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LETTER TO THE EDITOR

Xpert MTB/RIF Ultra for Detection of *Mycobacterium tuberculosis* in Cerebrospinal Fluid

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Tuberculous meningitis (TBM) is the most lethal manifestation of tuberculosis and requires rapid diagnosis and initiation of treatment to prevent death and serious neurological disability. The Xpert MTB/RIF assay (Xpert) (Cepheid, USA) is a fully automated nucleic acid amplification test that detects the *Mycobacterium tuberculosis rpoB* gene and associated mutations that confer rifampin resistance. Xpert was approved by the WHO in 2010 for the diagnosis of pulmonary and extrapulmonary tuberculosis (1). The next-generation Xpert MTB/RIF Ultra assay (Xpert Ultra) was approved by the WHO in March 2017 (1). Xpert Ultra includes two additional hybridization targets (IS*6110* and IS*1081* genes), as well as a larger reaction chamber, all of which boost the analytical sensitivity of Xpert Ultra to almost 8 times higher than that of Xpert (2). A number of studies have demonstrated a higher sensitivity of Xpert Ultra compared to that of Xpert for the detection of *M. tuberculosis* in pulmonary specimens (3–7). To date, only one study of the performance of Xpert Ultra for detecting *M. tuberculosis* in cerebrospinal fluid (CSF) has been published (8). The study included CSF samples from 23 HIV-infected patients with probable or definite TBM and reported sensitivities of 70%, 43%, and 43% for Xpert Ultra, Xpert, and mycobacterial culture, respectively.

Xpert Ultra became available at our laboratory in Uganda in October 2017. We have since included Xpert Ultra testing of CSF as part of the routine diagnostic investigation of 11 patients with suspected TBM admitted to the neurology ward of Mulago/Kiruddu National Referral Hospital. Using retrospective routine laboratory data, we present here the CSF results for these 11 patients. All of the patients had computed tomography (CT) imaging of the brain and fulfilled uniform case definition criteria for probable or definite TBM (9). Two patients had HIV infection and were not taking antiretroviral medication. Antituberculosis therapy (ATT) was started on all patients after CSF collection, except that for patient 7, who was started on ATT by the referring hospital 10 days prior to CSF collection. Our laboratory protocol is to apply uncentrifuged and undiluted CSF for Xpert and Xpert Ultra testing as previously described (10). Mycobacterial growth indicator tubes (MGIT) (Bactec MGIT 960; Becton, Dickinson and Company, USA) are inoculated with a CSF volume of 0.8 ml.

All CSF samples showed pleocytosis with lymphocytic predominance and elevated protein levels (>45 mg/dl) (Table 1). Most samples showed reduced glucose levels (<2.2 mmol/liter). Gram stain, Ziehl-Neelsen stain, India ink preparation, and routine bacterial cultures were negative for all samples. Cryptococcal antigen testing was done on CSF samples from patients with positive or unknown HIV 1/2 serology status at the time of lumbar puncture (patients 1, 2, 5, 8, 10, and 11), and all assay results were negative. Xpert Ultra detected *M. tuberculosis* in 7 of the 11 CSF samples (2 low, 2 very

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TABLE 1 CSF results of patients with tuberculous meningitis

Patient	HIV infection	CSF content[a]				Assay result for:		MGIT[b] (no. of days to growth)
		Cells (no. of WBC/μl)	Lymph (%)	Protein (mg/dl)	Glucose (mmol/liter)	Xpert MTB/RIF	Xpert MTB/RIF Ultra	
1	No	100	80	140	0.3	Low	Low	7
2	No	200	85	104	0.9	Low	Low	9
3	No	25	90	423	1.4	Very Low	Very Low	NG
4	No	10	85	178	0.9	Very Low	Trace	13
5	Yes	350	60	334	6.1	ND	Very Low	NG
6	No	50	90	312	0.8	ND	Trace	NG
7	No	25	80	109	0.4	ND	Trace	17
8	No	45	85	89	0.3	ND	ND	12
9	No	10	85	110	3.4	ND	ND	NG
10	Yes	220	75	129	2.1	ND	ND	NG
11	No	100	80	100	1.7	ND	ND	NG

[a]WBC, white blood cell; CSF, cerebrospinal fluid; lymph, lymphocyte.
[b]MGIT, mycobacterial growth indicator tube; ND, not detected; NG, no growth at 6 weeks.

low, and 3 trace). All 4 samples positive by Xpert were positive by Xpert Ultra. Xpert Ultra detected *M. tuberculosis* in 2 samples that were negative by Xpert and MGIT culture and in 1 sample that was negative by Xpert and positive by MGIT culture. Xpert and Xpert Ultra failed to detect *M. tuberculosis* in 1 sample that was positive by MGIT culture. Overall, 5 of the 11 CSF samples were positive by MGIT culture. Given that all patients were clinically ill with meningitis, it is unlikely that the two Xpert Ultra-positive/MGIT-negative samples are false positives. Both patients improved on ATT and were discharged to home. Patient 6 was lost to follow-up, and patient 5 is alive on ATT at 6 months. No rifampin resistance was detected by Xpert, Xpert Ultra, or MGIT culture.

Our observations of a higher rate of detection of *M. tuberculosis* in CSF by Xpert Ultra compared to Xpert and MGIT culture are very similar to the findings of Bahr et al. (8). Notably, the majority of our patients were HIV uninfected. Since we inoculated uncentrifuged CSF, the MGIT culture positivity rate may have been lower than what could have been achieved using the sediment after centrifugation of a large-volume CSF sample. We believe that Xpert Ultra has a very useful role for the rapid detection of *M. tuberculosis* and rifampin resistance in CSF. However, a trace-positive Xpert Ultra result cannot provide drug resistance information (2). *M. tuberculosis* cultures should be performed, at a minimum, on Xpert- and Xpert Ultra-negative CSF samples and on Xpert Ultra-trace-positive CSF samples for *M. tuberculosis* isolation and drug susceptibility testing. Studies with larger numbers of cases are needed to further define the performance of Xpert Ultra for the detection of *M. tuberculosis* in the CSF of patients with suspected TBM, including in those with and without HIV infection and in pediatric patients.

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