Clinical Microbiology and Infection 25 (2019) 1000–1005

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a diagnostic evaluation study

M. Tadesse [1, 2, 6, 7, *], G. Abebe [1, 2], A. Bekele [3], M. Bezabih [3], D. Yilma [4], L. Apers [5], B.C. de Jong [6], L. Rigouts [6, 7]

[1] Mycobacteriology Research Centre, Jimma University, Jimma, Ethiopia
[2] School of Medical Laboratory Sciences, Institute of Health, Jimma University, Jimma, Ethiopia
[3] Department of Pathology, Institute of Health, Jimma University, Jimma, Ethiopia
[4] Department of Internal Medicine, Institute of Health, Jimma University, Jimma, Ethiopia
[5] Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium
[6] Mycobacteriology Unit, Institute of Tropical Medicine, Antwerp, Belgium
[7] Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium

ARTICLE INFO

Article history:
Received 3 June 2018
Received in revised form
11 December 2018
Accepted 12 December 2018
Available online 22 December 2018

Editor: F. Allerberger

Keywords:
Diagnostic accuracy
Ethiopia
Extrapulmonary tuberculosis
Xpert MTB/RIF

ABSTRACT

Objectives: The diagnosis of extrapulmonary tuberculosis (EPTB) is often made on clinical suspicion alone, resulting in both under- and overdiagnosis and relatively poor outcomes. In this study, we evaluated the clinical utility of the Xpert MTB/RIF on routinely collected extrapulmonary specimens in Ethiopia.
Methods: This study was carried out at Jimma University Specialized Hospital, Southwest Ethiopia. Extrapulmonary specimens were collected from 572 patients clinically suspected of suffering from EPTB. All specimens were tested for TB by smear microscopy, culture, and Xpert MTB/RIF. The diagnostic accuracy of Xpert MTB/RIF was calculated and compared to a composite reference standard (CRS), comprising clinical and laboratory results.
Results: In total, 572 extrapulmonary specimens (279 lymph node, 159 pleural, 80 peritoneal, 45 cerebrospinal, and nine pericardial fluids) were tested. The pooled sensitivity and specificity of Xpert MTB/RIF were calculated to be 75% (95% CI 70–80) and 98% (95% CI 97–100) respectively when compared to the CRS. The highest sensitivity was documented for lymph node specimens (90%; 95% CI 86–94), moderate sensitivity for cerebrospinal fluid (53%; 95% CI 28–79), while the sensitivity was lowest for pleural (30%; 95% CI 17–44) and peritoneal (32%; 95% CI 12–51) fluids. Xpert MTB/RIF in addition detected rifampicin resistance in 13 patients, in perfect agreement with results from the line probe assay.
Conclusions: Xpert MTB/RIF may be used as initial diagnostic tool for testing of lymph node specimens from patients suspected of having TB lymphadenitis. The added value of Xpert MTB/RIF to diagnose pleural or peritoneal TB is limited by its poor sensitivity. **M. Tadesse, Clin Microbiol Infect 2019;25:1000**

Introduction

Ethiopia has reported a higher than average proportion of extrapulmonary tuberculosis (EPTB), dominated by TB lymphadenitis: 40% across Ethiopia compared to 15–20% worldwide [1,2]. The variable non-specific presentations, paucibacillary nature of the disease, non-uniform distribution of bacilli, difficulty in obtaining appropriate and adequate samples, and poor performance of conventional microbiological techniques in EPTB all contribute to challenges in diagnosing EPTB [2–4]. This problem particularly affects resource-limited settings, where the more sensitive methods of mycobacterial culture and histological examination are not widely available. These all lead to delayed or missed diagnosis with increased morbidity and mortality, or overdiagnosis leading to unnecessary TB treatment.

