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Xpert MTB/RIF Ultra improved the diagnosis of paucibacillary tuberculosis: A prospective cohort study

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SUMMARY

Objectives: We assessed the diagnostic performance of Xpert MTB/RIF Ultra (Xpert Ultra) in comparison to Xpert MTB/RIF (Xpert) for the detection of paucibacillary tuberculosis (TB).
Methods: Smear-negative sputum, pleural fluid and cerebrospinal fluid (CSF) were collected from TB suspects at Beijing Chest Hospital (Beijing, China) and were examined using smear, Xpert and culture. Xpert Ultra was tested using specimens stored at −80 °C. Drug susceptibility testing (DST) was conducted for all of the isolates recovered. The performances of Xpert Ultra and Xpert were evaluated using composite reference standard (CRS) as gold standard, which included clinical, laboratory, histopathological, radiological and follow-up features.
Results: Totally 689 cases were included. The direct head-to-head diagnostic performance comparison showed higher sensitivity of Xpert Ultra in contrast with Xpert among 292 smear-negative pulmonary TB (PTB) (70.89% vs 57.88%, $P=0.001$), 108 tuberculous pleurisy (61.11% vs 34.26%, $P<0.001$), and 43 tuberculous meningitis (44.19% vs 18.60%, $P=0.011$). The percentage of definite PTB, tuberculous pleurisy and tuberculous meningitis increased from 67.12% to 78.77%, 61.11% to 69.44% and 23.26% to 51.16%, respectively after integrating Xpert Ultra outcomes. The specificity of Xpert Ultra and Xpert was 96.75% (238/246) and 98.37% (242/246), respectively. Xpert Ultra and Xpert performed similarly in detecting rifampicin resistance.
Conclusion: Xpert Ultra has higher sensitivity but relatively reduced specificity compared with Xpert in diagnosis of paucibacillary TB. Performing Xpert Ultra would improve the definite diagnosis of smear-negative pulmonary tuberculosis, tuberculous pleurisy and tuberculous meningitis.

Introduction

Tuberculosis (TB) is the ninth leading cause of deaths worldwide with an estimated 10 million new cases and 1.3 million deaths in 2017.[1] Detection of acid-fast bacilli (AFB) using smear microscopy from clinical specimen is the most popular method for TB diagnosis worldwide, however, 30–60% of all pulmonary TB (PTB) cases in many high incidence settings are smear-negative.[2] According to the 2018 global tuberculosis report of the World Health Organization (WHO), the mortality rate for smear-negative PTB can reach up to 20%, which might largely be caused by delay in diagnosis.[1] Furthermore, 10–20% of TB transmission at the population level is attributed to smear-negative cases.[3] On the other hand, extrapulmonary TB (EPTB) accounted for 14% of the 6.3 million incidents reported by WHO in 2017.[1] Due to its paucibacillary nature, diagnosis of EPTB is extremely challenging. Therefore, improvement in the diagnostic efficiency and early diagnosis for both smear-negative PTB and EPTB are crucial.

The Xpert MTB/RIF (Xpert) (Cepheid, Sunnyvale USA) assay, a point-of-care (POC) technique, was a major step towards improved diagnosis of TB and resistance to rifampicin (RIF) globally. Despite its excellent sensitivity (98%) for smear-positive sputum samples,[4] Xpert demonstrated imperfect capacity for smear-negative sputum (67%), paucibacillary extrapulmonary samples (50.9–82.7%)[5–7] and TB/HIV co-infected patients (73.3%).[8] The Xpert MTB/RIF

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Ultra (Xpert Ultra) (Cepheid, Sunnyvale USA) assay was developed as a next-generation assay to improve the sensitivity for *Mycobacterium tuberculosis* (Mtb) detection and rifampin resistance diagnosis. Analytical studies showed that Xpert Ultra had a lower detection limit i.e. 15.6 bacterial colony forming units (cfu) per ml in contrast with 112.6 cfu per ml for Xpert.[9] Only a few studies have demonstrated that Xpert Ultra has an improved sensitivity in diagnosing of smear-negative PTB, tuberculous meningitis and pediatric TB in contrast with Xpert.[10–14] As a new diagnostic tool, Xpert Ultra shows tremendous promise for TB diagnosis, however, the performance data is still limited. WHO recommend using Xpert Ultra for TB diagnosis in 2018, but also suggested to extensively evaluate Xpert Ultra in different epidemiological and geographical settings with different patient populations, especially among EPTB patients.[15]

