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Six months therapy for tuberculous meningitis (Review)

Jullien S, Ryan H, Modi M, Bhatia R

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[Intervention Review]

Six months therapy for tuberculous meningitis

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ABSTRACT

Background

Tuberculous meningitis (TBM) is the main form of tuberculosis that affects the central nervous system and is associated with high rates of death and disability. Most international guidelines recommend longer antituberculous treatment (ATT) regimens for TBM than for pulmonary tuberculosis disease to prevent relapse. However, longer regimens are associated with poor adherence, which could contribute to increased relapse, development of drug resistance, and increased costs to patients and healthcare systems.

Objectives

To compare the effects of short-course (six months) regimens versus prolonged-course regimens for people with tuberculous meningitis (TBM).

Search methods

We searched the following databases up to 31 March 2016: the Cochrane Infectious Diseases Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library; MEDLINE; EMBASE; LILACS; INDMED; and the South Asian Database of Controlled Clinical Trials. We searched the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) and ClinicalTrials.gov for ongoing trials. We also checked article reference lists and contacted researchers in the field.

Selection criteria

We included randomized controlled trials (RCTs) and prospective cohort studies of adults and children with TBM treated with antituberculous regimens that included rifampicin for six months or longer than six months. The primary outcome was relapse, and included studies required a minimum of six months follow-up after completion of treatment.

Data collection and analysis

Two review authors (SJ and HR) independently assessed the literature search results for eligibility, and performed data extraction and 'Risk of bias' assessments of the included studies. We contacted study authors for additional information when necessary. Most data came from single arm cohort studies without a direct comparison so we pooled the findings for each group of cohorts and presented them separately using a complete-case analysis. When a study reported more than one cohort, the cohorts were analysed separately. We assessed the quality of the evidence narratively, as using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was inappropriate with no direct comparisons between short- and prolonged-course regimens.

Main results

Four RCTs, 13 prospective cohort studies, and one unpublished ongoing cohort study met our inclusion criteria, and included a total of 2098 participants with TBM. None of the included RCTs directly compared six months versus longer regimens, so we analysed all data as individual cohorts to obtain relapse rates in each set of cohorts.

We included 20 cohorts reported in 18 studies. One of these was reported separately, leaving 19 cohorts in the main analysis. We included seven cohorts of participants treated for six months with a total of 458 participants. Three studies were conducted in Thailand, two in South Africa, and one each in Ecuador and Papua New Guinea between the 1980s and 2009. We included 12 cohorts of participants treated for longer than six months (ranging from eight to 16 months), with a total of 1423 participants. Four studies were conducted in India, three in Thailand and one each in China, South Africa, Romania, Turkey, and Vietnam, between the late 1970s and 2011. The unpublished ongoing cohort study is conducted in India and included 217 participants.

The proportion of participants classified as having stage III disease (severe) was higher in the cohorts treated for six months (33.2% versus 16.9%), but the proportion with known concurrent HIV was higher in the cohorts treated for longer (0/458 versus 122/1423). Although there were variations in the treatment regimens, most cohorts received isoniazid, rifampicin, and pyrazinamide during the intensive phase.

Investigators achieved follow-up beyond 18 months after completing treatment in three out of the seven cohorts treated for six months, and five out of the 12 cohorts treated for eight to 16 months. All studies had potential sources of bias in their estimation of the relapse rate, and comparisons between the cohorts could be confounded.

Relapse was an uncommon event across both groups of cohorts (3/369 (0.8%) with six months treatment versus 7/915 (0.8%) with longer), with only one death attributed to relapse in each group.

Overall, the proportion of participants who died was higher in the cohorts treated for longer than six months (447/1423 (31.4%) versus 58/458 (12.7%)). However, most deaths occurred during the first six months in both treatment cohorts, which suggested that the difference in death rate was not directly related to duration of ATT but was due to confounding. Clinical cure was higher in the group of cohorts treated for six months (408/458 (89.1%) versus longer than six months (984/1336 (73.7%)), consistent with the observations for deaths.

Few participants defaulted from treatment with six months treatment (4/370 (1.1%)) versus longer treatment (8/355 (2.3%)), and adherence was not well reported.

Authors' conclusions

In all cohorts most deaths occurred in the first six months; and relapse was uncommon in all participants irrespective of the regimen. Further inferences are probably inappropriate given this is observational data and confounding is likely. These data are almost all from participants who are HIV-negative, and thus the inferences will not apply to the efficacy and safety of the six months regimens in HIV-positive people. Well-designed RCTs, or large prospective cohort studies, comparing six months with longer treatment regimens with long follow-up periods established at initiation of ATT are needed to resolve the uncertainty regarding the safety and efficacy of six months regimens for TBM.

2 April 2019

Up to date

All studies incorporated from most recent search

All eligible published studies found in the last search (31 Mar, 2016) were included and one ongoing study was identified (see 'Characteristics of ongoing studies' section)

PLAIN LANGUAGE SUMMARY

Six months therapy for patients with tuberculous meningitis

What is tuberculous meningitis and why is the duration of treatment important?

Tuberculous meningitis (TBM) is a severe form of tuberculosis, which affects the membranes that cover the brain and spine. It is associated with high rates of death and disability. While there are standardized international recommendations for treating people with pulmonary tuberculosis (tuberculosis of the lungs) for six months with antituberculous therapy, there is a wide range of differing recommendations and practices for treating people with TBM worldwide. Some specialists recommend nine months, 12 months, or even longer treatment for TBM in order to prevent relapse of the disease. Longer regimens have potential disadvantages: they are associated with poor adherence to treatment, which could contribute to increased relapse and development of drug resistance; and increased costs to patients and healthcare systems.

What the evidence shows

This Cochrane review assessed the effects of six-month regimens for treating people with TBM compared with longer regimens. Cochrane researchers examined the available evidence up to 31 March 2016 and they included 18 studies. None of the included studies directly compared people with TBM treated for six months with people with TBM treated for longer. Two of the included studies analysed two groups of participants treated for six months and longer than six months. Therefore, the review authors included information from seven groups of people treated for six months (458 people), 12 groups of people treated for longer than 6 months (1423 people), and one ongoing study of 217 people which was analysed separately due to methodological concerns. Although the treatment regimens in the included studies varied, most participants received standard first-line antituberculous drugs, and were followed up for more than a year after the end of treatment. The studies included adults and children with TBM, but few participants were HIV-positive.

Relapse was an uncommon event across both groups of studies, with only one death attributed to relapse in each group. Most deaths occurred during the first six months of treatment in both groups of studies, which showed that treatment duration did not have a direct impact on the risk of death in these studies. There was a higher death rate in participants treated for longer than six months, and this probably reflects the differences between the participants in the two groups of studies. Few participants defaulted from treatment, and adherence was not clearly documented.

They found no evidence of high relapse rates in people treated for six months, and relapse was uncommon in all patients irrespective of regimen. There may be differences between the participants treated for six months and longer than six months that could have led to bias (confounding factors), so further research would help determine if shorter regimens are safe. Most of the data were in patients without HIV, and so these inferences do not apply to patients who are HIV-positive.

BACKGROUND

Description of the condition

Tuberculosis (TB) is caused by infection with one of several mycobacterial species that belong to the *Mycobacterium tuberculosis* complex. TB is estimated to be the leading infectious cause of death worldwide alongside HIV, and approximately one-third of the world's population is thought to have latent TB. TB is associated with poverty. Low- and middle-income countries carry the greatest burden of the disease, and more than three-quarters of cases are reported in South-East Asia, the Western Pacific, and Africa (WHO 2015). Tuberculous meningitis (TBM) is a severe form of TB, which affects the meninges that cover the brain and spine. TBM is the main form of TB that affects the central nervous system (CNS), which accounts for approximately 1% of all cases of active TB, and 5% to 10% of extrapulmonary TB cases (TB involving organs other than the lungs) (Thwaites 2009; Török 2015). TBM prevalence is higher in populations with high overall TB prevalence. The World Health Organization (WHO) reported 0.8 million new extrapulmonary TB cases worldwide in 2013 out of 5.4 million people with a first episode of TB (WHO 2014). TBM mainly affects children and immunosuppressed people (Principi 2012).

TBM is a major contributor to the death and disability associated with TB. Death occurs in around 30% of people with TBM and 50% of people who survive TBM suffer from neurological deficits that cause disability despite antituberculous treatment (ATT) (Principi 2012). Early diagnosis and prompt treatment with ATT and corticosteroids are the main determinants of outcome in TBM (Prasad 2016; Thwaites 2013).

