Treatment outcomes in adult tuberculous meningitis: a systematic review and meta-analysis.

Anna M Stadelman*, Jayne Ellis*, Thomas HA Samuels, Ernest Mutengesa, Joanna Dobbin, Kenneth Ssebambulidde, Morris Rutakingirwa, Lillian Tugume, David R Boulware, Daniel Grint, Fiona V Cresswell

1. Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN 55455, USA
2. Hospital for Tropical Diseases, University College London Hospitals NHS Foundation Trust, London, UK
3. University College London Hospitals NHS Foundation Trust, London, UK
4. Hillingdon Hospital, The Hillingdon Hospitals NHS Foundation Trust, Uxbridge UB8 3NN, UK
5. Clinical Research Department, London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT
6. Infectious Diseases Institute, Makerere University, PO Box 22418, Kampala, Uganda
7. MRC-UVRI-London School of Hygiene and Tropical Medicine Uganda Research Unit, Entebbe, Uganda
8. Division of Infectious Diseases and International Medicine, Department of Medicine, University of Minnesota, Minneapolis, MN, USA
9. Tropical Epidemiology Group, Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, WC1E 7HT

* authors contributed equally.
Corresponding author: Anna Stadelman, Infectious Diseases Institute, Kampala, Uganda, Email: stad0110@umn.edu

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Abstract

Background: There is substantial variation in the reported treatment outcomes for adult tuberculous meningitis (TBM). Data on survival and neurological disability by continent and HIV serostatus are scarce.

Methods: We performed a systematic review and meta-analysis to characterize treatment outcomes for adult TBM. Following a systematic literature search (MEDLINE and EMBASE), studies underwent duplicate screening by independent reviewers in two stages to assess eligibility for inclusion. Two independent reviewers extracted data from included studies. We employed a random effects model for all meta-analyses. We evaluated heterogeneity by the $I^2$ statistic.

Results: We assessed 2,197 records for eligibility; 39 primary research articles met our inclusion criteria reporting on treatment outcomes for 5,752 adults with TBM. The commonest reported outcome measure was six-month mortality. Pooled six-month mortality was 24% and showed significant heterogeneity ($I^2>$95%; $p<0.01$). Mortality ranged from 2% to 67% in Asian studies and from 23% to 80% in sub-Saharan African studies. Mortality was significantly worse in HIV-positive adults at 57% (95%CI; 48-67%), compared with 16% (95%CI; 10-24%) in HIV-negative adults ($p<0.01$). Physical disability was reported in 32% (95%CI; 22-43%) of adult TBM survivors. There was considerable heterogeneity between studies in all meta-analyses with $I^2$ statistics consistently >50%.

Conclusions: Mortality in adult TBM is high and varies considerably by continent and HIV-status. The highest mortality is amongst HIV-positive adults in sub-Saharan Africa. Standardized reporting of treatment outcomes will be essential to improve future data quality and increase potential for data sharing, meta-analyses, and facilitating multi-center tuberculosis research to improve outcomes.
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**Article Main Point**

We found that mortality for adults with tuberculous meningitis was highest in HIV-positive adults and in sub-Saharan Africa. Over 90% of deaths occur in the first three months, indicating that 3-month mortality may be an acceptable randomized clinical trial endpoint.
Background:

In 2018, ten million cases of tuberculosis were reported globally;¹ tuberculosis meningitis accounts for 1-5% of these cases.² Tuberculous meningitis is the most severe form of tuberculosis and is responsible for a considerable burden of neurological sequelae and mortality; a systematic review of treatment outcomes in 1,636 children with tuberculous meningitis estimated a mortality of 19.3%.³ There is considerable variation in the reported outcomes for adult tuberculous meningitis across available studies, the reasons for which remain unclear. Two recent systematic reviews of adult tuberculous meningitis outcomes reported substantial heterogeneity in mortality, the proportion of deaths among those diagnosed with TBM, with pooled estimates of 22.8% and 24.7%.⁴ ⁵ However, neither review attempted to explain the variation in treatment outcomes by stratifying studies by HIV status and geographical location. In addition, Wen and colleagues excluded all investigational treatment studies effectively excluding major treatment randomised controlled trials (RCTs) investigating regimens that have now become the standard of care (e.g. adjunctive steroids and delayed antiretroviral therapy (ART) for those with HIV-associated tuberculous meningitis). Furthermore, there is a paucity of data in recent meta-analyses on drug resistance rates, treatment regimens, and steroid use. HIV co-infection has been shown to be a risk factor for death (Hazard Ratio 2.5; 95% CI 1.9-3.4) in Vietnamese adults with tuberculous meningitis,⁶ but this remains to be explored systematically in other regions.⁷ ⁹ Neurological disability in adult tuberculous meningitis survivors has not been studied in detail in meta-analyses. In two recent systematic reviews, prevalence of disability in adult tuberculous meningitis survivors varied between 29% and 50%.⁴ ⁵ However neither review provided data on the nature and severity of neurological sequelae in tuberculous meningitis survivors.