* Corresponding author. M. Tadesse, Mycobacteriology Research Centre, Jimma University, P.O. Box 378, Jimma, Ethiopia.
E-mail addresses: mulualemt.tadesse@gmail.com, mulualem.tadesse@ju.edu.et (M. Tadesse).

https://doi.org/10.1016/j.cmi.2018.12.018
1198-743X/

The Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) has been endorsed by the WHO for the initial diagnosis of individuals suspected of rifampicin-resistant or HIV-associated TB [5,6]. More recently, assessments of Xpert MTB/RIF have extended to various non-respiratory clinical samples from EPTB patients [7–10], showing highly heterogeneous sensitivity between specimen types, ranging from 25% to 96.6%. In 2013, the WHO recommended the use of Xpert MTB/RIF for some types of EPTB such as TB lymphadenitis and TB meningitis [11].

Xpert MTB/RIF has been nationally implemented in Ethiopia in selected laboratories for the initial diagnosis of TB and screening of drug-resistant TB [12]. In our previous study [13], we reported excellent sensitivity (87.8%) and specificity (91%) of Xpert MTB/RIF for the diagnosis of TB lymphadenitis using processed fine-needle aspirate (FNA). However, in that study, patients' clinical data sets were not considered and Xpert MTB/RIF has been compared to Löwenstein–Jensen culture and/or smear microscopy, which are known to be suboptimal reference standards for EPTB [3]. Therefore, in this study we investigated the use of Xpert MTB/RIF for diagnosing EPTB using a composite reference standard (CRS), composed of liquid culture (MGIT 960), smear microscopy, cytological and radiological findings, and treatment response.

Methods

Study population and specimen

This study was conducted at Jimma University Specialized Hospital, a public tertiary care hospital, southwest Ethiopia. Consecutive patients (age ≥15 years) with signs and symptoms suggestive of EPTB were included from September 2015 to June 2017. Site-specific extrapulmonary specimens were collected from patients with presumed EPTB and sent to the Mycobacteriology Research Centre (MRC) for laboratory diagnosis. The medical records of patients were examined for a clinical diagnosis: radiology findings, cytology reports, and/or clinical improvement after anti-TB treatment (ATT).

Laboratory processing of specimens

Upon receipt in the MRC, the specimen was divided in two parts: the first part was used for Xpert MTB/RIF and the second for culture and smear microscopy. For FNA (usually 0.5–1 mL volume), the volume was raised to 2 mL by addition of phosphate-buffered saline (PBS) and split in two prior to testing.

MGIT 960

Culture was performed using MGIT 960 (Becton Dickinson, Franklin Lakes, NJ, USA). Lymph node and blood-stained specimens were decontaminated by adding an equal volume of N-acetyl-L-cysteine–sodium hydroxide (1% final concentration), incubated for 15 min at room temperature, centrifuged for 15 min at 3000*g*, and the sediment resuspended in 1 mL of sterile PBS [14]. Specimens expected to be sterile (such as cerebrospinal fluid (CSF), pleural fluid, and peritoneal fluid) were directly centrifuged to concentrate the samples. MGIT tubes were inoculated with 0.5 mL of the processed specimens. For positive tubes, a smear was prepared to detect acid-fast bacilli, and MTBc was confirmed by a *p*-nitrobenzoic acid test [14].

Xpert MTB/RIF

The assay was performed as previously described [15]. If rifampicin resistance was detected by Xpert MTB/RIF, further drug susceptibility testing by the GenoType MTBDR*plus* line probe assay was performed on DNA extracted from a positive MGIT culture as per the manufacturer's instructions (Hain Lifescience, Nehren, Germany) [16].

Diagnostic classification for analysis

Based on clinical and laboratory findings, study participants were categorized as follows: (i) confirmed TB, defined as a positive culture of MTBc regardless of smear result; (ii) probable TB, culture negative but TB was suggested with the fulfilment of one of the following criteria: positive smear microscopy, cytological or radiological features suggestive of TB, or clinical improvement after ATT; (iii) non-TB, patients for whom no microbiological (smear-negative and culture-negative) or cytological evidence of TB could be found, and/or for whom an alternative diagnosis was available (none of the patients in this category received ATT); (iv) Indeterminate, patients not meeting the confirmed and probable TB criteria and/or patient medical records were lost or incomplete and clinical diagnosis of TB was not made. Indeterminate patients were excluded from analysis against the CRS (Fig. 1).

