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MAJOR ARTICLE

The Impact of GeneXpert Cerebrospinal Fluid Testing on Tuberculous Meningitis Diagnosis in Routine Care in Botswana

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Background. Tuberculous meningitis (TBM) disproportionately impacts high–HIV prevalence, resource-limited settings where diagnosis is challenging. The GeneXpert platform has utility in TBM diagnosis, but uptake remains limited. In Botswana, before the introduction of GeneXpert, tuberculosis (TB) testing was only available through mycobacterial culture at the National TB Reference Laboratory. Data describing routine use of Xpert MTB/RIF for cerebrospinal fluid (CSF) testing in resource-limited settings are scarce.

Methods. Electronic records for patients with CSF tested in government facilities in Botswana between 2016 and 2022 were obtained from a central online repository as part of ongoing national meningitis surveillance. Samples were excluded from 1 site where Xpert MTB/RIF is performed universally. The proportion receiving TB-specific investigation on CSF and the number positive for *Mycobacterium tuberculosis* following increased Xpert MTB/RIF capacity were determined.

Results. The proportion of CSF samples receiving TB-specific investigation increased from 4.5% (58/1288) in 2016 to 29.0% (201/693) in 2022, primarily due to increased analysis with Xpert MTB/RIF from 0.9% (11/1288) to 23.2% (161/693). There was an overall decline in the annual number of CSF samples analyzed, but the proportion with microbiologically confirmed TBM increased from 0.4% to 1.2%. The proportion of samples tested for TB that were collected from health care facilities >100 km from the National TB Reference Laboratory increased with Xpert MTB/RIF rollout from 65.9% (87/132) to 78.0% (494/633).

Conclusions. In Botswana, access to TB culture is challenging in remote populations; more accessible near-patient testing using Xpert MTB/RIF increased the number of patients receiving TB-specific testing on CSF and the number of confirmed TBM cases.

Keywords. TB meningitis; Ultra; Xpert MTB/RIF.

Globally, 1%–5% of people affected by tuberculosis (TB) have tuberculous meningitis (TBM). TBM is often associated with severe immunosuppression, specifically in the context of advanced HIV. Long-term sequelae are frequent, and the mortality of TBM is unacceptably high (up to 50% in adults), remaining unchanged for the past 2 decades [1, 2].

Diagnosis of TBM is difficult due to the paucibacillary nature of disease in cerebrospinal fluid (CSF). Limits of detection differ greatly between smear microscopy (10 000 colony-forming units [CFU]/mL), nuclear acid amplification testing (NAAT) including Xpert MTB/RIF and Xpert MTB/RIF Ultra (20–150 CFU/mL), and mycobacterial culture (1–10 CFU/mL) [3, 4], with sensitivity of smear microscopy, NAAT, and culture for diagnosis of TBM from CSF ranging between 9%–33%, 47%–76%, and 50%–70%, respectively [5, 6]. Time to result from the more sensitive tests is also highly variable. Results from Xpert MTB/RIF are available in 1–2 hours, whereas culture can take up to 6 weeks to yield a result, meaning it cannot inform immediate management decisions. In low-resource settings where the majority of TBM cases occur, diagnosis is further challenged by limited availability of culture and molecular diagnostics. As a result, patients are often empirically treated for TBM based on clinical presentation and CSF protein, glucose, and cell count, frequently resulting in inappropriate

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or unnecessary treatment [7]. Furthermore, in advanced HIV, TBM can present with atypical clinical and CSF findings, potentially delaying recognition of TBM and initiation of treatment [8]. Delayed TBM treatment increases morbidity, adverse neurological sequelae, and mortality.

