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Original article

Diagnostic accuracy of Xpert MTB/RIF and Xpert ultra tests in pulmonary and extrapulmonary tuberculosis compared to Löwenstein-Jensen culture

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ABSTRACT

Background: Tuberculosis (TB) is one of the leading causes of death worldwide. However, an accurate diagnosis contributes to timely treatment, reducing its adverse consequences. The aim of this research was to determine the diagnostic accuracy of the molecular test Xpert MTB/RIF and Xpert MTB/RIF Ultra (Xpert Ultra) for the diagnosis of pulmonary and extrapulmonary TB compared to Löwenstein-Jensen culture.

Methods: We conducted a cross-sectional study of diagnostic accuracy. We included samples from patients who attended a Peruvian laboratory between 2011 and 2022. The index test was the Xpert MTB/RIF and Xpert Ultra and the reference standard was Löwenstein-Jensen solid culture for *Mycobacterium tuberculosis*. We calculated sensitivity, specificity, and positive and negative likelihood ratios.

Results: We evaluated 1023 samples, of which 737 were pulmonary samples, 197 tested positive for the Xpert MTB/RIF and Xpert Ultra tests; and 151 tested positive for culture. The Xpert (MTB/RIF and Ultra) showed a joint sensitivity and specificity of: 97 % (95%CI: 93–99) and 93 % (95%CI: 91–95) in pulmonary samples, 100 % (95%CI: 29.2–100) and 98.3 % (95%CI: 94.1–99.8) in cerebrospinal fluid, 66.7 % (95%CI: 22.3–95.7) and 96.8 % (95%CI: 91–99.3) in pleural fluid, 100 % (95%CI: 15.8–100) and 94.3 % (95%CI: 80.8–99.3) in urine. For the detection of pulmonary TB, the Xpert MTB/RIF had a sensitivity and specificity of 97.1 % (95%CI: 89.9–99.6) and 95.6 % (95%CI: 92.9–97.5) and the Xpert Ultra of 97 % (95%CI: 88.5–99.6) 89.5 % (95%CI: 84.9–93.1) respectively.

Conclusion: Our results suggest that the Xpert MTB/RIF and the Xpert Ultra are tests with high diagnostic performance for the detection of pulmonary TB and adequate specificity in pulmonary, cerebrospinal fluid, pleural, and urine samples. However, the results for other samples were imprecise.

1. Introduction

According to the World Health Organization, tuberculosis (TB) is one of the leading causes of death worldwide.[1] Its presentations include pulmonary tuberculosis (PTB) and extrapulmonary tuberculosis (EPTB),[2] the latter constitutes around 15–20 % of all TB cases and often poses significant challenges for early diagnosis due to its variety of presentation.[3]

The diagnosis of TB relies on clinical and radiological criteria, although confirmation is bacteriological and/or histological, with the gold standard being culture in Löwenstein-Jensen medium.[4] However, this procedure requires an 8-week incubation period to obtain maximum

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sensitivity,[2] which could potentially delay treatment or subject patients to inadequate empiric therapy.[3] Delay in the diagnosis and treatment of TB increases the possibility of complications and mortality among patients, as well as its transmission in the population.[5,6]

The Xpert MTB/RIF and Xpert MTB/RIF Ultra (Xpert Ultra) diagnostic tests are real-time semi-automated polymerase chain reaction nucleic acid amplification technologies, capable of simultaneously detecting *Mycobacterium tuberculosis (MTB)* and its rifampicin resistance in less than 2 h,[7] whose results are presented in a way that is easy to interpret. Furthermore, it is a totally closed system, so there is a minimal risk of contamination and biological risk.[2] Xpert Ultra was developed to enhance the sensitivity of the Xpert MTB/RIF and it does this by incorporating two different multiple copy amplification objectives and a larger DNA reaction chamber than the Xpert MTB/RIF.[8] It is reported that the detection limit using Xpert Ultra improved to 15.6 CFU/ml of sputum compared to 112.6 CFU/mL for Xpert MTB/RIF,[9] referring to the lowest number of colony-forming units (CFU) per sample that can be reliably distinguished from negative samples with 95 % confidence.

