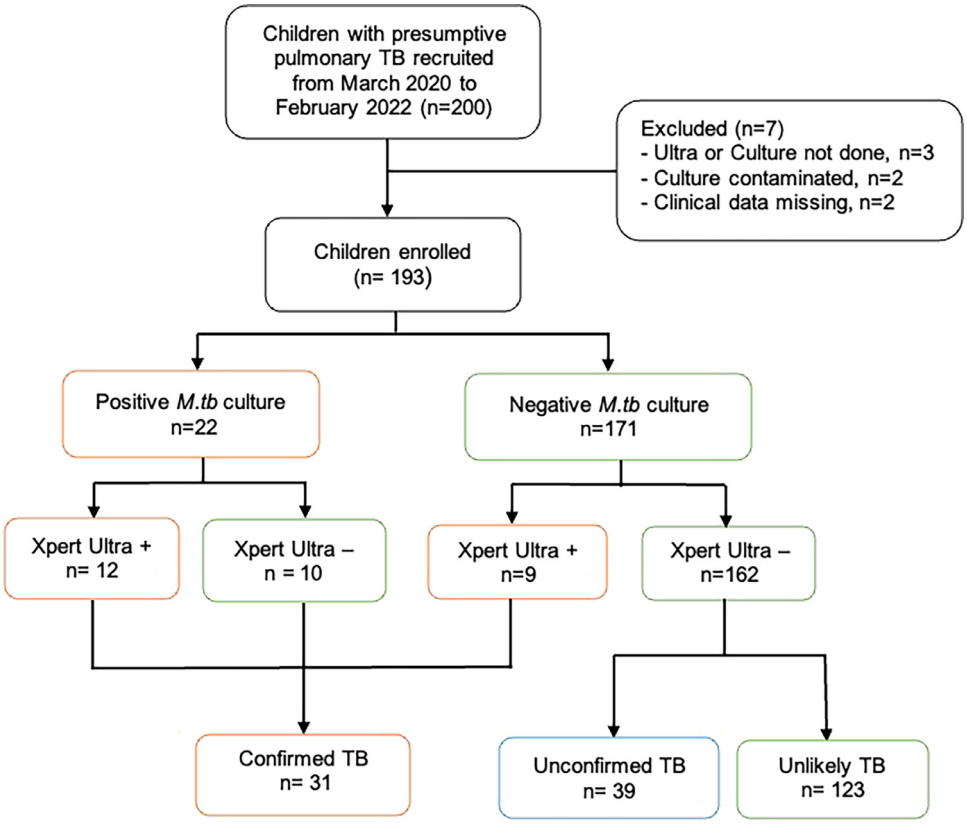

Figure 1. STARD diagram reporting the flow of participants in the study.

among the culture-confirmed childhood TB cases, while nine children had positive Ultra results among the children that were *M.tb* culture-negative (Figure 1). The median age of the 193 children was 4.0 years (interquartile range 1.1 to 9.2 years), 105 (54.4%) were aged <5 years, 88 (45.6%) were female, and 36 (18.7%) were found to be HIV positive. Overall, 31 (16.6%) had confirmed TB, 39 (20.2%) had unconfirmed TB, and 123 (63.2%) had unlikely TB. Detailed demographic and clinical characteristics of all children included in the analyses, by study site and overall, are presented in Table 1.

Diagnostic accuracy of Ultra

The pooled sensitivity and specificity of Ultra verified by culture were 55.0% (95% CI: 28.0–79.0%) and 95.0% (95% CI: 88.0–98.0%), respectively (Figure 2). The sensitivity of Ultra against culture was relatively higher in Ghana (80.0%; 95% CI: 28.0–99.0%) than in Mali (67.0%; 95% CI: 30.0–93.0%) and Benin (25.0%; 95% CI: 3.0–65.0%).