Easily accessible, rapid, and sensitive diagnostics are essential for improving outcomes from central nervous system infections [9]. Xpert MTB/RIF run on the GeneXpert platform was endorsed by the World Health Organization (WHO) for the diagnosis of pulmonary TB in 2011 following a large multinational clinical validation study [10]. In the 2013 policy update, the WHO made a strong recommendation based on very low-quality evidence that Xpert MTB/RIF should be used in preference to conventional microscopy and culture as the initial diagnostic test for CSF specimens from patients suspected of having TBM [11]. This recommendation was extended to Xpert MTB/RIF Ultra in 2017 [12]. Xpert MTB/RIF, and subsequently Xpert MTB/RIF Ultra, has been rolled out across many countries in Southern Africa including Botswana, where in many places it has replaced smear microscopy as the primary TB diagnostic in the context of pulmonary TB. However, data on its use for diagnosing extrapulmonary TB, especially TBM, are scarce [13–15].

We analyzed 6 years of national data from Botswana, a low-resource, high–HIV prevalence setting, to evaluate the impact of Xpert MTB/RIF rollout on the number of CSF Xpert MTB/RIF examinations, the number of microbiologically confirmed MTB diagnoses, and the characteristics of patients investigated for TBM.

METHODS

The Botswana National Meningitis Survey is an ongoing meningitis surveillance network monitoring trends in the etiology of central nervous system infections in Botswana. Botswana is an upper middle-income county in Southern Africa with an estimated HIV prevalence of 18.6% in adults aged 15–49 and an annual TB incidence of 235 per 100,000 in 2021 [16]. Compared with neighboring countries, Botswana has a relatively robust health care infrastructure, where 85% of the population live within 5 km of a health care facility [17]. Xpert MTB/RIF was initially introduced in Botswana between October 2012 and June 2013 at 13 centers as part of a research study using a stepped-wedge design [18]. Xpert MTB/RIF capacity was subsequently expanded following a donation from the World Bank. Currently 39 health facilities have GeneXpert platforms on site, including all 26 referral, district, and primary hospitals. In Botswana, the use of Xpert MTB/RIF on CSF has been advocated in national HIV/TB guidelines since 2016. Analysis of CSF using Xpert MTB/RIF and, since 2019, Xpert MTB/RIF Ultra was performed in 20 of these hospitals during the study period. Other tests advocated for use on CSF in the 2016 guidelines were microscopy, cell count and differential, CSF biochemistry, India ink stain, TB culture, and extended fungal culture. During the study period, manufacturer guidance for the use of Xpert MTB/RIF on CSF was followed. Data regarding whether the Xpert MTB/RIF or MTB/RIF Ultra was used during the transition period in 2019/2020 were not available; the terminology Xpert MTB/RIF is used throughout the manuscript to denote testing with either version. Culture for *Mycobacterium tuberculosis* is only performed at the National Tuberculosis Reference Laboratory (NTRL) in the capital, Gaborone.

Table 1. Laboratory Standard Procedures for Analysis of Cerebrospinal Fluid [19]

Tests performed on all samples:
• Macroscopic examination
• Total cell count using Neubauer counter
• Centrifugation of CSF at 3000 revolutions per minute for 3 min followed by gram stain, India ink stain, differential count (if CSF white cell count ≥10/mm^3), and culture using the sediment on:
◦ Sabouraud dextrose agar (incubation 10 d)
◦ Sheep blood agar (incubation 72 h)
◦ Chocolate agar (incubation 72 h)
Additional tests performed on all adult CSF samples
• Cryptococcal antigen testing (IMMY Lateral Flow Assay)
Additional tests performed on request:
• Acid-fast bacilli smear
• TB culture on Bactec 960 *Mycobacterium* Growth Indicator Tube (MGIT) automated culture system
• Xpert MTB/RIF Ultra

Abbreviations: CSF, cerebrospinal fluid; TB, tuberculosis.

Institutional review board approval was granted by the Health Research Development Council (HRDC reference number 6/14/1), London School of Hygiene and Tropical Medicine (LSHTM reference number 17322), and the University of Botswana (UB reference number UBR/RES/IRB/1631). This study used only retrospective, routine laboratory data; therefore, a waiver of informed patient consent was obtained.

