RESEARCH ARTICLE
Can improved diagnostics reduce mortality from Tuberculous meningitis? Findings from a 6.5-year cohort in Uganda [version 1; referees: 1 approved with reservations]

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Abstract

Background: Tuberculous meningitis (TBM) is the second most common cause of meningitis in sub-Saharan Africa and is notoriously difficult to diagnose. We describe the impact of improved TBM diagnostics over 6.5 years at two Ugandan referral hospitals.

Methods: Cohort one received cerebrospinal fluid (CSF) smear microscopy only (2010-2013). Cohort two received smear microscopy and Xpert MTB/Rif (Xpert) on 1ml unprocessed CSF at physician discretion (2011-2013). Cohort three received smear microscopy, routine liquid-media culture and Xpert on large volume centrifuged CSF (2013-2017) for all meningitis suspects with a negative CSF cryptococcal antigen. We compared rates of microbiologically confirmed TBM and hospital outcomes over time.

Results: 1672 HIV-infected adults presenting with suspected meningitis underwent lumbar puncture, of which 33% (558/1672) had negative CSF cryptococcal antigen and 12% (195/1672) were treated for TB meningitis. Over the study period, microbiological confirmation of TBM increased from 3% to 41% (P<0.01) and there was a decline in in-hospital mortality from 57% to 41% (P=0.27) amongst those with a known outcome. Adjusting for definite TBM diagnosis and antiretroviral therapy use, and using imputed data, assuming 50% of those with an unknown outcome died, the odds of dying were nearly twice as high in cohort one (adjusted odds ratio 1.7, 95% CI 0.7 to 4.4) compared to cohort three. Sensitivity of Xpert was 63% (38/60) and culture...
was 65% (39/60) against a composite reference standard.

**Conclusions:** As TBM diagnostics have improved, microbiologically-confirmed TBM diagnoses have increased and in-hospital mortality has declined. Yet, mortality due to TB meningitis remains unacceptably high and further measures are needed to improve outcomes from TBM in Uganda.

**Keywords**
Tuberculous meningitis, TBM, HIV, diagnosis, outcomes

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Introduction
Tuberculous meningitis (TBM) is the second most common cause of adult meningitis in sub-Saharan Africa, accounting for one to five percent of the 10.4 million tuberculosis (TB) cases reported worldwide in 2016. Despite treatment, TBM outcomes are poor with 19–28% mortality in HIV-uninfected persons and 40–67% mortality in HIV-infected patients in addition to long-term disability which is frequent among survivors.

Insidious symptom onset in persons with TBM leads to delay in seeking care and increasing disease severity at presentation correlates with higher mortality. Further, the paucibacillary nature of TBM increases the difficulty in confirming diagnosis once care is sought, also contributing to high mortality. Cerebrospinal fluid (CSF) smear microscopy for acid-fast bacilli (AFB smear) has poor sensitivity (~10–20%) in routine practice. Culture has improved sensitivity (~50–60%) but is not widely available in many resource constrained settings and commonly takes at least 2–3 weeks for liquid culture growth, which is too slow to guide decision-making at the time of presentation.

In 2013, the World Health Organization endorsed the Xpert MTB/RIF (Xpert) assay (Cepheid, Sunnyvale, California, USA), a cartridge-based, polymerase chain reaction assay with a run time of 113 minutes, as the preferred initial test to investigate TB meningitis on the basis of a meta-analysis of 13 studies. Of the two major studies included in the meta-analysis, Patel and colleagues reported 67% sensitivity against microbiologically proven TBM and 36% against consensus clinical case definitions, while Nhu and colleagues showed 59% sensitivity against the same case definitions. Additionally, use of a larger volume of centrifuged CSF improves sensitivity of Xpert. Yet, inadequate negative predictive value means that Xpert cannot substitute for clinical judgement.

