***Mycobacterium tuberculosis* blood stream infection prevalence, diagnosis, and mortality risk in seriously-ill HIV-positive adults: a systematic review and meta-analysis of individual patient data**

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***Mycobacterium tuberculosis* blood stream infection prevalence, diagnosis, and mortality risk in seriously-ill HIV-positive adults: a systematic review and meta-analysis of individual patient data**

**Abstract**

Word count: 300

**Background**

The clinical and epidemiological significance of HIV-associated *Mycobacterium tuberculosis* blood stream infection (MTB-BSI) is incompletely understood. We hypothesised that MTB-BSI prevalence has been underestimated, that MTB-BSI independently predicts death, and sputum Xpert has suboptimal diagnostic yield for MTB-BSI.

**Methods**

We conducted a systematic review and individual patient data (IPD) meta-analysis of studies performing routine mycobacterial blood-culture (TBBC). Harmonised inclusion criteria were applied to IPD: age ≥13 years, HIV-positivity, available CD4 count, a valid mycobacterial blood culture result (excluding patients with missing data from lost or contaminated blood cultures), and meeting WHO definitions for suspected tuberculosis (presence of screening symptom). Predicted probabilities of MTB-BSI from mixed-effects modelling were used to estimate prevalence. Estimates of diagnostic yield of sputum (Xpert or culture if Xpert unavailable) and urine-lipoarabinomannan for MTB-BSI were obtained by two-level random-effect meta-analysis, mortality hazard of MTB-BSI by mixed-effect Cox proportional-hazard modelling, and effect of treatment delay with propensity-score analysis. PROSPERO registration: CRD42016050022·

**Findings**

We identified 23 data sets for inclusion (20 published and 3 unpublished at time of search), and obtained data from 20, representing 96% of eligible IPD. 5751 patients met inclusion criteria. Predicted probability of MTB-BSI was 45% (95%CI 38-52%) for danger-sign positive tuberculosis inpatients with cohort median CD4 count of 76 cells/L. Diagnostic yield of sputum was 77% (95%CI 63–87%), rising to 89% (95%CI 80-94%) when combined with urine-lipoarabinomannan testing. Presence of MTB-BSI compared to absence in patients with HIV-associated tuberculosis increased hazard of death before 30-days (aHR2·5, 95%CI 2·1–3·1) but the effect waned after 30 days (aHR 1.25 95% 0.84-2.49). In a propensity-score matched cohort of participants with HIV-associated tuberculosis (n=630), mortality increased with anti-tuberculosis treatment delay >4 days in the subgroup with MTB-BSI (OR 3·2, 95%CI 1·1–10·3) but not convincingly in the overall cohort (OR 1.25 95% CI 0.68 – 2.25).

**Interpretation**

In critically-ill adults with HIV-tuberculosis, MTB-BSI is a frequent manifestation of tuberculosis and strongly predicts mortality within 30 days. Better diagnostic yield in patients with MTB-BSI can be achieved by parallel use of sputum-Xpert and urine-LAM. Anti-tuberculosis treatment delay may increase mortality hazard.

**Funding**

None.

**Research in context**

**Evidence before this study**

We did a systematic review of PubMed, Scopus, and Cochrane Database of Systematic reviews using combinations of search terms [*Blood stream infection, bacter?emia,*  *septic?emia*, sepsis, *tuberculosis*, *TB*, *mycobacter?emia*] on 15/09/2019 without date restriction to find studies which have attempted to systematically summarise available data on prevalence and mortality for HIV-associated tuberculosis blood stream infection. We identified one aggregate meta-analysis of HIV-associated tuberculosis blood stream infection which reports *M. tuberculosis* is a common cause of BSI in adults with HIV-infection. Two further aggregate data meta-analyses have highlighted the high prevalence of tuberculosis as a cause of sepsis, and community acquired blood stream infection, in sub-Saharan Africa.

However, all these analyses showed substantial between-study heterogeneity unexplained by study-level confounders. While some published cohort studies have linked positive TB blood culture with increased risk of death, others have found no significant association; the identified meta-analyses have not reported pooled mortality associations adjusted for individual patient characteristics. Consequently, there is uncertainty about the clinical and epidemiological importance of MTB-BSI.

**Added value of this study**

To address these uncertainties, we conducted an individual patient data (IPD) meta-analysis of healthcare facility-based studies which performed routine TB blood cultures taken from adults with HIV-infection.

Correcting for individual patient characteristics, we were able to explain substantial variation in probability of MTB-BSI and found prevalence to be higher than previously reported particularly in hospitalised patients with HIV-associated tuberculosis and WHO danger signs. We demonstrated a robust independent association of MTB-BSI with death before 30 days (compared to tuberculosis blood culture negative patients with HIV-associated tuberculosis). We found that sputum-Xpert and urine-LAM have marked heterogeneity in diagnostic yield in MTB-BSI patients, partly explained by a lower probability of obtaining samples in critically-ill patients rather than poor test diagnostic sensitivity. Analogous to non-tuberculosis sepsis in high income settings, we provide new evidence that anti-tuberculosis treatment delay is associated with 30-day / inpatient mortality in MTB-BSI patients.

**Implications of available evidence**

Tuberculosis in critically-ill PLWH is frequently a blood stream infection; tuberculosis bacteraemia is a common and important predictor of 30-day mortality. As with other causes of bacterial sepsis, providing prompt effective antimicrobial therapy may be vital in MTB-BSI. Urine-lipoarabinomannan testing should be routinely added to first-line diagnostic testing of sputum in HIV-positive, WHO danger-sign positive inpatients with suspected tuberculosis. MTB-BSI patients are an important population in which to validate WHO management guidelines for seriously ill PLWH suspected of having tuberculosis and warrant specific focus in the road map for future research and global response to sepsis. Interventional trials are urgently required to establish an evidence base for mortality reduction in MTB-BSI.

***Mycobacterium tuberculosis* blood stream infection prevalence, diagnosis, and mortality risk in seriously-ill HIV-positive adults: a systematic review and meta-analysis of individual patient data**

Total word count: 4088

**Introduction (471 words)**

In high HIV/tuberculosis burden settings *Mycobacterium tuberculosis* blood stream infection (MTB-BSI) may be common. When sought, tuberculosis is the most frequently identified community-acquired BSI in hospitalised adults in sub-Saharan Africa1 and in adult sepsis cohorts recruited in high-HIV burden settings.2-4 The high frequency of multi-organ, notably spleen, involvement in HIV-associated tuberculosis post-mortems5 is consistent with active blood-stream dissemination being near universal in fatal cases.

