A novel bedside rule-in test for tuberculous meningitis in HIV-infected adults

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Tuberculous meningitis (TBM) likely affects more than 100,000 people per year [1]. While this represents approximately 1% of all TB cases, TBM is disproportionately important because it kills or severely disables half of those affected. [2] Major risk factors for TBM are young age [3] and HIV infection.

Diagnosis of TBM is a challenge because clinical features are non-specific, laboratory tests are insensitive and mycobacterial culture is too slow to have meaningful clinical impact. Treatment delay is the strongest risk factor for death [2]; sensitive diagnostics with short turnaround times are urgently needed. Rapid nucleic acid amplification tests, such as Xpert MTB/RIF Ultra (Ultra) have shown good sensitivity (77%) against culture-confirmed TBM [4], but require large cerebrospinal fluid (CSF) volumes [5] and are not yet widely available, particularly close to the point of care in many high burden countries. [6]

In this edition of Clinical Infectious Diseases, Quinn and colleagues [7] present encouraging first results for a new point of care lateral flow assay, Fujifilm SILVAMP TB LAM assay (FujiLAM), for the diagnosis of TBM in adults, most of who were HIV-infected. FujiLAM testing takes 60 minutes, requires 0.2 mL of sample and does not require an instrument [8,9]. While FujiLAM was originally designed for testing urine, it is biologically plausible, as demonstrated here, that mycobacterial lipoarabinomannan (LAM) is present in CSF, however it was unclear whether the test would have useful sensitivity for TBM, or whether sample pre-treatment would be required for CSF.

Several findings are striking. FujiLAM had the same sensitivity as mycobacterial culture (79%), when compared with a microbiological reference standard (culture plus Ultra) in the subset of patients with all three tests. When compared with a reference standard of microbiologically confirmed plus clinically probable TBM, sensitivity of FujiLAM was 52%, nearly as high as that of Ultra (55%). FujiLAM was more likely to be positive in patients with high bacterial burden in CSF, as assessed by
Ultra semi-quantitative result, and in patients with advanced HIV infection and higher mortality, in keeping with previous studies based on urine samples from patients with pulmonary TB. [10,11] The authors also tested CSF with an earlier LAM assay, Alere Determine TB LAM, but sensitivity was significantly lower.

On the other hand, FujiLAM failed to detect 26% of cases with microbiologically-confirmed TBM which precludes its use as a rule-out test. As an illustration, a patient in the study by Quinn and colleagues, after initial clinical assessment and after ruling-out cryptococcal meningitis, had a 57% probability of TB. If the FujiLAM test was negative, then the probability that this patient had TBM was still 40% (Figure 1). Whilst there was incremental benefit from testing with both FujiLAM and Ultra, even this combination could not be used to rule out TBM in a population with a high pre-test probability. Early initiation of empiric treatment, based on clinical and radiological evaluation, will likely continue to be necessary for patients at high risk of TBM, including those with negative rapid microbiological tests. [12]

In contrast, since FujiLAM had excellent specificity, the likelihood that a patient in this population had TBM if the FujiLAM test was positive, increased from 57% to 97%, high enough to justify immediate initiation of treatment for TBM (Figure 1). Using the reference standard of microbiologically confirmed plus clinically probable TBM, only one false-positive FujiLAM test was identified, in a patient with non-tuberculous mycobacterial (NTM) meningitis. Whilst NTM meningitis is rare [13], clinicians should be aware of the possibility of false-positive results due to this cause.

The prospective study design and use of consensus case definitions for TBM are strengths of this study. However, the interpretation of the results of this manuscript are complicated by the inconsistent use of reference and index tests for CSF samples (due to insufficient CSF volume). The inability to do reference (Ultra and culture) and index (FujiLAM and AlereLAM) tests on all CSF
samples may have led to underestimation of the specificity of FujiLAM. Importantly, many patients were excluded from testing (including 326 patients with positive cryptococcal antigen tests and 160 with inadequate samples). Since cryptococcal and tuberculous meningitis may co-occur [14], the accuracy of FujiLAM in patients with cryptococcal meningitis requires investigation.

The authors identified that faint bands on the FujiLAM lateral flow test were the major source of inter-reader disagreement. Further work is required to investigate whether faint lines may result in difficulty in interpretation when the test is done by minimally trained users and in decentralized settings with different lighting conditions. There may be value in exploring the use of low-complexity strip readers (such as those used for glucose measurement) to deal with this concern. Additional studies are also needed to evaluate test accuracy with larger sample sizes as well as in children and in HIV-uninfected adults.

Several recent research reports [10,15–20] indicate that lower detection limits for LAM will translate into even higher diagnostic sensitivity and the development of next-generation point-of-care LAM assays should be prioritized. The key challenges in the development of such LAM point of care tests are to reach a high analytical sensitivity while keeping the test user-friendly, affordable, and at the same time highly specific. [21]

Rapid intervention with appropriate therapy is key to improving outcomes in TBM. For the first time, a true rapid point of care assay holds promise for bedside diagnosis of this infection. If clinical utility of FujiLAM can be demonstrated, the global health community should ensure commercial availability of FujiLAM at affordable cost.
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Potential conflicts of interest

T. B. reports a patent pending in the field of lipoarabinomannan detection and is a shareholder of Avelo Ltd and was previously employed by FIND. T.B. reports personal fees from Avelo Ltd outside the submitted work. M.P.N. has received grant funding to his institution to support studies of FujiLAM in adults with tuberculosis.
References:


Figure Legend

**Figure 1**: Fagan Nomogram illustrating pre-test TBM probability in the study population and post-test TBM probabilities for a positive FujiLAM (red) and negative FujiLAM (green) result.