Check for updates

RESEARCH ARTICLE

Can improved diagnostics reduce mortality from Tuberculous meningitis? Findings from a 6.5-year cohort in Uganda [version 1; referees: awaiting peer review]

Fiona V. Cresswell [1,2], Ananta S. Bangdiwala[3], Nathan C. Bahr [4], Emily Trautner [5], Edwin Nuwagira[6], Jayne Ellis[7], Radha Rajasingham[8], Joshua Rhein [2,8], Darlisha A. Williams[2], Conrad Muzoora[6], Alison M. Elliott[1,9], David B. Meya[2,10], David R. Boulware[8]

[1]Department of Clinical Research, London School of Hygiene and Tropical Medicine, London, WC1E 7HT, UK
[2]Infectious Diseases Institute, Kampala, Uganda
[3]Division Biostatistics, School of Public Health, University of Minnesota, Minneapolis, MN, 55455, USA
[4]Division of Infectious Diseases, Department of Medicine, University of Kansas, Kansas City, KS, 66160, USA
[5]University of Utah, Salt Lake City, UT, 84112, USA
[6]Mbarara University of Science and Technology, Mbarara, Uganda
[7]Doctors.net.uk, Abingdon, OX14 4SH, UK
[8]Division of Infectious Disease and International Medicine, Department of Medicine, University of Minnesota, Minneapolis, MN, 55455, USA
[9]Medical Research Council/Uganda Virus Research Institute and London School of Hygiene & Tropical Medicine Uganda Research Unit on AIDS, Entebbe, Uganda
[10]College of Health Sciences, Makerere University, Kampala, Uganda

Open Peer Review

Referee Status: *AWAITING PEER REVIEW*

Discuss this article

Comments (0)

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

Corresponding author: Fiona V. Cresswell (fiona.cresswell@lshtm.ac.uk)

Introduction

Tuberculous meningitis (TBM) is the second most common cause of adult meningitis in sub-Saharan Africa[1,2], accounting for one to five percent of the 10.4 million tuberculosis (TB) cases reported worldwide in 2016[3]. 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 is frequent among survivors[4–6].

Insidious symptom onset in persons with TBM leads to delay in seeking care and increasing disease severity at presentation correlates with higher mortality[7]. Further, the paucibacillary nature of TBM increases the difficulty in confirming diagnosis once care is sought, also contributing to high mortality[8]. Cerebrospinal fluid (CSF) smear microscopy for acid-fast bacilli (AFB smear) has poor sensitivity (~10–20%) in routine practice[7]. 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[8].

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[9]. 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[10–12]. Additionally, use of a larger volume of centrifuged CSF improves sensitivity of Xpert[10,13]. Yet, inadequate negative predictive value means that Xpert cannot substitute for clinical judgement[14].

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[15,16]. However for pulmonary TB, Xpert has not been shown to decrease mortality[16–18]. Yet, lessening diagnostic delay in persons with TBM may be more likely to lead to improved outcomes as compared to pulmonary TB given the high early mortality of TBM[19]. 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 enrolment 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[11]. In addition to the consensus case definitions, clinical TBM was defined as subjects without a positive microbiologic result, but who were treated empirically for TBM treatment due to high clinical suspicion. TBM treatment included 12 months of antituberculous therapy with 6–8 weeks of adjunctive corticosteroids as per Ugandan guidelines[20].

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 TBM with CSF AFB smear (Mulago Hospital only), Xpert MTB/Rif on large volume centrifuged CSF[13] 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

CSF Testing Performed	2010	2011	2012	2013	2014	2015	2016	2017
AFB smear		Cohort 1 (16th Nov 2010 – 28th May 2013)						
AFB smear **Xpert** (1ml uncentrifuged CSF)		Cohort 2 (1st April 2011 – 10 Nov 2013)						
AFB smear **Xpert** (large vol centrifuged CSF) **MGIT culture**					Cohort 3 (11th Nov 2013 – 28th May 2017)			

Figure 1. Timeline illustrating evolution of diagnostic testing.