Most settings with generalised HIV epidemics have no access to mycobacterial blood culture. Even where available, an average 3-week culture time-to-detection3,6-8 combined with high early mortality means that tuberculosis blood culture has limited diagnostic value. In contrast to other bacteraemic pathogens, no specific evidence base has been developed for treating patients with MTB-BSI.

The true prevalence of MTB-BSI is unknown; there is marked unexplained heterogeneity in aggregate data meta-analysis.9 Diagnostic performance of tuberculosis rapid tests in HIV-associated tuberculosis is variable;10 the relative utility of sputum Xpert MTB/RIF® (Cepheid, Sunnyvale, CA, USA) and urine-lipoarabinomannan (urine-LAM) depends on disease severity,11 and may be different in patients with MTB-BSI compared to less critically-ill tuberculosis-HIV populations.12 Further, while some studies link mycobacteraemia to high risk of death in HIV-associated tuberculosis,3,8,13 others find no significant independent association.14-16

World Health Organization (WHO) guidelines on HIV-associated tuberculosis do not address MTB-BSI directly, but do refer to ‘disseminated tuberculosis’, described as “disease not limited to one site”. In addition, guidance for managing ‘seriously ill people living with HIV and suspected of having tuberculosis’, largely based on expert opinion, is given (summarised in box 1).17

We hypothesised that a substantial proportion of inpatients with HIV-associated tuberculosis who are ‘seriously ill’ have MTB-BSI, and that they represent a group at particularly high risk of death, especially if effective treatment is delayed. If this is the case, patients with MTB-BSI are an important and specific population in which to validate the WHO algorithm. Heterogeneity in reported prevalence of MTB-BSI might be explained by differences in inclusion criteria, individual level variation in clinical factors such as CD4 count, or technical factors such as number of blood cultures.18 Lack of independent association of MTB-BSI with mortality in some studies could be the result of underpowering, or bias in application of the tuberculosis blood culture reference test.

We carried out an individual patient data (IPD) meta-analysis allowing harmonised individual patient inclusion criteria and adjustment for individual-level variables to address four questions. First, what is the prevalence of MTB-BSI amongst adult inpatients with HIV-associated tuberculosis who are seriously ill (having at least one WHO ‘danger sign’, listed in Box 1)? Second, what is the diagnostic yield of sputum Xpert, and urine-LAM, in patients with MTB-BSI? Third, what is the mortality risk associated with having a positive tuberculosis blood culture, and fourth what is the effect on mortality of delaying anti-tuberculosis treatment by 3-5 days as per the WHO algorithm, in patients with MTB-BSI?

**Box 1: Summary of WHO guidance for managing people living with HIV, suspected of having TB, and seriously ill**.

* TB suspected if cough, fever, night sweats, or weight loss present.
* *Seriously ill* defined as presence of any **danger signs**: respiratory rate > 30 per minute, temperature > 39oC, heart rate > 120 beats per minute, and inability to walk unaided.
* Hospital admission and parenteral antibiotics for bacterial infections in all cases.
* Xpert MTB/RIF on sputum and extra-pulmonary samples if extrapulmonary TB is suspected.
* If Xpert MTB/RIF negative or not available, and *no clinical improvement after 3-5 days*, start presumptive TB therapy.
* In addition, urine lateral flow lipoarabinomannan (uLAM) “may be used… regardless of CD4 count”.

**Methods [1293 words]**

**Search strategy and selection criteria**

We searched for studies where mycobacterial blood culture was performed in a prospectively defined patient population which included PLWH aged ≥13-years, excluding studies where CD4 count was not measured.

PubMed and Scopus were searched initially on 07 October 2016 and updated on 10 November 2018 without language or publication period limits using [(*Blood stream infection* OR *BSI* OR *bacter?emia* OR *septic?emia*) AND (*tuberculosis* OR *TB*)] OR [*mycobacter?emia*]. Reference lists and review articles were also searched. Researchers with interest in HIV-associated tuberculosis were contacted to identify unpublished cohorts. Abstracts were reviewed independently (JML, DAB) and, if potentially eligible according to either reviewer, full texts were obtained. Full texts were also reviewed independently with disagreements resolved by consensus after clarification of method details with primary authors.

**Data analysis**

Original investigators of identified studies were asked to provide primary data, and meta-data in the event of unclear data coding. Pre-specified variables (Table S1, appendix pp 2-3) were extracted and standardised. Original primary study case definitions for a final tuberculosis diagnosis, and microbiological identification standards, were accepted.

Primary studies were classified by inclusion criteria and setting (Table 1). Risk of bias assessment was by an adapted QUADAS-2 framework informed by a survey sent to primary study authors (Table S2, appendix pp 4-5). Two authors (DAB and JL) used the survey data to assess risk of bias as low, moderate or high across five domains (patient selection, reference test, recording of co-factors [i.e. covariates to be included in model], index test and mortality outcome) with disagreements resolved by consensus.

Harmonised inclusion criteria were applied to IPD: age ≥13 years, HIV-positivity, available CD4 count, a valid mycobacterial blood culture result (excluding patients with missing data from lost or contaminated blood cultures), and WHO tuberculosis screening symptom(s).17 All patients included met WHO definitions for suspected tuberculosis.17

***Data analysis: prevalence simulation***

MTB-BSI prevalence was assessed with mixed-effects logistic regression using *lme4* package in R.19 Random-intercept by primary study and fixed-effects for *a priori* specified variables were added to the model in the arbitrary, prespecified order shown in Table S5 (appendix pp 10) to the raw (unimputed) datasets. Continuous variables were standardised to mean 0 and standard deviation 1. Each nested model was compared by likelihood ratio test to: (i) a null model containing only a random-effect by study on the intercept; and (ii) the preceding model, giving associated p-values reported as LRTnull and LRTpreceding, respectively. The effect of models on heterogeneity was assessed using random effect variance (Tau squared, *τ* 2) and proportion of residual individual variance attributable to random effects (Variance Partition Co-efficient, VPC).20,21 Variance explained by fixed effects (R2*marginal*), and by total model (R2*conditional*), were calculated using *r.squaredGLMM()* function of R package *MuMIn*.22-24 The importance of clustering by primary dataset was further assessed by ΔAUC, the additional area under receiver operating characteristic curve (within sample discrimination) from including random effects by dataset (Table S3, appendix pp 6).20

All variables with LRTpreceding < 0.01 were included in the final model and the predicted probability of positive tuberculosis blood culture from this model was used to simulate population prevalence of MTB-BSI for given levels of the relevant fixed-effects (for example, assuming 2 blood cultures were performed prior to starting anti-tuberculosis treatment, and at a specific CD4 cell count level). An overall mean prevalence for MTB-BSI in an ‘average’ study was calculated (i.e., with random effect of 0), as well as for each primary study (including associated random effects) to visualise residual heterogeneity in MTB-BSI probability after adjusting for IPD-level covariates.