Statistical analysis

Xpert MTB/RIF diagnostic accuracy was calculated in comparison to the CRS made up of smear and culture results, radiological and cytological findings and clinical improvement after ATT. Any patient that was positive for any one component of the CRS was considered 'TB'. Overlapping 95% CI data were regarded as showing no significant difference between the results determined for the corresponding sample types.

Ethics approval

Ethics approval for this study was obtained from the Ethics Review Board of Jimma University, Ethiopia (Ref. No. RPGC/510/2014) and the Institute of Tropical Medicine, Antwerp, Belgium (Ref. no. 986/15). Written informed consent was obtained from each patient. For study participants who could not read and write, an impartial witness was co-signed.

Results

A total of 585 patients referred to the hospital with presumed EPTB were eligible. Of these, 572 patients provided sufficient volume of site-specific extrapulmonary specimens (one specimen per patient). These comprised 279 lymph node specimens, 45 CSF, 159 pleural, 80 peritoneal, and nine pericardial fluids. Of 572 patients, 226 (39.5%) were culture-positive 'confirmed TB' cases, 83 (14.5%) 'probable TB' cases were clinically, radiologically, and/or cytologically positive and received ATT with good response, and 155 (27%) were classified as 'non TB' cases because of no evidence for TB. In the remaining 108 (19%) patients, TB diagnosis was uncertain classifying them as 'indeterminate cases' (Fig. 1).

Demographic and clinical data

Of 572 patients, 295 (51.6%) were females; the mean age was 33.3 (±12 SD) years. HIV test results were available for 449 patients with 64 (14.3%) testing positive (Table 1).

Performance of Xpert MTB/RIF compared to MGIT culture

Overall, 226 (39.5%) of the 572 specimens were positive for MTBc by culture and 242 (42.3%) by Xpert MTB/RIF. The Xpert MTB/