We performed a systematic review and meta-analysis to characterize treatment outcomes, namely all-cause mortality and neurological sequelae, for adult tuberculous meningitis across a
range of epidemiological settings. We endeavored to perform a definitive review by including the best quality data available and performing a robust quality assessment of the studies included.

Methods:

Literature search strategy

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for the reporting of systematic reviews and meta-analyses. A systematic electronic search was conducted using MEDLINE and EMBASE with the aim of identifying all studies reporting treatment outcomes in adult tuberculous meningitis from 1988 to present. This time period corresponds to the WHO recommendation of standard quadruple therapy for the treatment of tuberculosis. Controlled and natural language terms identified key search concepts such as: “tuberculosis”, “meningitis”, “mortality”, “complications” and “outcome.” Full search strategies are presented in Appendix A. Searches were conducted on 9 July 2018.

Study selection

A two-stage sifting process was employed: (1) at title and abstract; and (2) at full text level according to eligibility criteria as detailed below. Sifting was performed in duplicate independently by two reviewers and any unresolved disagreements were resolved by a third, independent reviewer. Reference and citation checking were conducted for included articles.

Studies were eligible for inclusion if they (i) included adults (aged ≥ 15 years) with confirmed or suspected TB-meningitis; (ii) utilized diagnostic criterion to systematically evaluate patients for tuberculous meningitis; (iii) reported on at least one of the following outcome measures: neurological sequelae, in-hospital mortality, mortality at the end of follow-up (v) employing any
of the following study designs: consecutive case series, case control study, cohort study, randomized controlled study, systematic review, or meta-analysis.

The following exclusion criteria were applied: (i) studies with fewer than 10 participants; (ii) studies limited to specific complications or comorbidities (e.g. hydrocephalus, tuberculoma, or surgical intervention); (iii) studies not providing at least a backbone of standard fixed dose combination anti-tuberculous therapy; (iv) studies not specifying treatment given; (v) studies published before 1988; (vi) studies not written in English; (vii) any systematic review superseded by an updated systematic review; (viii) narrative reviews not adding new data or new analysis of data to existing knowledge.

Data extraction and data synthesis

Two authors independently extracted data on study characteristics, recruitment populations, and treatment outcomes from eligible studies using a standardized, piloted electronic data capture database (REDCap, Vanderbilt University, USA). We captured data on geographical region, number of HIV-positive participants, British Medical Research Council (MRC) tuberculous meningitis grade at presentation, treatment regimens utilized, use of corticosteroids, and outcomes reported at specified time points for each study. Any unresolved disagreements in extraction were resolved by a third, independent reviewer.

We used each study’s definition of neurological sequelae as reported in the study. For articles that utilized the modified Rankin Scale or the Barthel index, “disability” was defined as ‘any disability that impeded the patient’s ability to carry out tasks they once performed’. This is was represented as a score of >2 on the modified Rankin Scale or <80 on the Barthel Index.

For systematic reviews, individual study level data were not extracted or analyzed, only the summary estimates were recorded for comparison, and citation checking was performed to ensure all relevant source manuscripts had been identified.
Data analysis

We used the proportion of all-cause deaths and neurological sequelae within each study to define outcomes of tuberculous meningitis for the meta-analyses. As such, all meta-analyses used random effects models and employed the DerSimonian and Laird method on Freeman-Tukey transformed proportions, which is the established approach for this type of analysis.\(^\text{11-13}\) We graphically displayed data in forest plots, which display point estimates of tuberculous meningitis outcomes in each study, with 95% confidence intervals. We generated pooled effect estimates by inverse-variance weighting each individual point estimate such that the estimates with lower variances contributed more to the pooled estimate.\(^\text{13}\) The overall pooled estimate for mortality was stratified by follow-up outcome reporting time. Inter-study and sub-group heterogeneity were assessed with the \(I^2\) statistic. All analyses were conducted in Stata version 15·1 (StataCorp, College Station, TX, USA) with the "metaprop" command.\(^\text{14}\)

Quality assessment

The 39 articles included in the meta-analysis were assessed for study quality using the Downs and Black tool, a 27-item quality assessment checklist.\(^\text{15}\) Each study was scored on a 32-point scale for items that examined quality of reporting, external validity, internal validity (bias and confounding), and study power. Study power was estimated according to sample size methodology. Studies were scored as follows; 0 if no sample size calculation was made or reported in the manuscript (given for observational studies); 3 if a power calculation was done but there were insufficient numbers of patients recruited; 5 if the power calculation was done and sufficiently powered. Systematic reviews meeting the inclusion criteria were not assessed for risk of bias. As treatment outcomes were of interest in these analyses and not treatment or intervention efficacy, we included all studies regardless of quality assessment score.
Role of funding source

The Fogarty International Center of the National Institutes of Health, USA provided funding fellowship support to the lead author of the study. The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results:

Search results, studies, and participants included

Our searches yielded 2,562 reports, after removal of duplicates (n=365), 2,197 studies underwent title and abstract screening, and 264 full texts were reviewed (Figure 1). 39 studies met our eligibility criteria for inclusion and analysis (Table 1). These 39 studies were published between 1995 and 2018 of which: 10 (26%) were case series, 21 (54%) were cohort studies, and eight (21%) were randomized controlled trials. Studies arose from 18 countries including a range of epidemiological settings; 24 (62%) were from high-TB burden settings and 15 (38%) were from low-TB burden settings. A total of 26 (67%) studies were conducted in Asia, and five (13%), five (13%), and two (5%) in Europe, Africa, and the Americas, respectively (Figure 2). Study quality scores ranged from eight to 32, with a score of 32 indicating the highest quality. Median quality score for included articles was 18 (IQR; 15-20). Our meta-analysis includes reported treatment outcomes for 5,752 adults with tuberculous meningitis. Participant age ranged from 15 to 88 years. Seven studies included 1,078 HIV-positive patients: 302 (28%) from Africa, and 776 (72%) from Asia. MRC tuberculous meningitis grade was reported in 29 studies, in which 28% (1354/4761) of participants presented with MRC grade I disease, 48% (2302/4761) with grade II, and 20% (967/4761) with grade III. A total of 37 studies (n=5,623
participants) reported the classification or uniform case definition of enrolled participants. Of those, 40% (2,243/5,623) were microbiologically-confirmed tuberculous meningitis, 49% (2,741/5,623) were suspected tuberculous meningitis, the latter of which included 21% (1,013/5,623) with probable tuberculous meningitis and 12% (663/5,623) with possible tuberculous meningitis according to the uniform case definition. Only 12 studies reported on drug resistance rates; 10 studies included patients with multi-drug resistant tuberculosis (n=49) and 12 studies included patients with mono-drug resistant tuberculosis of which 10 studies included isoniazid resistance (n=112 participants); six studies included rifampin resistance (n=12 participants), and one study included streptomycin resistance (n=1 participant).

The most common treatment regimen was standard four-drug therapy of rifampicin, isoniazid, pyrazinamide, and ethambutol (RHZE) with no additional anti-tuberculous drugs (n=17 studies). Seven studies used streptomycin in addition or in replacement for ethambutol (Table 1). Median treatment duration was nine months (IQR; 9-12 months). Corticosteroids were given to all patients in 19 studies, and to some participants in 10 studies (Table 1). Treatment outcomes by corticosteroid use was examined in a meta-analysis with included studies, but this was not the aim nor design of our meta-analysis and a significant amount of heterogeneity in mortality between studies was unexplained (Appendix B). A Cochrane meta-analysis on corticosteroid use in TBM was published in 2016.17

Mortality assessment and outcomes

A wide range of mortality end-points were reported: 15% (6/39) studies reported one-month mortality, 5% (2/39) studies reported two-month mortality, 8% (3/39) studies reported three-month mortality, 18% (7/39) studies reported six-month mortality, 13% (5/39) studies reported 12-month mortality, and 2% (1/39) reported five-year mortality. Other reported outcomes included in-hospital mortality (n=6 studies) and median-time to death (n=4 studies). In the six studies which reported on ‘in-hospital mortality’, only one study reported on the length of
hospitalization which ranged from 4-10 days until death or discharge. Five studies did not define the ‘in-hospital mortality’ in terms of time frame.

To investigate time-specific mortality, articles were grouped by follow-up outcome reporting time point. Articles that reported outcomes less than or equal to three months were included in the three-month reporting category to summarize ‘early’ mortality. Articles that reported outcomes greater than three months to six months were included in the six-month reporting category. Articles that reported outcomes greater than six months were included in the 12-month reporting category. Of articles reporting outcomes at three, six, and 12 months, pooled mortality was 23% (95% CI; 14-35%), 23% (95% CI; 14-33%), and 25% (95% CI; 17-33%), respectively (Figure 3). There was significant heterogeneity ($I^2 = 95\%; p<0.01$) for all outcome reporting timepoints. There was no marked heterogeneity in mortality between outcome reporting timepoints ($p=0.60$), but it was included in the pooled analysis resulting in a pooled mortality of 24% (95% CI; 19-29%).

**Mortality endpoints by HIV status**

Seven studies reported mortality for HIV-positive adults. For HIV positive adults, pooled mortality was 57% (95% CI; 48-67%), compared with 16% (95% CI; 10-24%) in HIV-negative adults (Figure 4). HIV status explained a significant amount of the observed heterogeneity in tuberculous meningitis mortality ($p<0.01$).

**Mortality endpoints by geographical region**

Most studies reporting on tuberculous meningitis mortality were conducted in India and the Asian continent ($n=27; 70\%$) where pooled mortality ranged from 2-67% (Figure 2). The countries reporting the highest tuberculous meningitis mortality were located in sub-Saharan Africa where mortality ranged from 23-80%. Continent (Africa vs. Asia) explained a significant amount of the observed heterogeneity in tuberculous meningitis mortality ($p=0.02$).
Temporal variation in mortality endpoints

To investigate changes in tuberculous meningitis treatment outcomes over time, we conducted a temporal analysis in which individual studies were allocated to one of five time periods and stratified analyses conducted. Time periods were sub-divided into five-year windows from 1995 onwards, and pooled mortality analyzed within each time window. Highest pooled mortality was 31% (95% CI; 14-51%) in articles published from 2006-2010, though there was no significant variation by time window (Appendix C). In earlier time periods, the heterogeneity in survival was greatest and heterogeneity appears to have reduced in the more recent time periods.