There is evidence that use of Xpert for diagnosis of pulmonary TB reduces diagnostic delay, increases the rate of same day treatment, and decreases usage of empiric treatment. However for pulmonary TB, Xpert has not been shown to decrease mortality. Yet, lessening diagnostic delay in persons with TBM may be more likely to lead to improved outcomes as compared to pulmonary TB given the higher early mortality of TBM. Whether routine use of Xpert for investigation of suspected TBM has made an impact on mortality has not yet been investigated.

Herein we describe TBM diagnosis and outcomes over a 6.5-year period in prospective cohorts at two Ugandan referral hospitals.

Methods
Study population
Adults presenting with symptoms of meningitis to Mulago National Referral Hospital, Kampala, and Mbarara Regional Referral Hospital, Mbarara, Uganda were assessed for eligibility for enrollment in two consecutive clinical trials investigating cryptococcal meningitis (www.clinicaltrials.gov; NCT01075152 – Cryptococcal Optimal Antiretroviral Timing, NCT01802385 – Adjunctive Sertraline for the Treatment of Cryptococcal Meningitis) beginning November 22, 2010. Patient screening continued until 28th May 2017. Baseline demographics, clinical and outcome data on all screened patients were routinely collected as part of the screening process. Any patient who received testing for TBM was eligible to be included in this study.

Microbiologically proven (definite) TB meningitis was defined as any positive AFB smear, culture or Xpert result from CSF testing. Consensus uniform case definitions were used to categorise patients as definite, probable, possible or not TBM. In addition to the consensus case definitions, clinical TBM was defined as subjects without a positive microbiologic result, but who were treated empirically for TB treatment due to high clinical suspicion. TB treatment included 12 months of antituberculous therapy with 6–8 weeks of adjunctive corticosteroids as per Ugandan guidelines.

Cohort definitions and diagnostic tests used
Cohort one (16th November 2010 until 28th May 2013) received only CSF AFB smear testing (Figure 1). If available, 1mL cryopreserved CSF was later tested with Xpert MTB/Rif when Xpert became available. Cohort two (1st April 2011 until 10th November 2013) underwent CSF AFB smear and Xpert MTB/Rif on a 1mL sample of uncentrifuged CSF. Testing was performed at physician discretion when there was lymphocytic pleocytosis and/or high degree of clinical suspicion. In the period of overlap of cohort one and two (April 2011–May 2013), Xpert testing was not being done on a routine basis; subjects were included in cohort two when Xpert was done in real-time and in cohort one if Xpert was not done, or only done at a later date on cryopreserved specimens.

In cohort three (11th November 2013 until 28th May 2017) all cryptococcal antigen negative (IMMY, Norman, Oklahoma, USA) patients were systematically investigated for the presence of TB meningitis, irrespective of physician discretion. Subjects had comprehensive testing for TB with CSF AFB smear (Mulago Hospital only), Xpert MTB/Rif on large volume centrifuged CSF and CSF Mycobacteria Growth Inhibitor Tube culture (MGIT, Becton Dickinson, Franklin Lakes, USA). AFB smear was discontinued in Mbarara in 2013 as the sensitivity was deemed too low to justify further use. In patients with a confirmed diagnosis of cryptococcal meningitis (CM), if TBM co-infection was suspected, patients would be investigated for TBM at the physician’s discretion.

Assessment of outcome
In-hospital outcome was determined from case report forms, hospital medical records or follow-up telephone calls with the patient or their surrogate where hospital outcome was unknown. The outcome was categorised as discharged alive, deceased prior to hospital discharge or unknown (i.e. self-discharged against medical advice in an imminently terminal patient, hospital outcome undetermined, transferred to another facility).