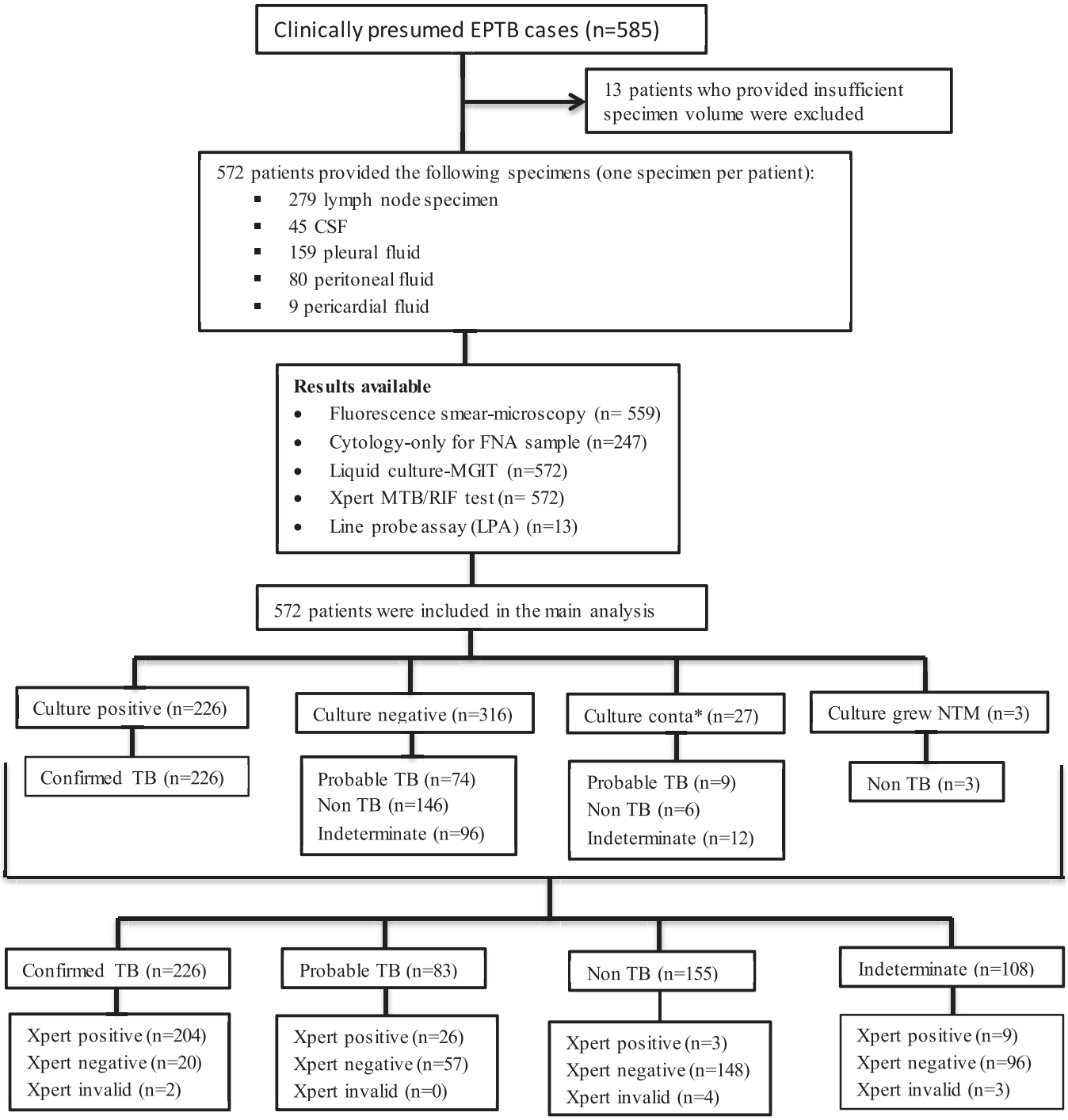

Fig. 1. Flowchart explaining the overall patient flow and diagnostic classifications. Indeterminate cases, i.e. patients with uncertain diagnosis were excluded from CRS reference standard. CSF, cerebrospinal fluid; CRS, composite reference standard; EPTB, extrapulmonary tuberculosis; NTM, non-tuberculous mycobacteria; *conta, contamination.

RIF and culture positivity rate was highest in lymph nodes (75.6% and 70.6% respectively) and modest in CSF (17.8% each). The Xpert MTB/RIF result was invalid for nine (1.6%) tests performed: less than the 27 (4.7%) contaminated MGIT tubes (Table S1). In nine of 27 culture contaminated cases, MTBc was detected by Xpert MTB/RIF and in all nine cases TB was clinically diagnosed (Table S2). Xpert MTB/RIF gave positive results in 29 (9.2%) of 316 culture-negative patients; for 17 of these patients, TB was clinically confirmed while for three cases an alternative diagnosis was made and TB was ruled out. In the remaining nine, no detailed clinical data were obtained and no confident diagnosis of TB could be made.

Overall, the pooled sensitivity and specificity of Xpert MTB/RIF were calculated to be 91% (95% CI 87.3–94.8) and 90.6% (95% CI 87.4–93.8) when compared to culture. The sensitivity of Xpert MTB/RIF (91%; 95% CI 87–95) was significantly higher than smear microscopy performed on the same specimen (47%; 95% CI 40.6–53.6; data not shown. Xpert MTB/RIF had the highest sensitivity on lymph node specimen (94.6%; 95% CI 91–98) followed by CSF (75%; 95% CI 45–100), while it was lowest for pleural (69%; 95% CI 44–94) and peritoneal fluids (71%; 95% CI 38–98%), with non-overlapping CIs between lymph node and pleural or peritoneal fluids (Table 2).