Neurological disability

Functional outcomes among survivors was a pre-specified endpoint in 24 studies; 10 studies reported on functional outcomes using the modified Rankin Scale score (n=6) or the Barthel index (n=5), and 10 studies reported on neurocognitive disability without using a specified scale or measurement tool, and five studies reported using “clinical assessments”.

The timing and method of neurological assessments varied between studies; the most commonly used outcome assessment being physical disability conducted at the end of follow up. In this analysis, participants were considered disabled if there was any indication of functional disability as reported by the modified Rankin Scale or Barthel Index. Of the studies utilizing the modified Rankin Scale, the pooled proportion of patients experiencing some level of physical disability was 26% (95% CI; 18-35%) with considerable heterogeneity (Appendix D). Of the studies using the Barthel Index the proportion of patients experiencing some level of physical disability was 32% (95% CI; 22-43%) with only moderate heterogeneity.
Discussion:

In this rigorous systemic review and meta-analysis, we reviewed treatment outcomes for over six thousand adults with tuberculous meningitis, and our data clearly demonstrate that the mortality and neurological sequelae associated with tuberculous meningitis remains unacceptably high. Although there was significant heterogeneity between studies ($I^2 > 95\%$), overall risk of death was 23\% at three months, and 25\% at 12 months. In patients that did survive, neurological sequelae were common, affecting nearly one third of all patients. Furthermore, our temporal analysis of treatment outcomes indicate that prognosis has improved little over time. Our results are in concordance with two recently published systematic reviews which reported overall mortality associated with adult tuberculous meningitis to be 23\% and 25\%, and risk of neurological sequelae to be 29\% and 50\%, respectively. Our study expands on the current literature through sub-group meta-analyses to evaluate differential treatment outcomes by HIV status and geographical region.

We have demonstrated that patients with HIV-associated tuberculous meningitis have three-fold higher mortality compared to HIV-negative cohorts; mortality in HIV-negative cohorts ranged between 10-24\% compared to 48-67\% in HIV-positive cohorts ($p < 0.01$). Pathogenesis research is urgently needed to investigate the disproportionate mortality associated with HIV co-infection in tuberculous meningitis, and to identify potential interventions or preventative measures.

Secondly, our data demonstrate that despite adoption of standardized treatment regimens for tuberculous meningitis, considerable global disparities in treatment outcomes exist. Pathogenesis work has shown that even within a Vietnamese population a single genetic polymorphism significantly impacts on corticosteroid responsiveness and survival from TBM.$^{18}$ The extent of the heterogeneity observed in this meta-analysis raises the possibility that genetic or other latent factors may contribute to outcome and the current one-size-fits all approach to
treatment may be effective in some individuals/populations and less effective in others. Our sub-
group meta-analyses indicate that patients in the African continent have a higher mortality
compared to all other continents. This may in part be explained by the higher co-prevalence of
HIV. However, given the considerable resource limitations including a lack of intensive care
facilities typical of many settings in sub-Saharan Africa, it is likely that the management of
commonly encountered complications of tuberculous meningitis including hyponatraemia, raised
intracranial pressure, hydrocephalus, stroke, and nosocomial infections are suboptimal. Further
research is needed to determine the attributable mortality due to a lack of supportive or critical
care in sub-Saharan Africa. Our systematic literature review highlights the historical paucity of
clinical studies published from this continent. In order to address the devastatingly poor
outcomes from HIV-associated meningitis, particularly for those in sub-Saharan Africa, we need
to design, fund and deliver more clinical research.

Our meta-analyses of follow-up time-specific mortality at three, six, and twelve months,
highlight that over 90% of tuberculous meningitis deaths occur in the first three months. This
may justify that three-month mortality is a reasonable RCT endpoint, potentially making study
trial follow-up shorter and cheaper, and therefore accelerating research outputs. However, the
considerable heterogeneity found in these analyses as well as inconsistencies in reporting
outcomes, indicates that further evidence is needed to justify a three-month clinical trial
endpoint. Clinical studies to identify drivers of early mortality in tuberculous meningitis may
inform the design of treatment intensification strategies and other adjunctive interventions.

Concerningly, our results demonstrate that minimal improvements in survival have been
made over time. There are a number of temporal factors which may have affected outcomes in
certain time periods including the height of the HIV epidemic in the 1990-2005 period, ART
rollout in the 1995 to 2010 windows, the increasing availability of more rapid diagnostics in the
form of the Xpert MTB/Rif assay in 2010 to 2020 windows facilitating the diagnosis of
tuberculous meningitis where it was previously unconfirmed, and lastly gradually increasing rates of anti-tuberculous drug resistance worldwide. Reporting bias, which may have varied over time, must also be considered.