Statistical methods
Comparisons of categorical and continuous demographic and clinical characteristics by cohort were performed using Fisher’s
exact tests and Kruskal-Wallis tests, respectively. Sensitivity of Xpert MTB/Rif was evaluated against a *composite reference standard* (any positive CSF test - AFB smear, Xpert or culture i.e. definite TBM according to the uniform case definition)

A separate analysis was conducted against the *uniform case definition* of probable or definite TBM. Concordance between Xpert MTB/Rif and culture was evaluated with a kappa statistic and McNemar’s test. Invalid tests (e.g. culture contamination, Xpert error) were counted as negative results. Mortality was first compared by cohort for participants with a known outcome using Fisher’s exact test. Data for patients with unknown outcome was imputed to assume first that 50% within each cohort died, or that 75% died (both within the expected mortality range for this population). Odds ratios and 95% confidence intervals were computed from multivariable logistic regression models with these imputed data, adjusted for 1) ART status, and 2) ART status and definite TBM diagnosis. Imputations were repeated with new random assignments to confirm results. Analyses were conducted using SAS version 9.4 (The SAS Institute, Cary, NC) and p-values <0.05 were considered statistically significant.

**Ethics**

Institutional review board approvals for the studies were obtained locally in Uganda [ASTRO: Mulago Hospital Research Ethics Committee (approval number, MREC 429); COAF: Makerere University School of Medicine Research and Ethics Committee (approval number, REC Ref No. 2009–022)], from the University of Minnesota (USA), and by the Uganda National Council of Science and Technology Written informed consent for screening or participation in the studies was obtained from all participants or from their surrogates (e.g. family member or guardian) where the patient had altered mental status and did not have the capacity to provide consent.

**Results**

**Participant characteristics**

Over the study period, 1672 patients with meningitis symptoms were assessed and underwent lumbar puncture: 1058 (63%) had a positive CSF cryptococcal antigen test, 558 (33%) had negative CSF cryptococcal antigen test (data missing, n=56). A total of 195 subjects were treated for TBM. Overall 61% were male, median age was 35 years (IQR 30–42), 96% were HIV-positive, median CD4 count was 78 cells/μL (IQR 26–191) and the majority (69%) presented with British Medical Research Council severity grade II disease, see Table 1. Baseline characteristics were similar between cohorts with the exception of antiretroviral (ART) experience; 0% of participants were on ART in cohort one compared to 61% in cohort three (P<0.01).

Among the 76 cases of microbiologically proven TBM in this population with advanced HIV infection, 33% (25/76) had an acellular CSF (white cells <5 cells/μL) at presentation, and 4% (3/76) had a normal CSF profile (CSF cells <5 cells/μL, protein <45 mg/dL, and glucose >2.2mmol/l).

**Method of diagnosis**

Microbiological confirmation of TBM was made in 38% (74/195) of cases. The proportion of cases with microbiologically confirmed TBM (definite TBM) increased significantly, from 3% (1/33) in cohort one to 87% (13/15) in cohort 2 and 41% (60/147) in cohort 3 (P<0.01). Categorisation by uniform case definition is summarised in Table 2.

There was a marked difference in physician threshold for empiric TBM therapy between the two clinical sites. In cohort three, Mulago Hospital recorded 44 cases of which 77% (34/44) were microbiologically confirmed and 23% (10/44) were empirically treated, whilst Mbarara Hospital recorded 103 cases of which 25% (26/103) were microbiologically confirmed and 75% (77/103) were empirically treated.

**Diagnostic accuracy of Xpert MTB/Rif**

Xpert MTB/Rif was positive in 51 of 455 tested (11%), MGIT culture positive in 39 of 321 (12%) tested, AFB stain positive on 5 of 818 tested (1%), as summarised in Table 2.
Diagnostic accuracy of Xpert and MGIT were analysed in cohort three, when both assays were done routinely, and 60 participants had a microbiologically confirmed diagnosis (composite reference standard). Sensitivity of Xpert was 63% (38/60) against the composite reference standard and 54% (38/71) against the uniform case definition (probable or definite TBM). Sensitivity of MGIT culture was 65% (39/60) against the composite reference standard of definite microbiologically confirmed TBM and 55% (39/71) against uniform case definition for probable or definite TBM.

Concordance between Xpert MTB/Rif and MGIT culture was analysed in the 118 with both Xpert and MGIT culture results available. Either Xpert or MGIT culture was positive in 56 patients, of which only 30% (17/56) were positive by both modalities (kappa 0.23 95% CI [0.04, 0.41], p=0.01 (Figure 2). Neither method diagnosed significantly more cases than the other (p=0.42).