In the analysis using the cMRS, the diagnostic yield of Ultra and culture irrespective of the respiratory sample type or country were 67.7% (95% CI: 48.6–83.3%) and 70.9% (95% CI: 51.9–85.8%), respectively. In addition, the diagnostic yield of Ultra against the cMRS, using sputum samples, was 63.6% (95% CI: 30.8–89.1%), relative to a yield of 66.7% (95% CI: 41.0–86.7%) with GA. Also, against the cMRS, the diagnostic yield of culture was 72.7% (95% CI: 39.0–94.0%) and 61.1% (95% CI: 35.7–82.7%) with sputum and GA, respectively (Table 2). When stratified by country, the diagnostic yield of Ultra against the cMRS was comparable between Ghana (83.3%; 95% CI: 35.9–99.6%) and Mali (80.0%; 95% CI: 51.9–95.7%), with both relatively higher than in Benin (15.5%; 95% CI: 12.2–73.8%). On the other hand, the diagnostic yield of culture against the cMRS was comparable between Benin (80.0%; 95% CI: 44.4–97.5%) and Ghana (83.3%; 95% CI: 35.9–99.6%), while both were relatively higher than the diagnostic yield of culture against cMRS in Mali (60.0%; 95% CI: 32.3–83.7%).

Rifampicin resistance detected by Ultra

Among the 21 children with positive Ultra results, three (14.3%) were also found to have Rifampicin resistance.

Discussion

In this multicenter study, we report the performance of Ultra for diagnosis of pulmonary TB using fresh respiratory samples obtained from ambulant children aged less than 15 years, who were investigated under routine conditions in tertiary-level hospitals, in three West African countries. Overall, we found that the pooled sensitivity and specificity of Ultra relative to *M.tb* culture were 55.0% and 95.0%, respectively. The sensitivity of Ultra relative to culture in our study is lower than reports from previous similar multicenter research studies, where sensitivities of 66.3% and 64.3% against culture were reported using fresh and stored respiratory samples, respectively [16,17]. The sensitivity of Ultra in our study is also lower than in a research study involving hospitalized children and from a recently published updated Cochrane review of Ultra accuracy, where the sensitivity of Ultra was reported to be greater than 70% [18,19].

These results suggest that the sensitivity of Ultra for diagnosis of TB in children, based on routine practices and procedures within the national public health systems in West Africa, is lower than in the more controlled research settings where stricter methodological requirements are applied. It is not clear what factors may have contributed to the relatively lower sensitivity of Ultra in our pragmatic study. However, it is possible that clinical, operational, logistics, pre-analytical, and/or other yet-to-be-identified factors, which

Table 1
Demographic and clinical characteristics of study participants.

Study site	Benin	Ghana	Mali	All children
Number (%)	66 (34.2)	66 (34.2)	61 (31.6)	193 (100)
Age, Median years, (IQR)	4.3 (1.5-9.2)	4.5 (1.2-10.0)	3.8 (1.0-8.3)	4.0 (1.1-9.2)
<5 years, n (%)	34 (51.5)	37 (56.1)	34 (55.7)	105 (54.4)
Sex, n (%)				
Female	27 (40.9)	32 (48.5)	29 (47.5)	88 (45.6)
HIV status, n (%)				
Negative	50 (75.8)	36 (54.6)	20 (32.8)	106 (54.9)
Positive	14 (21.2)	17 (25.8)	5 (8.2)	36 (18.7)
Unknown	2 (3.0)	13 (19.6)	36 (59.0)	51 (26.3)
Clinical presentation, n (%)				
Cough >2 weeks	33 (50.0)	15 (22.7)	40 (65.6)	88 (45.6)
Fever	49 (74.2)	49 (74.2)	48 (78.7)	146 (75.7)
Lethargy	18 (27.3)	21 (31.8)	20 (32.8)	59 (30.6)
Past history of TB	1 (1.5)	3 (4.6)	1 (1.6)	5 (2.6)
Respiratory sample type[a], n (%)				
Gastric aspirate	39 (59.1)	44 (84.6)	32 (52.5)	115 (64.2)
Sputum	27 (40.9)	8 (15.4)	29 (47.5)	64 (35.8)
Diagnosis, n (%)				
Confirmed TB	10 (15.2)	6 (9.1)	15 (24.6)	31 (16.1)
Unconfirmed TB	6 (9.1)	26 (39.4)	7 (11.5)	39 (20.2)
Unlikely TB	50 (75.8)	34 (51.5)	39 (63.9)	123 (63.7)

IQR, interquartile range; HIV, human immunodeficiency virus; TB, tuberculosis.
[a] Total number of respiratory samples for 'All children' is 179 because the samples were collected for only 52/66 children in Ghana; the remaining 14 children had samples collected for TB detection tests by fine-needle aspiration.