Systematically (i.e. variables missing for a whole study dataset) and sporadically missing data (i.e. variables which were available for a given dataset but were missing for individuals) were multiple-imputed using generalised linear mixed models (GLMMs) to account for clustering by primary study, using the *hmi* package in R.25 Missing observations in each variable from the set [heart rate, respiratory rate, temperature, ability to walk unaided, early mortality, patient setting, age, sex, CD4 count, MTB-BSI, haemoglobin] were imputed with all the other variables in the set as predictors, using logistic or linear GLMMs as appropriate. Five imputations were carried out, resulting in five complete versions of the data.

Mean predicted prevalence values and 95% confidence intervals were calculated from pooled bootstraps, with resampling stratified by primary study. 1000 replicates from each of the five imputed versions of the data were pooled and confidence intervals derived from their quantiles.26 To assess the effect of bias on our results, a sensitivity analysis was carried out whereby any study with high or unknown risk of bias in any domain was excluded and this process repeated.

Finally, a 95% prediction interval for mean prevalence of MTB-BSI in a new unobserved study was estimated from 1000 simulations carried out in each of the five imputed versions of the data using *bootMer()* in *lme4*,19 capturing uncertainty in parameter estimates, random-variation between studies, conditional variation in the binary outcome, and variance from imputation of missing data.27

***Data analysis: performance of surrogate rapid diagnostics***

To assess the utility of rapid diagnostics to identify tuberculosis in those with MTB-BSI we defined:

* *sputum diagnostic yield* as proportion of MTB-BSI patients who had a positive sputum test result, using an aggregate sputum variable of Xpert or MTB culture as surrogate if Xpert unavailable (which assumes that the Xpert would be positive for all sputum culture positive patients);
* *urine-LAM diagnostic yield* as proportion of MTB-BSI patients who had a positive urine-LAM; and
* *composite diagnostic yield*, as proportion who had either test positive.

We restricted this analysis to studies which collected IPD on sputum Xpert/culture or urine-LAM. Protocol specified analyses of chest-radiology and sputum microscopy were abandoned due to lack of obtained data. Pooled estimates of diagnostic yield were obtained by two-level random-effect meta-analysis using a normal-binomial GLMM method in the R packages *meta* and *lme4·*19,28 Heterogeneity was explored using meta-regression on prespecified study-level covariates, with role of covariates assessed by likelihood ratio testing nested models. Factors associated with availability of sputum or urine were assessed in univariable mixed-effect logistic regression. Because absence of a diagnostic test was thought to be a likely determinant of diagnostic yield, these analyses were carried out on the unimputed data and the proportion of participants with available test included as a covariate.

***Data analysis: mortality association of MTB BSI***

To assess the independent mortality risk of MTB-BSI in patients with HIV-tuberculosis, we constructed mixed-effect Cox proportional hazard models using *survival* package in R,29 with random intercept by study and *a priori* specified fixed-effects: age, sex, CD4 count, inpatient status versus outpatient, presence of WHO danger signs, antiretroviral therapy (ART) at baseline, and MTB-BSI (defined as positive blood culture). The proportional hazards assumption was checked by chi-squared test of a nonzero slope of scaled Schoenfeld residuals against time. Missing data were imputed using the strategy described above; confidence intervals on model parameters were constructed by pooling 1000 nonparametric cluster bootstrap replicates from five imputed dataset as before. Unadjusted hazard ratios for all the fixed effect variables were determined using models including only the variable of interest and a random intercept by study; adjusted hazard ratios were determined using a model including all the fixed effect variables along with random intercept. Cox regression was used in preference to protocol specified logistic regression because observations on date of death were more complete than anticipated.

***Data analysis: post-hoc exploration of anti-tuberculosis treatment delay***

Finally, we explored an association between time to anti-tuberculosis treatment (ATT) and mortality in patients with MTB-BSI. To reflect the 3-5 day observation period in the WHO algorithm (box 1), anti-tuberculosis treatment delay was defined as >4 days between blood culture collection and ATT start, and other cut-offs were explored by sensitivity analysis. Mortality was defined as death before discharge from hospital or by 30-days follow-up. Because of a high proportion of missing data in the start date of ATT variable (1059/2460 [43%] of participants, Figure S10, appendix pp 22) and concern that imputing these missing values may be invalid, a complete case analysis was undertaken; patients without a final tuberculosis diagnosis, without complete observations, and patients starting ATT ≥24-hours before blood culture, were excluded. We calculated a propensity score for anti-tuberculosis treatment delay using logistic regression with variables: age, CD4 count, ≥1 WHO danger sign, TBBC result, and primary study. Patients without and with anti-tuberculosis treatment delay were matched 2:1 by propensity score nearest neighbour on logit distance without calliper restrictions. Association between anti-tuberculosis treatment delay and mortality was assessed in the whole matched cohort, and in pre-specified sub-groups (MTB-BSI patients, danger sign positive patients, patients with CD4 < 100 cells/mm3) by Fisher’s exact test.

All analysis was carried out in R (R Foundation for Statistical Computing, Vienna, Austria). The meta-analysis protocol was registered on PROSPERO [CRD42016050022].

**Role of the funding source**

There was no direct funding for this study. The corresponding author had full access to the data in the study and had final responsibility for the decision to submit for publication.