Outcomes
Hospital outcome was known for 142 participants, 53 had unknown outcomes or self-discharged against medical advice. Median time to death was 3 days (IQR 1–9 days) among those known to have died, and median length of hospitalization was 7 days (IQR 4–10 days) for participants known to have survived to hospital discharge. Among those with known outcomes, there was a non-significant decline in mortality from 57% in cohort one to 41% in cohort three (p=0.27) (Table 3). Assuming that 50% of those with unknown outcome died, and adjusting for ART status and definite TBM diagnosis at hospitalization, the odds of dying were approximately twice as high for cohort one (aOR 1.7 95% CI [0.7, 4.4]) and cohort two (1.8 [0.6, 5.6]) as compared to cohort three. Assuming that 75% of those with unknown outcome died, adjusted odds of death increase further, cohort one (4.0 [1.5, 10.9]) and cohort two (2.0 [0.6, 6.7]) compared to cohort three (Table 3, Figure 3).

Discussion
Rapid molecular diagnostics have been predicted to reduce TB-related mortality21 but no prior studies have looked at the impact of Xpert on TB-related mortality. Here we report clinical outcomes among hospitalized Ugandans treated for TB meningitis over a 6.5-year period. In-hospital mortality
Figure 2. Venn diagram Illustrating the overlap of positive MGIT culture and Xpert test results in the n=118 samples tested with both assays. A total of 118 adults were tested with both MGIT culture and Xpert, of which 22 were positive by MGIT culture, 17 by Xpert and 17 by both tests. Neither test performed better than the other, p=0.423 by McNemar’s. A kappa statistics value of 0.23 95%CI [0.04, 0.41], p=0.01, suggests only slight agreement of the two assays.
Table 3. Hospital outcomes.

| Diagnostics used | Cohort 1 Nov 2010 to May 2013 | Cohort 2 Apr 2011 to Nov 2013 | Cohort 3 Nov 2013 to May 2017 | Total | P-value
|------------------|------------------------------|------------------------------|------------------------------|-------|----------
| N in TBM case cohort | 33 | 15 | 147 | 195 |

Outcome of hospitalization

<table>
<thead>
<tr>
<th>Unknown</th>
<th>Known</th>
<th>Discharged Alive</th>
<th>Died</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 (79%)</td>
<td>7 (21%)</td>
<td>3 (43%)</td>
<td>4 (57%)</td>
</tr>
<tr>
<td>4 (27%)</td>
<td>11 (73%)</td>
<td>4 (36%)</td>
<td>7 (64%)</td>
</tr>
<tr>
<td>23 (16%)</td>
<td>124 (84%)</td>
<td>73 (59%)</td>
<td>51 (41%)</td>
</tr>
</tbody>
</table>

Odds Ratio (Mortality) and 95% CI (on imputed data)

Assuming 50% of unknowns died

| Adjusted for ART status | 1.5 (0.6, 3.6) | 2.0 (0.7, 6.2) | 1 |
| Adjusted for ART status and confirmed TBM | 1.7 (0.7, 4.4) | 1.8 (0.6, 5.6) | 1 |

Assuming 75% of unknowns died

| Adjusted for ART status | 3.3 (1.3, 8.4) | 2.5 (0.8, 7.8) | 1 |
| Adjusted for ART status and confirmed TBM | 4.0 (1.5, 10.9) | 2.0 (0.6, 6.7) | 1 |

Overall median (IQR) time in hospital was 7 (4, 10) days among those who were known to be discharged alive, and 3 (1, 9) days among those who were known to have died in hospital.

*P-value from Fisher’s exact test comparing KNOWN discharged alive vs KNOWN died; Odds ratios are the odds of being discharged alive, assuming 50% and 75% of those with unknown outcome died.

was high in the cohort overall (44%), similar to other research settings with high HIV prevalence7,19,22,23. The adjusted model on imputed data found odds of in-hospital mortality were almost two fold higher in the earliest cohort, tested by CSF smear microscopy only, than that of that of the most recent cohort in whom Xpert (and culture) are routinely performed. Severity of TBM at presentation was similar over the study period and TBM treatment recommendations have not changed for Uganda, though other confounding factors may exist.