In this study, we focused on the performance of Xpert Ultra by evaluating its efficiency for testing paucibacillary samples. We compared the diagnostic performance of Xpert Ultra with Xpert on a large number of smear-negative sputum and non-respiratory specimens in a TB high-burden and HIV low-burden setting.

Material and methods

Ethical approval and informed consent

The study was approved by the Ethics Committee of the Beijing Chest Hospital, Capital Medical University. Written informed consent was obtained from all the patients.

Study design and oversight

The objective of this study was to compare the diagnostic performance of Xpert Ultra with Xpert on smear-negative sputum, pleural fluid and cerebrospinal fluid (CSF) using the composite reference standard (CRS) as control, which was composed of clinical, laboratory, histopathological, and radiological and follow-up features. Sputum and CSF specimen from TB suspects were consecutively collected during July to December 2017 at Beijing Chest Hospital (Beijing, China), which is the only national level TB referral center in China and patients were followed up to a minimum of 6 months. Eligible participants were patients with pulmonary TB symptoms had no anti-TB drugs taken in the past 6 months. Adults who were offered lumbar puncture as a part of routine care for suspected brain infection were eligible for enrolment. At least 3 ml of un-centrifuged CSF was used for mycobacterial targeted diagnostic tests. Besides, the following tests were also performed on CSF: routine biochemistry, microscopy (Gram stain), bacterial and fungal culture, viral antibody, cryptococcal antigen latex agglutination test (CLAT). Pleural fluid samples were prospectively collected from July 2015 to December 2016 in a cohort study "Appropriate course of the treatment of tuberculous pleurisy" (ChiCTR-IOR-15006408) and stored in "Beijing Bio-Bank of clinical resources on Tuberculosis" (Beijing Chest Hospital). Eligibility for enrollment was based on standard clinical criteria, including TB symptoms, chest pain, radiological evidence of pleural effusion, thoracoscopic examination suggested TB, no previous treatments with any anti-TB drugs in the past 6 months. Furthermore, all of the patients were followed up for a minimum of 12 months. Among all the 242 tuberculous pleurisy patients recruited, the bacteriologically confirmed cases and some clinically diagnosed cases were consecutively recruited in this study.

Patient categories

Based on the CRS, PTB and tuberculous pleurisy suspects were categorized into three groups: (1) definite cases: a biological specimen was positive by any of the smear microscopy, culture and Xpert, as well as Xpert Ultra after being performed, (2) clinically diagnosed case: active TB was diagnosed according to the histopathological/thoracoscopic or radiological examinations by clinician, responded well to anti-TB therapy at months of follow-up, (3) non-TB: alternative diagnosis established and clinical resolution without anti-TB treatment. Tuberculous meningitis patients were categorized as definite, probable, possible, and not tuberculous meningitis using the uniform clinical case definitions described by Marais and colleagues.[16]

New cases were defined as patients with TB but never treated for TB. Previously treated cases were defined as patients which had received 1 or more months' anti-TB treatment in the past.