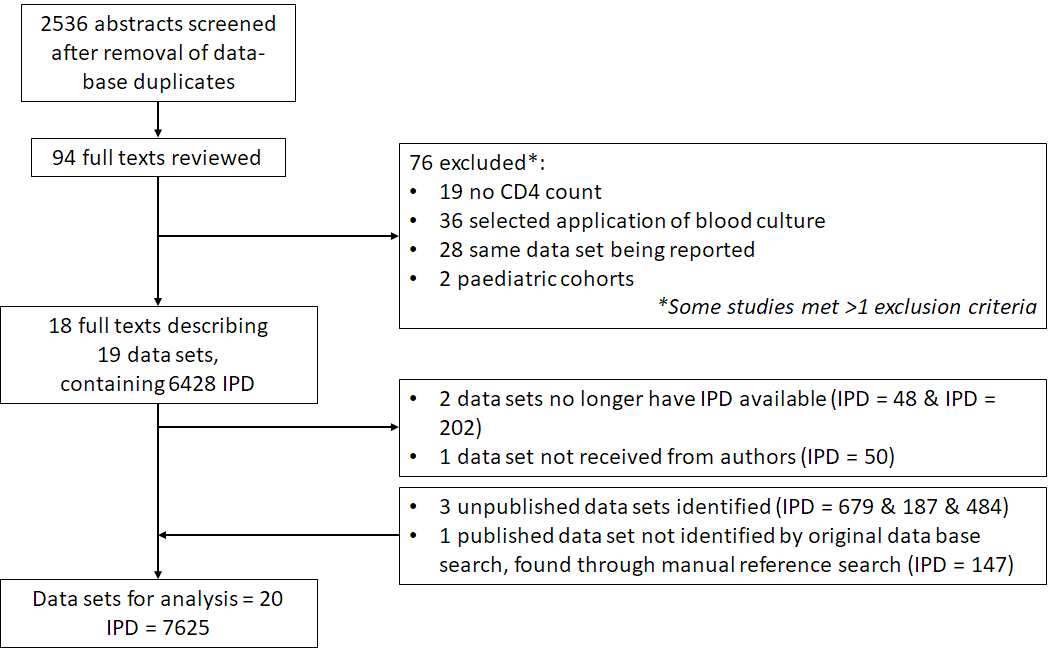
**Results (1194 words)**

The database search identified nineteen datasets for inclusion; four additional datasets were identified from other sources (3 unpublished, 1 missed by database search terms). Responses were obtained from all primary study authors; IPD was lost for two datasets; one dataset was not received. The 20 received datasets represented 96·2% of the sought IPD (Figure 1). Risk of bias was assessed to be generally low except for the domain ‘patient selection’ which was moderate for most studies (Figure S1, appendix pp 7; Table S2, appendix pp 4-5). Application of the harmonised IPD level inclusion criteria left 5,751 patients for analyses. Characteristics of these patients are shown in Table S4 (appendix pp 9), missing data by study in Figure S2 (appendix pp 8). No data from high-income settings met inclusion criteria; 74% of included patients were recruited in sub-Saharan Africa.

Compared to the MTB-BSI prevalence reported in the original publications (Table 1; mean proportion 0·177, coefficient of variation 61·3%), the proportion of patients with MTB-BSI after application of harmonised IPD inclusion criteria was higher, but no less heterogeneous (Table S4, appendix pp 9; mean proportion 0·196, coefficient of variation 61·9%, both in in raw [unimputed] analysis). Mixed-effect logistic regression models (Table S5, appendix pp 10) showed that 6/8 *a priori* selected variables were associated with MTB-BSI (CD4 count, presence of danger signs, hospitalisation status, receiving TB treatment prior to blood culture, number of blood cultures performed, and final diagnosis was TB) and two were non-significant (ART status and year of recruitment). Inclusion of the six significant predictor variables reduced heterogeneity between datasets compared to the null model containing no fixed-effects (τ2 reduced from 0·79 to 0·49, VPC reduced from 0·19 to 0·13), explained substantial total variance (R2conditional increasing from 0·19 to 0·73), and improved within-sample predictive accuracy (ROC AUC increasing from 0·75 to 0·91), while reducing importance of random-effects for predictive accuracy (ΔAUC reducing from 0·25 to 0·01).

The final model, following imputation of missing data, was used to simulate prevalence of MTB-BSI in patients diagnosed with HIV-associated tuberculosis when two blood cultures are collected prior to start of ATT. Inpatients with ≥1 WHO danger sign and CD4 counts below 100 cells/mm3 had the highest predicted probability of MTB-BSI (Figure 2A). For a hospitalised patient with danger signs and CD4 count of 76 cells/mm3 (the median for inpatients), population mean predicted probability of MTB-BSI (i.e., across all datasets) was 0·45, 95% CI 0·38 to 0·52 (Figure 2B). The 95% prediction interval for mean probability of MTB-BSI in a new study was 0·14 to 0·78 (Figure 2B), wider, as would be expected, than the population predicted probability and reflecting remaining between-study heterogeneity despite the inclusion of covariates (Table 4). In sensitivity analysis excluding studies with high or unknown risk of bias, the estimated prevalence of TB-BSI in patients with HIV-associated tuberculosis was similar to the main analysis, but 7% lower, with confidence intervals that overlapped the original estimates: 0.38 95% CI 0.31 to 0.41; the prediction interval for a new study mean was 0.18 to 0.59.

**Figure 1. Identification of primary data sets**



**Table 1. Identified primary datasets**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Dataset ID†** | **1st author** | **Source** | **Data** | **Site** | **Design** | **Dates** | **Primary study population category** | **Reported MTBSI %\*** | **n IPD available** | **n met inclusion$** |
| Brazil 2004 | Bacha | DS | Received | 3o care hosp | cohort | 2001 -02 | Suspected TB IP | 29·5% | 53 | 44 |
| Brazil 1997 | Grinsztejn | DS | Not received | 3 specialist ID centres | cohort | 1992-94 | Suspected TB | 38·0% | NA | NA |
| S.E.Asia 2010 | Varma | DS | Received | HTS OPCs | cohort | 2006-08 | OP | 1·8% | 2009 | 1338 |
| India 2008 | Singh | DS | Received | 3o care hosp | cohort | 2005-06 | Suspected TB IP | 30·8% | 52 | 36 |
| Ivory Coast 1993 | Vugia | DS | No IPD | 3o care hosp | cohort | 1991 | Febrile IP | 4·0% | NA | NA |
| Kenya 1995 | Gilks | DS | No IPD | 3o care hosp | cohort | 1992 | Suspected TB IP | 22·9% | NA | NA |
| Malawi 2012 | Bedell | DS | Received | OP clinics | cohort | 2010 | Suspected TB OP | 2·3% | 469 | 411 |
| Malawi 2013 | Feasey | DS | Received | 2o care hosp | cohort | NA | Febrile IP | 8·7% | 104 | 90 |
| South Africa 2015 | Lawn | DS | Received | 2o care hosp | cohort | 2012-13 | IP | 9·6% | 427 | 338 |
| South Africa 2009 | Shah | DS | Received | 3o and 2o care hosps | cohort | NA | Suspected TB IP | 8·6% | 498 | 264 |
| South Africa 2001 | Von Gottberg | DS | Received | 3o care hosp | cohort | 1998 | Suspected TB IP | 22·5% | 45 | 44 |
| South Africa 2018 | Schutz | PC | Received | 2o care hosp | cohort | 2014-17 | Suspected TB IP | NA | 679 | 615 |
| South Africa 2017 | Griesel | PC | Received | 2o care hosps | cohort | 2011-14 | Suspected TB IP | 23·6% | 484 | 444 |
| South Africa 2006 | Wilson | RS | Received | 2o care hosp | cohort | 2002 | Suspected TB IP & OP | 24·5% | 147 | 141 |
| South Africa 2014 | Nakiyingi | DS | Received | 2o care hosps + OPCs | cohort | 2011 | Suspected TB IP & OP | 9·5% | 513 | 483 |
| Uganda 2014 | Nakiyingi | DS | Received | 2o care hosps + OPCs | cohort | 2011 | Suspected TB IP & OP | 15·6% | 524 | 479 |
| Tanzania 2012 | Crump | DS | Received | 3o care hosps | cohort | 2006-10 | Febrile IP | 5·70% | 411 | 145 |
| Tanzania 2011 | Munseri | DS | Received | 2o + 3ocare hosps | RCT | 2007-08 | Suspected TB IP | 15·9% | 258 | 230 |
| Vietnam 2004 | Louie | DS | Received | 3o care hosp | cohort | 2000 | IP | 12·3% | 100 | 61 |
| Uganda 2009 | Jacob | DS | Received | 3o care hosps | cohort | 2006 | Sepsis IP | 22·1% | 150 | 98 |
| Uganda 2013 | Jacob | DS | Received | 3o care hosps | cohort | 2008-09 | Sepsis IP | 23·4% | 427 | 315 |
| Zambia 2014 | Andrews | DS | Received | 3o care hosp | RCT | 2012 | Sepsis IP | 37·8% | 88 | 58 |
| Zambia 2017 | Andrews | PC | Received | 3o care hosp | RCT | 2012-13 | Sepsis IP | 20·6% | 187 | 117 |