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)[11]. A separate analysis was conducted against the *uniform case definition* of probable or definite TBM[11]. 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); COAT: 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.

Table 1. Demographics, HIV details and outcomes of cohort.

Diagnostics used	N with data	Cohort 1 Nov 2010 to May 2013 AFB smear	Cohort 2 Apr 2011 to Nov 2013 AFB smear Xpert	Cohort 3 Nov 2013 to May 2017 AFB smear Xpert Culture	Total	P-value*
N in TBM case cohort		33	15	147	195	
Demographics						
Sex	195					0.58
Male		18 (55%)	8 (53%)	92 (63%)	118 (61%)	
Age	195					0.33
Median (IQR)		33 (29, 38)	35 (29, 40)	35 (30, 43)	35 (30, 43)	
HIV details						
HIV status, n (%)	195					1.00
HIV-positive		32 (97%)	15 (100%)	141 (96%)	188 (96%)	
ART status, n (%)	179					<0.01
On ART		0 (0%)	4 (27%)	80 (61%)	84 (47%)	
ART naive		32 (100%)	11 (73%)	52 (39%)	95 (53%)	
CD4	131					0.30
Median (IQR)		12 (7, 121)	148 (54, 169)	78 (26, 206)	78 (26, 191)	
TBM details						
MRC severity grade, n (%)	191					0.13
I		9 (27%)	4 (31%)	20 (14%)	33 (17%)	
II		22 (67%)	7 (54%)	102 (70%)	131 (69%)	
III		2 (6%)	2 (15%)	23 (16%)	27 (14%)	

*P-values from Fisher's exact tests for categorical variables and Kruskal-Wallis tests for continuous variables.

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 microbiologic-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 mortality[21] but no prior studies have looked at the impact of Xpert on TBM-related mortality. Here we report clinical outcomes among hospitalized Ugandans treated for TB meningitis over a 6.5-year period. In-hospital mortality

Table 2. Methods of Diagnosis.

	Cohort 1	Cohort 2	Cohort 3		
	AFB smear	AFB smear Xpert	AFB smear Xpert Culture	Total	P-value$
All meningitis patients screened					
Total number	471	71	1130	1672	
Cryptococcal Antigen positive	269	31	758	1058	
Cryptococcal Antigen negative	187	38	333	558	
TBM diagnostic tests performed					
CSF AFB smear microscopy*					
N AFB performed	466	71	281	818	
N AFB positive	1 (0%)	0 (0%)	4 (2%)	5 (1%)	
CSF TB culture					
N TB culture performed	0	0	321	321	
N TB culture positive	0	0	39 (12%)	39 (12%)	
CSF Xpert MTB/Rif					
N Xpert performed (realtime)	0	71	384	455	
N Xpert positive	0	13 (18%)	38 (10%)	51 (11%)	
Uniform case definition					
Definite	1 (3%)	13 (87%)	60 (41%)	74 (38%)	<.01
Probable	5 (15%)	2 (13%)	11 (7%)	18 (9%)	
Possible	22 (67%)	0 (0%)	53 (36%)	75 (38%)	
Not	5 (15%)	0 (0%)	23 (16%)	28 (14%)	

Prior to November, 2013 any patient not prospectively tested with Xpert was considered in Cohort 1

*AFB smear was initially performed on all meningitis patients regardless of CSF Cryptococcal antigen result. From October 2013, it was only performed on those with a negative Cryptococcal antigen, and was later stopped altogether in Mbarara.