Table 1
Demographic and clinical characteristics of patients referred to Jimma University Specialized Hospital with presumed extrapulmonary tuberculosis

Characteristics	All study patients ($N = 572$)	Confirmed TB ($n = 226$)	Probable TB ($n = 83$)	Non TB ($n = 155$)	Indeterminate ($n = 108$)
Age					
15–25	205 (35.8)	93 (41.2)	28 (33.7)	47 (30.3)	37 (34.3)
26–35	179 (31.3)	71 (31.4)	28 (33.7)	46 (29.7)	34 (31.5)
36–45	92 (16.1)	32 (14.2)	11 (13.3)	2 9 (18.7)	20 (18.5)
46–55	57 (10.0)	23 (10.2)	8 (9.6)	16 (10.3)	10 (9.3)
≥56	39 (6.8)	7 (3.1)	8 (9.6)	17 (11.0)	7 (6.5)
Gender					
Male	277 (48.4)	100 (44.2)	39 (47)	90 (58.1)	48 (44.4)
Female	295 (51.6)	126 (55.8)	44 (53)	65 (41.9)	60 (55.6)
HIV status					
Positive	64 (11.2)	20 (8.8)	8 (9.6)	21 (13.5)	15 (13.9)
Negative	385 (67.3)	176 (77.9)	63 (75.9)	91 (58.7)	55 (50.9)
Unknown[a]	123 (21.5)	30 (13.3)	12 (14.5)	43 (27.7)	38 (35.2)
Specimen type					
Lymph node	279 (48.8)	197 (87.2)	30 (36.1)	38 (24.5)	14 (13.0)
CSF	45 (7.9)	8 (3.5)	7 (8.4)	21 (13.5)	9 (8.3)
Pleural	159 (27.8)	13 (5.8)	30 (36.1)	64 (41.3)	52 (48.1)
Peritoneal	80 (14.0)	7 (3.1)	15 (18.1)	30 (19.4)	28 (25.9)
Pericardial	9 (1.6)	1 (0.4)	1 (1.2)	2 (1.3)	5 (4.6)
Smear result[b]					
Positive	117 (20.9)	106 (47.1)	10 (12.3)	0	0
Negative	442 (79.1)	119 (52.9)	71 (87.7)	147 (100)	106 (100)

CSF, cerebrospinal fluid.
[a] 123 patients were not asked for HIV test or the result was not available.
[b] Smear result for 13 patients was not available.

Table 2
Performance of Xpert MTB/RIF test with respect to different specimen types compared to culture and CRS

Specimen type	Culture as a reference standard				CRS as a reference standard			
	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95%CI)	NPV % (95% CI)	Sensitivity % (95% CI)	Specificity % (95%CI)	PPV % (95% CI)	NPV % (95% CI)
Lymph node	94.4 (91–98)	71.5 (60–83)	91 (87–95)	80.4 (70–91)	89.8 (86–94)	92 (84–100)	98.5 (97–100)	60.4 (48–73)
CSF	75 (45–100)	94 (87–100)	75 (45–100)	94 (87–100)	53 (28–79)	100	100	74 (58–91)
Pleural	69 (44–94)	96.5 (93–99)	64.3 (39–89)	97 (94–100)	30 (17–44)	100	100	67 (58–77)
Peritoneal	71 (38–98)	94 (88–100)	56 (23–88)	97 (92–100)	32 (12–51)	100	100	66 (52–80)
Pooled	91 (87–95)	90.6 (87–94)	87.6 (83–92)	93.4 (91–96)	75 (70–80)	98 (96–100)	98 (97–100)	66 (60–72)

Calculation of sensitivity and specificity for pericardial fluid was not possible due to small number of this specimen in our study. PPV, positive predictive value; NPV, negative predictive value; CSF, cerebrospinal fluid; CRS, composite reference standard; CI, confidence interval.

The Xpert MTB/RIF specificity varied less across the different specimen types, with fluid specimens (pleural, peritoneal, and CSF) showing the highest specificity (≥94%) and lymph nodes the lowest (71.5%; 95% CI 60–83) (Table 2).