**Footnotes:**

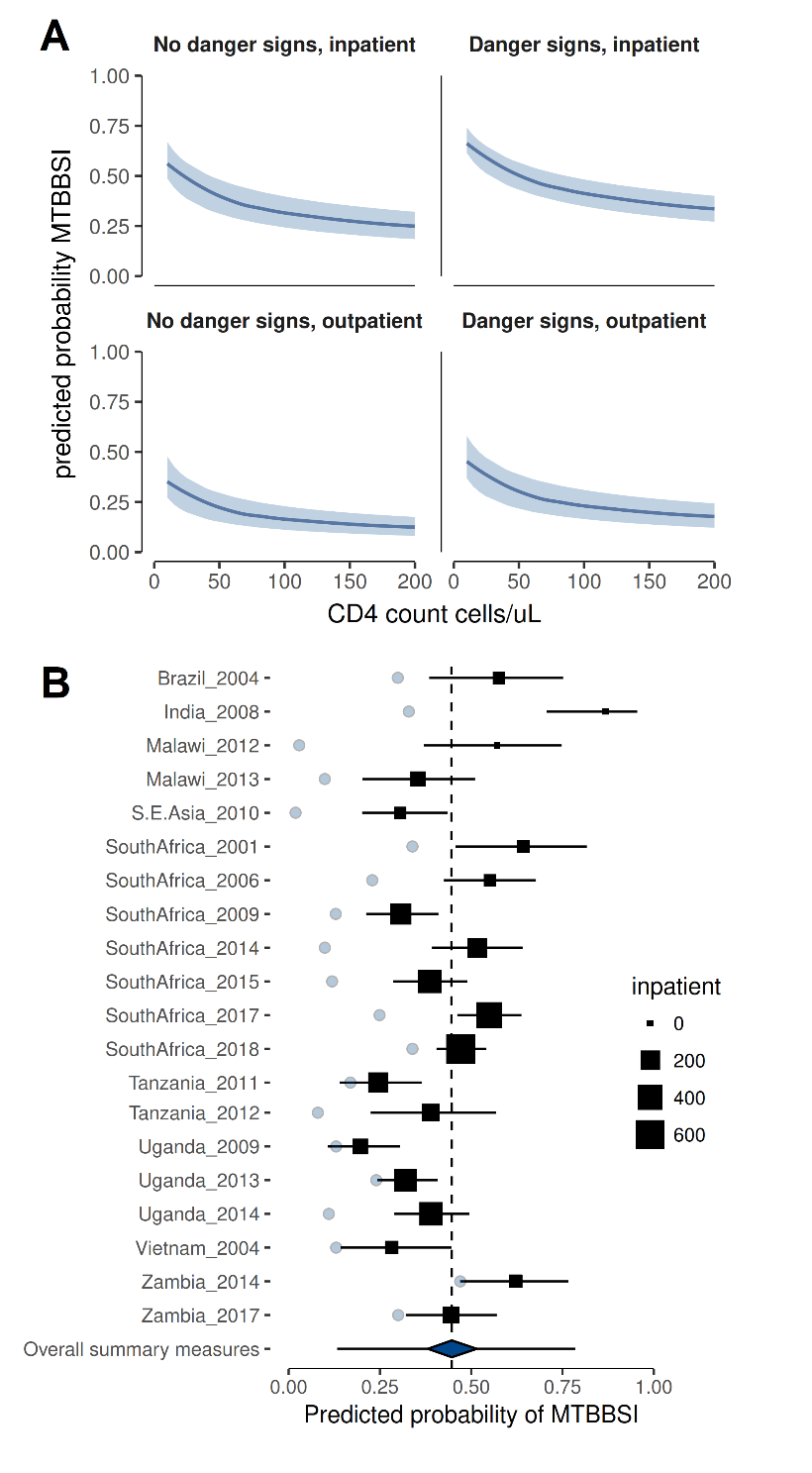
DS = database search; PC = personal contact; RS = manual reference search; hosp = hospital; HTS = HIV testing service; OPC = outpatient clinic; 1o = primary; 2o = secondary; 3o = tertiary; OP = outpatient; IP = inpatient; NA = not available.

All included studies performed mycobacterial blood culture in prospectively defined patient population of PLWH aged ≥13-years and measured CD4 count.

**†** Full citations in table S12 of supplementary appendix, pp 25-26.

\*Disaggregated HIV-positive sample if available

$ IPD level inclusion criteria were: Age ≥13 years, confirmed HIV-infection, available CD4 count, at least one valid mycobacterial blood culture result (excluding patients with missing data from, for instance, lost or contaminated blood cultures), and at least one WHO TB screening symptom.