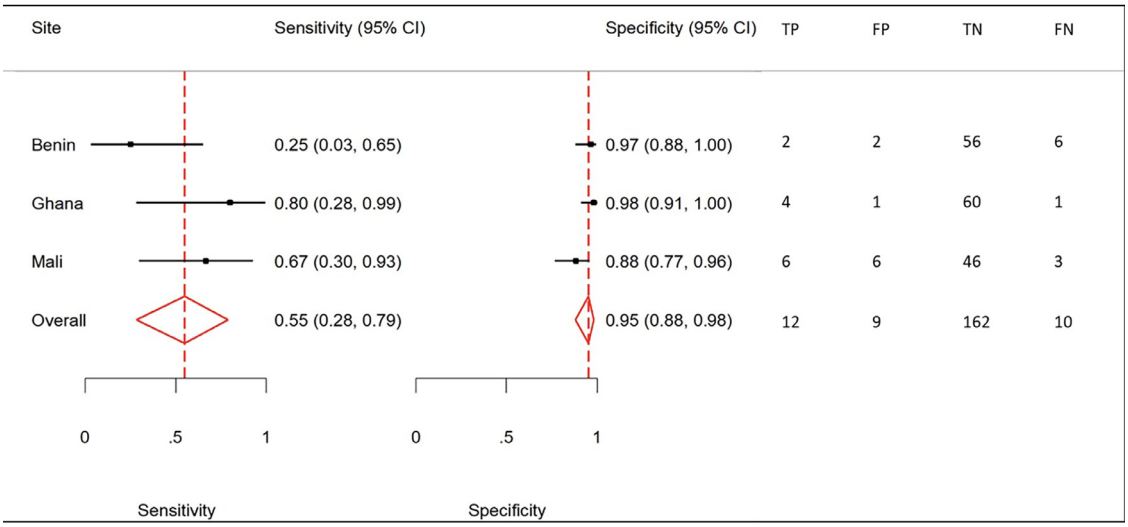

Figure 2. Diagnostic accuracy of Ultra verified by mycobacterial culture.

may not be optimal within national health systems in resource-limited settings, could affect the performance of the Ultra [8]. In addition, the results could also be due in part to our study population being children who were recruited from outpatient TB clinics. Such children probably have milder TB disease with relatively lower bacterial load when compared with children hospitalized with TB disease as in-patients. However, these results highlight the need for operational research, preferably using quantitative and qualitative approaches, to investigate the factors in the pathway toward diagnosis of TB in children within public health systems.

We also determined the diagnostic yield of Ultra against the cMRS that combines positive culture or Ultra results in the subgroup of children with confirmed TB [14]. This is because *M.tb* culture is recognized as an imperfect reference standard in children and because any positive Ultra test, even in children with negative culture results, is an indication for TB treatment initiation in the real-life clinical setting in which our study was conducted. We found that the diagnostic yield of Ultra and culture against the cMRS were 67.7% and 70.9%, respectively. These results from our pragmatic study suggest that the diagnostic yield of Ultra is comparable to that of culture in the sub-group of children with confirmed TB. We also reported that nine children with positive Ultra results were culture-negative. These children were classified as confirmed TB in accordance with the revised case definition for TB in children [10] and were treated for TB accordingly. The high rate of positive result discordance between culture and Ultra observed in our study probably also reflects the nature of our study population being symptomatic but ambulant children recruited in outpatient childhood TB clinics, as previously highlighted. In such population, it has been suggested that multiple diagnostic tests and or multiple samples might be required to reach sufficient sensitivity [20]. Taken together, these findings support the assertions made in previous childhood TB diagnosis studies conducted in our setting and other parts of Africa that culture of respiratory samples in children, where it is available, is advisable because it could have incremental benefits when combined with Xpert assay [16,21].

The pooled specificity of 95.0% for Ultra reported in our study is comparable with the specificity of 95.4% and 98.1% using fresh

Table 2
Diagnostic yield of Ultra and culture against the composite microbiological reference standard.