TBM is diagnosed clinically by recognition of meningitis together with findings suggestive of *M. tuberculosis* infection (Principi 2012). A "bacteriologically confirmed TBM case" implies confirmation of the diagnosis by identification of *M. tuberculosis* in the person's cerebrospinal fluid (CSF) by microscopy, cell culture, or molecular methods. A case diagnosed as TBM by a health worker without laboratory confirmation is defined as a "clinically diagnosed TBM case" (WHO 2013). The disease severity at presentation is classified into three stages according to the British Medical Research Council (MRC) (MRC 1948), based on the Glasgow Coma Scale (GCS) (Teasdale 1974) and neurological signs.

- Stage I: non-specific signs and symptoms but no neurological focal signs and GCS of 15.
- Stage II: minor neurological focal signs such as cranial nerve palsies or GCS of 11 to 14.
- Stage III: severe neurological deficits such as paresis or GCS equal to or less than 10.

Such classification facilitates comparison between findings from different studies and is useful to predict prognosis.

Description of the intervention

Without treatment, TBM leads to death. To effectively treat people with TBM, ATT must eliminate active TB bacilli to prevent neurological sequelae and death, eliminate dormant bacilli to prevent relapse, and prevent the emergence of drug resistance (Woodfield 2008). In contrast to pulmonary TB, there are no standardized international recommendations for treating people with TBM. There is a wide range of differing recommendations and practices for treating people with TBM worldwide (Appendix 1). This is partly due to the limited existing evidence regarding the optimal choice and dose of antituberculous drugs, as well as the most appropriate duration of treatment for people with TBM. Most data on treating TBM have been extrapolated from pulmonary TB (Heemskerk 2011).

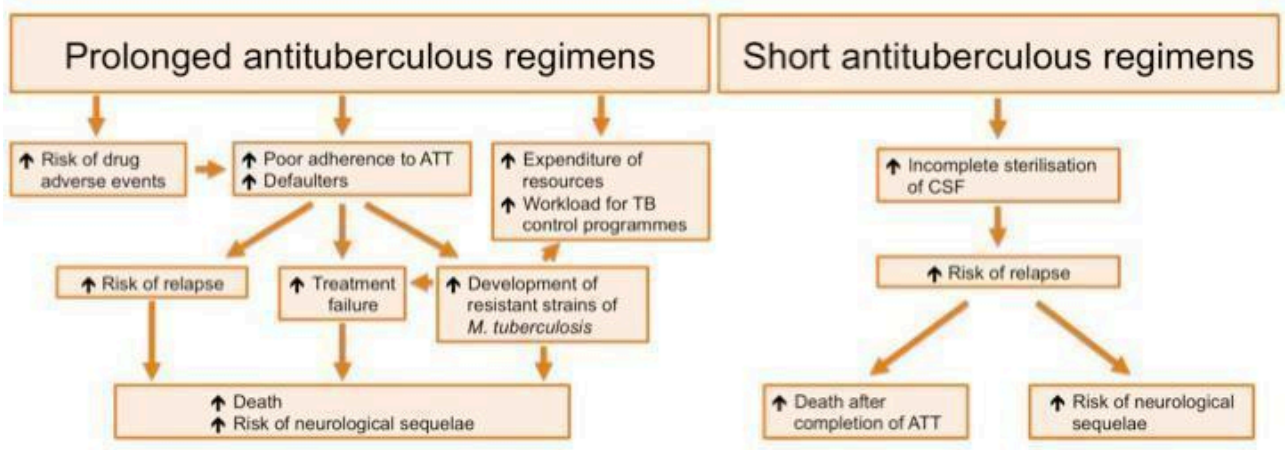
Regarding treatment duration, two main concerns have led to the perception that treatment longer than the six months regimen for pulmonary TB is needed for people with TBM to ensure microbiological cure and prevent relapse. Firstly, the blood-brain barrier hinders the penetration of antituberculous drugs to reach adequate drug concentration in the infected site, meaning that it may take longer to eradicate viable bacilli in the person's CNS (Thwaites 2013). The second argument concerns relapse rates. In 2013, 0.3 million cases of TB relapse after previous cure of the disease were reported (WHO 2014). Although relapse rates of 5% are generally considered acceptable for pulmonary TB regimens, this may not be the case for TBM, in which relapse can lead to severe neurodisability and death (Donald 2010a). Furthermore, reliable parameters for monitoring response to treatment in TBM are lacking, in contrast to pulmonary TB where sputum microscopy and culture are used. Consequently, some specialists recommend 12 months treatment for drug-sensitive TBM, consisting of a two months intensive phase with isoniazid, rifampicin, pyrazinamide, and either ethambutol or streptomycin, followed by a 10 months continuation phase with isoniazid and rifampicin (Török 2015).

All international guidelines, including the WHO guidelines (WHO 2010a), recommend the use of isoniazid, rifampicin, and pyrazinamide, usually with a fourth drug such as ethambutol or streptomycin, as first-line antituberculous drugs in people with TBM. Isoniazid is highly active against rapidly replicating mycobacteria and has good CSF penetration. Rifampicin kills both rapidly replicating and slow or non-replicating bacilli, while pyrazinamide has strong bactericidal effect against intracellular mycobacteria. Thus, both rifampicin and pyrazinamide are critical drugs to sterilize lesions by killing dormant bacteria and those in remote sites such as the CSF, which is essential to reduce the risk of relapse (Donald 2010b; Thwaites 2005a). The introduction of rifampicin allowed the shortening of pulmonary TB treatment (Zumla 2014). Although rifampicin has poor CSF penetration, its importance in TBM treatment has being emphasized in a trial in which mortality rate was higher among participants with rifampicin-resistant TBM (Thwaites 2005b).

How the intervention might work

There is uncertainty about the effectiveness of short-course regimens of six months ATT in people with TBM. Some study authors report that six months were adequate for treating TBM (Donald 1998; van Toorn 2014), while prolonged regimens have disadvantages. Prolonged regimens may increase the risk of drug-related adverse events and are associated with poor adherence to treatment and default. Poor adherence increases the risk of relapse leading to potential neurological disability and death, and facilitates the development of drug-resistant bacterial strains (van Loenhout-Rooyackers 2001). Finally, long regimens lead to greater expenditure of resources and greater workload for TB control programmes. Short-course regimens may not be long enough to eliminate dormant bacilli from the CNS, and may lead to higher relapse rates. Higher relapse rates may increase neurodisability and death after completion of ATT (Figure 1).

Figure 1. Possible disadvantages of prolonged and short-course antituberculous regimens for treating people with TBM.



Abbreviations: ATT: antituberculous treatment; CSF: cerebrospinal fluid; *M. tuberculosis: Mycobacterium tuberculosis;* TB: tuberculosis; TBM: tuberculous meningitis

Relapse is the most daunting possible consequence of using short treatment regimens. There is uncertainty around the lag time between completion of treatment and relapse. However, most relapses seem to occur within the first six months after completing ATT (Jullien 2015). Thus, at least six months of follow-up are required to adequately assess this outcome, and longer follow-up periods are desirable for detecting all cases of relapse. Defaulters may be at increased risk of relapse due to inadequate dosing with ATT, particularly during the intensive phase of treatment, although direct evidence for this association is lacking in people with TBM (Conde 2009). The number of deaths and neurological deficits are reduced by early diagnosis and prompt ATT. Indeed, most of the deaths associated with TBM will occur during the first weeks of disease (Yaramiş 1998). In preliminary work for this Cochrane Review, Jullien 2015 attributed deaths occurring after six months of treatment mainly to complications of TBM and comorbidity, such as secondary infection. Few deaths were associated with relapse. Finally, longer regimens expose patients to the risk of adverse effects of antituberculous drugs for longer.

Why it is important to do this review

The most appropriate duration of treatment for people with TBM is uncertain. Although several studies have reported safe outcomes in adults and children with TBM treated with six months regimens (Donald 1998; van Toorn 2014), there are concerns about whether six months regimens would be sufficient to sterilize CSF and thus prevent relapse. Most international guidelines recommend prolonged-course ATT of nine to 12 months for people with drug-sensitive TBM. In practice, more than four antituberculous drugs are sometimes used, and regimens may be prolonged up to 24 months for fear of relapse. Treatment is also prolonged in people for whom supervision and follow-up are doubtful (Principi 2012). On the one hand, TBM treatment duration must be long enough to eliminate dormant bacilli to prevent relapse. On the other hand, treatment should be as short as possible to avoid disadvantages related to prolonged regimens. Reducing the duration of TBM therapy from prolonged-course regimens to short-course regimens could have several benefits, including reduced drug toxicity and improved adherence to treatment, with fewer consequent relapses and lower risk of developing drug-resistant strains. Additionally, short-course regimens would reduce the use of resources and workloads in TB control programmes, which are often overburdened in settings where TB incidence is high (Conde 2009; van Loenhout-Rooyackers 2001).