A systematic review conducted in 2020 reported that in pulmonary samples (7 studies), Xpert MTB/RIF showed a sensitivity of 84.7 % (78.6–89.9) and a specificity of 98.4 % (97.0–99.3) for MTB detection, whereas Xpert Ultra showed a sensitivity of 90.9 % (86.2–94.7) and a specificity of 95.6 % (93.0–97.4). However, of the 7 studies analyzed, 3 were reported to have a high risk of bias in the patient selection domain 10.

In 2021, Kohli M. et al. conducted a systematic review and meta-analysis evaluating the diagnostic accuracy of Xpert MTB/RIF and Xpert Ultra in extrapulmonary samples. For cerebrospinal fluid (CSF) samples (30 studies included), the Xpert MTB/RIF showed a sensitivity of 71.1 % (62.8–79.1) and a specificity of 96.9 % (95.4–98.0). For pleural fluid samples (25 studies included), it had a sensitivity of 49.5 % (39.8–59.9) and a specificity of 98.9 % (97.6–99.7).[11] Regarding Xpert Ultra, for CSF samples (6 studies included), it showed a sensitivity of 89.4 % (79.1–95.6) and a specificity of 91.2 % (83.2–95.7). For pleural fluid samples (4 studies included), it had a sensitivity of 75.0 % (58.0–86.4) and a specificity of 87.0 % (63.1–97.9), with these last two values having low and very low certainty evidence.[11] Other extrapulmonary samples, such as urine or bone tissue, have been scarcely evaluated.

Therefore, there remains a need for high-quality evidence supporting the diagnostic accuracy of Xpert in diverse samples, to facilitate evidence-based clinical decision-making for early and accurate TB diagnosis. The aim of this study was to determine the diagnostic accuracy of the molecular tests Xpert MTB/RIF and Xpert Ultra for the diagnosis of PTB and EPTB compared to Löwenstein-Jensen culture.

2. Methods

2.1. Study design and population

We conducted a cross-sectional diagnostic accuracy study. We followed the Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines for reporting diagnostic accuracy studies.[12]

The study was conducted using data from the 18 branches of ROE Clinical Laboratory located in Lima, Peru. This is a private laboratory with ISO 9001 and NTP ISO 15189 quality certifications. The laboratory performs MTB cultures, and the Xpert MTB/RIF test was conducted between years 2012 and 2018, while the Xpert Ultra test has been used since 2019, in addition to other laboratory analyses.[13] The information from the results is entered into their database by trained laboratory personnel.

For our study, we included samples from patients with suspected PTB or EPTB for which both tests (Xpert and MTB culture in Löwenstein-Jensen medium) were requested to confirm or rule out these pathologies between January 1, 2012, and December 31, 2022.

2.2. Index tests

The index tests used were the Xpert MTB/RIF and Xpert Ultra. Both tests were processed following the manufacturer's recommendations. The result was considered positive when the detection of the rop B gene, marked with five signaling molecules (probes A to E), was observed with a cycle threshold (CT) of up to 39.0 for probes A, B, and C, and up to 36.0 for probes D and E. It was considered negative when the gene was not detected.[8] Unlike the Xpert MTB/RIF, the Xpert Ultra incorporates two amplification targets for the detection of MTB (IS*6110* and IS*1081*) as well as a larger DNA reaction chamber, aiming to improve its sensitivity.[8]

The following samples were collected: respiratory samples (sputum and bronchoalveolar lavage), urine, lymph node tissue biopsy, cerebrospinal fluid (CSF), and pleural fluid. The details of the procedures can be found in Supplementary Material 1.

2.3. Reference standard

MTB Culture: After sample collection, they were inoculated into test tubes containing Löwenstein-Jensen solid culture medium. Subsequently, the tubes were placed in incubators for culture. A temperature of $35 \pm 2\,^{\circ}C$ was maintained. The tubes were observed twice a week, and it was considered negative when no colonies formed up to 45 days. Culture was performed only if requested by the treating physician.