Procedures

For sputum specimen, 1 ml of raw sputum was used for Xpert, 1 mL for solid culture, and 1.5 ml for liquid culture and Xpert Ultra. The sputum were decontaminated with N-acetyl-L-cysteine-sodium hydroxide (BBL MycoPrep; Becton Dickinson, Sparks, MD) for 20 min, then neutralized with sterile saline phosphate buffer (PBS; pH 6.8) to a final volume of 45 ml, and then centrifuged at $3000\times g$ for 15 min at 4 °C. The pellet was resuspended in 1.5 ml of PBS, 0.5 mL of which was inoculated into the mycobacteria growth indicator tube (MGIT) 960 system (Becton, Dickinson and Company, USA) while the remaining 1 mL was stored at −80 °C for Xpert Ultra testing until culture result was obtained or at the end of the follow-up term. For CSF samples, 0.5 mL was used for liquid culture, 0.1 mL for solid culture, 1 mL for Xpert testing and 1 mL for Xpert Ultra testing. For pleural fluid samples, a minimum of 50 ml pleural fluid was collected from each patient. The samples were centrifuged ($3000\times g$ at 4°C for 20 min) and 0.5 mL of the resuspended pellet was used for liquid culture, 0.1 mL for solid culture, 1 mL for Xpert testing, and 1 mL for Xpert Ultra assay.

Xpert and Xpert Ultra

The Xpert and Xpert Ultra assays were performed as per the manufacturer's instructions. Briefly, 1 ml specimen was mixed with 2 ml sample reagent, vortexed for at least 10 s, and incubated at room temperature for 10 min. The mixture was again vortexed for another 10 s and incubated at room temperature for 5 min. A total of 2 ml of the mixture was transferred into the Xpert/Xpert Ultra cartridge and loaded into the GeneXpert instrument. The automatic detection procedure was then run. For an invalid result, the Xpert Ultra or Xpert test was repeated using the same sample.

An additional semi-quantitative category of "trace-positive" was introduced for Xpert Ultra to identify the paucibacillary samples, which indicated that the amplification of IS6110/IS1081 sequence was successful but not the *rpoB* gene.[9] WHO suggests[15] that a trace-positive result is sufficient to initiate therapy in cases with known or suspected HIV infection, children and extrapulmonary TB cases, however, the trace-positive outcome for sputum is not considered very reliable. Therefore, here, we adopted the conditional-trace approach for sputum examination recommended by Dorman S but with some changes.[10] We reclassified all the "trace-positive" as a tuberculosis-negative outcome for sputum examination to avoid evident decrease of specificity

Drug susceptibility testing

For the positive cultures acquired in this assay, we performed drug susceptibility testing (DST) with proportion method using Lowenstein-Jensen medium. The critical concentration used was 40 μg/ml for RIF.