A study that reviewed treatment duration for people with TBM by comparing case series of adults and children, showed similar completion and relapse rates between six months regimens including at least isoniazid, rifampicin, and pyrazinamide and longer regimens (van Loenhout-Rooyackers 2001). In this review, we have included more recent studies, and performed 'Risk of bias' assessments and appraised the quality of the evidence.

This review was prompted as part of work with the Central TB Division, Ministry of Health and Family Welfare in India, and the All India Institute of Medical Sciences in New Delhi in preparation for the Indian Extra-Pulmonary TB (INDEX-TB) guidelines (INDEX-TB 2016). There was uncertainty and debate as to whether six to nine months of treatment is as safe as longer regimens for treating people with TBM (Jullien 2015), with varying views on what the literature showed. As we knew there were no randomized controlled trials (RCTs), we sought to summarize and critically appraise evidence from observational studies. The initial systematic review found several observational studies that reported low numbers of relapse with short regimens, but did not include all the available evidence for longer regimens. In this Cochrane Review, we examined the effects of six months (short-course) and longer than six months (prolonged-course) regimens on TBM outcomes.

OBJECTIVES

To compare the effects of short-course (six months) regimens versus prolonged-course regimens for people with tuberculous meningitis (TBM).

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs), quasi-RCTs, and prospective cohort studies. As our preliminary work (Jullien 2015) suggested a lack of studies that directly compared short-course and prolonged-course treatment, we included prospective cohort studies in which all participants were treated with the same duration of antituberculous treatment (ATT).

Types of participants

Adults and children with a diagnosis of presumed drug sensitive tuberculous meningitis (TBM) as defined by the study authors, from all settings and countries.

Types of interventions

Short-course regimens

ATT regimens of six months that included rifampicin.

Prolonged-course regimens

ATT regimens of more than six months that included rifampicin.

Types of outcome measures

Primary outcomes

- Relapse: the number of participants in each treatment group who had new symptoms and signs of TBM after resolution of disease and completion of ATT. We included studies with a minimum of six months follow-up after completion of ATT[a].

Secondary outcomes

- Death from any cause.
- Death after six months of ATT. We were interested in this outcome in order to discriminate the number of deaths that may have been related to duration of treatment.
- Clinical cure: the number of participants in each treatment group who completed treatment according to the original treatment plan without evidence of treatment failure at the end of treatment (WHO 2013)[b].
- Default: the number of participants in each treatment group who discontinued ATT before the end of treatment, or participants whose treatment was interrupted for eight weeks or more consecutively (WHO 2013).
- Poor adherence: the number of participants in each treatment group who did not adhere to the prescribed treatment regimen, as reported by study authors, but who did not meet the definition of default given above.

[a]Long follow-up periods are required to reliably detect all cases of relapse. We chose to include studies with a minimum of six months follow-up as we considered studies with shorter follow-up periods would be likely to miss cases of relapse.

[b]The World Health Organization (WHO)'s definitions for TB outcomes are primarily based on the assessment of pulmonary TB patients, so sputum smear and culture status are important factors in defining outcomes. Generally, repeating cerebrospinal fluid (CSF) sampling and culture at the end of ATT in TBM participants is not done routinely, therefore CSF smear/culture status is not part of the definition of cure or successful treatment in practice. Our definition of 'clinical cure' is broadly equivalent to the definition of 'treatment completed' in the WHO's nomenclature.

We considered the outcomes for this Cochrane Review carefully. Although treatment failure is an important outcome in TBM, there is currently no accepted definition of TBM treatment failure. In this review, we defined treatment failure as referring to participants who failed to improve with ATT, or deteriorated following initial improvement while on ATT. Importantly, this definition excluded participants who deteriorate after completing ATT; we classified these participants as relapses for the purposes of this review. In our preliminary work for the TB-INDEX guidelines, we included treatment failure as a secondary outcome (INDEX-TB 2016; Jullien 2015). During this work, it became apparent that this outcome was not directly related to the duration of treatment, as by definition it can occur at any point during ATT. Furthermore, treatment failure was not well defined or described in many of the included studies, was not reported consistently, and participants were described as having treatment failure usually received longer treatment. Thus, we decided not to include treatment failure as a primary or secondary outcome in this review, although we did provide the information in the 'Results' section for completeness.

For our inclusion criteria, we also considered length of follow-up carefully. Long follow-up periods are required to reliably detect all cases of relapse. Therefore, we excluded studies with short follow-up to limit detection bias, as this could lead to underestimation of the number of relapses, which was the primary outcome of this review.

Adverse events

- All adverse effects related to the ATT.
- Drug toxicity leading to the discontinuation or modification of the treatment regimen

Search methods for identification of studies

We attempted to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and ongoing).

Electronic searches

We searched the following databases for relevant studies using the search terms and strategy detailed in Appendix 2: the Cochrane Infectious Diseases Group (CIDG) Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library issue 3 2016; MEDLINE (Pubmed, 1966 to 31 March 2016); EMBASE (OVID, 1980 to 31 March 2016); LILACS (1982 to 31 March 2016); INDMED (http://indmed.nic.in/, 31 March 2016); and the South Asian Database of Controlled Clinical Trials. We also searched the WHO International Clinical Trials Registry Platform (ICTRP; http://www.who.int/ictrp/en/) and ClinicalTrials.gov for ongoing trials (both accessed on 31 March 2016).

Searching other resources

We checked the reference lists of all studies identified by the above methods for other potentially relevant studies. We contacted researchers at the National Institute for Research in Tuberculosis, Chennai, to identify unpublished studies (grey literature).

Data collection and analysis

Selection of studies

Two review authors (SJ and HR) independently screened the titles and abstracts of the studies identified by the literature searches to identify studies that met eligibility criteria, and removed duplicate reports. We retrieved the full-text articles of the studies we identified as potentially eligible. SJ and HR independently assessed the full-text articles for study eligibility using an eligibility form based on the predefined inclusion and exclusion criteria, and resolved any disagreements by discussion. Where eligibility was unclear we attempted to contact the study authors for clarification. We excluded studies that did not meet the inclusion criteria and listed them and their reasons for exclusion in the 'Characteristics of excluded studies' table. We constructed a study flow diagram to illustrate this process.

Data extraction and management

One review author (SJ) piloted the data extraction form on two studies. Based on the results of the pilot, we modified and finalized the data extraction form. Two review authors (SJ and HR) independently extracted data from the included studies according to the agreed data extraction tool. We compared the data extracted by the two review authors to identify any possible errors. We resolved any discrepancies through discussion and by referring to the original articles. We extracted the following data.

- Country, when the study was conducted, study design, inclusion and exclusion criteria applied, and the number of participants recruited.
- Participant characteristics: age, gender, epidemiological data such as known contact with TB patient, duration of symptoms at presentation, clinical severity of the disease according to the British Medical Research Council (MRC) scale, comorbidity (HIV, other immunosuppression disease and other diseases), and diagnostic methods used (for example, CSF testing, neuroimaging, chest X-ray, purified protein derivative (PPD) skin test) along with number of bacteriologically confirmed and clinically-diagnosed TBM cases.
- Intervention data: description of drugs, dose, route of administration in both the intensive and continuation phase, and duration of ATT for both phases. Administration of other drugs or therapeutic procedures.
- Outcome data.

For the primary outcome we extracted the following data.

- Relapse:
  - number of relapse cases, stratified by age and HIV status, if available;
  - clinical severity of relapse;
  - clinical severity at original diagnosis;
  - method of diagnosing relapse;
  - time between end of treatment and relapse.

For the secondary outcomes we extracted the following data.

- Death from any cause:
  - number of deaths, stratified by clinical severity, age, HIV status, if available.
- Death after six months of ATT treatment:
  - number of deaths after six months, stratified by clinical severity, age and HIV status if available;
  - time from start of ATT until death;
  - cause of death, if specified.
- Clinical cure:
  - number of cases cured at end of treatment;
  - number of cases cured stratified by clinical severity, age, HIV status if available.
- Default:
  - number of defaulters, stratified by clinical severity, age and HIV status if available;
  - method of monitoring adherence during treatment (clinical history, direct observation, tablet counting).
- Poor adherence:
  - number of participants not receiving prescribed ATT regimen but not meeting the definition of default;
  - method of monitoring adherence during treatment (clinical history, direct observation, tablet counting).