Our analysis has several limitations. Firstly, although we only included studies which employed a pre-specified diagnostic criterion for tuberculous meningitis, there was considerable variation in the quality of diagnostic criteria used, and diagnostics have changed over time. We chose not to restrict diagnostic criteria to microbiologically confirmed tuberculous meningitis, because doing so would have restricted our meta-analysis to 40% (n=2,243) of adults, and furthermore we wanted our results to be generalizable to real world clinical settings where confirmation rates are often only moderate. We do however recognize that misclassification of undifferentiated meningitis cases as tuberculous meningitis is common, especially when left to physician discretion; as may have been the case in some of the patients included in our meta-analysis and therefore this would undermine the accuracy of our outcome estimates. Secondly, in the spirit of generalizability we chose to include case-series, which are primarily descriptive and not wholly representative of the populations they are drawn from. Although this may have posed some unmeasurable bias, we believe that this would not have substantially impacted our results since mortality and neurological sequelae, our outcomes of interest, would not have measured differently or changed based on study design. Thirdly, the specific antituberculous regimen utilised and drug resistance rates within the cohorts was inconsistently reported in studies therefore we were unable to conduct stratified meta-analyses based on drug resistance patterns. The International Tuberculous Meningitis Research Consortium paper on standardized methods for enhanced quality and comparability of tuberculous meningitis studies, specify that it is essential to document the dose, route of administration, and duration of all antituberculosis drugs used in tuberculous meningitis studies. There remain several outstanding questions concerning the optimal treatment of tuberculous meningitis, and therefore to facilitate cross
study comparisons and interrogate differences in study outcomes basic information about the treatment provided is essential.

Finally, there was a considerable lack of standardization of reporting on treatment outcomes. This was particularly marked with respect to reporting of neurological sequelae; firstly, neurological sequelae were rarely reported (only 10/39 (26%) studies including any data on neurological sequelae), the tools used were inconsistent (nine tools in total) and the time-points for assessment were rarely reported. This inconsistent reporting hampered comparison of data across studies. Given the importance of neurological disability in tuberculous meningitis and the importance of developing a standardized evidence base against which to assess new treatments, the International Tuberculous Meningitis Research Consortium recommend that the modified Rankin Score should be used as the first line tool, which should be recorded at 12 months from antituberculosis treatment initiation in all adults. We support this recommendation, and in addition would suggest that mortality be routinely reported on at three, six, and 12 months if possible, to improve study comparability.

The strengths of this work include its size, with 39 individual studies included studies from Asia, Africa, Europe and the Americas making our estimates broadly generalizable to a range of settings. Our systematic review is larger than two previously published systematic reviews of adult tuberculous meningitis. In comparison to Wen et al, we decided to include randomized control trials in our systematic review which enable us to include the highest quality of trial evidence, and we also reported drug resistance rates within each included study. In comparison to Wang et al, we ascertained variation in treatment outcomes geographically, and reported on the nature and severity of reported neurological sequelae. Overall, we assessed a wide range of co-variates to investigate the heterogeneity in treatment outcomes observed. To our knowledge, this is the most extensive critical appraisal of tuberculous meningitis outcomes to date.
In conclusion, adult tuberculous meningitis is associated with considerable neurological morbidity and mortality and remains a major challenge in TB endemic regions. The worst outcomes are observed by those with HIV co-infection in sub-Saharan Africa where risk of death is three-fold higher. Our study was limited by suboptimal reporting on diagnostic criteria utilised, drug resistance rates, details of treatment regimens used, as well highly variable outcome reporting. Adoption of standardized reporting systems across tuberculous meningitis studies would not only facilitate across study comparisons, but overall would also improve the quality of research outputs and support collaborative research across centres with an aim of improving tuberculous meningitis outcomes globally.