2.4. Statistical analysis

The data were exported to Microsoft Excel and subsequently analyzed using the Stata V17 statistical package. To describe categorical variables, we used frequencies and percentages, and for quantitative variables, measures of central tendency and dispersion.

To perform the analysis, we considered the results of Xpert MTB/RIF and Xpert Ultra as the index test and compared them with the reference standard (MTB culture). For the diagnosis of EPTB, we grouped both tests (Xpert MTB/RIF and Xpert Ultra) due to the limited number of positive tests with Xpert Ultra. For the diagnosis of PTB, we conducted independent analyses.

For the analyses, contingency tables were used, and sensitivity, specificity, and likelihood ratios (LR) positive, negative, and the area under the ROC curve (AUC-ROC) were calculated with their respective 95 % confidence intervals (95 % CI). By consensus among the authors, we considered 95 % CIs with an interval less than 10 % to be very precise and those between 10 % and 20 % to be precise. Finally, when zero values were present in the contingency tables, they were modified to 0.5 solely for the calculation of positive or negative LR.[14]

2.5. Ethics

The protocol was submitted to and approved by the Ethics Committee of Hospital III Daniel Alcides Carrión EsSalud (Tacna, Peru). Subsequently, permission was obtained from the management of the ROE laboratory for access to their database. Anonymity of each individual was ensured during data collection and cleaning. Informed consent was not requested due to the observational and retrospective nature of the study.

3. Results

3.1. Population characteristics

Out of the 8300 samples processed between 2011 and 2022 to confirm suspected TB with Xpert MTB/RIF, Xpert Ultra, and/or culture, 7277 were excluded from the study (7170 had no culture requested, and 107 had no final result reported), so 1023 samples were finally included.

The median age of the patients was 61 years (interquartile range: 41

to 75), and 52.2 % were male. Out of the 1023 samples, 289 were extrapulmonary samples, with the most common origins being CSF (12 %), pleural fluid (9.8 %), and urine (3.6 %) (Table 1).

3.2. Diagnostic accuracy of Xpert MTB/RIF and Xpert Ultra for pulmonary tuberculosis

In pulmonary samples, the Xpert MTB/RIF test exhibited a sensitivity and specificity of 97.1 % (95 % CI: 89.9–99.6) and 95.6 % (95 % CI: 92.9–97.5) respectively. On the other hand, the Xpert Ultra test demonstrated a sensitivity of 97 % (95 % CI: 89.5–99.6) and specificity of 89.5 % (95 % CI: 84.9–93.1) (Table 2).

3.3. Diagnostic accuracy of Xpert MTB/RIF and Xpert ultra in extrapulmonary samples

A combined analysis of Xpert tests (MTB/RIF and Ultra) yielded a sensitivity of 100 % (95 % CI: 29.2–100) and specificity of 98.3 % (95 % CI: 94.1–99.8) in CSF samples. Likewise, in pleural fluid samples they presented a sensitivity of 66.7 % (95 % CI: 22.3–95.7) and specificity of 96.8 % (95 % CI: 91–99.3). Urine samples yielded a sensitivity of 100 % (95 % CI: 15.8–100) and specificity of 94.3 % (95 % CI: 80.8–99.3).