Laboratory records from all laboratories performing CSF analysis are uploaded to a national electronic health record system termed the Integrated Patient Management System (IPMS). All CSF samples with results stored on IPMS from samples collected between January 1, 2016, and December 31, 2022, were extracted from an online repository in collaboration with the Botswana Ministry of Health and Wellness. The details of the CSF analysis are described in Table 1. Samples from patients admitted to the national referral hospital in Gaborone were excluded from the analysis because universal Xpert MTB/RIF Ultra testing and TB culture of CSF samples were introduced in 2021 as part of a research study. Data on standard CSF evaluation, TB-specific data, and HIV-related data were extracted as separate data sets from the online repository and merged through deterministic linkage of laboratory records using unique patient identifiers, either a 9-digit national identification number or a hospital identification number. Results were then de-duplicated before analysis.

Data were analyzed using STATA, version 16.0. Patient demographics, CSF test results, and HIV-related data were described using frequencies, percentages, or medians and interquartile ranges (IQRs), as appropriate. Clinical and CSF characteristics were compared for those patients who underwent investigation for TBM and those who did not using the Wilcoxon rank-sum test for medians and the chi-square test for proportions. Comparisons were also made between patients who underwent TB investigation before and after the scale-up of Xpert Ultra capacity. The cutoff chosen for this was 2020, when Xpert MTB/RIF consistently became the most commonly used modality for investigating for TBM in Botswana and the more sensitive Xpert MTB/RIF Ultra had replaced the original Xpert MTB/RIF. Maps were made using R, with geospatial data of TB analysis plotted using the tmap package.

Study outcomes were the number and proportion of CSF samples undergoing TB-specific investigations (microscopy, TB culture, or Xpert MTB/RIF) and the number and proportion of positive results from TB-specific investigations. All semiquantitative results from CSF analysis with Xpert MTB/RIF were considered positive.

RESULTS

Between January 1, 2016, and December 31, 2022, a total of 6934 CSF samples were investigated, of which 1114 (16.1%) were investigated using TB-specific investigations: 787 Xpert MTB/RIF, 340 smear microscopies, and 177 mycobacterial cultures (Table 2). Although there was an overall decline in the total number of CSF samples received for analysis during the study period from 1288 in 2016 to 693 in 2022, the number of patients receiving TB-specific analyses increased from 58/1288 (4.5%) in 2016 to 201/693 (29.0%) in 2022, largely due to an increase in Xpert MTB/RIF, which comprised 15.5% of all tests performed in 2016 and 78.1% in 2022 (Figure 1). Although the test positivity rate of mycobacterial culture was highest (8.0%) compared with Xpert MTB/RIF (6.7%) and smear microscopy (1.2%), more samples were tested using Xpert and more microbiologically confirmed TBM diagnoses were made by Xpert MTB/RIF: 53 positive Xpert MTB/RIF tests compared with 14 mycobacterial cultures and 4 positive smears (Table 2).

Patients whose CSF was investigated with a TB-specific investigation had a higher median age (39.1 vs 35.2 years) and higher HIV prevalence (61.3% vs 51.0%) compared with those who did not have TB-specific investigations. The group that had TB-specific investigations also had higher rates of CSF pleocytosis, raised CSF protein >1 mg/mL, and an extraneural sample positive for *M. tuberculosis*.

Laboratory characteristics from patients who underwent TB testing between 2016–2017 and 2020–2022 were compared to assess the impact of scaling up the use of Xpert MTB/RIF on CSF in Botswana. In the group that underwent testing between 2016 and 2017, the proportion of those tested who were HIV positive (70.5%) was higher than in 2020–2022 (58.6%). Among those patients who received testing between 2016 and 2017, there was a higher proportion of patients with a CSF pleocytosis >100 cells/mL and lymphocytic predominance in cellular CSF.

