Central nervous system infection, particularly meningitis, caused by *Mycobacterium tuberculosis* occurs in around 1% of all cases of tuberculosis (TB) and accounts for at least 5% of extrapulmonary tuberculosis diagnoses (1). It is more common in children and patients with HIV, and delayed diagnosis is associated with poor outcomes (2). Laboratory diagnosis of tuberculous meningitis (TBM) is challenging due to the effects of paucibacillary disease. Examining large volumes of cerebrospinal fluid (CSF) improves the sensitivity of smear and culture (3), but volumes submitted for mycobacterial culture are often small. Thus, in the majority of patients, TBM is diagnosed on the basis of clinical symptoms, cell counts, and protein concentration in the CSF rather than microbiological confirmation. The clinical value of culture remains limited to diagnostic confirmation and drug susceptibility testing; cultures may take several weeks to yield a positive result, and negative results do not exclude TBM.

Xpert MTB/RIF is an automated real-time molecular assay for rapid diagnosis of tuberculosis (TB) and detection of rifampin resistance. It was first endorsed by the World Health Organization (WHO) in December 2010. A recent systematic review reported the successful use of the Xpert MTB/RIF test on CSF samples, with a median sensitivity of 85% (4). The review included 10 studies representing a total of 126 positive CSF samples; one study from Vietnam contributed 103 positive samples (5). The second-largest study was conducted in Italy, including a total of 150 CSF samples, 11 of which were TB culture positive (6). Despite its wide availability, studies investigating the diagnostic performance of Xpert MTB/RIF for TBM in resource-rich settings are lacking. This study used routine retrospective data to determine the sensitivity and specificity of Xpert MTB/RIF compared to liquid Mycobacterium Growth Indicator Tube (MGIT)-based culture of CSF samples.

All CSF samples referred for Xpert MTB/RIF testing to the National Mycobacterium Reference Laboratory (NMRL), London, United Kingdom, between January 2011 and January 2015 were included in this analysis. The following data were extracted from the laboratory database: age, gender, and Xpert MTB/RIF culture and smear results. CSF samples for which Xpert/RIF testing was attempted, consisting of 741 samples with 740 valid Xpert MTB/RIF results and 1 test failure, were included in the analysis. Any CSF or central nervous system culture results from the same patient determined within 3 months of the index sample were reviewed. Only aliquots of >500 μl underwent Xpert MTB/RIF testing to ensure sufficient sample volumes for culture. Microscopy was performed at the NMRL if microscopy results were not available from the referring laboratory, and then up to 1.5 ml of the primary sample was centrifuged, and any supernatant in excess of 600 μl was removed and the centrifuged sample was mixed with Cepheid sample reagent. Following incubation for 15 min, 2 ml of the preparation was transferred into an Xpert MTB/RIF cartridge per the manufacturer's instructions. The remaining CSF was inoculated into a Bactec MGIT tube (Becton Dickinson, Oxford, United Kingdom) and Kirchner medium and incubated for 8 weeks.

Sensitivity and specificity data and corresponding 95% confidence intervals (95% CI) were calculated from the Xpert MTB/RIF results using two gold standards: first, comparison with the culture result from the same sample (Table 1); second, comparison with a composite of the culture result from the same sample and any sample collected within 7 days of the index sample (Table 1).
Samples with a positive Xpert MTB/RIF result and a negative culture result were excluded if the patient was receiving antituberculosis treatment at the time of sampling. A total of 740 samples from 698 patients were analyzed. The median of the ages of the patients was 46 years (range, 0 to 93 years), and 59% were male. TBM was confirmed by culture of the primary specimen in 37 of 740 cases (4.5%). Inclusion of a further 8 samples with a contemporary positive result from CSF or central nervous system cultures for M. tuberculosis increased the prevalence to 5.5% in this series. Seven of 740 specimens were smear positive, and 4 were positive by both culture and Xpert MTB/RIF. Of the remaining 3 specimens, all were culture and Xpert MTB/RIF negative for M. tuberculosis; a nontubercular mycobacterium strain was cultured in one case. Based on the Xpert MTB/RIF and culture results from the same sample, the Xpert MTB/RIF sensitivity, specificity, positive predictive value, and negative predictive value were calculated as 54% (95% CI, 38 to 70%), 98% (95% CI, 97 to 99%), 60% (95% CI, 44 to 77%), and 97% (95% CI, 96 to 98%).

Table 2 takes into account contemporary positive culture results for Xpert MTB/RIF-positive samples (n = 5) and for Xpert MTB/RIF-negative samples (n = 3), improving sensitivity to 56% (95% CI, 40 to 70.4%) and specificity to 99% (95% CI, 98 to 99%).

Overall, Xpert MTB/RIF’s sensitivity for detecting M. tuberculosis in CSF was 55%. This is similar to the 59% determined by Nhu et al. in their study of 379 patients with probable TBM (5) and the figure of 62% determined by Patel at al. in their South African study of over 200 predominantly HIV-positive patients (6). However, it is significantly lower than the 85% sensitivity reported in an Italian study that included only 11 M. tuberculosis cases (7). These studies utilized clinical diagnosis as well as culture as the reference standard, reflecting the difficulties in diagnosing M. tuberculosis microbiologically. Unfortunately, clinical and laboratory information, such as cell count data, is rarely provided to the NMRL by the referring hospital, making it impossible to use a composite reference standard such as that proposed by Marais et al. (8). Differences in reference standards make head-to-head comparisons with the other studies difficult.

The Vietnamese study was conducted in a tertiary specialist hospital. An M. tuberculosis case series from the same hospital reported mortality in excess of 30%, possibly reflecting advanced stages of M. tuberculosis disease. Bacillary burden might be higher in advanced cases of M. tuberculosis, resulting in a high sensitivity of laboratory diagnosis. Patel et al. noted lower (42%) Xpert sensitivities in HIV-negative patients with TBM. In contrast, our study included samples from routine clinical practice, drawn from general and specialist hospitals across England. Both the prevalence of M. tuberculosis and the bacillary burden of patients presenting with M. tuberculosis are highly context specific. Differences in the use of centrifugation and in sample volumes might explain the differences in sensitivities of Xpert MTB/RIF seen in different settings: Bahr et al. reported a sensitivity of 72% in comparing Xpert analysis of centrifuged CSF directly with Xpert analysis performed on 2 ml of unprocessed CSF (sensitivity, 28%) and against microscopy and culture (9). Median CSF sample quantities in this Ugandan study were large (6 ml), whereas the NMRL is typically sent quantities of 0.5 to 1 ml.

Culture sensitivity is also a function of sample volume. To address the issue of false-negative culture results that are due to low CSF volumes, this study took account of other culture results determined within 7 days of the sample received for Xpert MTB/RIF testing. It is still possible that low culture volumes and undiscovered TB treatment account for a proportion of Xpert MTB/RIF “false-positive” results. If samples had been submitted with fuller clinical details, including HIV status, imaging findings, and cell counts, we would have been able to employ a more robust reference standard.

A sensitivity of 55% compared to a suboptimal reference standard (culture) is unlikely to impact heavily on clinical decision-making. At best, a positive test result will confirm clinical suspicion and enable a clinician to stop broad-spectrum antibiotics. In settings with a high prevalence of rifampin resistance, Xpert MTB/RIF results may confer some value regarding rpoB mutations. Bahr et al. (9) concluded that a positive culture or Xpert result should be the laboratory diagnostic standard but that a negative Xpert MTB/RIF result should not outweigh a high level of clinical suspicion (10).

REFERENCES