**Figure 2. Predicted probability of BSI in patients with HIV-associated tuberculosis.**

**Footnotes:**

Based on final model shown in Table 4, following imputation of missing data. All predictions assume 2 tuberculosis blood cultures sent prior to start of anti-tuberculous therapy. **A**. Simulated probability of positive tuberculosis blood culture for PLWH diagnosed with TB at varying covariate levels. Mean predicted probabilities (solid line) and 95% confidence interval (shading) **B**. Predicted probability (as squares) and 95% confidence interval (whiskers) of positive tuberculosis blood culture for danger sign positive inpatients diagnosed with tuberculosis, with a CD4 count of 76 cells/mm3 (the median across datasets). Square size is proportional to number of hospitalised patients in each study. Population mean and 95% confidence interval (all datasets) are shown with dashed line and blue diamond and 95% prediction interval for mean predicted probability of MTB-BSI in a new, unobserved dataset is shown by whiskers around the diamond. Also shown for comparison are the tuberculosis blood culture positivity rates originally reported for each primary study (blue circles).

Next, we estimated diagnostic yield of sputum and urine-LAM testing for patients with MTB-BSI, using the aggregate sputum variable of Xpert or culture if Xpert was not available, and without imputation of missing data (because presence or absence of diagnostic test is a clinically relevant variable that was thought *a priori* to be likely associated with diagnostic yield). In fourteen studies collecting sputum, 545 (84%) of 652 patients with MTB-BSI had a valid sputum sample; 464 (85%) of 545 were positive. Of 554 patients with MTB-BSI, 422 (76%) in the eight studies collecting urine-LAM had a valid urine-LAM result; 304 (72%) of 422 tested positive. In the studies testing both sputum and urine-LAM, 480 (98%) of 492 patients with MTB-BSI had a valid sputum or urine-LAM result, with 424 (88%) of 480 patients having at least one positive test. Availability and results of diagnostic testing stratified by study is shown in Figure S3 (appendix pp 12) and Table S6 (appendix pp 11). All studies performing Xpert used G4 cartridges, and all urine-LAM testing used Alere Determine™ TB LAM Ag test (Alere Inc., Waltham, MA, USA).

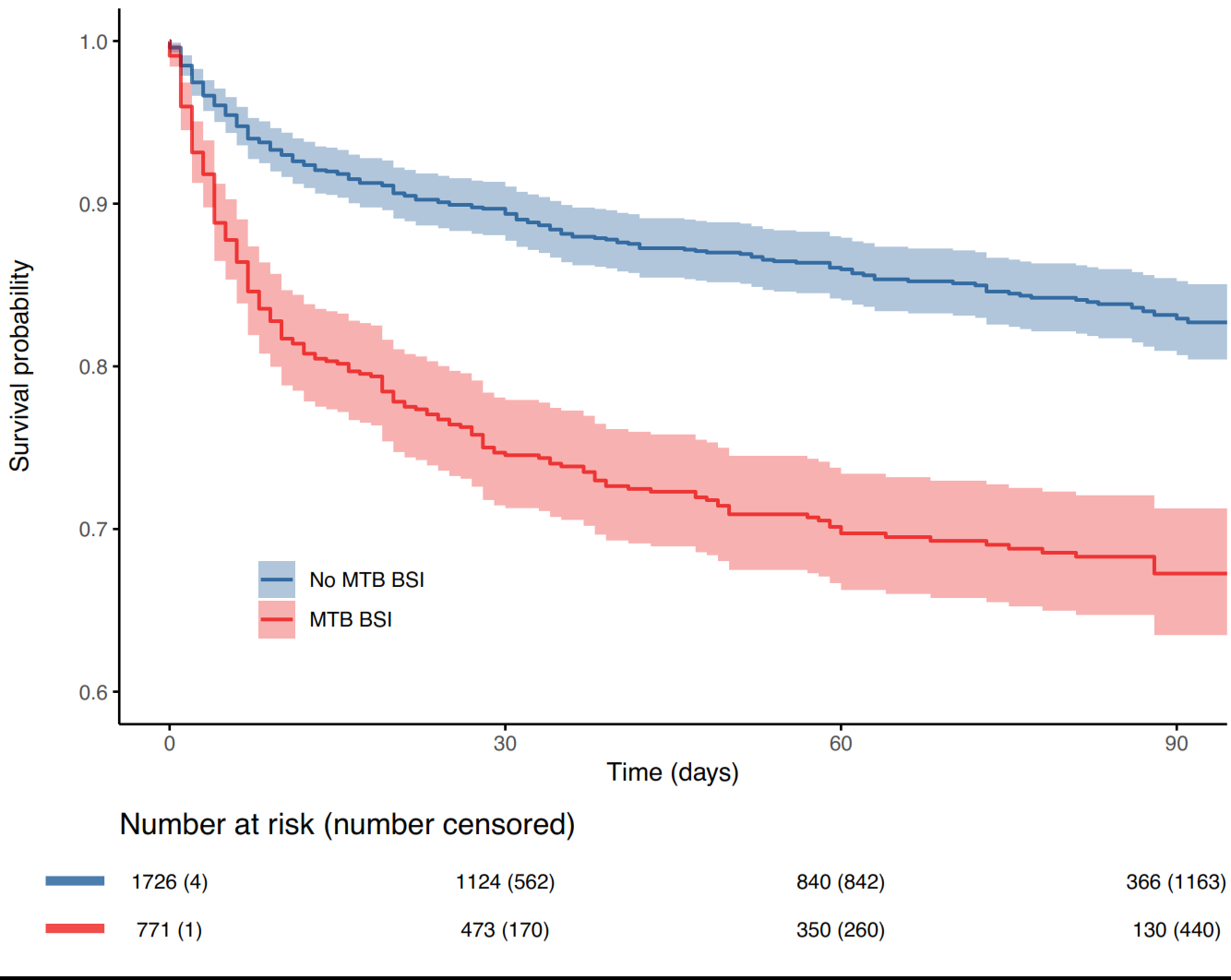
Pooled summary diagnostic yield of urine-LAM was lower than sputum (52% [95% CI 35-69%] versus 77% [95% CI 63–87%], Figure S4A-B, appendix pp 13); composite diagnostic yield (urine-LAM plus sputum) was highest at 89% (95% CI 80-94%, Figure S4C, appendix pp 13). There was significant heterogeneity across studies. Meta-regression showed that proportion with available test explained significant heterogeneity in diagnostic yield of sputum and urine-LAM respectively (both p < 0·0001). Restricting the analysis to the four studies which performed sputum Xpert (avoiding use of culture result as surrogate) reduced sputum diagnostic yield point estimate while increasing uncertainty (72% [95% CI 30-94%], Figure S5, appendix pp 14).