There was significant regional variability in the number of CSF samples submitted for analysis and the proportion that underwent testing with a TB-specific investigation (Figure 2). Hospitals from the 3 largest urban centers in Botswana outside the capital, Francistown, Maun, and Molepolole, submitted the highest proportion of CSF samples for TB-specific investigation, 21.3%–61.3%, 5.4% (43/796) of which were positive. Smaller hospitals tended to send fewer samples and to send a lower proportion of these samples for TB investigation; 8.4% of samples from smaller hospitals received TB testing, with 7.8% (25/320) of these being positive. Samples collected >500 km from NTRL were significantly less likely to receive TB culture than those collected in facilities <500 km from NTRL, 0.4% (4/917) compared with 2.9% (173/6017), and significantly more likely to be analyzed with Xpert MTB/RIF 21.8% (200/917) vs 9.8% (590/6017) (Table 3). The proportion of samples tested for TB that were collected from health care facilities >100 km from NTRL increased with the rollout of Xpert MTB/RIF, from 65.9% (87/132) in 2016–2017 to 78.0% (494/633) in 2020–2022 ($P < .01$) (Table 2).

DISCUSSION

This study, using robust national surveillance data from Botswana, demonstrates relatively low rates of investigation for TBM, even after the introduction of Xpert MTB/RIF testing. Over time, the rollout of Xpert MTB/RIF increased the proportion of CSF samples undergoing investigation with TB-specific tests, and this increased the overall number of microbiologically confirmed TBM diagnoses. Between 2016 and 2022, 16.1% of CSF samples had investigations for TBM, and 13.9% were tested using relatively sensitive cultures and/or Xpert MTB/RIF. In comparison, the cheap, easy-to-use, and widely available CSF cryptococcal antigen lateral flow (CrAg) assay was used on 63.9% of these CSF samples. The difference in cost might inform this discrepancy to some extent. CrAg costs ~$2 and Xpert MTB/RIF Ultra $7.97; therefore, CrAg testing is performed more indiscriminately on CSF samples. However, the major cause of limited TB-specific testing is likely to be due to the small numbers of clinicians initiating investigation for TB. This highlights the potential for expanding diagnostic coverage for TBM if a cheaper, more rapid, easy-to-use, and true point-of-care test for TB becomes available. There are extremely limited data describing the routine use of Xpert MTB/RIF in the context of TBM in resource-limited settings. Botswana is

Table 2. Results of TB-Specific Investigations Performed on CSF Samples in Botswana Between 2016 and 2022

		Microscopy			TB Culture			Successful Xpert MTB/RIF or Xpert MTB/RIF Ultra			Patients With Positive TB-Specific Investigation on CSF		
	Total No. of CSF Samples Analyzed	Total Performed, No.	Negative, No. (%)	Positive, No. (%)	Total Performed, No.	Negative, No. (%)	Positive, No. (%)	Total Performed, No.	Negative, No. (%)	Positive, No. (%)	Total Performed, No.	Negative, No. (%)	Positive, No. (%)
2016	1288	49	48 (98.0)	1 (2.0)	4	3 (75.0)	1 (25.0)	11	8 (72.7)	3 (27.3)	58	53 (91.4)	5 (8.6)
2017	1233	56	56 (100)	0	25	23 (92.0)	2 (8.0)	17	16 (94.1)	1 (5.9)	74	71 (96.0)	3 (4.1)
2018	1123	49	48 (98.0)	1 (2.0)	34	31 (91.2)	3 (8.8)	91	84 (92.3)	7 (7.7)	138	125 (91.9)	11 (8.1)
2019	1057	70	70 (100)	0	40	39 (97.5)	1 (2.5)	137	133 (97.1)	4 (2.9)	211	206 (97.6)	5 (2.4)
2020	869	44	43 (97.7)	1 (2.3)	32	28 (87.5)	4 (12.5)	206	188 (91.3)	18 (8.7)	247	225 (91.1)	22 (8.9)
2021	671	25	25 (100)	0	10	9 (90.0)	1 (10.0)	164	151 (92.1)	13 (7.9)	185	170 (93.4)	14 (7.6)
2022	693	41	40 (97.6)	1 (2.4)	31	29 (93.6)	2 (6.5)	161	154 (95.7)	7 (4.4)	201	193 (96.0)	8 (4.0)
Total	6934	334	330 (98.8)	4 (1.2)	176	162 (92.1)	14 (8.0)	787	734 (93.3)	53 (6.7)	1114	1043 (93.4)	68 (6.1)

Abbreviations: CSF, cerebrospinal fluid; TB, tuberculosis.