4. Discussion

4.1. Xpert in the diagnosis of PTB

Currently, conventional laboratory techniques for TB diagnosis, such as direct microscopy, are not very sensitive. Moreover, traditional culture methods are time-consuming, requires sophisticated biosafety measures, and demand trained laboratory personnel.[15] Faced with this challenge, molecular techniques have substantially improved the field of TB diagnosis. In our study, we were able to identify over 97 % of patients with culture confirmed PTB using the Xpert MTB/RIF and Xpert Ultra tests. These findings are similar to those reported in other studies, which found sensitivity ranging from 84.7 % to 90.0 % for Xpert MTB/RIF and up to 97.6 % for Xpert Ultra.[10,16] However, the performance of the tests may vary depending on the population to be evaluated and the environment in which they are performed.[17] For instance, in patients with HIV and TB co-infection, the bacillary load is extremely low, resulting in low sensitivity of smear microscopy. Nonetheless, Xpert exhibits a good diagnostic profile and could be more useful in this scenario.[16]

When analyzing the performance of Xpert MTB/RIF compared to Xpert Ultra in the diagnosis of PTB, the sensitivity between both tests was similar, although the aim of developing Xpert Ultra was to improve test sensitivity,[8] our results do not show differences. A systematic review reported that the sensitivity of Xpert MTB/RIF was 85 % and Xpert Ultra was 88 %, showing limited superiority.[18] This situation changes in contexts where the bacillary load is lower, for example in patients with HIV, where Xpert Ultra has shown much higher sensitivity (69 %) compared to Xpert MTB/RIF (61.8 %).[19]

Table 1
Characteristics of the study population (n = 1023).

Characteristics	n (%)
Sex (n = 811)	
Female	388 (47.8)
Male	423 (52.2)
Age in years (n = 746)[a]	61 (41–75)
Xpert MTB/RIF (n = 615)	
Negative	520 (84.6)
Positive	95 (15.4)
Xpert Ultra (n = 408)	
Negative	306 (75.0)
Positive	102 (25.0)
Culture (n = 1023)	
Negative	872 (85.2)
Positive	151 (14.8)
Sample origin (n = 1023)	
Pulmonary	737 (72.0)
CSF	123 (12.0)
Pleural fluid	100 (9.8)
Urine	37 (3.6)
Lymph node biopsy	16 (1.6)
Bone	10 (1.0)
Year (n = 1023)	
2012 a 2014	239 (23.4)
2015 a 2017	272 (31.1)
2018 a 2019	223 (25.5)
2020 a 2022	289 (33.0)

CSF: Cerebrospinal Fluid.
[a] Median and interquartile range.

4.2. Xpert in the diagnosis of EPTB

This study managed to evaluate the diagnostic performance of Xpert (MTB/RIF and Ultra) in multiple extrapulmonary samples. We identified high sensitivity of the test in most extrapulmonary samples except for pleural fluid samples (67 %), which is consistent with literature reports.[10,20,21] As well as with the systematic review by Aggarwal et al., which included 74 studies, reporting sensitivity and specificity of 52 % (95 % CI: 43–60) and 99 % (95 % CI: 97–99) for Xpert MTB/RIF and 68 % (95 % CI: 55–79) and 97 % (95 % CI: 97–99) for Xpert Ultra.[22] However, when a composite reference standard (clinical response to treatment and laboratory tests) is used, the sensitivity of both tests decreases even more. This shows the limited utility of Xpert for the diagnosis of pleural TB, probably due to the very low load of acid-fast bacilli in pleural fluid samples.

Despite finding high specificity in almost all extrapulmonary samples, we found that samples from lymph node biopsy had the lowest specificity (69 %). This contrasts with the results obtained in the systematic review by Denkinger CM et al., which found a specificity of 93.6 % in the detection of lymph node TB; perhaps because the reported values are the product of an analysis using a composite reference standard (which could include another molecular test, treatment response, smear microscopy).[23] Although the gold standard is culture, using a composite standard could improve the specificity of the test, especially when clinical response to empirical TB treatment is included. In our results, 25 patients tested positive on Xpert Ultra but had negative culture. Although we did not have access to the patients' histories to determine if they indeed had TB, our hypothesis is that Xpert Ultra identified TB cases that traditional culture could not.