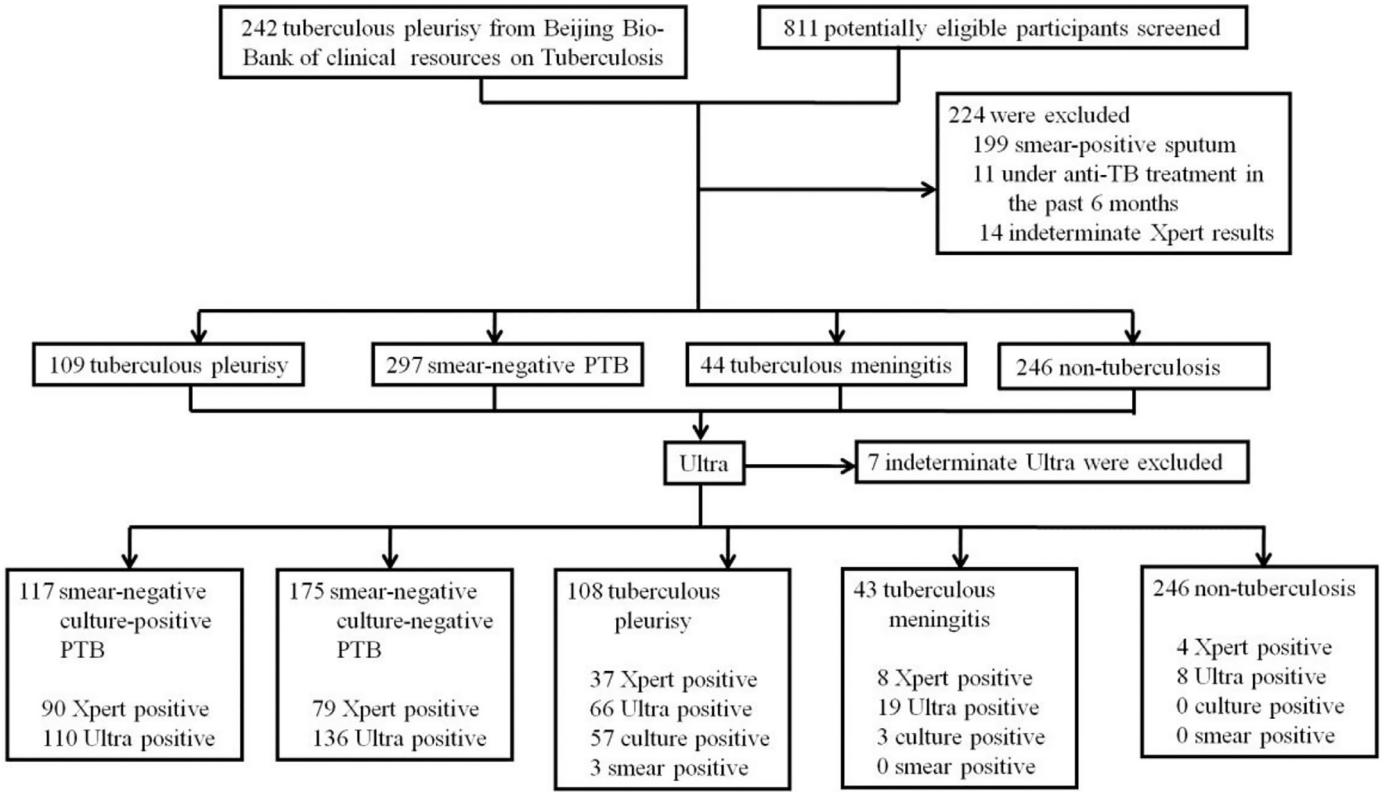

Fig. 1. Study flow chart.
PTB: pulmonary tuberculosis.

Statistical analysis

The statistical analysis was conducted using the SPSS, version 19.0 software (IBM,Armonk, NY, USA). The Pearson χ^2 test was used to compare the sensitivity between the different diagnostic tools. Differences were considered statistically significant at $P < 0.05$.

Results

Participants

Totally, 811 PTB and tuberculous meningitis suspects were recruited. 224 participants were excluded from the analysis, including 199 smear-positive cases, 11 with history of anti-TB treatment in the past 6 months, and 14 with indeterminate Xpert results (Fig. 1). Therefore, 587 participants were enrolled including: 297 smear-negative PTB (119 culture-positive, 178 culture-negative but clinically diagnosed), 44 tuberculous meningitis (10 definite tuberculous meningitis and 34 probable or possible tuberculous meningitis) and 246 non-TB cases. Furthermore, 109 tuberculous pleurisy (57 culture-positive, 52 culture-negative) were also recruited from the cohort study.

A total of 7 indeterminate Xpert Ultra results were excluded (3 smear-negative culture-negative sputum, 2 smear-negative culture-positive sputum, 1 pleural fluid and 1 CSF). Thus, the final sample size for analysis was 689 patients, which included 443 (64.30%) TB patients (Fig. 1). The other 246 (35.70%) cases were classified as “non-TB” patients, including 124 pneumonia, 71 lung cancer, 10 lymphoma, 9 pulmonary abscess, 7 non-tuberculous mycobacterial infection, 8 pulmonary fungal infection, 10 viral meningitis and 7 cryptococcal meningitis cases. All patients were HIV-negative. Basic characteristics of the enrolled patients are shown in Table 1.