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| First Author | Year | Study Design | Country  | N | Diagnostic Criteria | HIV N (%) | Confirmed TBM N (%) | Suspected TBM N (%) | MDR TB N (%) | INH mono-R N (%) | Antituberculous treatment | Steroids | Outcome(s) and Time point reported |
|--------------|------|--------------|----------|---|---------------------|-----------|---------------------|--------------------|---------------|----------------|-----------------------------|----------|---------------------------------|
| **AFRICA**   |      |              |          |   |                     |           |                     |                    |              |                 |                             |          |                                 |
| Luma 20      | 2013 | Case Series  | Cameroon | 54| 2 a b               | 54 (100%) | 1 (2%)              | 53 (98%)           |              |                | 2RHZE/6-8RH                |          | All received steroids: unspecified drug(s), dose, & duration |
| Marais 21    | 2011 | Cohort      | South Africa | 120 | 2 a b c d e f | 106 (88%) | 47 (39%)           | 73 (61%)           | 3 (3%)        | 3 (3%)        | RHZE                        |          | In-hospital and 6-month mortality |
| Thinyane 22  | 2015 | Case Series | Lesotho  | 22 | 2 a b e f          | 15 (68%)  | 0 (0%)             | 22 (100%)          |              |                | RHZE                        |          | Mortality at the end of follow up |
| Cresswell 23 | 2018 | Cohort      | Uganda   | 195| 2 a b c d          | 106 (54%) | 74 (38%)           | 93 (48%)           | 0 (0%)        | 0 (0%)        | RHZE                        |          | In-hospital mortality |
| Raberahona 24| 2017 | Case Series | Madagascar | 75| 1                   | 3 (4%)    | 8 (11%)           | 44 (59%) probable 23 (31%) possible |              |                | 2RHZE/6RH + S if prior TB (n=2) |          | Mortality at 8 months |
| **SOUTH AMERICA** |      |              |          |   |                     |           |                     |                    |              |                 |                             |          |                                 |
| Gonzalez-Duarte 25 | 2011 | Cohort    | Mexico | 64 | 2 a c f           | 14 (22%)  | 44 (69%)           | 20 (31%)           |              |                | 2RHZE/RH - mean time of therapy was 11.9 ± 7 months |          | 57 (78%) received steroids, unspecified drug(s), dose & duration |
| Alarcon 26   | 2013 | Cohort      | Ecuador | 310| 2 a b d e f g h | 2 (1%)    | 140 (45%)         | 170 (55%)          |              |                | 2RHZE + E or S or quinolone / 10RH (quinolone given to some) |          | Steroids given to patients with severe disease, unspecified drug(s), dose & duration |
| **ASIA**     |      |              |          |   |                     |           |                     |                    |              |                 |                             |          |                                 |
| Torok 27     | 2008 | Cohort      | Vietnam | 58 | 2 b d e f         | 58 (100%) | 54 (93%)           | 4 (7%)             | 4 (7%)        |                | 3RHZE + S if prior TB/6RH |          | D (0·3–0·4mg/kg) tapered over 6-8 weeks |
| Torok 28     | 2011 | RCT         | Vietnam | 253| 2 a b d e f       | 253 (100%) | 158 (62%)         | 95 (38%)           | 4 (2%)        |                | 3RHZE + S if prior TB/6RH |          | D (0·3–0·4mg/kg) tapered over 6-8 weeks |
| Heemskerk 6  | 2016 | RCT         | Vietnam | 817| 1                 | 349 (43%) | 407 (50%)         | 214 (26%)          | 174 (21%)   | 15 (2%)       | 86 (11%) | 2RHZE/6RH + S if prior TB + L in one trial arm |          | D (0·3–0·4mg/kg) for 6-8 weeks |
| Thwaites 29  | 2002 | Cohort      | Vietnam | 56 | 2 a b d           | 11 (20%)  | 56 (100%)         | 0 (0%)             | 0 (0%)        | 3 (5%)        | 3RHZE/6RHZ if HIV+ 3RHZS/6RHZ if HIV- |          | Not given |

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| Author(s) | Year | Study Type | Country | N | TB Treatment | Mortality and Neurological Outcomes at | Notes |
|-----------|------|------------|---------|---|--------------|--------------------------------------|-------|
| Thwaites | 2004 | RCT        | Vietnam | 545 | 3RHZS/6RHZ if HIV+ or prior history of TB | D (0.3-0.4mg/kg) tapered over 4 weeks, then oral treatment (4mg/day) tapered for 4 weeks | Mortality and neurological outcomes at 9 months |
| van Laarhoven | 2017 | Cohort    | Indonesia | 608 | 2RHZE (n=47: high dose R) (n=25: M instead of E) | 91% received steroids Drug, dose, and duration not specified | Mortality at 12 months |
| Singh    | 2016 | Cohort    | India   | 141 | 2RHZS/7HE | D (0.3-0.4mg/kg) tapered over 4 weeks, then oral treatment (4mg/day) tapered for 4 weeks | Neurological outcomes at 9 months |
| Tai      | 2016 | Cohort    | Malaysia | 36  | 2RHZE/10RH | Not specified | Neurological outcomes at 9 months |
| Chen     | 2014 | Cohort    | Taiwan  | 38  | 2RHZE/10-16RHE | Not specified | Neurological outcomes at 3 months |
| Kalita   | 2014 | RCT       | India   | 60  | RHZE | D (12-16mg) P (60-80mg) tapered 6-8 weeks | Mortality and neurological outcomes at 18 months |
| Sheu     | 2012 | Case Series | Taiwan | 91  | RHZE +/- S | Neither D 12-16mg/day or P 60-80mg/day over 1.5-2 months | In-hospital mortality and neurological outcomes |
| Wasay    | 2014 | Case Series | Pakistan | 404 | RHZE +/- C and/or S for drug toxicity | Unspecified regimen given to all patients | Mortality and neurological outcomes at 2 months |
| Chotmongkol | 1996 | RCT        | Thailand | 59  | 2RHZS/4RH | 29 (52%) P 60mg tapered over 5 weeks | Mortality and neurological outcomes at 6 and 18 months |
| Lu       | 2001 | Cohort    | China   | 36  | RHZE | Unspecified steroid given to patients with clinical deterioration | Mortality and neurological outcomes at 3 and 6 months |
| Wang     | 2002 | Cohort    | China   | 41  | RHZE | Unspecified steroid given to 9 patients | Mortality at 6 months |
| Chotmongkol | 2003 | Cohort    | Thailand | 45  | 2RHZS/4RH | Not given | Mortality at 6 months |
| Thwaites | 2003 | Cohort    | Vietnam | 21  | 3RHZS/6RHZ | Not given | Mortality and neurological outcomes at 9 months |
| Study | Year | Design | Location | n | Mortality | Neurological outcomes | Treatment Details |
|-------|------|--------|----------|---|-----------|----------------------|-------------------|
| Malhotra | 2009 | RCT | India | 91 | 0% | 73% | 2RHZE or S/7RH |
| Hsu | 2010 | Case Series | Taiwan | 108 | 0% | 62% | D (0.3-0.4mg/kg) tapered over 4 weeks, then oral treatment (4mg/day) tapered for 4 weeks OR MP 5 days OD of either 1 g (weight>50 kg) or 20 mg/kg (<50kg). |
| Sharma | 2013 | Case Series | India | 42 | 0% | 38% | RHZE |
| Sun | 2014 | Cohort | China | 33 | 0% | 26% | RHZE +/- PAS + L if in trial arm 2 |
| Kalita | 2014 | Case Series | India | 34 | 0% | 0% | 9RHZE/9RH |
| Imam | 2015 | Case Series | Qatar | 80 | 0% | 45% | RHZE + 4% received S, M, and A |
| Zhang | 2016 | Cohort | China | 401 | 0% | 202% | RHZE + L |
| Kalita | 2016 | RCT | India | 57 | 0% | 39% | 6RHZE + L in trial arm/12RH for following year |
| Li | 2017 | Case Series | China | 154 | 0% | 18% | 2-4RHZE/6-12RH |
| Mai | 2018 | RCT | Vietnam | 120 | 0% | 26% | 3RHZE/6RH |
| EUROPE | | | | | | | |
| Cagatay | 2004 | Cohort | Turkey | 42 | 5% | 32% | |
| Doganay | 1995 | Cohort | Turkey | 72 | 0% | 72% | |