Characteristics	n/N	Sensitivity % (95% CI)
Test		
Ultra	21/31	67.7 (48.6-83.3)
Culture	22/31	70.9 (51.9-85.8)
Respiratory sample (Ultra)		
Gastric aspirate	12/18	66.7 (41.0-86.7)
Sputum	7/11	63.6 (30.8-89.1)
Respiratory sample (Culture)		
Gastric aspirate	11/18	61.1 (35.7-82.7)
Sputum	8/11	72.7 (39.0-94.0)
Country (Ultra)		
Benin	4/10	15.5 (12.2-73.8)
Ghana	5/6	83.3 (35.9-99.6)
Mali	12/15	80.0 (51.9-95.7)
Country (Culture)		
Benin	8/10	80.0 (44.4-97.5)
Ghana	5/6	83.3 (35.9-99.6)
Mali	9/15	60.0 (32.3-83.7)

CI, confidence interval; n, number of test positive; N, number of children with confirmed tuberculosis based on positive culture and/or Ultra results.

and stored respiratory samples, respectively, reported from other studies [16,17]. This is also comparable to the specificity of 97% reported in studies involving hospitalized children and from the new Cochrane review [18,19,22].

Due to the difficulties in obtaining good-quality sputum samples from children, studies have evaluated the use of other respiratory specimens including nasopharyngeal aspirates and/or GAs for diagnosis of pulmonary TB in children. The recently published Cochrane systematic review that updated evidence on the diagnostic accuracy of Ultra found that its sensitivity varies by specimen type, with sputum having the highest sensitivity (75.3%), followed by GA (70.4%) and stool (56.1%) [19]. In our study, we found that the diagnostic yield of Ultra verified by the cMRS was marginally lower with sputum (63.6%) than with GA (66.7%).

Our study had some limitations. The number and proportion of children diagnosed with TB, especially confirmed TB, are small and vary between the hospitals. While this further highlights the challenge with microbiological confirmation of TB in children, which is an exception rather than the rule, it also suggests possible heterogeneity across the hospitals. Therefore, we used random-effect meta-analysis to account for the heterogeneity in our analysis. Also, the recruitment of eligible children at the three hospitals in this descriptive pragmatic study was probably impacted by the nationwide lockdowns and movement restrictions imposed across West Africa during the period of the study because of the COVID-19 pandemic. Furthermore, the probable impact of the COVID-19 pandemic on the quality of screening, sample collection, and laboratory testing at the various national health systems during the period of the study cannot be completely ruled out.

Conclusion

The sensitivity of Ultra in children with TB that were investigated routinely in tertiary-level hospitals in three West African countries is lower than the sensitivity reported under more systematic research conditions. This constitutes a practical challenge for reliable diagnosis of TB and the timely initiation of treatment in children. Furthermore, our paper highlights the urgent need for operational research on how to improve the diagnosis of childhood TB within national public health systems in West Africa and the need for new diagnostics with improved sensitivity for rapid detection of childhood TB in general.

Declaration of competing interest

None declared.

Funding

The work was supported by a European and Developing Countries Clinical Trials Partnership (EDCTP) grant to the West African Networks of Excellence for TB, AIDS, and Malaria (WANETAM) consortium (Reference number: EDCTP-RegNet2015-1049). The funder had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Ethical approval and informed consent

The study was approved by the respective ethics committees of the CNHU-PPc, Cotonou, Republic of Benin, University of Sciences, Techniques and Technologies of Bamako, Bamako, Mali, and KBTH, Accra, Ghana. Written informed consent was obtained from a literate parent or legal guardian. In the case of an illiterate parent or legal guardian, informed oral consent was attested by an independent witness. Older children aged ≥7 years additionally provided assent for study participation.

Acknowledgements

The authors would like to thank the field, clinic and laboratory teams who facilitated the recruitment and investigation of the children at each hospital; the West Africa Regional Network for TB Control (WARN-TB) and the West Africa Pediatric TB Network (WApTBNet) for their continuous support; Binta Saidy, Juka Jones, Lamin Saidy and Bai Lamin of MRC Unit The Gambia at LSHTM for the general data management support; and the parents/guardians and families of the children who participated in the study.

Author contributions

ABD and TT conceptualized the study. ABD, AF, KAO, MT, AS, BD, AOE, and TT contributed to the study design and oversaw the study planning, implementation, and data collection. ABD, VFE, NM, and TT analyzed and interpreted the data. ABD, VFE, NM, and TT wrote the first draft of the manuscript. KAO, BO, IA, AOE, BD, BG, DA, RO, and AOK provided additional input into the manuscript. All authors provided input into the manuscript and approved the final manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2024.01.003.

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