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Xpert Ultra's place in the diagnosis of tuberculous meningitis – Authors' reply

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In response to our study on the performance of GeneXpert MTB/Rif Ultra (Ultra) for diagnosis of TB meningitis,[1] Singh and Sankar reported their experience using low volume CSF.[2] In addition, Boyles discussed his group's prior work on thresholds of disease likelihood above which treatment should be started for TB meningitis and adapted it to Ultra using our data. He reports Ultra is likely to be more useful in ruling out TB meningitis in a broader range of patients than was GeneXpert MTB/Rif (Xpert).

Understanding how best use Ultra will be crucial to harnessing the potential of this new test for diagnosis of TB meningitis and understanding effect on clinical outcomes. Proper utilization of a low volume CSF to maximize diagnostic yield in meningitis is an important question requiring further research. We applaud Singh and Sankar's efforts to contribute to this field and hope to see full publication of their findings. Our study used large volumes of centrifuged CSF whenever possible in order to maximize yield based on published experience and the assays' analytical sensitivity.[3–5]

Molecular or microbiologic tests for TB meningitis, a pauci-bacillary disease, must have a low limit of detection. Analytical sensitivity thresholds of MGIT culture, Ultra, and Xpert are ~10, ~15, and 100 CFU/mL, respectively. Molecular tests are more rapid than culture and detect non-viable bacilli. although none of these tests alone have adequate sensitivity to rule-out TB meningitis[1,4–6] In our prior systematic evaluation of the effect of CSF volume on Xpert performance, centrifuging CSF (median volume 6mL, IQR 4–10mL) improved sensitivity to 72% versus 28% for 2mL uncentrifuged CSF[5]. Patel and colleagues reported

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similar findings.[4] CSF concentration puts a larger number of bacilli into a fixed volume, allowing the limit of detection to be reached more easily.

Yet, Singh and Sankar's efforts reflect a common problem of inadequate available CSF volume. In devising an algorithm, assays with poor sensitivity (AFB smear, Lowenstein-Jensen culture) should not be used if more sensitive alternatives are available. Limiting the use of such tests means that a higher proportion of the bacilli present are available for detection by more sensitive assays.

Dr. Boyles proposes a four-stage approach to determine the clinical benefit of Ultra for diagnosis of TB meningitis centered around the use of clinical prediction rules and clinical decision thresholds translated to easy to use tools for clinicians which could be studied for effect. We applaud Dr. Boyles' thoughtful approach to determining the benefit of Ultra in a real-world clinical context and agree that his approach has excellent potential.

While we acknowledge obtaining large volume CSF is not always possible – multiple studies have supported the idea that obtaining larger CSF volumes should be the goal for maximal detection of TB meningitis.[1,4,5] More research on diagnostic algorithms in a variety of geographic settings and populations is needed, such work would inform Dr. Boyles' efforts to determine clinical benefit of Ultra.

References

1. Bahr NC, Nuwagira E, Evans EE, et al. Diagnostic accuracy of Xpert MTB/RIF Ultra for tuberculous meningitis in HIV-infected adults: a prospective cohort study. Lancet Infect Dis 2017.
2. Singh S, Sankar MM. Diagnostic algorithm for low-volume CSF samples in tuberculous meningitis. Lancet Infect Dis 2017; 17(12): 1236–7. [PubMed: 29173879]
3. Chakravorty S, Simmons AM, Rowneki M, et al. The New Xpert MTB/RIF Ultra: Improving Detection of Mycobacterium tuberculosis and Resistance to Rifampin in an Assay Suitable for Point-of-Care Testing. MBio 2017; 8(4).
4. Patel VB, Theron G, Lenders L, et al. Diagnostic accuracy of quantitative PCR (Xpert MTB/RIF) for tuberculous meningitis in a high burden setting: a prospective study. PLoS Med 2013; 10(10): e1001536. [PubMed: 24167451]
5. Bahr NC, Tugume L, Rajasingham R, et al. Improved diagnostic sensitivity for tuberculous meningitis with Xpert((R)) MTB/RIF of centrifuged CSF. Int J Tuberc Lung Dis 2015; 19(10): 1209–15. [PubMed: 26459535]
6. Bahr NC, Marais S, Caws M, et al. GeneXpert MTB/Rif to Diagnose Tuberculous Meningitis: Perhaps the First Test but not the Last. Clin Infect Dis 2016; 62(9): 1133–5. [PubMed: 26966284]