Performance of Xpert MTB/RIF compared to CRS

Xpert MTB/RIF identified 90.3% (204/226 specimens) of all 'confirmed TB' cases – including 101 smear-negative TB cases – and 31.3% (26/83) of 'probable TB' cases (Table S3). Using the CRS as comparator, the pooled sensitivity of Xpert MTB/RIF significantly decreased (91% compared to culture and 75% compared to the CRS with non-overlapping CIs). This drop largely results from comparing fluid specimens (CSF, pleural fluid, and peritoneal fluid). Indeed, the sensitivity differed markedly between specimen types when compared against the CRS, being the highest for lymph node specimens (90%; 95% CI 86–94), modest for CSF (53%; 95% CI 28–78) and lowest for pleural (30%; 95% CI 17–44) and peritoneal (32%; 95% CI 12–51) specimens (Table 2).

The Xpert MTB/RIF specificity was excellent for all types of specimens tested ranging from 92% to 100%. Overall, the specificity was 90.6% (95% CI 87–94) when compared to culture and improved to 98% (95% CI 96–100) when compared to the CRS (Table 2).

Detection of rifampicin resistance

Xpert MTB/RIF testing for rifampicin resistance showed an 'invalid' result in two cases. After a single repeat test, both cases were found to be rifampicin sensitive. In total, rifampicin resistance was detected in 16 patients. Of these, two patients were culture negative and one was contaminated, and thus the line probe assay result was not available for these three cases. In the remaining 13, Xpert MTB/RIF rifampicin-resistant cases Line probe assay (LPA) results were in full agreement, and all 13 were also found to be isoniazid resistant.

Discussion

Our study confirms previous observations on variability in sensitivity of Xpert MTB/RIF across different specimen types, with the highest sensitivity for TB detection in lymph node specimens, moderate sensitivity in CSF, and lower sensitivity in fluid specimens such as pleural and peritoneal [11,17–19]. Our pooled sensitivity of 91% compared to culture was reduced to 75% when compared to the CRS, whereas the specificity improved from 91% against culture to 98% against the CRS. Although culture is considered the best reference standard for pulmonary TB, it may miss cases of EPTB due to the paucibacillary nature of the disease. Thus, when Xpert MTB/

RIF is evaluated against culture alone, the number of false-positive EPTB cases (classified as positive by Xpert MTB/RIF and negative by culture) may be overestimated, leading to underestimating the specificity of Xpert MTB/RIF. The use of a CRS reclassifies these to true positives and increases the specificity. The other drawback of using culture alone as a reference standard is that both culture and Xpert MTB/RIF are likely to pick up cases with a higher bacterial load, and both are likely to miss cases with a lower bacterial load [2]. This dependency could lead to an overestimation of the Xpert MTB/RIF sensitivity, which could be corrected for by bringing in clinical and treatment outcome data.

For lymph node specimens, the sensitivity of Xpert MTB/RIF compared to culture or the CRS was not statistically different. More than 88% of TB lymphadenitis cases defined by the CRS were confirmed by Xpert MTB/RIF. Hence, a negative Xpert MTB/RIF result in lymph node specimens should guide for an alternative diagnosis. This is likely to be because the bacillary load in lymph node specimen sampled directly from the site of disease (lymph node) is above the limit of detection of Xpert MTB/RIF. Besides, lymph node specimens are relatively easy to obtain, with 1 mL being sufficient for accurate performance of Xpert MTB/RIF.

For CSF, the sensitivity of Xpert MTB/RIF was modest (75%) compared to culture and reduced to 53% compared to the CRS. Hence, even though a negative Xpert MTB/RIF does not rule-out TB meningitis, it could still significantly speed up and improve its diagnosis in settings where liquid culture or better tools are not available. Although not attempted in our current study, a South African study showed a significant increase in the sensitivity of Xpert MTB/RIF using a CSF pellet after centrifugation [20].

