Comment

Diagnostic tests for tuberculous meningitis

Tuberculous meningitis is the most serious manifestation of tuberculosis, with mortality in approximately 50% of HIV co-infected people.[1] A major factor contributing to the poor outcome of tuberculous meningitis is delayed diagnosis due to a lack of rapid, accurate diagnostic tests. Until recently, these tests were restricted to smear microscopy of cerebrospinal fluid (CSF) and microbiological culture. The former tends operationally to be of low sensitivity and the latter often renders a result too late to be clinically meaningful. The diagnosis of drug-resistant disease presents further difficulties.

Around a decade ago, the advent of a semi-automated nucleic acid amplification test for tuberculosis (Xpert TB/RIF, or Xpert), which relies on a single copy gene to ascertain *Mycobacterium tuberculosis*, was widely hailed as an advance, and in 2015, WHO recommended this test be used in the evaluation of tuberculous meningitis.[2] However, performance of Xpert for this indication is variable, with sensitivity to detect microbiologically confirmed tuberculous meningitis ranging from 45% to 67%, making it unsuitable as a rule-out diagnostic test.[3,4] However, sensitivity of this test to detect tuberculosis has been advanced by the introduction of Xpert MTB/RIF Ultra (Xpert Ultra), whose amplification targets are repetitive genomic sequences. This could be an important advance in the diagnosis of tuberculous meningitis.

In *The Lancet Infectious Diseases*, two studies investigating performance of Xpert Ultra in tuberculous meningitis are presented. Fiona Cresswell and colleagues[5] report a prospective study comparing the performance of Xpert Ultra, Xpert, and mycobacteria growth indicator tube (MGIT) culture against a published case definition and composite reference standard in patients with HIV-associated tuberculous meningitis in Uganda. Consistent with preliminary work from the same group,[3] the study infers that Xpert Ultra has significantly higher sensitivity than Xpert or MGIT culture when compared against the uniform case definition, and significantly higher sensitivity than Xpert when compared against the composite biological reference standard. Joseph Donovan and colleagues[6] present data from a randomised diagnostic study comparing Xpert and Xpert Ultra in HIV-infected and HIV-uninfected patients with tuberculous

meningitis in Vietnam, showing that sensitivity of Xpert Ultra was not superior to Xpert when compared against the published case definition.

The cerebrospinal bacillary load in tuberculous meningitis rarely exceeds 100–1000 colonies per mL. Thus, results of diagnostic tests that rely on detection of *M tuberculosis* are influenced by the volume, and preparation, of CSF taken, with diagnostic yields increasing with higher volume removed and whether concentration techniques have been applied.[7] In Cresswell and colleagues' study,[5] a median volume of 8 mL (IQR 5–11) of CSF was centrifuged and the resuspended cell pellet divided into four 0·5 mL aliquots, three of which were used in Xpert Ultra, Xpert, and culture. In Donovan and colleagues' study,[6] 6 mL of CSF was collected, centrifuged, and tested by either Xpert or Xpert Ultra using 0·2 mL of resuspended pellet, Ziehl-Neelsen smear (0·1 mL), and MGIT (0·2 mL). Given that Xpert Ultra relies on a multigene copy, it is unsurprising that the test would exhibit greater sensitivity than Xpert with equivalent volumes of CSF. The higher sensitivity against a clinical reference standard in Uganda[5] might be explained by a higher volume of CSF used for testing. In Uganda, all participants were HIV co-infected,[5] compared with 31 in Vietnam (17 [26%] of 65 tested by Xpert Ultra and 14 [23%] of 62 tested by Xpert).[6] In HIV co-infection, CSF bacterial count tends to exceed that of HIV-uninfected patients; this might account for differences in diagnostic performance. The type of tuberculosis strain in different locations might also affect the sensitivity of Xpert Ultra; in Vietnam, lineage 2 is most prevalent, whereas in Uganda, strains of lineage 4 predominate. Given that Xpert Ultra relies on detection of IS*6110* and IS*1081* insertion sequences, the numbers of which vary between strains, this might influence geographical variation. Standardisation of volume and processing of CSF in studies comparing performance of Xpert Ultra against other tests in different settings might be advantageous and will go some way to ensuring that results yielded represent actual differences in respective clinical utility of Xpert Ultra rather differences in sampling technique.

In the Ugandan study,[5] performance of Xpert Ultra was compared with a composite reference standard that included Ziehl–Neelsen staining of acid-fast bacilli, Xpert, Xpert Ultra, or MGIT culture. Ziehl–Neelsen

staining is the most widely available and simple test for tuberculous meningitis diagnosis, but its sensitivity also varies remarkably by geographical location. In Vietnam, the sensitivity of smear was 87·5% (95% CI 79·0–92·9) in patients with definite or probable tuberculous meningitis.[6] This parameter was not reported in Cresswell and colleagues' study, but sensitivity in the same setting has been previously found to be 24%.[8] A comparison of new diagnostic tests against varying composites could contribute to observed differences in performance of Xpert Ultra in different populations. In Uganda, only when more than 4 mL CSF was available were all three components of the microbiological composite assessed; a sensitivity analysis to understand the influence of each of these and their effect on the sensitivity of Xpert Ultra would have been interesting. The exceptional diagnostic performance of smear microscopy in Vietnam has been a consistent feature of studies from this group and cannot be achieved elsewhere—could sharing of technical expertise improve performance of Ziehl–Neelsen staining across different populations?

Despite these differences and limitations, these studies suggest that rapid and accurate diagnostics for tuberculous meningitis are gradually improving. Nothing, however, can be concluded from either study regarding the ability of Xpert Ultra to diagnose drug-resistant tuberculous meningitis: in Uganda, no drug sensitivity testing was done and all results available from Xpert Ultra were indeterminate, whereas in Vietnam, drug resistance testing was done but did not form part of the STARD checklist. Multidrug-resistant tuberculous meningitis has a very poor prognosis that can only feasibly be ameliorated by tailored therapy; rapid drug sensitivity testing must, therefore, be considered a vital function of tuberculous meningitis diagnostic tests. Novel discovery technologies, such as metagenomic sequencing and mass spectroscopy, might uncover diagnostic biomarkers. Whatever the approach, the quest for rapid diagnostics would benefit from a standardised, cross-disciplinary, and collaborative approach to ensure the journey itself is a speedy one.

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What is the best regimen to treat latent tuberculosis infection?

The adequate management of people with latent tuberculosis infection is necessary to ensure a clinical benefit to the individual as well as achieve a public health result: reduce tuberculosis incidence and render tuberculosis elimination an achievable goal.[1,2] Despite the efforts of WHO and other stakeholders, the current technology renders latent tuberculosis infection identification and treatment an endeavour difficult to implement in resource-limited settings because of differing priorities and resources.[2]

Currently, latent tuberculosis infection diagnosis is primarily done through contact tracing and screening of groups that are high risk (ie, screening before start of anti-tumour necrosis factor treatment, pre-transplant, and screening of migrant or health-care workers). Additionally diagnostic tests are used, such as the Mantoux or