We found high sensitivity and specificity of Xpert (MTB/RIF and Ultra) for diagnosing TB in CSF samples, similar to those reported in a systematic review including 30 studies (sensitivity 85 %, 95 % CI: 70–93 and specificity 98 %, 95 % CI: 97–99).[24] On the other hand, the study conducted by Pink et al.[25] which included 740 CSF samples, reported much lower sensitivity (55 %). Although the type of patient included in the analysis is not reported, it is important to consider this, as patients with immunosuppressive diseases tend to be more predisposed to developing TB meningitis and are the same patients who tend to have lower bacillary load, which evidently would reduce the sensitivity of the test.[9,18,23,26] The possible heterogeneity of patients among studies could explain why sensitivity and specificity may vary between studies.

Other factors that may explain the differences in sensitivity and specificity results of Xpert MTB/RIF for the diagnosis of EPTB in different reports could be due to the fact that some use only solid and liquid culture as the diagnostic standard,[20] others use a composite standard of positive cytology + Acid-fast bacillus and/or solid MTB culture,[27] and finally, other studies use another composite standard consisting of clinical presentation, radiological pattern, histology, cytology, and culture.[28] It is evident that a better definition of the gold standard for EPTB diagnosis is needed.

Table 2
Diagnostic accuracy of the Xpert MTB/RIF and Xpert Ultra for the diagnosis of TBP and EPTB, considering the Löwenstein-Jensen MTB solid culture as a reference standard.

Variable	TB prevalence - % (95 % CI)	TB patients (TP, FN)	Patients without TB (TN, FP)	Sensitivity - % (95 % CI)	Specificity - % (95 % CI)	AUC ROC - (95 % CI)	LR positive - (95 % CI)	LR negative - (95 % CI)
All samples by Xpert MTB/RIF and Xpert Ultra (n = 1023)	15 (13–17.1)	151 (145, 6)	872 (820, 52)	96 (92–99)[a]	94 (92–96)[a]	0.95 (0.93–0.97)	16.1 (12.3–21)	0.04 (0.19–0.09)
Pulmonary Samples								
Xpert MTB/RIF and Xpert ultra (n = 737)	18 (16–21)	135 (131, 4)	602 (561, 41)	97 (93–99)[a]	93 (91–95)[a]	0.95 (0.93–0.97)	14.2 (10.6–19.2)	0.03 (0.01–0.08)
- Xpert MTB/RIF (n = 432)	16 (13–19.8)	69 (67,2)	363 (347,2)	97.1 (89.9–99.6)[a]	95.6 (92.9–97.5)[a]	0.96 (0.94–0.99)	22 (13.6–35.6)	0.03 (0.01–0.12)
- Xpert Ultra (n = 305)	22.7 (17–26.7)	66 (64,2)	239 (214,25)	97 (89.5–99.6)[a]	89.5 (84.9–93.1)[a]	0.93 (0.90–0.96)	9.27 (6.48–15.5)	0.03 (0.01–0.13)
Extrapulmonary samples								
Xpert MTB/RIF and ultra (n = 286)	5.6 (3.2–8.9)	16 (14, 2)	270 (260, 10)	87.5 (61.7–98.4)	96.3 (93.3–98.2)[a]	0.92 (0.86–1.00)	23.6 (12.5–44.6)	0.13 (0.04–0.48)
- CSF (n = 123)	2 (1–7)	3 (3, 0)	120 (118, 2)	100 (29.2–100)	98.3 (94.1–99.8)[a]	0.99 (0.98–1.00)	60.0 (15.2–237.0)	0.14°
- Pleural fluid (n = 100)	6 (2–13)	6 (4, 2)	94 (91, 3)	66.7 (22.3–95.7)	96.8 (91–99.3)[a]	0.82 (0.61–1.00)	20.9 (6.0–72.8)	0.34 (0.11–1.07)
- Urine (n = 37)	5 (1–18)	2 (2, 0)	35 (33, 2)	100 (15.8–100)	94.3 (80.8–99.3)[b]	0.97 (0.93–1.00)	17.5 (4.6–67.2)	0.14°
- Lymph node biopsy (n = 16)	19 (4–46)	3 (3, 0)	13 (9, 4)	100 (29.2–100)	69.2 (38.6–90.9)	0.85 (0.72–0.98)	3.3 (1.4–7.4)	0.29°
- Bone (n = 10)	20 (3–56)	2 (2, 0)	8 (8, 0)	100 (15.8–100)	100 (63.1–100)	1.00 (1.00–1.00)	13.3°	0.18°