$P-value from Fisher's exact test
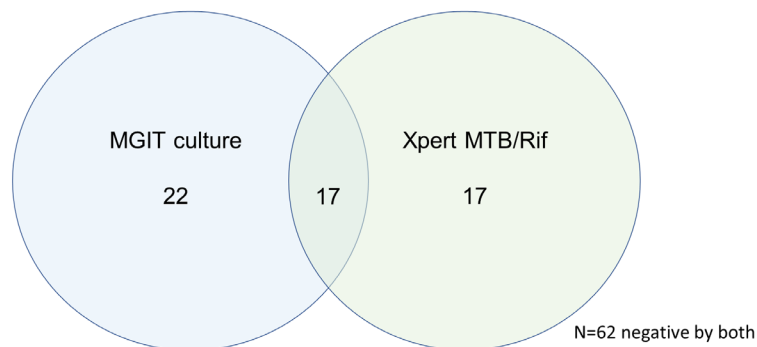
Figure 2. Venn diagram Illustrating the overlap of positive MGIT culture and Xpert test results in the n=118 samples tested with both assays. A total of 118 adults were tested with both MGIT culture and Xpert, of which 22 were positive by MGIT culture, 17 by Xpert and 17 by both tests. Neither test performed 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 AFB smear	Cohort 2 Apr 2011 to Nov 2013 AFB smear Xpert	Cohort 3 Nov 2013 to May 2017 AFB smear Xpert Culture	Total	P-value*
N in TBM case cohort	33	15	147	195	
Outcome of hospitalization					
Unknown	26 (79%)	4 (27%)	23 (16%)	53 (27%)	
Known	7 (21%)	11 (73%)	124 (84%)	142 (73%)	
Discharged Alive	3 (43%)	4 (36%)	73 (59%)	80 (56%)	0.27
Died	4 (57%)	7 (64%)	51 (41%)	62 (44%)	
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 prevalence[7,19,22,23]. 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 naïve subjects[24]. 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 2030[25]. Initiating treatment in the early stage of disease is the single most important factor in improving outcomes[7]. 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 Xpert[26]. Ultra appears to be significantly more sensitive than Xpert or culture for the diagnosis of TB (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 bacilli[13,27]. Neither test performed better than the other (P=0.42).
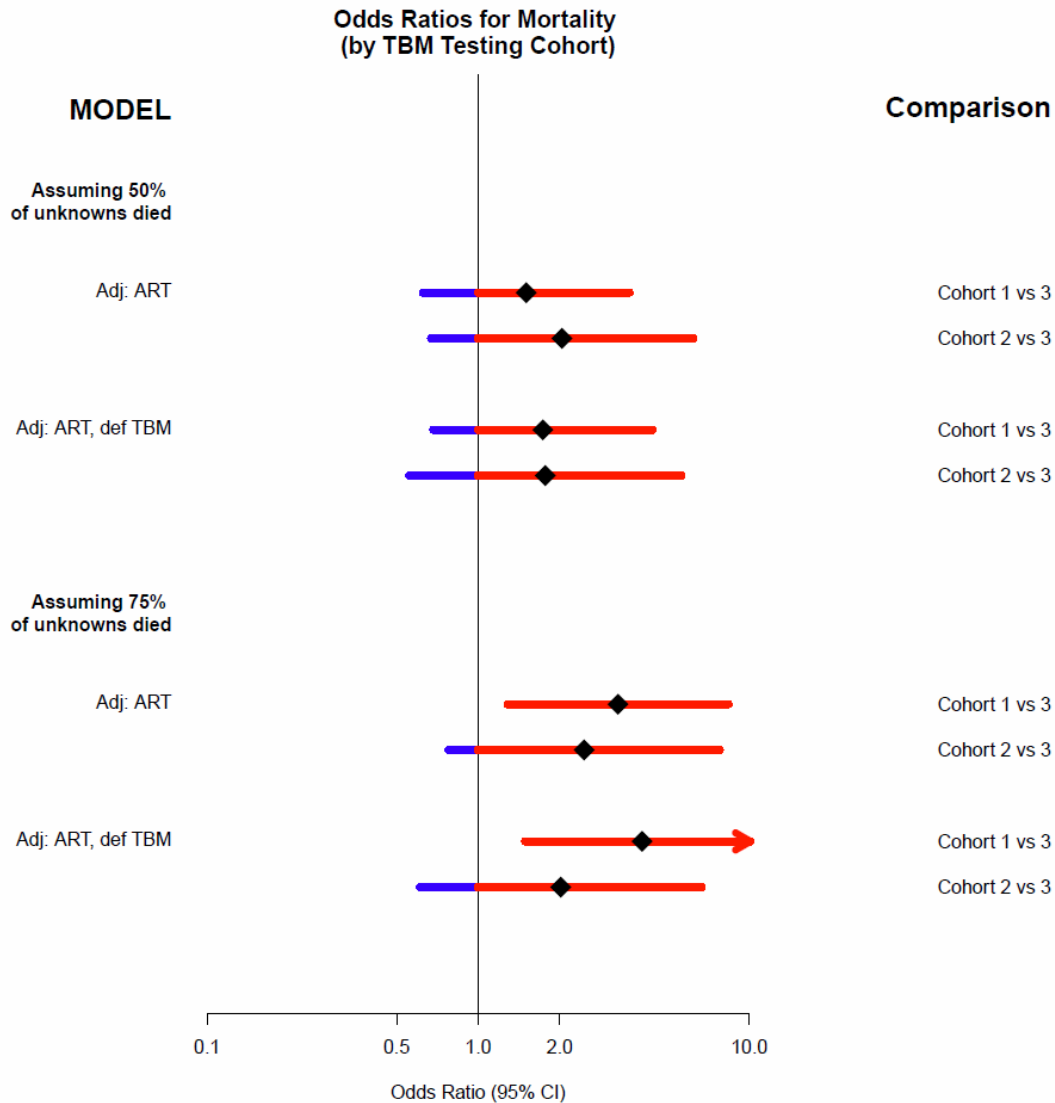
Figure 3. Illustration of odds of dying in cohort one and two compared to cohort three in a multivariate model. Odds ratios (and 95% confidence intervals) for death by the end of hospitalization comparing cohorts 1 and 2 to cohort 3, computed from multivariable logistic regression models with imputed 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[14].