Yield of Xpert Ultra in the smear-negative PTB diagnosis

Among the 292 smear-negative sputum from TB cases, 117 were positive for culture, 169 for Xpert, 207 for Xpert Ultra. 51 and 14 trace-positive outcomes for PTB case or non-TB cases were reclassified as tuberculosis-negative. The direct head-to-head performance comparison for Mtb detection showed higher sensitivity of Xpert Ultra than Xpert among smear-negative sputum (70.89%, 207/292 vs 57.88%, 169/292; $P=0.001$), either in smear-negative culture-positive samples (87.18%, 102/117 vs 76.92%,90/117; $P=0.041$) or in smear-negative culture-negative samples (60.00% 105/175 vs 45.14%, 79/175; $P=0.009$) (Table 2). Totally 230 patients demonstrated bacteriological evidence of Mtb in this assay, among them, Xpert Ultra had 90.00% (207/230) sensitivity, which was higher than both Xpert (73.48%, 169/230; $P<0.001$) and culture (50.87%, 117/230; $P<0.001$) (Fig. 2). Xpert Ultra detected 38 additional PTB cases which increased the Mtb detection rate by 13.01% (38/292) in contrast with Xpert. Its sensitivity gain, compared with Xpert, was more apparent among participants with lower sputum bacillary burden e.g. smear-negative culture-negative patients (14.86%, 26/175) than among smear-negative culture-positive cases (10.26%, 12/117; $P<0.001$). The specificities of Xpert Ultra and Xpert were 96.60% (199/206) and 98.06% (202/206), respectively. Two lung cancer, 1 pneumonia and 1 hemolytic staphylococcus infection were misdiagnosed as TB by Xpert, while another 1 lung cancer and 2 pneumonia cases were misdiagnosed as TB by Xpert Ultra.

Yield of Xpert Ultra in EPTB diagnosis

Among 108 pleural fluid samples, 3 were positive for smear, 57 for culture, 37 for Xpert and 66 for Xpert Ultra (including 26 trace-positive outcomes). Overall, Xpert Ultra (61.11%, 66/108) had higher sensitivity than Xpert (34.26%, 37/108; $P<0.001$) for tuber-

Table 1
Demographic and clinical characteristics of the study participants.

Characteristics	Smear-negative pulmonary tuberculosis	Tuberculous pleurisy	Tuberculous meningitis	Non-tuberculosis
Total	**292**	**108**	**43**	**246**
Age, median (range), yr	47(14–89)	37(15–89)	33(15–83)	55(17–86)
Gender				
Male	192/292 (65.75)	86/108 (80)	24/43 (56)	149/246(60.57)
Female	100/292 (34.25)	22/108 (20)	19/43 (44)	97/246(39.43)
History of tuberculosis	145/292 (49.66)	11/108 (10)	20/43 (47)	23/246(9.35)
HIV status				
HIV-negative	292/292(100)	108/108(100)	43/43(100)	246/246(100)

Table 2
Sensitivities and specificity of Xpert Ultra and Xpert assay for the detection of *Mycobacterium tuberculosis* in paucibacillary respiratory and non-respiratory specimens.

Specimen type	Sensitivity		Specificity	
	Xpert Ultra*n*/*N* (%)	Xpert*n*/*N* (%)	Xpert Ultra*n*/*N* (%)	Xpert*n*/*N* (%)
Smear-negative sputum	207/292 (70.89)	169/292 (57.88)	199/206(96.60)	202/206(98.06)
Culture-positive	102/117 (87.18)	90/117 (76.92)		
Culture-negative	105/175 (60.00)	79/175 (45.14)		
Pleural fluid	66/108(61.11)	37/108 (34.26)	22/23(95.65)	23/23(100)
Culture-positive	48/57 (84.21)	28/57 (49.12)		
Culture-negative	18/51 (35.29)	9/51 (17.65)		
Cerebrospinal fluid	19/43(44.19)	8/43 (18.60)	17/17(100)	17/17(100)
Bacteriologically-positive	19/22 (86.36)	8/22 (36.36)		