In addition, we extracted data on treatment failure (number of participants in each treatment group who failed to improve with ATT, or deteriorated following initial improvement while on ATT), on neurological sequelae (number of participants in each treatment group with neurological sequelae as described by the original study authors), and on follow-up (length of follow-up after completing ATT, the way participants were followed-up, and number and characteristics of losses to follow-up).

For each established outcome, we extracted the number of participants assigned and the numbers analysed in each treatment group. For dichotomous outcomes, we extracted the number of participants experiencing the event. For count data outcomes, we extracted the number of events in the intervention and control group. From our preliminary work, we knew that relapse and default are relatively uncommon. Therefore we did not attempt a time-to-event analysis for these outcomes as the results are likely to be misleading.

For the purposes of analysis in this review, we categorized treatment groups to six months or more than six months based on the duration of treatment they were scheduled to receive.

Assessment of risk of bias in included studies

Based on our preliminary work, we anticipated there would be no studies with a direct comparison between short and prolonged ATT. We treated the included studies as observational cohort studies for the purpose of analysis in our review. The Cochrane 'Risk of bias' assessment tool, Higgins 2011, and the Downs and Black checklist for assessment of methodological quality, Downs 1998, are inadequate to assess the quality of single-arm observational cohort studies. Therefore, we devised a 'Risk of bias' assessment tool to appraise the reliability of the outcome data from each study, based on the domains included in the 'Risk Of Bias In Non-randomized Studies - of Interventions' (ROBINS-I) tool (Sterne 2016), which applies to non-randomized, observational cohort studies. As no direct comparison is made between cohorts treated with six and more than six months of ATT, we did not assess participant selection and allocation. At least two review authors independently assessed each included study for potential sources of bias that could have affected the reliability of the outcome data,

and resolved any discrepancy through discussion. We classified our judgments as either low, high, or unclear risk of bias based on the following criteria.

- Detection bias for outcomes that occurred during the follow-up period, after completing ATT (relapse, death after six months of ATT):
  - low risk: the study authors attempted to see all participants (for example, by giving them a clinic appointment, a telephone call, or home visit) at least once at 18 months of follow-up after the end of ATT or beyond;
  - unclear risk: poorly described method of follow-up, or follow-up between six and 18 months;
  - high risk: passive follow-up or follow-up with for less than six months.
- Detection bias for outcomes that occurred during ATT (death, clinical cure, default, adherence to treatment):
  - low risk: all participants had clear methods of follow-up during ATT, through regular visits, hospital-based treatment or Directly Observed Therapy (DOT) programmes;
  - unclear risk: unclear method of follow-up during ATT;
  - high risk: passive follow-up, not hospital-based.
- Attrition bias for outcomes occurring during the follow-up period, after completing ATT (relapse, death after six months of ATT):
  - low risk: less than 5% of participants lost to follow-up at the end of the follow-up period;
  - unclear risk: between 5 and 10% of participants lost to follow-up at the end of the follow-up period;
  - high risk: more than 10% of participants lost to follow-up at the end of the follow-up period.
- Attrition bias for outcomes occurring during ATT (death, clinical cure, default, adherence to treatment):
  - low risk: less than 5% of participants lost to follow-up during ATT;
  - unclear risk: between 5 and -10% of participants lost to follow-up during ATT;
  - high risk: more than 10% of participants lost to follow-up during ATT.
- Performance bias for all outcomes: ATT received for longer than planned could reduce the probability of relapse if clinicians gave prolonged ATT to the participants they judged were at higher risk of relapse. Thus we considered:
  - low risk: less than 5% of participants had duration of treatment prolonged, with reasons given;
  - unclear: between 5 and 10% of participants had duration of treatment prolonged, or no reasons given;
  - high risk: more than 10% of participants had duration of treatment prolonged.
- Confounding bias for all outcomes:
  - factors that may have affected the main outcomes but were unrelated to the duration of treatment, including poor adherence to ATT (which could lead to relapse and treatment failure), and co-interventions such as steroids and surgical treatment.

We summarized the results of the assessment for the group of cohorts that received six months ATT and the group of cohorts that received prolonged ATT regimens, in 'Risk of bias' graphs and tables, with supporting evidence from the study reports (and the 'Characteristics of included studies' tables).

Measures of treatment effect

We stated in our protocol, Jullien 2016, that we would calculate the risk ratio (RR) for dichotomous outcomes and the rate ratio for count data outcomes, and that we would present the effect estimates with 95% confidence intervals (CIs). This was not possible, as we did not find any trials that directly compared short versus prolonged course regimens. Therefore, we presented the findings separately for each group of cohorts.

Dealing with missing data

Where data from the study reports were insufficient, unclear, or missing, we attempted to contact the study authors for additional information. For all included studies, we performed a complete-case analysis, which means that we only analysed the available data.

Assessment of heterogeneity

We assessed clinical and methodological diversities by looking at the variability in participants, interventions, and risk of bias of the included cohorts.

Assessment of reporting biases

We planned to construct funnel plots to assess publication bias, but this was not possible as no comparative trials met the inclusion criteria of this review.

Data synthesis

Although we planned to conduct meta-analyses, this was not possible. Instead we synthesized results narratively and in tables. We attempted to assess the quality of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) principles (Guyatt 2011), but this was not possible due to the lack of direct comparison between short- and prolonged-course regimens. Instead, we constructed a modified 'Summary of findings' table to summarize findings of both groups of cohorts, and assessed the quality of the evidence narratively. We used Review Manager (RevMan 2014) to gather and synthesise our findings.

Subgroup analysis and investigation of heterogeneity

We could not conduct formal subgroup analyses. Instead we explored heterogeneity between trials narratively by considering differences between study populations and intervention, such as: age group of participants, clinical severity of the disease at presentation, HIV status, time of the study, and length of follow-up.

Sensitivity analysis

We did not perform a sensitivity analysis as we were unable to conduct meta-analyses.

RESULTS

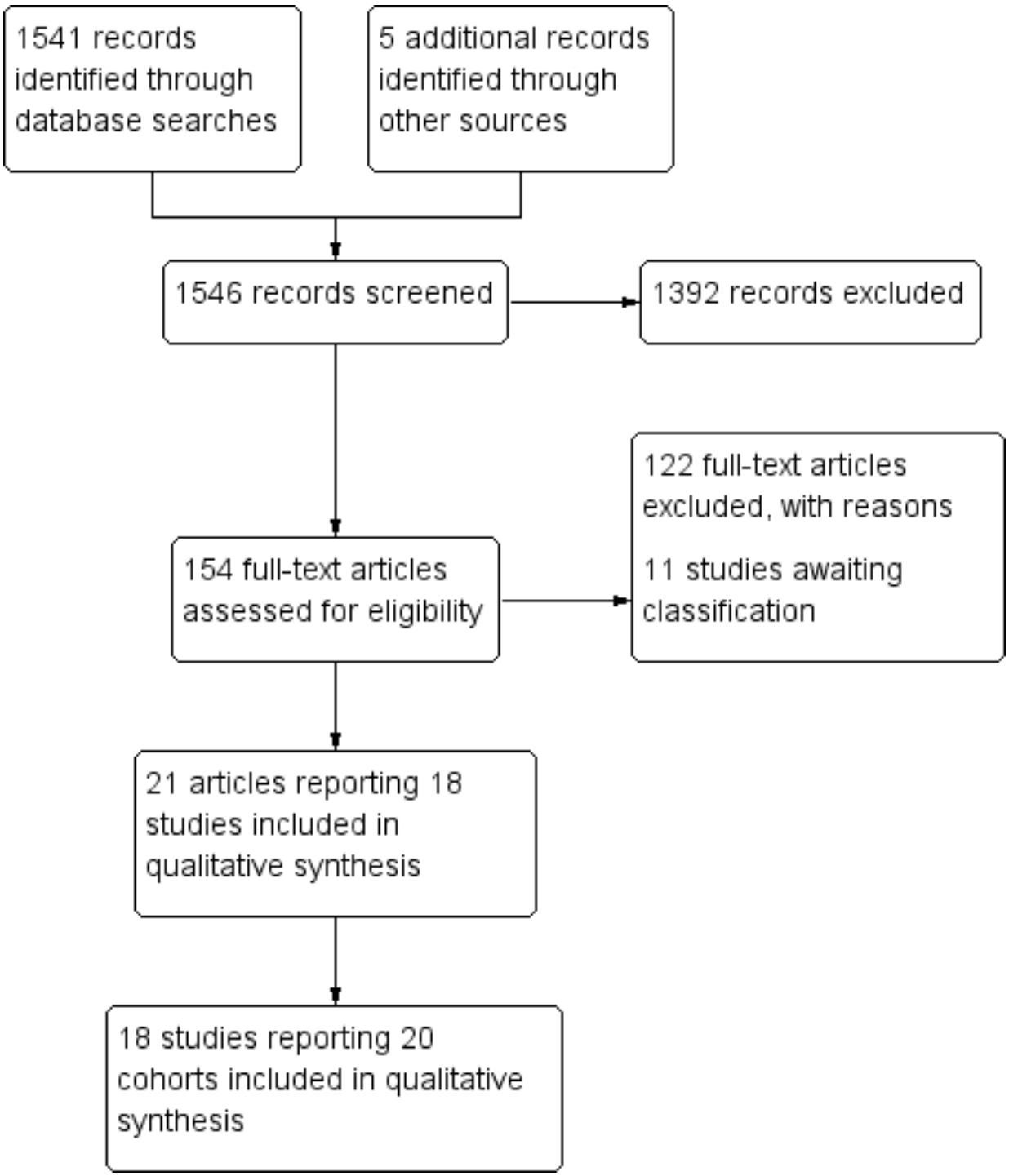
Description of studies

Results of the search

We conducted the literature search up to the 31 March 2016 and identified 1541 studies. We identified five additional records