Limitations of this 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[4].

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 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

References

1. Jarvis JN, Meintjes G, Williams A, *et al.*: **Adult meningitis in a setting of high HIV and TB prevalence: findings from 4961 suspected cases.** *BMC Infect Dis.* 2010; **10**: 67.
   PubMed Abstract | **Publisher Full Text** | **Free Full Text**

2. Durski KN, Kuntz KM, Yasukawa K, *et al.*: **Cost-effective diagnostic checklists for meningitis in resource-limited settings.** *J Acquir Immune Defic Syndr.* 2013; **63**(3): e101–8.
   PubMed Abstract | **Publisher Full Text** | **Free Full Text**

3. World Health Organization: **Global Tuberculosis Report 2017**. Geneva: World Health Organisation, 2017.
   Reference Source

4. Woldeamanuel YW, Girma B: **A 43-year systematic review and meta-analysis: case-fatality and risk of death among adults with tuberculous meningitis in Africa.** *J Neurol.* 2014; **261**(5): 851–65.
   PubMed Abstract | **Publisher Full Text**

5. Mai NT, Thwaites GE: **Recent advances in the diagnosis and management of tuberculous meningitis.** *Curr Opin Infect Dis.* 2017; **30**(1): 123–8.
   PubMed Abstract

6. Brancusi F, Farrar J, Heemskerk D: **Tuberculous meningitis in adults: a review of a decade of developments focusing on prognostic factors for outcome.** *Future Microbiol.* 2012; **7**(9): 1101–16.
   PubMed Abstract | **Publisher Full Text**

7. Wilkinson RJ, Rohlwink U, Misra UK, *et al.*: **Tuberculous meningitis.** *Nat Rev Neurol.* 2017; **13**(10): 581–598.
   PubMed Abstract | **Publisher Full Text**