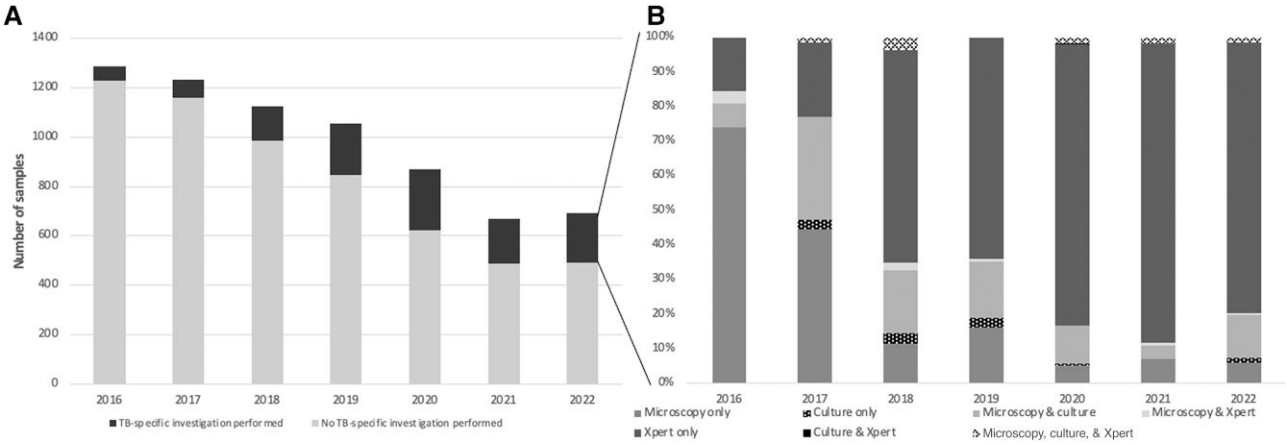

Figure 1. A, Number of CSF samples analyzed each year in Botswana, 2016–2022, with the proportion receiving TB-specific investigation represented in black. Samples from Princess Marina Hospital, Gaborone, were excluded as universal Xpert MTB/RIF Ultra was implemented since 2020. B, Yearly variation of the proportion of TB-specific investigations performed on CSF each year excluding Princess Marina Hospital, Gaborone, 2016–2022. Abbreviations: CSF, cerebrospinal fluid; TB, tuberculosis.

almost uniquely placed to generate these data as a low-resource, high–HIV prevalence Southern African country where routinely collected data are available through electronic health records and patients can be linked through a national identification number.

Previous epidemiological data on adult meningitis etiology in Botswana between 2004 and 2015 reported that cases of TBM only accounted for 1% of all microbiologically confirmed diagnoses nationwide. This contrasted with data from neighboring South Africa, where 25% of adult central nervous system infections were microbiologically confirmed as TBM [8, 20]. While TB incidence in South Africa is more than double that of Botswana, this is unlikely to explain a 25-fold difference in confirmed TBM diagnosis among people presenting with central nervous system infections. A more likely explanation is under investigation for TBM in Botswana as TB culture is only available in the capital, Gaborone, up to 1000 km away from some clinics, and Xpert MTB/RIF was not routinely performed on CSF in 2004–2015.

TB-specific testing was more likely to be performed when clinical features suggestive of TBM such as immunosuppression and pleocytosis were present. However, in the period between 2020 and 2022 there was a trend toward more widespread testing and an increase in test positivity from 6.1% to 7.0%. This suggests that the threshold for clinicians to order TB-specific tests was reduced, likely due to easier access through decentralization of TB testing and more widespread use of Xpert MTB/RIF Ultra, which, unlike culture, can deliver immediate results that influence treatment decisions. TB culture, which was the most sensitive test used for diagnosis of TBM pre–Xpert MTB/RIF, was only performed on 4 CSF samples collected >500 km from NTRL in the 7 years of observation, indicating access barriers. While we have focused on the impact of Xpert MTB/RIF, TB culture remains a key component of investigation for TB meningitis. Sensitivity estimates are higher than Xpert MTB/RIF Ultra, and culture can provide information on antimicrobial susceptibility. However, limited CSF volumes often restrict multiple analyses, and rapid tests that can immediately inform clinician decision-making are often prioritized.