Mortality and neurological outcomes at 6 and 18 months.
| Sutlas 54 | 2003 | Cohort | Turkey | 61 | 2 b d e f g h | 0 (0%) | 19 (31%) | 42 (69%) | 1RHZES/2-3RHZE/4-9RHZ (if no tuberculoma present)/10-12RH | P (1mg/kg/day) for 1 month, tapered for 4 months | Mortality at 12 months |
|----------|------|--------|--------|----|--------------|--------|----------|----------|------------------------------------------------|------------------------------------------------|----------------------|
| Sengoz 55 | 2008 | Cohort | Turkey | 121 | 2 a b d e f g h | 0 (0%) | 52 (43%) | 69 (57%) | 4 (3%) | 2RHZ + E or S/7-10RH | 2D (16 mg/day) for those with neurological deficits | Mortality at the end of follow up |
| Miftode 50 | 2015 | Cohort | Romania | 127 | 1 | 0 (0%) | 25 (20%) | 35 (28%) | 70 (55%) | 2-3RHZE/7-9RH | All received: unspecified drug, dose, & duration | In-hospital mortality and neurological outcomes |

1 Diagnostic Criteria Legend:  
1 = Uniform case definition  
2 = Other criteria used to diagnose and categorise patients including: a = suggestive CSF picture, b = microscopy, c = Xpert / PCR, d = culture, f = evidence of extra-neural, TB, g = response to treatment, h = other (history of TB or contact with a TB-infected individual, positive mantoux reaction, IGM AB in the CSF, biopsy, etc.)

2 Some participants were considered 'suspected' as well as 'confirmed' TBM

3 TB treatment (given to all unless specified otherwise): Number of months placed in front of regimen code: R = rifampicin, H = isoniazid, Z = pyrazinamide, E = ethambutol, S = streptomycin, L = levofloxacin, M = moxifloxacin, C = ciprofloxacin, A = amikacin, PAS = paraaminosalicylic acid, P = prednisolone, D = dexamethasone, MP = methylprednisolone. Where no duration of antituberculous therapy or steroids is stated it means it was not clearly specified in the paper.

* van Laarhoven et al. includes some data from 3 clinical trials in Indonesia (Ruslami R, Lancet Infect Dis, 2013, Yunivita V, Int J Intimicrob, 2016, Dian S, Antimicrob Agents Chemother, 2018). The primary studies were excluded from the review to avoid duplication of data.

+ Treatment information was taken from Chotmongkol 1996 as they were from the same authors, hospital, and decade.
Figure 1. Flow Diagram of Study Selection Process

- Records identified through database searching (n = 2562)
- Additional records identified through other sources (n = 3)
- Records after duplicates removed (n = 2197)
- Records screened (n = 2197)
- Records excluded (n = 1934)
- Full-text articles assessed for eligibility (n = 264)
  - Full-text articles excluded (n = 225)
    - Non-tuberculous meningitis (n = 13)
    - No systematic diagnostic criteria for diagnosing tuberculous meningitis (n = 25)
    - Did not report at least one outcome of interest (n = 9)
    - Ineligible study type or study type not specified (n = 10)
    - Fewer than 10 study participants (n = 3)
    - Non-English articles (n = 27)
    - Study conducted before 1988 (n = 8)
    - Study sample limited to patients with specific complications or comorbidities (n = 5)
    - Full text unable to be located (n = 27)
    - No disaggregated tuberculous meningitis data (n = 6)
    - No disaggregated adult data (n = 58)
    - No specified treatment drugs, doses, and duration (n = 30)
    - Narrative reviews or new analysis of existing data (n = 2)
    - Any systematic review superseded by an updated systematic review (n = 2)