through other resources. By screening titles, abstracts, and keywords, we selected 154 records and attempted to retrieve the full-text articles of these studies. By contacting the first author of one of these potentially eligible studies for clarification, we were granted access to the database of an ongoing prospective observational cohort of participants with tuberculous meningitis (TBM), which met our inclusion criteria (Alvarez-Uria 2012; NCT02454569). Although some of the participants included in our analysis have also been presented in Alvarez-Uria 2013 and Alvarez-Uria 2015, all the data we present in this review come from the larger database provided by the study author. Overall, 18 studies presented in 21 records met the inclusion criteria of this review (see the 'Characteristics of included studies' table). We had insufficient information to decide inclusion or exclusion of 11 studies (see the 'Characteristics of studies awaiting classification' table). We presented the reasons for excluding the remaining 122 reports in the 'Characteristics of excluded studies' table. We illustrated this process in the study flow diagram (Figure 2).

Figure 2. Study flow diagram.



Included studies

We included 17 published studies and one unpublished ongoing cohort. Of the published studies, four were randomized controlled trials (RCTs) and 13 were non-randomized prospective cohort studies. None of the included RCTs compared six months antituberculous treatment (ATT) versus ATT given for more than six months for TBM, so we analysed all as single cohorts. Overall, we identified seven cohorts treated for six months, and 12 cohorts treated for longer than six months. Any comparisons between regimens of six months and regimens of greater than six months are entirely observational.

Cohorts treated for six months

See Table 1 for a full description of the included cohorts.

Setting and time

The seven cohorts were from single tertiary centres in Thailand (Chotmongkol 1991; Chotmongkol 1996; Jacobs 1992), South Africa (Donald 1998; van Toorn 2014), Ecuador (Alarcón 1990), and Papua New Guinea (Biddulph 1990). Four studies were conducted in the 1980s (Alarcón 1990; Biddulph 1990; Chotmongkol 1991; Jacobs 1992), two in the 1990s (Chotmongkol 1996; Donald 1998), and one between 2006 and 2009 (van Toorn 2014).

Participants

The seven cohorts included 109 adults (three studies) and 349 children (five studies) diagnosed with TBM. Only van Toorn 2014 reported HIV status, and none of the seven cohorts reported data on malnutrition. Six studies used the British Medical Research Council (MRC) criteria to assess clinical severity (MRC 1948), but only five of them (256 participants) reported disaggregated data: stage I (mild): 30 participants; stage II (moderate): 141 participants; and stage III (severe): 85 participants.

ATT regimens

In all seven studies the intensive phase included at least two months of isoniazid, rifampicin, and pyrazinamide. Four studies also gave streptomycin (Biddulph 1990; Chotmongkol 1991; Chotmongkol 1996; Jacobs 1992), and two gave ethionamide (Donald 1998; van Toorn 2014). Five studies gave a two months intensive phase with three or four drugs, followed by a four months continuation phase with isoniazid and rifampicin only (Alarcón 1990; Biddulph 1990; Chotmongkol 1991; Chotmongkol 1996; Jacobs 1992), while the two cohorts from South Africa gave four drugs for the whole six months (Donald 1998; van Toorn 2014).

Drugs were given orally except streptomycin, which was given intramuscularly. There was some variation between studies in the dosages used (see the 'Characteristics of included studies' table). Dosages were given as a single daily administration, except in Biddulph 1990, in which antituberculous drugs were given twice weekly during the continuation phase. Drugs were given under Directly Observed Therapy (DOT) in Donald 1998 and under trial conditions in Chotmongkol 1996. In van Toorn 2014, half of the participants were hospital-based during ATT and the other half were home-based. In the remaining four studies, drugs were self administered under condition of being recruited in a prospective observational cohort with the purpose of describing TBM outcomes (Alarcón 1990; Biddulph 1990; Chotmongkol 1991; Jacobs 1992).

Corticosteroids

Overall, 344 participants from the seven cohorts received corticosteroids. Different regimens were given to either all participants or only to those with moderate and severe presentation of TBM or with neurological complications, or as part of a RCT to assess the use of corticosteroids (Chotmongkol 1996), during the first four to eight weeks of ATT.

Diagnosis: clinical, radiological, and microbiological characteristics

Diagnosis of TBM was based on characteristic clinical features (see Table 2), typical cerebrospinal fluid (CSF) findings (elevated cell count with predominance of lymphocytes, low glucose content, and elevation of protein content), and the presence of acid-fast bacilli in CSF evidenced by microscopy examination or culture (see Table 3). Only one cohort reported 5/28 participants with a previous history of TB (Alarcón 1990). Four cohorts reported known contact with an infectious TB patient (Alarcón 1990; Biddulph 1990; Donald 1998; Jacobs 1992). The diagnosis of TBM was bacteriologically confirmed in 56 participants and clinically based in 198 participants among the 254 participants with disaggregated data. Only one study reported performing drug sensitivity testing (Donald 1998).

Cohorts treated for longer than six months

See Table 4 for a full description of the included cohorts.

Setting and time

The 12 cohorts were from different geographical settings: India (Iype 2014; Ramachandran 1989; Ramachandran 1997; Sharma 2013a), Thailand (Jacobs 1992; Phuapradit 1987), South Africa (van Toorn 2014), China (Lau 2005), Ecuador (Alarcón 1990), Romania (Anastasatu 1993), Turkey (Doğanay 1995), and Vietnam (Török 2011a). Doğanay 1995 was conducted in university hospitals, Lau 2005 was performed in tertiary and secondary hospitals and chest clinics, and the remaining studies were conducted in tertiary hospitals. Five studies were multicentric (Doğanay 1995; Lau 2005; Ramachandran 1989; Ramachandran 1997; Török 2011a). The earliest study was started in 1977 (Ramachandran 1989), followed by three studies conducted in the 1980s (Alarcón 1990; Jacobs 1992; Phuapradit 1987), four in the 1990s (Anastasatu 1993; Doğanay 1995; Lau 2005; Ramachandran 1997), and four between 2001 and 2011 (Iype 2014; Sharma 2013a; Török 2011a; van Toorn 2014).

Participants

The 12 cohorts included 893 adults (six studies) and 530 children (seven studies) diagnosed with TBM. Three cohorts included 122/736 HIV-positive people (Lau 2005; Török 2011a; van Toorn 2014); Iype 2014 and Sharma 2013a excluded people with HIV, and the remaining seven cohorts did not report the HIV status of the participants. Ramachandran 1989 and Ramachandran 1997 reported data on severe malnutrition and included 147/395 children with severe malnutrition according to the growth standards from the Indian Council of Medical Research. Eleven studies used the MRC criteria to assess clinical severity, with disaggregated data in nine cohorts: stage I (mild): 371 participants; stage II (moderate): 743 participants; and stage III (severe): 231 participants (Alarcón 1990; Doğanay 1995; Iype 2014; Jacobs 1992; Lau 2005; Phuapradit 1987; Ramachandran 1989; Ramachandran 1997; Sharma 2013a; Török 2011a; van Toorn 2014).

ATT regimens

Twelve cohorts assessed the effects of more than 20 regimens of between eight and 16 months of duration. All of them comprised at least isoniazid and rifampicin (except two participants in Jacobs 1992), with up to five antituberculous drugs.