The total number of CSF samples submitted for analysis annually declined during the study period, from 1288 in 2016 to 693 in 2022. A plausible explanation for this is improved antiretroviral therapy (ART) coverage, reducing the number of presentations with suspected central nervous system infections. Botswana is a leader in ART programming in Africa. It was the first African country to offer free ART to its citizens and has recently become one of the first countries globally to surpass the UNAIDS 95–95–95 targets, with recent data demonstrating a decline in the number of cryptococcal meningitis cases [21].

This study has several limitations. Detailed individual patient-level data were not available, including data on changes to management from the results of TB-specific investigations. Some patients may have already been treated empirically when results became available, and therefore the impact of test positivity on management is not known. While this study was not designed to report TBM incidence in Botswana but rather to describe the changes in TB-specific investigation following the rollout of Xpert MTB/RIF, the frequency of TBM diagnosis is likely underestimated in our study for several reasons. First, electronic data capture was not complete due to unreliable internet connectivity and power interruptions, and during these periods results were disseminated locally on paper. These paper records were not captured as part of this analysis, and triangulation against other reliable datasets

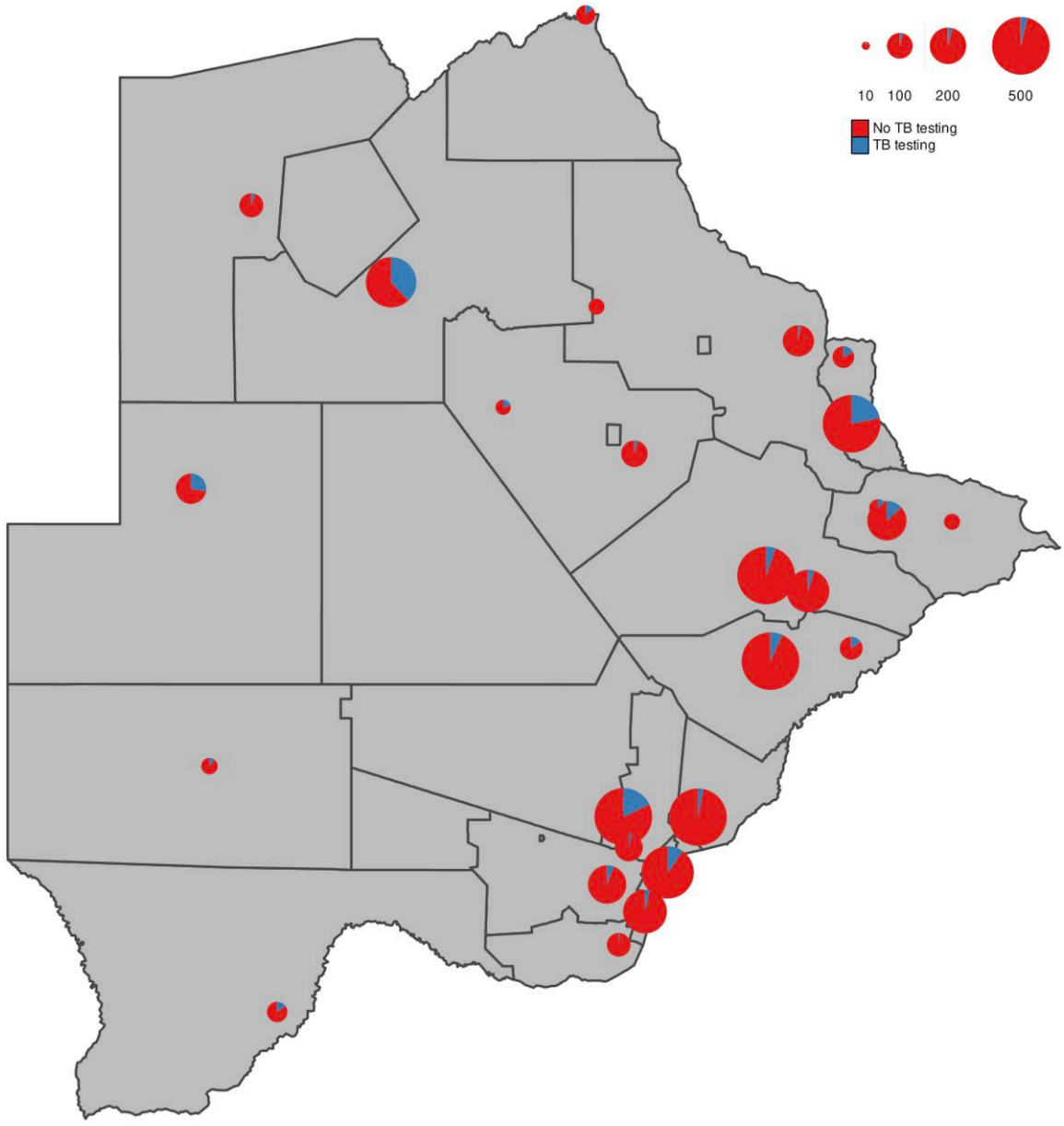

Figure 2. Geospatial size and frequency representation of the number of CSF samples analyzed in government health care facilities in Botswana and the proportion that undergo TB testing in Botswana. Abbreviations: CSF, cerebrospinal fluid; TB, tuberculosis.