- Studies included in qualitative synthesis (n = 42)
- Studies included in quantitative synthesis (meta-analysis) (n = 39)
**Figure 2. Tuberculous Meningitis Mortality by Country**

Pooled mortality for tuberculous meningitis by country. Mortality for countries with only one study reflect the reported mortality for that one study.
Figure 3. Tuberculous Meningitis Mortality by Outcome Reporting Timepoint

| Study                        | Mortality (95% CI) | % Weight |
|------------------------------|-------------------|----------|
| **3 Months**                 |                   |          |
| Lu et al (2001)              | 0.14 (0.05, 0.29) | 2.42     |
| Thwaite et al (2002)         | 0.43 (0.30, 0.57) | 2.57     |
| Shau et al (2010)            | 0.15 (0.09, 0.24) | 2.69     |
| Marais et al (2011)          | 0.16 (0.09, 0.24) | 2.71     |
| Luma et al (2013)            | 0.14 (0.00, 0.07) | 2.73     |
| Wasy et al (2014)            | 0.18 (0.14, 0.22) | 2.85     |
| Milhous et al (2015)         | 0.06 (0.00, 0.11) | 2.74     |
| Thyane et al (2015)          | 0.23 (0.06, 0.45) | 2.20     |
| Kalita et al (2016)          | 0.06 (0.01, 0.10) | 2.58     |
| Cresswell et al (2016)       | 0.32 (0.25, 0.39) | 2.80     |
| Mai et al (2018)             | 0.09 (0.05, 0.16) | 2.70     |
| **Subtotal (P < 0.05, p < 0.01)** | 0.23 (0.14, 0.35) | 28.86   |
| **6 Months**                 |                   |          |
| Chotmongkol et al (1996)     | 0.12 (0.05, 0.23) | 2.59     |
| Wang et al (2002)            | 0.45 (0.37, 0.59) | 2.46     |
| Chotmongkol et al (2003)     | 0.02 (0.00, 0.12) | 2.50     |
| Mahora et al (2009)          | 0.33 (0.23, 0.44) | 2.69     |
| Gonzalez Duarte et al (2011) | 0.36 (0.24, 0.49) | 2.61     |
| Marais et al (2011)          | 0.38 (0.29, 0.47) | 2.73     |
| Shama et al (2013)           | 0.17 (0.07, 0.31) | 2.48     |
| Kalita et al (Jan, 2014)     | 0.06 (0.01, 0.20) | 2.40     |
| Kalita et al (March, 2014)   | 0.36 (0.26, 0.50) | 2.59     |
| **Subtotal (P = 0.06, p < 0.01)** | 0.19 (0.10, 0.32) | 2.58     |
| **12 Months**                |                   |          |
| Dogaray et al (1995)         | 0.10 (0.04, 0.19) | 2.64     |
| Sultas et al (2000)          | 0.29 (0.17, 0.41) | 2.59     |
| Thwaite et al (2003)         | 0.24 (0.08, 0.47) | 2.17     |
| Cagatay et al (2004)         | 0.07 (0.01, 0.19) | 2.48     |
| Thwaite et al (2004)         | 0.37 (0.32, 0.41) | 2.66     |
| Topk et al (2008)            | 0.37 (0.54, 0.79) | 2.58     |
| Hsu et al (2010)             | 0.23 (0.10, 0.37) | 2.44     |
| Topk et al (2011)            | 0.58 (0.22, 0.85) | 2.82     |
| Ataor et al (2013)           | 0.16 (0.14, 0.23) | 2.83     |
| Chen et al (2014)            | 0.21 (0.10, 0.35) | 2.44     |
| Imam et al (2015)            | 0.05 (0.01, 0.12) | 2.66     |
| Heeman et al (2016)          | 0.28 (0.20, 0.36) | 2.87     |
| Zhang et al (2016)           | 0.05 (0.03, 0.07) | 2.85     |
| Li et al (2017)              | 0.21 (0.15, 0.29) | 2.77     |
| Rabarshina et al (2017)      | 0.28 (0.18, 0.40) | 2.65     |
| van Laakmeen et al (2017)    | 0.44 (0.40, 0.48) | 2.58     |
| Mai et al (2018)             | 0.09 (0.05, 0.16) | 2.73     |
| **Subtotal (P = 0.05, p < 0.01)** | 0.25 (0.17, 0.33) | 45.52   |

Heterogeneity between groups: p = 0.96
Overall (P = 0.05, p < 0.01); 0.24 (0.19, 0.29) 100.00

Forest plots depicting mortality due to tuberculous meningitis at three, six, and 12 months. One study was excluded because outcome timepoint was not reported.
Figure 4. Tuberculous Meningitis Mortality by HIV Status

Forest plot depicting mortality due to tuberculous meningitis stratified by HIV status. HIV status explains a significant amount of heterogeneity in tuberculous meningitis mortality (p<0.01).