Similar to most previous reports [7,17,18], we found a low sensitivity and high specificity of Xpert MTB/RIF on fluids, whether compared to culture or the CRS. The poor sensitivity in such fluids is probably due to the paucibacillary nature of the disease. Some studies suggested tissue biopsies rather than fluids as the sample of choice for the diagnosis of paucibacillary TB [7,17], even though the more invasive nature of the former restricts its widespread use. In our study, except for lymph node samples, the sensitivity of Xpert MTB/RIF significantly reduced when compared against the CRS, with only around 15% of probable TB cases being detected in fluid specimens. Hence, a negative Xpert MTB/RIF in pleural or peritoneal fluid does not exclude a diagnosis of EPTB. Patients whose symptoms and signs strongly suggest disseminated EPTB should be started on ATT, despite a negative Xpert MTB/RIF. Where available, other diagnostic approaches such as measurement of interferon gamma and adenosine deaminase could be considered to improve the diagnosis of pleural TB [21].

Nevertheless, the high pooled specificity highlights the utility of Xpert MTB/RIF as a rule-in test for EPTB diagnosis, providing sufficient confidence for the clinician to initiate ATT following a positive Xpert MTB/RIF result. Unlike its sensitivity, the Xpert MTB/RIF specificity varied less across different specimen types. Compared to culture, the specificity of Xpert MTB/RIF was low for lymph node specimens (72%), most likely to be due to underperformance of culture, i.e. non-viable growth of MTBc bacilli from these specimen types, while DNA amplification was not hampered. In 29 cases, Xpert MTB/RIF was positive while culture remained negative. Of these, 17 patients had either radiologically or cytologically proven TB or a clinical response when treated with ATT, and no obvious reason was found to explain the negative culture. In nine patients, no clinical data were available to resolve the observed discrepancy. For the remaining three cases, TB was ruled out (CRS-negative), though administrative errors or sample switch could have contributed for this discrepancy. Nevertheless, taking into account that Xpert MTB/RIF is less prone to cross contamination, being a 'closed' test system (single cartridge, real-time PCR technology), these Xpert-positive but culture- or CRS-negative cases are likely to represent true-positive cases.

Apart from providing bacteriological confirmation of disease, rapid detection of rifampicin resistance in extrapulmonary specimens is another added benefit of Xpert MTB/RIF. WHO has recommended that all rifampicin-resistant cases should start second-line TB regimens. Therefore, rifampicin-resistant EPTB cases diagnosed by Xpert MTB/RIF should be referred for second line-LPA and/or phenotypic susceptibility testing.

Our study has some shortcomings. The sample size for certain specimen types such as CSF and pericardial fluid was limited, urging for caution when interpreting results for each category of specimens separately. Also, the medical records of a significant number of patients were lost or incomplete and the TB diagnosis remained uncertain. These cases were excluded from the CRS analysis. Finally, we believe that even though the use of a CRS may introduce a minor degree of selection bias and may be difficult to standardize, this consideration outweighs the risk of misclassification when using culture alone as a reference.

Conclusions

In EPTB, Xpert MTB/RIF is likely to be of greatest utility when testing lymph node specimens. Xpert MTB/RIF has modest sensitivity in CSF, but it could still be considered as the initial diagnostic test for diagnosis of TB meningitis as it provides rapid diagnosis. However, there is still a need to evaluate and confirm the utility of Xpert MTB/RIF on a large sample size with specimens such as CSF, other body fluids, and urine, which are easier to obtain.

Transparency declaration

The authors declare that they have no conflict of interests relevant to this article. This work was supported by interuniversity cooperation between Jimma University and Flemish Universities (VLIR-OUS project). The funders had no role in study design, data analysis and interpretation, or the decision to prepare the manuscript and submit for publication.

Acknowledgments

We are grateful to the patients who consented to take part in this study. We would also like to thank the staff of Mycobacteriology Research Centre of Jimma University for the assistance and guidance during data collection.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2018.12.018.