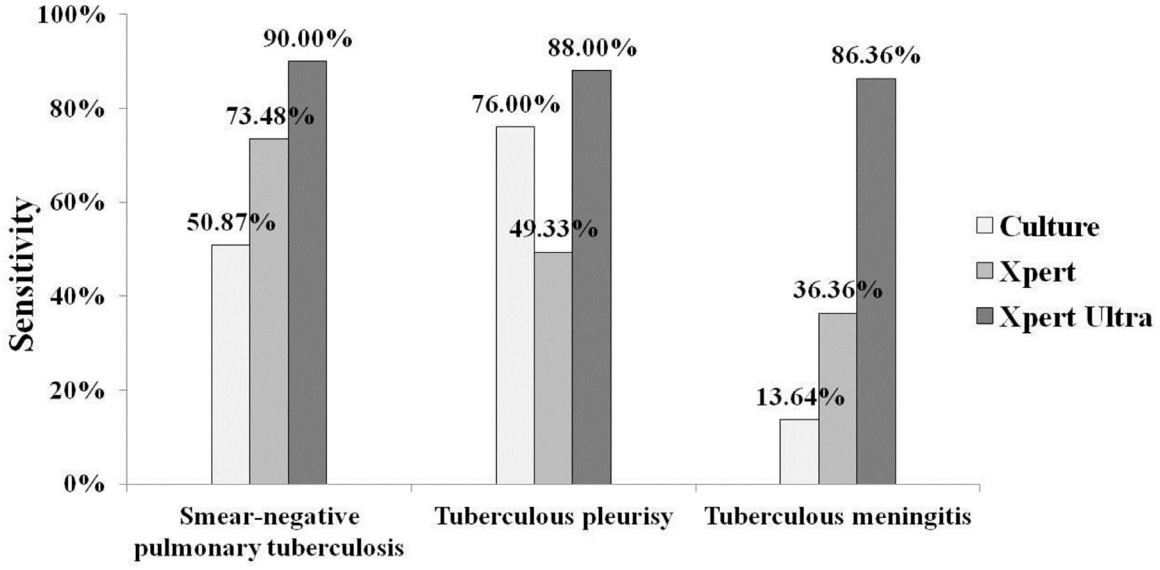

Fig. 2. The sensitivity of each method among bacteriologically confirmed tuberculosis.

culous pleurisy. Xpert Ultra was also more sensitive than Xpert among culture-confirmed tuberculous pleurisy (84.21%, 48/57 vs 49.12%, 28/57; $P<0.001$) (Table 2). After integrating the Xpert Ultra outcomes, 75 patients were classified as definite tuberculous pleurisy. Among them, Xpert Ultra had 88.00% (66/75) sensitivity, which was significantly higher than Xpert (49.33%, 37/75; $P<0.001$) but only slightly higher than culture (76.00%, 57/75; $P=0.056$) (Fig. 2). Among these confirmed cases, 9 were detected by Xpert Ultra only, while 0 by Xpert only and 8 by culture only. The specificities of Xpert Ultra and Xpert were 95.65% (22/23) and 100% (23/23), respectively. One lung adenocarcinoma case was misdiagnosed as TB by Xpert Ultra.

Among the 43 CSF samples of tuberculous meningitis patients, 0 were positive for smear, 3 for culture, 8 for Xpert and 19 for Xpert Ultra (including 12 trace-positive outcomes). Sensitivity of Xpert Ultra was superior to Xpert among the 43 tuberculous meningitis (44.19%, 19/43 vs 18.60%, 8/43; $P=0.011$). Xpert Ultra had 86.36% (19/22) sensitivity for definite tuberculous meningitis, which was higher than both Xpert (36.36%, 8/22; $P=0.001$) and culture (13.64%, 3/22; $P<0.001$) (Fig. 2). Without Xpert Ultra assay, 23.26% (10/43) of the enrolled tuberculous meningitis patients were classified as definite tuberculous meningitis, whereas this percentage increased to 51.16% (22/43) by considering the Xpert Ultra outcomes. Among the 22 definite tuberculous meningitis cases, 2 were positive for Xpert only, 0 for culture only, while 12 for Xpert Ultra only. The specificities of Xpert Ultra and Xpert both were 100% (17/17).