Drugs were given orally except streptomycin, which was given intramuscularly. The cohorts used different drug dosages (see the 'Characteristics of included studies). Intermitent regimens (twice or thrice weekly) were administered in three studies throughout the course of treatment (Iype 2014; Ramachandran 1997; Sharma 2013a), and in two studies during the intensive or continuation phase only (Anastasatu 1993; Ramachandran 1989). The remaining studies gave single daily doses. In Iype 2014 and Sharma 2013a, drugs were given under DOT; while in Anastasatu 1993, Ramachandran 1997, and Török 2011a, participants received ATT under trial conditions. In van Toorn 2014, half of the participants were hospital-based during ATT and the other half were home-based. In the remaining studies, drugs were self-administered under the condition of being recruited to a prospective observational cohort with the purpose of describing TBM outcomes.

Corticosteroids

All studies considered corticosteroids, except Anastasatu 1993 in which authors did not report whether participants received corticosteroids or not. Overall, 1001 participants received corticosteroids. Different regimens were given to either all participants or only to those with moderate and severe presentation of TBM or with neurological complications, or as part of RCTs to assess the use of corticosteroids (Török 2011a), during the first four to eight weeks of ATT.

Diagnosis: clinical, radiological, and microbiological characteristics

Similarly to the cohorts of participants receiving six months of ATT, diagnosis of TBM was based on characteristic clinical features (see Table 5), typical CSF findings, and presence of acid-fast bacilli in CSF evidenced by microscopy examination or culture (see Table 6). Three participants out of 72 presented a previous history of TB in Doğanay 1995. Five studies reported known contact with an infectious TB patient (Iype 2014; Jacobs 1992; Lau 2005; Ramachandran 1989; Ramachandran 1997). The diagnosis of TBM was bacteriologically confirmed in 470 participants, clinically-based in 794 participants among the 1264 participants with disaggregated data from eight studies. Four studies performed drug sensitivity testing (Ramachandran 1989; Ramachandran 1997; Török 2011a; Visudhiphan 1989).

Outcomes

Although some studies used different definitions of relapse, default, clinical cure, and poor adherence, we collected and presented the data according to the definitions we established in our protocol, Jullien 2016 (see the 'Types of outcome measures' section).

Primary outcome

All included studies reported relapse.

Secondary outcomes and adverse events

All studies reported death from any cause and clinical cure. We were able to extract data on death after six months of ATT in all the cohorts receiving six months of ATT and in eight cohorts receiving prolonged ATT. We extracted data on default in five and six cohorts of participants treated for six months and more than six months respectively. One cohort study of six months ATT and two cohort studies of more than six months ATT reported poor adherence.

Authors of the included studies did not report adverse events uniformly. Some studies collected all adverse events while some others reported only the cases requiring discontinuation of ATT due to drug toxicity, or adverse effects secondary to corticosteroids. Overall, 13 studies reported adverse events related to ATT, and 14 studies reported drug toxicity leading to the discontinuation or modification of the treatment regimen.

Additional cohort

All participants in the Alvarez-Uria 2012 cohort come from the Vicente Ferrer HIV Cohort Study (VFHCS), which is an ongoing long-term prospective cohort study of all HIV-positive patients who have attended Rural Development Trust (RDT) hospitals in the district of Anantapur, India (NCT02454569). Therefore such data reflect a cohort of participants in a 'real-world' setting. We presented these data separately as it would be misleading to pool findings from this cohort with the other cohorts. We reported the findings of all consecutive participants diagnosed with TBM between 23 December 2010 and 30 September 2014, which corresponded to 217 participants co-infected with HIV and TBM. There were three children (aged 8, 9, and 13 years) and 214 adults older than 18 years, with a mean age of 38 years. Data on clinical severity were not reported.

Local policy stated that participants without previous TB should receive six months of treatment while participants with previous TB should be treated for eight months. However, some clinicians treat patients with TBM for longer, independently of the condition of the patient according to the main investigator. Thereby, 20 participants were treated for six months (including one participant with previous TB) and 75 were treated for between seven to 16.7 months (including 19 participants with previous TB). The remaining 122 participants either died before the sixth month of ATT or received interrupted treatment, and the study authors therefore classified them as defaulters. Authors reported data on relapse, death, clinical cure and default, but did not reported data on poor adherence and adverse events.

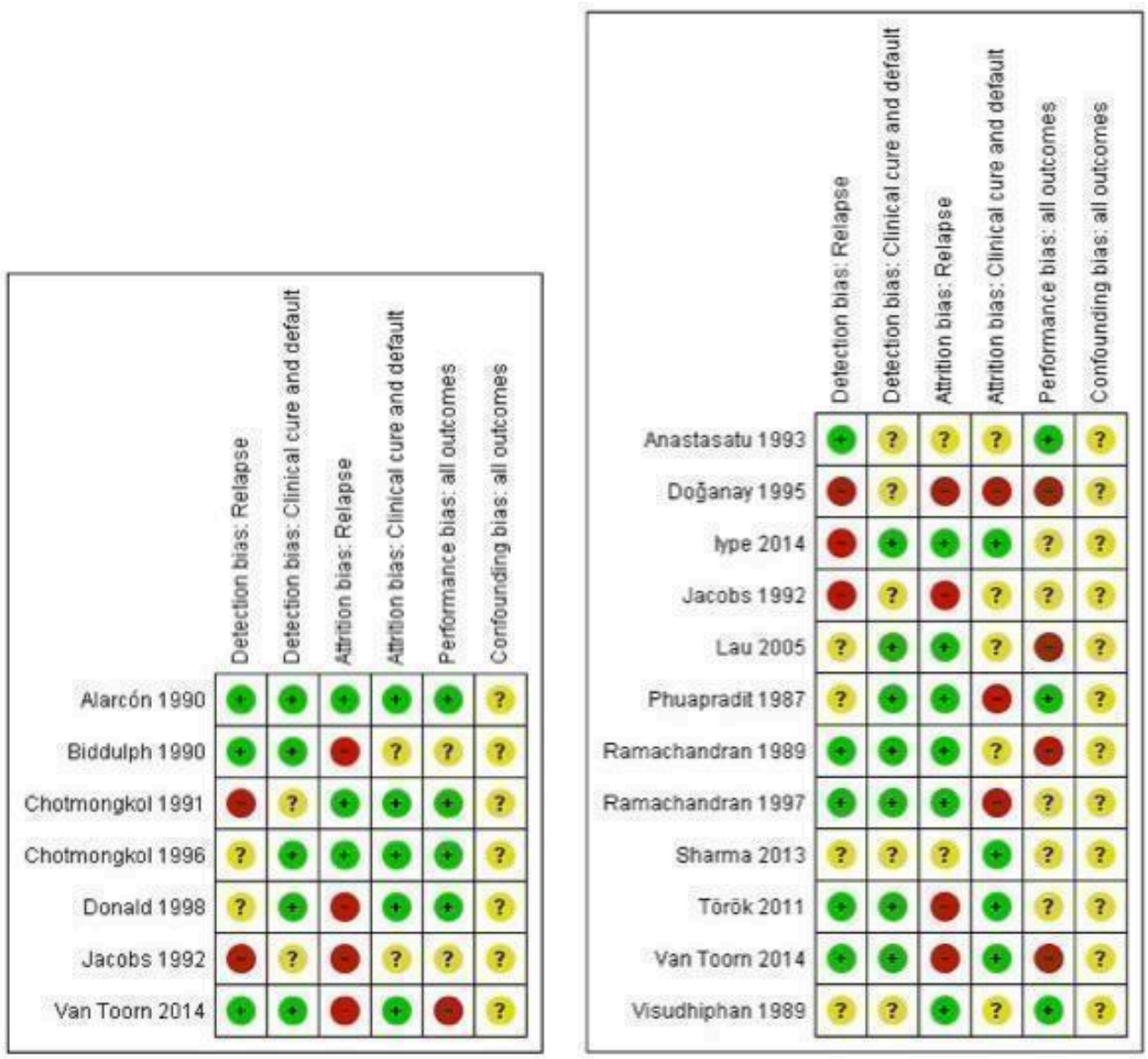
Excluded studies

We have listed the reasons for excluding 122 studies in the 'Characteristics of excluded studies' section.

Risk of bias in included studies

See Figure 3 for a summary of the 'Risk of bias' assessment of both group of cohorts receiving six months and more than six months of ATT. The 'Risk of bias' tables provide further details for supporting evidence in the 'Characteristics of included studies' table.

Figure 3. 'Risk of bias' summary for the cohorts treated for six months (left) and the cohorts treated for longer than six months.