Inability to provide sputum and urine were both associated with MTB-BSI (OR 1·82, 95%CI 1·39 – 2·38; and OR 1·76, 95%CI 1·24-2·47 respectively) and death (OR 2·74, 95%CI 1·90-3·91; OR 5·22, 95%CI 3·54-7·66 respectively) in univariable analysis of unimputed data (Table S7 and S8, appendix pp 15).

Next, we constructed mixed-effect Cox proportional hazards models to identify factors associated with mortality amongst patients diagnosed with tuberculosis (n=2497; Table S9, appendix pp 16), following multiple imputation of missing data. Having MTB-BSI gave a strong unadjusted hazard of mortality (Figure 3) compared to mycobacterial blood culture negative patients with HIV-associated tuberculosis. Since scaled Schoenfeld residuals of sex and presence of MTB-BSI showed a significant interaction with time, coefficients were modelled separately for 0-30 days and 31 – 100 days follow-up. This post-hoc decision (which was not included in our protocol) was made after inspection of the plot of the time varying estimates the coefficient of presence of MTB BSI against time (Supplementary appendix Figure S6, appendix pp 17). MTB-BSI significantly increased the hazard of death before 30 days (HRday0-30 2·48 (95% CI [2·05 – 3·08]) but not after (HRday31-100 1·25 (95% CI [0·84 – 2·49]) in the final model (Table 2). By comparison, urine-LAM status showed weak pooled mortality association, with between-study heterogeneity (Figure S7, appendix pp 18). After adjusting for age, sex, WHO danger signs, CD4 count, and ART status in a *post-hoc* mixed-effect Cox proportional hazards model (equivalent to that used for MTB-BSI above), positive urine-LAM was not significantly associated with mortality (HR 1·24, 95%CI 0·86 – 2·36; Table S10, appendix pp19) in those with a diagnosis of HIV-associated tuberculosis.

Finally we examined the association of time-to-ATT on early mortality (defined as 30-day or inpatient death), in an unimputed analysis. In danger sign positive MTB-BSI patients, early mortality was increased in both participants who started ATT before enrolment and who started ATT > 4 days after enrolment compared to those who started ATT 0-4 days after enrolment (Figure S8A, appendix pp 20). We hypothesised that any causal relationship between time-to-ATT and early mortality was confounded by more urgent treatment in patients at higher risk of death, making shorter time-to-ATT appear harmful, and therefore used propensity score analysis to adjust for this (causal assumptions are shown in a directed acyclic graph in Figure S9, appendix pp 21). From 1208 patients who met inclusion criteria for analysis, 630 patients (420 without and 210 with anti-tuberculosis treatment delay) were matched 2:1 by propensity score for anti-tuberculosis treatment delay, defined as >4 days from blood culture collection to starting ATT (Figures S10, S11 and Table S11, appendix pp 22-23). In patients with MTB-BSI, 13 (27%) of 49 with anti-tuberculosis treatment delay died, compared to 10 (10%) of 98 who experienced no anti-tuberculosis treatment delay (OR 3·2, 95%CI 1·2 to 8·8, p=0·015, Figure S8B, appendix pp 20). This effect size was sensitive to the cut-off used to define anti-tuberculosis treatment delay, progressively reducing when treatment delay was classified as >4, >3, or >2 days (Figure S12, appendix pp 24).

**Figure 3. Pooled Kaplan-Meier curve (solid lines) and 95% confidence intervals (shaded areas) for all patients with tuberculosis diagnosed by any means (n = 2497) stratified by presence (red) or absence (blue) of MTB-BSI.**



**Footnote:**

This plot is generated using a simple pooling of all data, without imputation of missing data.

**Table 2.** **Adjusted hazard ratio of death in patients with a final diagnosis of tuberculosis (n= 2497).**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | | **HR (95% CI)** | **aHR (95% CI)** |
| Outpatient (vs inpatient) | | 0.13 (0.00 – 0.23) | 0·17 (0·07 – 0·33) |
| Age (per 5 years increase) | | 1.11 (1.05-1.15) | 1·12 (1·04 – 1·17) |
| ART at baseline | | 0.98 (0.54 – 1.37) | 0·99 (0·56 – 1·62) |
| Presence of one or more WHO danger signs | | 1.46 (0.95-2.03) | 1·29 (0·80 – 1·63) |
| CD4 count (per 100 cell/mm3 increase) | | 0.81 (0.69 – 0.92) | 0·83 (0·68 – 0·96) |
|  | **MTB-BSI positive\*** | | |
| For death during 0-30 days follow-up | | 2.82 (2.43-3.38) | 2·48 (2·05 – 3·08) |
| For death during 31-100 days follow-up | | 1.38 (0.95 – 2.76) | 1·25 (0·84 – 2·49) |
|  | **Sex, male versus female\*** | | |
| For death during 0-30 days follow-up | | 1.45 (1.19 – 2.04) | 1·27 (1·02 – 1·87) |
| For death during 31-100 days follow-up | | 0.60 (0.41 – 1.22) | 0·56 (0·39 – 1·13) |

**Footnote:**

This table shows the unadjusted and adjusted hazard ratio from Cox proportional hazard model following imputation of missing data. Unadjusted HR includes a random-effect term by dataset.

\*Scaled Schoenfeld residuals of sex and presence of MTB-BSI showed a significant interaction with time, coefficients were therefore modelled separately for 0-30 days and 31-100 days follow-up.

**Words = 1130**

**Discussion**

The results presented here indicate MTB-BSI is a common form of disease in hospitalised patients with advanced HIV-associated tuberculosis in low- and middle-income settings. Previous reports of MTB-BSI prevalence are under-estimates: most studies relied on a single blood culture, did not account for false negative results from antimicrobial carry-over in plasma, and included patients with unobserved blood culture status (e.g., due to contamination) in the denominator. Using modelling and simulation to account for this, we estimate MTB-BSI prevalence to be 45% (95%CI 38%-52%) in danger-sign positive patients with HIV-associated tuberculosis at a median inpatient CD4 count (76 cells/mm3) if two blood cultures are taken, rising to a majority at lower CD4 counts. Substantial heterogeneity in reported MTB-BSI prevalence is explained by these technical and clinical co-factors.