demonstrated that they accounted for up to 10% of all laboratory records. Private hospitals and 1 hospital linked to a mining development do not upload data to the electronic IPMS, and data from these sites were not captured. We also are unable to comment on any intersite variation regarding pre-analytical processing of CSF that may have impacted the yield of Xpert MTB/RIF such as sample volume or prior centrifugation.

In addition to potential missed diagnoses resulting from our study methodology including only electronic records, all currently available TBM investigations have imperfect sensitivity, and furthermore a significant proportion of patients will never receive any TB-specific investigation for TBM. As such, TBM case frequency will be markedly under-reported, and due to limited clinical data in our data set, we were unable to reliably utilize uniform clinical case definitions for TBM to attempt to correct for this.

Despite some encouraging trends toward increased testing for TBM in patients presenting with suspected central nervous system infections, the rates of investigation remain comparatively low despite excellent Xpert MTB/RIF availability. This study demonstrates that the introduction of decentralized rapid molecular testing for TBM with relatively modest sensitivity increased the rate of TB-specific investigations and the number of

Table 3. (1) Comparison of Laboratory Data of Patients who Underwent Investigation for Suspected TBM With TB-Specific Investigations and Those who Did Not; (2) Comparison of Patients who Received TB Testing Before and After the Widespread Rollout of Xpert MTB/RIF and Xpert MTB/RIF Ultra