Cohorts treated for six months

Detection bias

Three of the seven cohorts conducted routine follow-up at greater than 18 months after completion of treatment, and we classified them as at low risk of detection bias for relapse and death after six months (Alarcón 1990; Biddulph 1990; van Toorn 2014). Five cohorts presented a clear method of follow-up during treatment and were at low risk of detection bias for death during treatment, clinical cure, default, and adherence (Alarcón 1990; Biddulph 1990; Chotmongkol 1996; Donald 1998; van Toorn 2014).

Attrition bias

Three cohorts followed up more than 95% of survivors, and we classified them as at low risk of attrition bias for relapse, and death after treatment (Alarcón 1990; Chotmongkol 1991; Chotmongkol 1996). Five cohorts had less than 5% loss to follow-up during treatment and were at low risk of attrition bias for death during treatment, clinical cure, default, and adherence (Alarcón 1990; Chotmongkol 1991; Chotmongkol 1996; Donald 1998; van Toorn 2014).

Performance bias

In four cohorts, more than 95% of the participants received the planned six months treatment, with few participants receiving prolonged treatment for specific reasons stated by the study authors (for example, modified and prolonged ATT due to severe adverse event), and we considered them as at low risk of performance bias (Alarcón 1990; Chotmongkol 1991; Chotmongkol 1996; Donald 1998).

Confounding bias

In all the cohorts, we identified factors that may affect the main outcomes but that are not related to the duration of ATT, such as poor adherence and administration of corticosteroids. It is unclear how these factors would affect the findings and have classified them as unclear risk of confounding bias.

Cohorts treated for longer than six months

Detection bias

Five of the 12 cohorts conducted routine follow-up at greater than 18 months after completion of treatment and we classified them as at low risk of detection bias for relapse and death after six months of treatment (Anastasatu 1993; Ramachandran 1989; Ramachandran 1997; Török 2011a; van Toorn 2014). Seven cohorts presented a clear method of follow-up during treatment and were at low risk of detection bias for death, clinical cure, default, and adherence (Iype 2014; Lau 2005; Phuapradit 1987; Ramachandran 1989; Ramachandran 1997; Török 2011a; van Toorn 2014).

Attrition bias

Six cohorts followed-up more than 95% of survivors and we judged them as at low risk of attrition bias for relapse and death after six months of treatment (Iype 2014; Lau 2005; Phuapradit 1987; Ramachandran 1989; Ramachandran 1997; Visudhiphan 1989). Four cohorts had less than 5% loss to follow-up during treatment and we considered them as at low risk of attrition bias for death during treatment, clinical cure, default, and adherence (Iype 2014; Sharma 2013a; Török 2011a; van Toorn 2014).

Performance bias

In three cohorts, it is very likely that all participants received the planned duration of treatment, with only one participant in one cohort receiving longer treatment due to severe adverse event, and we considered them as at low risk of performance bias (Anastasatu 1993; Phuapradit 1987; Visudhiphan 1989).

Confounding bias

In all the cohorts, we identified factors that may have affected the main outcomes but that were not related to the duration of ATT, such as poor adherence and administration of corticosteroids. It is unclear how these factors would affect the findings and we have classified them as at unclear risk of confounding bias.

Additional cohort

We have presented our 'Risk of bias' assessment of the cohort reported by Alvarez-Uria 2012 in the corresponding 'Risk of bias table' (see the 'Characteristics of included studies' table). There was high risk of detection bias and unclear risk of attrition bias for outcomes that occurred during the follow-up period, which ranged from one to 51 months. For outcomes that occurred during ATT, the risk of detection and attrition biases was low. We considered there was a high risk of performance bias as participants were treated from six to 16.7 months based on the decision of clinicians.

Effects of interventions

See Figure 4 for the 'Summary of findings' table. We summarized the findings of the Alvarez-Uria 2012 cohort separately in Table 7.

Figure 4. 'Summary of findings' table.

	Cohorts treated for 6 months		Cohorts treated for longer than 6 months	
Baseline characteristics				
Number of cohorts	7		12	
Participants	458 participants 109 adults and 349 children		1423 participants 893 adults and 530 children	
HIV status	0/159 participant HIV-positive (1 study)		122/825 participants HIV-positive (5 studies)	
Clinical severity	Grade I: 32/256 (12.5%) Grade II: 139/256 (54.3%) Grade III: 85/256 (33.2%)		Grade I: 367/1308 (28.1%) Grade II: 720/1308 (55.0%) Grade III: 221/1308 (16.9%)	
Previous TB treatment	5/28 (1 study) Not reported in 430 participants (6 studies)		3/72 (1 study) Not reported in 1351 participants (11 studies)	
ATT regimens	4 different regimens		More than 20 different regimens	
Longer ATT received than regimen planned	27 participants (7.3%)		32 participants (4.8%) and 166 individualized ATT	
Length of FU (months)	From 4 to 45		From 6 to 84	
Outcomes	**Number of events**	**Number of participants (studies)**	**Number of events**	**Number of participants (studies)**
Relapse	**3** (0.8%)	**369** (7 studies)	**7** (0.8%)	**915** (11 studies)
Death from any cause	**58** (12.7%)	**458** (7 studies)	**447** (31.4%)	**1423** (12 studies)
Death after 6 months of ATT	**8** (1.7%)	**458** (7 studies)	**39** (5.9%)	**662** (8 studies)
Clinical cure (end ATT)	**408** (89.1%)	**458** (7 studies)	**984** (73.7%)	**1336** (12 studies)
Default	**4** (1.1%)	**370** (5 studies)	**8** (2.2%)	**358** (6 studies)
Poor adherence	**3** (1.9%)	**159** (1 study)	**0** (0%)	**181** (2 studies)

Abbreviations: ATT: antituberculous treatment; FU: follow-up; HIV: human immunodeficiency virus.

We have provided more details in Table 8 and Table 9 for cohorts treated for six months, and in Table 10 and Table 11 for cohorts treated for longer than six months.

Relapse

Six months ATT

Up to the end of follow-up, 3/369 participants (0.8%) from seven cohorts had relapsed. These three participants were from three different studies (Alarcón 1990; Biddulph 1990; Donald 1998), had received different regimens, and relapsed between three weeks and three months after completing ATT. Their HIV status is unknown. They consisted of one adult (34 years of age), who died, and two children (one year and 11 years), who both recovered. In Biddulph 1990, 5/7 children who had relapsed of TB infection from any organ in the whole cohort had missed doses, but authors did not report whether the case of TBM relapse was one of these five children. The child who relapsed in Donald 1998 had ethionamide stopped and the dosages of isoniazid, rifampicin, and pyrazinamide halved due to poor appetite and nausea after three months of treatment.

More than six months ATT

In 11 cohorts, 7/915 (0.8%) had relapsed during the follow-up period. These participants arise from three different studies (Iype 2014; Ramachandran 1997; Török 2011a), and they all received nine-month ATT with different regimens. They consisted of three children and four adolescents or adults. The HIV status was negative for one participant as Iype 2014 excluded HIV-positive people, and unknown for the remaining six participants: three in which the HIV status was not reported (Ramachandran 1997), and three in Török 2011a, in which there were 98/545 HIV-positive people, but the status of those who relapsed was not specified. They all recovered except one child who died. This child had culture-positive CSF with fully sensitive *M. tuberculosis* on drug sensitivity testing at initial diagnosis and again at relapse, was retreated for nine months, and died 10 months after completing the second ATT regimen, despite having normal CSF analysis and negative CSF cultures.

Additional cohort

None of the 18 participants treated for six months and followed up for 30.5 months on average presented relapse. From the 71

participants treated for longer than six months and followed-up for a mean of 25 months, seven relapsed with fatal outcome in two cases. Time to relapse was between five days and 31 months.

We have presented the profile of all participants who relapsed after completing ATT in Table 12.

Death from any cause

Six months ATT

Overall, 58/458 participants (12.7%) who received or planned to receive six months ATT regimen across the seven cohorts, died from any cause. The proportion of death in each cohort ranges from 9/159 (5.7%) in van Toorn 2014 to 9/28 (32.1%) in Alarcón 1990. Alarcón 1990 is the cohort with higher proportion of participants with severe TBM at presentation (14/28; 50%), and the nine participants who died had severe disease. The van Toorn 2014 cohort receiving six months of ATT did not include any HIV-positive participant and is the most recent study, conducted between 2006 and 2009, while the other cohorts were conducted between 1984 and 1994.

More than six months ATT

Among participants who received or planned to receive more than six months ATT, 465/1423 participants (32.7%) died from any cause among the 12 cohorts, ranging from 0% (0/44) in Anastasatu 1993 to 45.7% (249/545) and 50% (4/8) in Török 2011a and Jacobs 1992 respectively. In Anastasatu 1993, the absence of death in uncertain as there were five participants without outcome reported. In Török 2011a, 18% of the participants were HIV-positive, which may explain the higher proportion of deaths in this cohort.