Although we lack data regarding time to treatment initiation, in this research setting Xpert results were obtained within 24 hours, leading to prompt treatment in the 51 subjects who were positive by Xpert MTB/Rif in real-time and presumably contributing to reduced mortality. The proportion of ART experienced subjects increased significantly over time with the roll out of ART treatment in Uganda and because the parent trial in cohort one enrolled only ART naive subjects24. Although ART status was not associated with mortality, we did adjust for ART in multivariable models due to the large discrepancy in ART status between cohorts.

Despite a non-significant decline in mortality, a current case-fatality rate of 41% remains unacceptably high and highlights the remaining work required to achieve the WHO goal of reducing TB-related deaths by 90% by 203025. Initiating treatment in the early stage of disease is the single most important factor in improving outcomes7. Earlier presentation to the hospital is essential for prompt diagnosis and treatment initiation, yet, 83% of our cohort presented with MRC grade II or III disease.

Once the patient presents to care, an affordable, rapid, and reliable test that can effectively confirm or rule out TBM is crucial for prompt diagnosis. In this predominantly HIV-positive TBM cohort, sensitivity of Xpert was 63% against the composite reference standard. Thus, even though results were available rapidly, Xpert missed over one in three cases. The next generation assay Xpert MTB/Rif Ultra has an analytic limit of detection of 15 colony forming units (CFU)/ml, compared to 113 CFU/ml for Xpert26. Ultra appears to be significantly more sensitive than Xpert or culture for the diagnosis of TBM (95% versus 45% and 45% respectively, P<0.001)27. Whether Ultra can reduce diagnostic delay and improve outcome from TBM requires further prospective evaluation.

Where both Xpert and MGIT had been done, less than a third (23%, 17/74) of confirmed cases were positive by both modalities. This is consistent with prior findings and is likely due to the relatively higher sensitivity of culture versus Xpert, and the ability of Xpert to detect dead TB bacilli13,27. Neither test performed better than the other (P=0.42).
Figure 3. Illustration of odds of dying in cohort one and two compared to cohort three in a multivariate model. Odds ratios (and 95% confidence intervals) for death by the end of hospitalization comparing cohorts 1 and 2 to cohort 3, computed from multivariable logistic regression models with imputed data, adjusted for (1) ART status, and (2) ART status and definite TBM diagnosis. Data for patients with unknown outcome was imputed to assume that 50% within each cohort died, or that 75% died.

Until a highly sensitive assay is widely available, there is likely to be on-going heterogeneity in clinical practice regarding initiation of empiric therapy for TBM. In our study, Mulago Hospital participants were treated for TBM on an empiric basis in under one quarter of cases as opposed to over three quarters of cases at Mbarara Hospital. Though empiric TBM therapy is potentially life-saving, significant risks such as side effects, drug-interactions and adjunctive steroids in an already immunosuppressed population need to be considered. Ideally, a rapid, accurate test allows therapy for TB meningitis to be started promptly only in those who actually have TBM. Overall, the proportion with microbiologically confirmed TBM increased significantly from 3% in cohort one to 41% in cohort three (P<0.01). In cohort two, Xpert was only performed in cases where there was extremely high index of suspicion and empiric treatment was given only twice in those with a negative Xpert (4%, 2/56). The low number of empiric diagnoses during this period were likely due to over-confidence in Xpert’s ability to rule-out TBM. As understanding regarding the limitations of Xpert for the diagnosis of TBM became known, empiric TBM treatment rose.

Limitations of study include missing data on hospital outcomes and time to starting TB treatment, unbalanced numbers in each cohort including smaller numbers in earlier cohorts and lack of long-term outcome data. When imputing data in the model we assumed that either 50% or 75% of patients with unknown outcome actually died, which is a clinically reasonable judgment for this population.