Yield of Xpert Ultra in rifampicin resistance detection

177 participants had culture-positive samples and had phenotypic drug susceptibility test results. Xpert Ultra provided interpretable rifampicin drug susceptibility test results for 138 participants (77.97%), whereas Xpert provided results for 118 participants

Table 3
Sensitivities and specificity of Xpert Ultra and Xpert assay for rifampicin resistance detection in comparison with drug susceptibility testing.

Specimen type	Sensitivity		Specificity	
	Xpert Ultra*n*/*N* (%)	Xpert*n*/*N* (%)	Xpert Ultra*n*/*N* (%)	Xpert*n*/*N* (%)
Sputum	16/16 (100)	15/16 (93.75)	74/74(100)	74/74(100)
Pleural fluid	6/6 (100)	6/6 (100)	23/23(100)	23/23(100)
Total	22/22(100)	21/22(95.45)	97/97(100)	97/97(100)

(66.67%). Comparison among samples with phenotypic DST outcomes and eligible Xpert and Xpert Ultra results was performed (Table 3). 16 sputum and 6 pleural fluid samples showed rifampicin resistance. Sensitivity of Xpert Ultra (100%, 16/16) was slightly higher than Xpert (93.75%, 15/16, $P = 0.310$) in detection of RIF resistance in sputum samples. The specificities for both were 100% (74/74) (Table 3). Xpert Ultra and Xpert both were 100% concordant with the phenotypic DST for detecting RIF resistance in pleural fluid samples. The overall sensitivity of Xpert Ultra (100%, 22/22) was slightly higher than Xpert (95.45%, 21/22, $P = 0.312$) in detecting rifampicin resistance in pleural fluid samples, but the difference was not significant.

Discussion

This study compared Xpert and Xpert Ultra head-to-head using paucibacillary samples exclusively. We focused on smear-negative sputum, pleural fluid and CSF of TB patients, since they often had low yields for bacterial examinations. Both conventional laboratory diagnostics and nucleic acid amplification techniques including Xpert assay are far from ideal for these specimen testing. Failing to find Mtb from clinical specimen often causes delayed diagnosis, and consequently, leads to increase in disease transmissions, mortality and disabilities. Xpert assay has advanced the TB diagnosis during the past decade, however, the impact of Xpert Ultra still remains undiscovered.

In this study, Xpert Ultra outperformed Xpert in diagnosing smear-negative PTB and paucibacillary EPTB. The sensitivity of Xpert Ultra reached 87.18% for smear-negative culture-confirmed PTB when compared to 76.92% sensitivity of Xpert, which was in line with the results of published studies that evaluated diagnostic efficiency of Xpert Ultra to date.[10–14] Greater added value of Xpert Ultra compared with Xpert for Mtb detection were observed among smear-negative culture-negative PTB cases (14.86%, from 45.14% to 60.00%) than among smear-negative culture-positive PTB cases (10.26%, from 76.92% to 87.18%). This result indicates that Xpert Ultra is highly beneficial for paucibacillary PTB patient.

Tuberculous pleurisy is the second most common form of EPTB as well as the main cause of pleural effusion in many countries.[17] A definitive diagnosis of tuberculous pleurisy relies on identification of Mtb from pleural fluid. Unfortunately, this is accomplished among a very low number of cases by conventional testing. Meta-analysis found that the pooled sensitivity of Xpert was 51% compared to culture, and the pooled sensitivity was 22.7% when a composite reference standard (CRS) was deployed.[7,18] In this study, the sensitivity of Xpert was 49.12% (28/57) when compared to culture and 34.26% (37/108) when compared to CRS, which confirmed poor sensitivity of Xpert for pleural fluid testing, even among culture proven cases. On the other hand, Xpert Ultra increased the sensitivity of Xpert from 34.26% to 61.11% among all the 108 tested cases, and also from 49.12% to 84.21% among the 57 culture confirmed pleurisy cases. Given the critical importance of a definitive TB diagnosis, Xpert Ultra takes a major step forward for tuberculous pleurisy diagnosis.