Rapid diagnostics had marked heterogeneity in diagnostic yield in patients with MTB-BSI, partly explained by increased risk of unobtained samples in more critically-ill patients. However, the combination of sputum and urine-LAM testing obtained a pooled diagnostic yield of 0·89 (0·80 to 0·94) in studies where both tests were available. These studies often had dedicated staff to collect spontaneous and/or induced sputum and so managed to obtain sputum from a very high proportion of patients; this may be unlikely in routine practice. The addition of urine-LAM testing to sputum-Xpert reduces mortality in hospitalised PLWH suspected of having tuberculosis with CD4 count <100 cells/mm3 or severe anaemia – sub-groups at highest risk of MTB-BSI.30

MTB-BSI independently predicted mortality before 30 days on meta-analysis, with adjusted hazard ratio 2·5 (95%CI 2·1 to 3·1). Previous studies which found no mortality association of MTB-BSI may have been underpowered15,16 or biased by selective application of the index test.14 By comparison, the association of urine-LAM with mortality was less clear in this meta-analysis. Non-availability of urine for testing was associated with death, raising the possibility of missing-data bias, but imputation of missing urine-LAM data did not affect results. It may be that urine-LAM positivity has a less direct causal relationship to death than positive tuberculosis blood culture, and therefore the mortality association of tuberculosis blood culture is more robust to differences in comparator group case-mix between studies: urine-LAM may have less prognostic information in more critically-ill cohorts, yet strong prognostic significance in a wider patient population.

Finally, we found an association between early mortality (30-day or inpatient) and both very early and delayed time-to-tuberculosis-treatment, an effect often seen in (non-mycobacterial) sepsis literature where both the shortest and longest time-to-antimicrobial therapy groups have the highest risk of death,31-33 likely due to confounding by disease severity.34,35 By accounting for this with propensity score matching we provide evidence that delaying ATT is associated with early mortality in patients with MTB-BSI (OR 3·2, HR 1·2 to 8·8).

A major limitation of this study is variation in inclusion criteria of the primary data sets, identified as the largest source of potential bias. Even after adjusting for technical and clinical factors, heterogeneity persisted between primary studies in MTB-BSI prevalence estimates. Subsequent adjustment for final diagnosis of tuberculosis had the largest reduction in variance attributable to random effects between studies. Consequently, we limited our prevalence estimates to patients with HIV-associated tuberculosis and did not estimate prevalence in other protocol specified sub-groups (patients with suspected tuberculosis and patients with sepsis syndrome). Variations in study design and conduct could also explain heterogeneity in sputum diagnostic performance; two studies had explicit biases – exclusion of patients unable to produce sputum despite induction,36 and exclusion of smear-positive patients.37 Datasets where the primary study aim was testing performance of diagnostics had highest observed diagnostic yield, while cohorts recruited to explore mortality associations had lower yield. We relied on sputum culture as a surrogate for Xpert testing which will have overestimated sensitivity (and therefore diagnostic yield) of sputum testing. Several studies had systematically missing data on co-factors. Missing data was multiply imputed accounting for clustering by data set, and uncertainty associated with imputation accounted for in confidence intervals; this will have reduced risks from missing data bias at the expense of greater imprecision. This method could not, of course, account for measurement error; in particular it seems likely that measurement error is an explanation for the absence of an independent association between ART status and MTB-BSI prevalence and death. We imputed 5 datasets; more may have been desirable but fitting the mixed effect models on more imputed datasets became computationally infeasible in a reasonable timeframe. There are other limitations: 74% of included patients were recruited in sub-Saharan Africa; care is warranted in attempting to generalise findings to elsewhere. We assessed risk of bias using a modified QUADAS-2 framework but classifying risk of bias in observational IPD meta-analyses is a difficult task with no gold standard tool; bias may have been under or overestimated. Finally, the analysis suggesting a mortality association of anti-tuberculosis treatment delay was designed after protocol registration and data collection, and is limited by sample size and the possibility of unmeasured confounding.

Our findings have several implications. Firstly, when the WHO algorithm for managing seriously ill patients is being applied to patients with HIV-associated tuberculosis, it is *de facto* being applied to patients with the highest risk of MTB-BSI. The recommendations contained in the algorithm therefore must be valid for patients with MTB-BSI. Sputum testing with Xpert is the central rapid-diagnostic step recommended in the WHO algorithm. Sensitivity of tuberculosis diagnostics in PLWH have substantial unexplained heterogeneity on meta-analysis.10,38-40 Our results show that marked variation in sample availability has an even greater effect on diagnostic yield in critically-ill MTB-BSI patients. We found probability of obtaining sputum and urine was reduced in the sickest patients, a significant concern for the *seriously-ill patient* algorithm, as reliance on these rapid diagnostics may be delaying treatment in patients at greatest risk of death. Our results support routine use of both sputum-Xpert *and* urine-LAM in parallel for danger-sign positive inpatients, to help off-set this risk.

The WHO algorithm recommends delaying presumptive anti-tuberculosis treatment for 3-5 days when rapid tests are non-diagnostic. Our study raises a concern that this delay is associated with an increase in early mortality. Trials of presumptive tuberculosis therapy in PLWH had negative results;41-43 but recruited ambulant (danger-sign negative) outpatients, so will have largely excluded patients with MTB-BSI, in whom the benefit of early empirical therapy is most likely.

MTB-BSI accounts for a disproportionate burden of disease in seriously ill PLWH. Tuberculosis remains the major cause of in-hospital death in HIV-positive adults; MTB-BSI is a major predictor of this mortality. Risk-benefit and utility of rapid diagnostics and empirical therapy are different for MTB-BSI compared to non-bacteraemic HIV-associated tuberculosis, and require specific evidence. Trials of tuberculosis treatment in PLWH have almost exclusively recruited sputum smear-positive ambulant outpatients.44 Consequently, there is a profound limitation of data supporting current management of HIV-associated MTB-BSI. Pragmatic interventional studies assessing early empiric treatment and/or intensified therapy strategies for MTB-BSI are needed.

**Contributors**

JML, DAB, GD, NF, DL, CS & GM conceived the study. JML & DAB designed and coordinated the study performed literature searches, analysis, and wrote the first manuscript draft, which was reviewed by all authors. Manuscript was revised based on comments from co-authors, including suggestions for additional and novel analyses. DAB, NF, CS, ADK, STJ, BA, PK, SL, LM, HB, DH, RB, MvL, RZ, JAC, DA, ELC, KG, SS, RG, GaM, MM, AMW, CMP, EAT, PM, SD, NM, MS, KC, CMH, JV, AvG, LS, DW & GrM collected and curated primary study data and meta-data. All authors approved the final version of the manuscript.

**Declaration of interests**

David Alland is on the Scientific Advisory Board of Specific Technologies and receives a portion of the licensing income paid by Cepheid to Rutgers University for sales of the Xpert Ultra assay. Neil Martinson has received institutional grants for collection of specimens for Roche and Becton Dickinson, and from Pfizer for assessing incident pneumonia. All other authors declare no competing interests.

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