8. Boulware DR: **Utility of the Xpert MTB/RIF assay for diagnosis of tuberculous meningitis.** *PLoS Med.* 2013; **10**(10): e1001537.
   PubMed Abstract | **Publisher Full Text** | **Free Full Text**

9. Denkinger CM, Schumacher SG, Boehme CC, *et al.*: **Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis.** *Eur Respir J.* 2014; **44**(2): 435–46.
   PubMed Abstract | **Publisher Full Text**

10. 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 Abstract | **Publisher Full Text** | **Free Full Text**

11. Marais S, Thwaites G, Schoeman JF, *et al.*: **Tuberculous meningitis: a uniform case definition for use in clinical research.** *Lancet Infect Dis.* 2010; **10**(11): 803–12.
    PubMed Abstract | **Publisher Full Text**

12. Nhu NT, Heemskerk D, Thu do DA, *et al.*: **Evaluation of GeneXpert MTB/RIF for diagnosis of tuberculous meningitis.** *J Clin Microbiol.* 2014; **52**(1): 226–33.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

13. Bahr NC, Tugume L, Rajasingham R, *et al.*: **Improved diagnostic sensitivity for tuberculous meningitis with Xpert(®) MTB/RIF of centrifuged CSF.** *Int J Tuberc Lung Dis.* 2015; **19**(10): 1209–15.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

14. 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 Abstract | **Publisher Full Text** | **Free Full Text**

15. Yoon C, Cattamanchi A, Davis JL, *et al.*: **Impact of Xpert MTB/RIF testing on tuberculosis management and outcomes in hospitalized patients in Uganda.** *PLoS One.* 2012; **7**(11): e48599.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

16. Theron G, Zijenah L, Chanda D, *et al.*: **Feasibility, accuracy, and clinical effect of point-of-care Xpert MTB/RIF testing for tuberculosis in primary-care settings in Africa: a multicentre, randomised, controlled trial.** *Lancet.* 2014; **383**(9915): 424–35.
    PubMed Abstract | **Publisher Full Text**

17. Boehme CC, Nabeta P, Hillemann D, *et al.*: **Rapid molecular detection of tuberculosis and rifampin resistance.** *N Engl J Med.* 2010; **363**(11): 1005–15.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

18. Boehme CC, Nicol MP, Nabeta P, *et al.*: **Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study.** *Lancet.* 2011; **377**(9776): 1495–505.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

19. Török ME, Yen NT, Chau TT, *et al.*: **Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)--associated tuberculous meningitis.** *Clin Infect Dis.* 2011; **52**(11): 1374–83.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

20. Uganda National Tuberculosis and Leprosy Control Programme: **Manual for Management and Control of Tuberculosis and Leprosy**. 2017.
    Reference Source

21. Ramsay A, Steingart KR, Pai M: **Assessing the impact of new diagnostics on tuberculosis control.** *Int J Tuberc Lung Dis.* 2010; **14**(12): 1506–7.
    PubMed Abstract

22. Heemskerk AD, Bang ND, Mai NT, *et al.*: **Intensified Antituberculosis Therapy in Adults with Tuberculous Meningitis.** *N Engl J Med.* 2016; **374**(2): 124–34.
    PubMed Abstract | **Publisher Full Text**

23. Ruslami R, Ganiem AR, Aarnoutse RE, *et al.*: **Rifampicin and moxifloxacin for tuberculous meningitis--authors' reply.** *Lancet Infect Dis.* 2013; **13**(7): 570.
    PubMed Abstract | **Publisher Full Text**

24. Boulware DR, Meya DB, Muzoora C, *et al.*: **Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis.** *N Engl J Med.* 2014; **370**(26): 2487–98.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

25. World Health Organization: **The End TB Strategy**. Geneva, Switzerland: World Health Organisations, 2015.
    Reference Source

26. 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): pii: e00812-17.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

27. 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.* 2018; **18**(1): 68–75.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**