References

[1] Berg S, Schelling E, Hailu E, Firdessa R, Gumi B, Erenso G, et al. Investigation of the high rates of extrapulmonary tuberculosis in Ethiopia reveals no single driving factor and minimal evidence for zoonotic transmission of Mycobacterium bovis infection. BMC Infect Dis 2015;15:112.
[2] Purohit M, Mustafa T. Laboratory diagnosis of extra-pulmonary tuberculosis (EPTB) in resource-constrained setting: state of the art, challenges and the need. J Clin Diagn Res 2015;9:EE01.
[3] Norbis L, Alagna R, Tortoli E, Codecasa LR, Migliori GB, Cirillo DM. Challenges and perspectives in the diagnosis of extrapulmonary tuberculosis. Expert Rev Anti Infect Ther 2014;12:633–47.
[4] Solovic I, Jonsson J, Korzeniewska-Kosełа M, Chiotan D, Pace-Asciak A, Slump E, et al. Challenges in diagnosing extrapulmonary tuberculosis in the European Union, 2011. Euro Surveill 2013;18:20432.
[5] World Health Organization. Roadmap for rolling out Xpert MTB/RIF for rapid diagnosis of TB and MDR-TB. Geneva: WHO; 2010. p. 1–12.

[6] Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M, et al. Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev 2013;1.
[7] Tortoli E, Russo C, Piersimoni C, Mazzola E, Dal Monte P, Pascarella M, et al. Clinical validation of Xpert MTB/RIF for the diagnosis of extrapulmonary tuberculosis. Eur Respir J 2012;40:442–7.
[8] Lawn SD, Zumla AI. Diagnosis of extrapulmonary tuberculosis using the Xpert® MTB/RIF assay. Expert Rev Anti Infect Ther 2012;10:631–5.
[9] Hillemann D, Rüsch-Gerdes S, Boehme C, Richter E. Rapid molecular detection of extrapulmonary tuberculosis by the automated GeneXpert MTB/RIF system. J Clin Microbiol 2011;49:1202–5.
[10] Vadwai V, Boehme C, Nabeta P, Shetty A, Alland D, Rodrigues C. Xpert MTB/RIF: a new pillar in diagnosis of extrapulmonary tuberculosis? J Clin Microbiol 2011;49:2540–5.
[11] World Health Organization. Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children: policy update. Geneva: WHO; 2013.
[12] Ethiopian Ministry of Health/Ethiopian Public Health Institute. Implementation guideline for GeneXpert MTB/RIF assay in Ethiopia. Ethiopia: Addis Ababa; 2014.
[13] Tadesse M, Abebe G, Abdissa K, Aragaw D, Abdella K, Bekele A, et al. GeneXpert MTB/RIF assay for the diagnosis of tuberculous lymphadenitis on concentrated fine needle aspirates in high tuberculosis burden settings. PLoS One 2015;10, e0137471.
[14] WHO. Laboratory services in tuberculosis control. 1998. Geneva, Switzerland.
[15] Helb D, Jones M, Story E, Boehme C, Wallace E, Ho K, et al. Rapid detection of Mycobacterium tuberculosis and rifampin resistance by use of on-demand, near-patient technology. J Clin Microbiol 2010;48:229–37.
[16] Global Laboratory Initiative. Mycobacteriology laboratory manual. Geneva: WHO Stop TB Partnership; 2014.
[17] Suzana S, Ninan MM, Gowri M, Venkatesh K, Rupali P, Michael JS. Xpert MTB/Rif for the diagnosis of extrapulmonary tuberculosis – an experience from a tertiary care centre in South India. Trop Med Int Health 2016;21:385–92.
[18] Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M, Steingart KR. Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. Eur Respir J 2014;44:435–46.
[19] Penz E, Boffa J, Roberts D, Fisher D, Cooper R, Ronksley P, et al. Diagnostic accuracy of the Xpert® MTB/RIF assay for extra-pulmonary tuberculosis: a meta-analysis. Int J Tuberc Lung Dis 2015;19:278–84.
[20] Bahr NC, Tugume L, Rajasingham R, Kiggundu R, Williams DA, Morawski B, et al. Improved diagnostic sensitivity for tuberculous meningitis with Xpert MTB/RIF of centrifuged CSF. Int J Tuberc Lung Dis 2015;19:1209–15.
[21] Meldau R, Peter J, Theron G, Calligaro G, Allwood B, Symons G, et al. Comparison of same day diagnostic tools including Gene Xpert and unstimulated IFN-γ for the evaluation of pleural tuberculosis: a prospective cohort study. BMC Pulm Med 2014;14:58.