	Total (n = 6934), % (No.)	Did Not Receive TB Testing (n = 5820), % (No.)	Received TB Testing (n = 1114), % (No.)	*P* Value	Samples Analyzed With TB-Specific Investigations in Early Xpert MTB/RIF Rollout Period (n = 132), % (No.)	Samples Analyzed With TB-Specific Investigations in Late Xpert MTB/RIF Rollout Period (n = 633), % (No.)	*P* Value
Age, median (IQR), y	36.1 (19.6–46.0)	35.2 (15.6–45.6)	39.1 (29.3–48.3)	<.01	38.4 (31.7–45.1)	39.9 (29.1–47.8)	.63
Female	45.3 (3137)	45.3 (2634)	45.2 (503)	.94	44.7 (59)	42.3 (268)	.62
HIV-positive	52.7 (3651)	51.0 (2968)	61.3 (683)	<.01	70.5 (93)	58.6 (371)	.01
CD4, median (IQR),[a] cells/μL	204 (58–455)	207 (58–458)	196 (53–421)	.21	163 (47–400)	202 (53–456)	.33
CD4 <200 cells/μL (if CD4 known)	49.,4 (1515)	50.9 (1227)	50.6 (288)	.51	55.4 (46)	49.8 (149)	.37
CSF WCC >10 cells/mm^3 (if CSF WCC known)[b]	20.9 (1097)	20.1 (880)	24.8 (217)	<.01	29.4 (30)	24.4 (120)	.29
CSF WCC >100 cells/mm^3 (if CSF WCC known)[b]	9.5 (499)	9.2 (405)	10.7 (94)	.17	17.7 (19)	10.4 (51)	.04
Lymphocytic pleocytosis	36.8 (313)	37.2 (250)	35.6 (63)	.70	41.7 (150)	31.5 (79)	.01
CSF protein, median (IQR),[c] mg/mL	0.65 (0.31–1.59)	.63 (0.30–1.50)	0.75 (0.36–1.80)	<.01	1.31 (0.41–3.48)	0.81 (0.35–1.80)	.28
CSF protein >1 mg/mL (if CSF protein known)	35.9 (584)	34.4 (463)	43.4 (121)	<.01	53.9 (14)	41.9 (129)	.26
CSF glucose, median (IQR),[d] mmol/L	3.36 (2.42–4.23)	3.38 (2.46–4.24)	3.24 (2.35–4.13)	.14	3.09 (2.05–3.77)	3.37 (2.35–4.32)	.06
CSF glucose <2.2 mmol/L (if CSF glucose known)	20.8 (749)	20.7 (604)	21.6 (145)	.60	26.0 (19)	21.4 (82)	.38
Extraneural sample with *M.Tb* detected in last 3 mo[e]	1.7 (115)	1.5 (88)	2.4 (27)	.03	2.3 (3)	2.8 (18)	.72
Distance >100 km from sample collection site to TB culture facility (National TB Reference Laboratory)	66.2 (4590)	64.9 (3775)	73.2 (815)	<.01	65.9 (87)	78.0 (494)	<.01

Abbreviations: CSF, cerebrospinal fluid; IQR, interquartile range; TB, tuberculosis; TBM, tuberculous meningitis; WCC, white cell count.

[a]CD4 count was unknown in 55.7% (3865/6934) of patients overall, in 57.0% (3320/5820) of those who did not have TB testing, and in 48.9% (545/1114) of those who did ($P < .01$). Among those who had TB testing, CD4 count was unknown in 37.1% (49/132) of those who had TB testing in 2016–2017 and 52.7% (334/633) of those who had testing in 2020–2022 ($P < .01$).

[b]CSF WCC was unknown in 24.3% (1677/6934) of patients overall, in 24.7% (1439/5820) of those who did not have TB testing, and in 21.4% (238/1114) of those who did ($P = .06$). Among those who had TB testing, CSF WCC was unknown in 22.7% (30/132) of those who had TB testing in 2016–2017 and 22.4% (142/633) of those who had testing in 2020–2022 ($P = .68$).

[c]CSF protein was unknown in 76.6% (5308/6934) of patients overall, in 76.9% (4473/5820) of those who did not have TB testing, and in 75.0% (835/1114) of those who did ($P = .42$). Among those who had TB testing, CSF protein was unknown in 80.3% (106/132) of those who had TB testing in 2016–2017 and 76.9% (504/633) of those who had testing in 2020–2022 ($P = .86$).

[d]CSF glucose was unknown in 48.1% (3338/6934) of patients overall, in 49.8% (2896/5820) of those who did not have TB testing, and in 39.7% (442/1114) of those who did ($P < .01$). Among those who had TB testing, CSF glucose was unknown in 44.7% (59/132) of those who had TB testing in 2016–2017 and 39.3% (249/633) of those who had testing in 2020–2022 ($P = .25$).

[e]The source of the extraneural sample was sputum in 69.6% (80/115), gastric aspirate in 11.1% (13/115), pleural fluid in 1.7% (2/115), pus in 1.7% (2/115), and unknown in 11.3% (18/115).

microbiologically confirmed TBM diagnoses. Whether the increase in diagnoses translates into improved patient outcomes is currently unknown.

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