Here we present important data on rates of diagnostic confirmation and TBM mortality during a period of TB
diagnostic evolution. There has been a significant increase in microbiological confirmation and a modest, albeit non-significant, decline in mortality since introduction of Xpert and culture in our study setting. An on-going multifaceted approach is needed to further reduce death and disability from TBM.

Consent
Written informed consent for publication of the anonymised data was obtained from the participants or their surrogates.

Data availability
The database contains individual level data and as such is not available through an open-access data repository. The database is stored on a secure server at the University of Minnesota. Researchers interested in accessing the data can contact the corresponding author (FVC), the last author (DRB) or the Division of Biostatistics at the University of Minnesota. Data access will be granted to active researchers in the field with the agreement of the authors.

Competing interests
No competing interests were disclosed.

Grant information
FVC is supported by the Wellcome Trust [210772/Z/18/Z]. ASB, DBM, and DRB are supported by Fogarty International Center and National Institute of Neurologic Diseases and Stroke [R01NS086312].

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

Thank you for the opportunity to review this article which describes the investigation, treatment and outcomes of a cohort of mostly HIV infected adults in Uganda who were suspected of having TB meningitis. It is well written and easily reproducible by others.

The title asks the question of whether improved diagnostics can reduce mortality in TBM. It might be better to say 'Have improved diagnostics improved outcomes?' My view of the data is that it provides very limited evidence that improved diagnostics have improved outcomes of TBM in this cohort. The small improvements in outcome over time are statistically non-significant and due to the observational design are likely to be influenced by numerous unmeasured confounding factors. For example, the experience of clinician may well have changed over time, we know that empiric treatment was used differently in the 2 centres but it might also have changed over time. Part of the work-up of a patient with suspected TBM is a search for extra-neural TB and we do not know how this changed over time although it is likely that Xpert MTB/RIF was used for non-CSF samples in later cohorts compared to earlier, the same might be said for urine LAM.

My view as a reader is therefore that this data does not provide convincing evidence that the change in diagnostics was the driver of the small changes in mortality. It must be remembered that new diagnostics also have the potential to worsen outcomes, particularly if clinicians miss-interpret negative tests as ruling out the condition as might well occur with Xpert MTB/RIF and TBM.

I think that this well written work definitely deserves to be published but feel that the conclusions should reflect a greater level of uncertainty.

Minor points:

The abstract says that all 1672 patients were HIV infected but in the results section is says 96% were HIV infected so there is a discrepancy.

Last line, para 1 of introduction, probably remove word ‘to’.

Last line. Para 3 of introduction- It is not that Xpert cannot substitute for clinical judgement- Xpert is used to enhance clinical judgement, it’s just that the poor sensitivity means that when negative it has limited influence on decision making.
Statistical methods- the uniform case definition is probable or definite TBM- do the authors think this is a reasonable reference standard for other tests? My view is that the threshold for treating TBM is very low and that patients with possible/probably or definite TBM should receive treatment and therefore this would be a more appropriate reference standard- what are your views on that?

Methods- Not clear if there were 76 or 74 microbiologically proven cases

Discussion- Para 1, repeat of ‘that of’

Discussion- Para 4, First sentence implies that tests are the only answer to the diagnosis of TBM, what about clinical prediction rules relying on clinical data- although so far they have not been very successful, neither have tests so a robust CPR may negate the need for tests.

Discussion- Para 5, Do the authors really think there are dead bacilli in CSF? Some of the authors have argued the opposite in their recent paper on Xpert Ultra so you can’t have it both ways.

Is the work clearly and accurately presented and does it cite the current literature? Yes

Is the study design appropriate and is the work technically sound? Yes

Are sufficient details of methods and analysis provided to allow replication by others? Yes

If applicable, is the statistical analysis and its interpretation appropriate? Yes

Are all the source data underlying the results available to ensure full reproducibility? Yes

Are the conclusions drawn adequately supported by the results? Partly

**Competing Interests:** No competing interests were disclosed.

**Referee Expertise:** Clinical management of patients with HIV and meningitis. The interpretation of tests and thresholds for treatment.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.