n: total samples, CI: Confidence Interval, CSF: Cerebrospinal Fluid, FN: false negative, FP: false positive, TB: Tuberculosis, LR: Likelihood Ratio, TN: true negative, TP: true positive.
[a] Confidence intervals range <10 % (very precise).
[b] Confidence intervals range between 10 % and <20 % (precise), ° To calculate them, the cells with values of 0 were replaced by 0.5. Confidence intervals for LR+ and LR-in these cases could not be calculated.

4.3. Implications

Early detection of *MTB* and initiation of appropriate treatment are important to reduce mortality rates from PTB or EPTB. Unfortunately, traditional diagnostic methods such as smear microscopy and culture have serious limitations in providing accurate and timely diagnosis.[16] Faced with this problem, Xpert MTB/RIF and Xpert Ultra provide accurate results and can enable prompt initiation of TB treatment.[10]

Our study supports the utility of Xpert MTB/RIF and Xpert Ultra for the diagnosis of pulmonary TB. On the other hand, the implementation of Xpert presents significant challenges, particularly related to cost and the technical and operational support requirements associated with the assay and its results.[29] However, in the long term, Xpert MTB/RIF testing could be less expensive than implementing cultures and drug susceptibility testing.[16] This is because early diagnosis can reduce hospital stay and the risk of complications among patients, that in the long run could generate more economic burden for healthcare systems.

While molecular tests for EPTB offer novel possibilities in early diagnosis, we consider that studies are needed to define a composite gold standard composed of microbiological tests and clinical response to treatment. This could help provide a diagnostic profile closer to reality.

4.4. Study limitations

Our study has limitations that should be considered when interpreting the results. Firstly, the total number of samples for each type of tissue was small. Second, we lacked clinical information about the patients who provided the samples, which may lead to results being influenced by variables we were unable to analyze (prior treatment, comorbidities). Third, due to the limited number of molecular tests included in the analysis, the results of the Xpert MTB/RIF and Xpert Ultra had to be grouped to analyze the diagnostic profile in EPTB. This may represent a limitation when interpreting our results. Finally, although we acknowledge that solid culture is the gold standard for PTB diagnosis, due to lack of additional variables, we could not perform a sub-analysis with a composite standard.

5. Conclusion

Our study suggests that Xpert MTB/RIF and Xpert Ultra have high sensitivity and specificity for the diagnosis of PTB, as well as high specificity in samples of CSF, pleural fluid, and urine. The implementation of Xpert represents a significant challenge for healthcare systems that should be taken into account to optimize early TB diagnosis.

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CRediT authorship contribution statement

Miguel Hueda-Zavaleta: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Juan Gomez-de-la-Torre:** Conceptualization, Writing – original draft, Validation, Writing – review & editing. **Claudia Barletta-Carrillo:** Data curation, Writing – original draft, Writing – review & editing. **Cinthya Flores-Flores:** Data curation, Writing – original draft, Writing – review & editing. **Nilver Piscoche-Botello:** Data curation, Writing – original draft, Writing – review & editing. **Cecilia Miranda-Visalot:** Data curation, Writing – original draft, Writing – review & editing. **Ada Mendoza-Farro:** Data curation, Writing – original draft, Writing – review & editing. **Sujey Gomez-Colque:** Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Álvaro Taype-Rondán:** Formal analysis, Writing – original draft, Validation, Writing – review & editing. **Cesar Copaja-**

Corzo: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Cesar Copaja-Corzo reports financial support was provided by Universidad San Ignacio de Loyola. Cesar Copaja Corzo reports a relationship with Universidad San Ignacio de Loyola that includes: employment. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cegh.2024.101730.

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