Tuberculous meningitis accounts for approximately 1% of TB disease, but bears a very high mortality risk between 20% and 50%.[19] Tuberculous meningitis is also a paucibacillary disease,[11] which makes it very difficult to be diagnosed. Prognosis of tuberculous meningitis worsens with later presentation, which would be exacerbated by delay of diagnosis and treatment initiation. In 2013, WHO recommended Xpert assay as the preferred initial test for diagnosis of tuberculous meningitis. [20] However, the sensitivity of Xpert is still not optimal. The only published evaluation of Xpert Ultra for tuberculous meningitis diagnosis[11] showed that it could successfully detect 95% of the definite cases among HIV-infected adults. In accordance with this report, Xpert Ultra demonstrated superior sensitivity (86.36%) over Xpert (36.36%) and culture (13.64%) for definite tuberculous meningitis in HIV-negative adults in this study. Furthermore, the integration of Xpert Ultra assay greatly changed the tuberculous meningitis classification composition in our study. The percentage of definite tuberculous meningitis patients increased from 23.26% (10/43) to 51.16% (22/43) when counted in the Xpert Ultra outcomes. According to our study, implementing Xpert Ultra as the initial diagnostic tests could benefit more patients, and can dramatically reduce the delay of appropriate treatment.

The “trace-positive” category accounted for a significant proportion of positive outcomes for pleural fluid and CSF specimen when using Xpet Ultra. However, although increased sensitivity was also acquired with sputum by including the “trace-positive” outcomes, obvious decrease in specificity was incurred [from 96.6% (199/206) to 89.8% (185/206)]. Dorman et al. [10] reported a conditional-trace approach to make compensation for the decreased specificity of Xpert Ultra. According to their recommendation, for participant with a history of tuberculosis, Xpert Ultra trace-positive result was reclassified as negative outcome, which can improve Xpert Ultra specificity and retain most of Xpert Ultra’s sensitivity in the smear-negative group. In a high TB burden country like China, about one fifth of the population had been infected with tuberculosis, however, patients with subclinical symptoms have not been detected. Therefore, this scenario would affect the specificity of Ultra Xpert when it is applied in China. In this assay, we reclassified all the trace-positive as tuberculosis-negative outcome to trade-off between increased sensitivity and decreased specificity. Increased on-site evaluations from other high burden countries are needed to justify this operation.

In this assay, both Xpert and Xpert Ultra assays were very in accordance with the phenotypic DST when considering the rifampicin resistance detection. Xpert Ultra (100%, 22/22) had slightly higher sensitivity than Xpert (95.45%, 21/22), whereas the difference was not significant. Both Xpert and Xpert Ultra assays had 100% specificity in this study. Although small number of rifampicin resistant cases were detected, our study implied that more drug resistant patients will be diagnosed after implementation of highly sensitive molecular tests, which is especially important for paucibacillary TB patients.

This study has several limitations. First, although this is a prospective cohort study, we did the Xpert Ultra assay with frozen samples due to our interest on paucibacillary samples. A higher sensitivity was reported for fresh samples (59.0%) compared with frozen samples (31.4%) by Xpert, however, there was no significant difference.[5] In this study, Xpert Ultra had obviously higher

sensitivity than Xpert which was performed with fresh samples. These outcomes demonstrated that the performance of Xpert Ultra with frozen samples was robust. Second, plural fluid was not recruited consecutively in this study. To guarantee enough bacteria-positive cases being enrolled, we included all the bacterially confirmed TB pleurisy cases collected in a cohort study (ChiCTR-IOR-15006408), but only consecutively recruited part of the clinically diagnosed TB cases (about 30%). Thus, the overall sensitivity for tuberculous pleurisy detection did not reflect the realistic disease condition, but only outlined the sensitivity difference between Xpert and Xpert Ultra assay.

In conclusion, Xpert Ultra has higher sensitivity, but slightly reduced specificity compared to Xpert in diagnosis paucibacillary tuberculosis. Performing Xpert Ultra would improve the definite diagnosis of smear-negative pulmonary tuberculosis, tuberculous pleurisy and tuberculous meningitis.

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Conflict of interests

No conflict of interests to disclose.

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