Additional cohort

Overall, 131/217 (60.4%) participants died; 71.8% of them occurred during the first six months of ATT, and 13.7% in defaulters.

Death after six months of ATT

Six months ATT

In participants that received six months regimens, death after six months of ATT coincides with death after completing treatment. All seven cohorts reported the timing of death and it was therefore possible to disaggregate the data to report the number of deaths that occurred after six months of treatment. Overall, 8/458 participants (1.7%) died after completing six months of ATT, which corresponded to 13.8% of the total number of deaths from any cause. Of these eight deaths, one was attributed to relapse, six to complications of TBM related to severe neurological sequelae, and there was no cause reported for the remaining death (see Table 13).

More than six months ATT

Amont eight cohorts of participants receiving more than six months ATT, there were 39/662 participants (5.9%) who died after six months of ATT, corresponding to 8.7% of the total number of participants who died from any cause. One of these deaths was attributed to relapse, while 33 were due to complications of TBM related to severe neurological sequelae or non TB causes, and there were five deaths of unknown cause (see Table 13). The two cohorts with higher number of participants dying after six months of ATT were Ramachandran 1989 (19/180 deaths) and Ramachandran 1997 (12/215), which are two cohorts with long follow-up (42 to 84 months, and 51 months). In addition, the Török 2011a cohort reported 50/296 deaths after completing the nine-month treatment, meaning that there were at least 50 participants who died after six months of ATT. The authors of the original paper could not determine how many of these deaths could be attributed to relapse. Finally, Lau 2005 reported three deaths during the second year from the start of ATT, attributable to causes no related to TBM. There is a lack of reporting to say how many of the 23 deaths reported during the first year occurred after the six months of ATT.

Additional cohort

Among the survivors who completed at least six months of ATT, 19/89 (21.3%) participants died after six months of treatment: 3/18 (16.7%) were treated for six months and 16/71 (22.5%) were treated for longer than six months of ATT. Only two of these deaths were attributed to relapse in participants who were treated for 9.1 months and 10 months.

Clinical cure

Six months ATT

In participants that received six months ATT, 408/458 (89.1%, seven cohorts) achieved clinical cure at the end of ATT. These findings were homogeneous across five cohorts. Alarcón 1990 presented the lowest proportion of cases who achieved clinical cure (20/28; 71.4%), and van Toorn 2014 the highest proportion (153/159; 96%), which is consistent with the findings exposed in deaths of any cause outcome.

More than six months ATT

In participants that received more than six months ATT, 989/1371 (72.1%, 12 studies) had achieved clinical cure at the end of ATT. There was high heterogeneity between the studies. The lowest proportions of participants with clinical cure are reported at 50% (4/8) in Jacobs 1992 and at 62.8% (336/535) in Török 2011a, which included 18% of HIV-positive participants. The highest clinical cure rates were in Anastasatu 1993 with 100% clinical cure (by complete-case analysis, as authors did not report the final outcome for five participants), and van Toorn 2014 with 96% (24/25) in participants either HIV-positive or with *M. tuberculosis* with monoresistance to isoniazid.

Additional cohort

Overall, 94/217 (43.3%) participants achieved clinical cure at the end of ATT, which comprised of 19 participants treated for six months and 75 participants who were treated for longer.

Default

Six months ATT

We were able to extract data on the number of participants who met our definition of default from five of the seven cohorts. There were 4/370 (1.1%) cases of default. The four cases came from the same cohort (Chotmongkol 1991), in which the study authors reported that these participants received 2, 2, 3, and 4 months of ATT respectively, and correspondence via letter after a mean period of 16.5 months indicated that all had fully recovered.

More than six months ATT

Six of the 12 cohorts reported data on default. There were 8/355 (2.3%) cases of default in this group: seven of them during the first

six months of ATT, and the remaining one at an unclear time from the start of ATT.

Additional cohort

Overall, there were 30/217 (13.8%) defaulters. It is not possible to classify these participants according to the duration of treatment that they were originally planned to receive, from the data available.

Poor adherence

One cohort that only received six months ATT reported poor adherence for 3/159 participants (1.9%; van Toorn 2014), and two cohorts that received prolonged ATT reported on this outcome, with no cases reported cases with poor adherence (Lau 2005; van Toorn 2014).

All adverse effects related to the ATT

We have described the adverse events as reported in the included studies (see Table 14). We are aware that some adverse events may be attributed to co-intervention such as corticosteroids, or to complications of the TBM itself.

Six months ATT

Three cohorts reported disaggregated data on adverse effects related to ATT. There was inconsistency in the way the three cohorts reported the adverse events. Chotmongkol 1991 only reported one case of severe adverse event (severe hepatitis) among 29 participants, while Alarcón 1990 and Donald 1998 reported 24 and 32 adverse events respectively among 28 and 95 participants, which comprised a more comprehensive list of adverse events, ranging from mild and transient elevation of transaminases to severe elevation of transaminases and uric acid. van Toorn 2014 reported adverse events for all participants that received six and more than six months of treatment. Biddulph 1990 reported all adverse effects for the whole cohort of participants with TB from any organ, without disaggregated data for those with TBM.

More than six months ATT

Nine cohorts reported a comprehensive list of adverse effects related to treatment, although there was inconsistency in the methods the study authors used to detect adverse events. In some studies investigators actively looked for adverse events, while in other studies investigators only reported on participants who reported symptoms.

Drug toxicity leading to the discontinuation or modification of the treatment regimen

Six months ATT

There were 13/197 (6.6%) participants from four cohorts who had their ATT interrupted due to hepatotoxicity or significant nausea and vomiting (Alarcón 1990; Chotmongkol 1991; Donald 1998; Jacobs 1992). In van Toorn 2014, drug toxicity led to discontinuation of ATT in 17/184, without disaggregated data between participants receiving six and more than six months of ATT.

More than six months ATT

There were 216/1299 (16.6%) participants from 10 cohorts who had their ATT discontinued or modified due to a range of adverse events (see Table 14). There was inconsistency across the cohorts on how these participants were managed.

Additional TB outcomes reported by studies

Six months ATT

None of the cohorts reported treatment failure.

Four cohorts reported 123/358 participants with neurodisability after treatment completion. There is high inconsistency across studies regarding the neurological sequelae reported and in the way of diagnosing them.

More than six months ATT

Three cohorts reported data on treatment failure. In Doğanay 1995, one participant is reported to died due to treatment failure after five months of therapy, and ATT was modified in another participant due to "inadequate clinical response". In Iype 2014, four participants developed treatment failure (three during the fourth month of therapy, and one with isoniazid resistance open case of pulmonary TB during the nine month of therapy). Török 2011a reported 89 participants with "onset of new focal neurologic signs or a fall in the Glasgow coma score of two points or more for two or more days after more than seven days of clinical stability or improvement at any time after randomization", after a median of 41 days in the dexamethasone group and 38 days in the placebo group from starting treatment. Although the study authors defined these cases as relapse, they did not meet our definition of relapse as they deteriorated during ATT; we classified them as treatment failure. Lack of an agreed definition of treatment failure in TBM, and differences in monitoring of participants during therapy, are likely to have led to the marked discrepancy in reporting of this outcome between studies.

Nine cohorts reported 352/1304 participants with neurodisability at the end of treatment. There is high inconsistency across studies in the neurological sequelae reported and in the way of diagnosing them.

DISCUSSION

Summary of main results

The seven cohorts treated for six months included 458 participants from Thailand, South Africa, Ecuador, and Papua New Guinea, and only one study was conducted after the year 2000. The 12 cohorts treated for longer (eight to 16 months) included 1423 participants from India, Thailand, South Africa, China, Romania, Turkey, and Vietnam, with four conducted between 2001 and 2011. The proportion of participants classified as having stage III disease (severe) was higher in the cohorts treated for six months, but the proportion with known concurrent HIV was higher in the cohorts that were treated for longer. The diagnosis was confirmed on culture in 56/254 (22%) participants treated for six months versus 470/1264 (37%) treated for longer (in studies where this was clearly stated). Although there were variations in the treatment regimens, most cohorts received isoniazid, rifampicin, and pyrazinamide during the intensive phase.

Three out of the seven cohorts treated for six months and five of the 12 cohorts treated for longer achieved follow-up beyond 18 months after completing treatment. All studies had potential sources of bias

in their estimation of the relapse rate, and comparisons between the cohorts could be confounded.

Relapse was an uncommon event in both groups of cohorts of participants treated for six months and longer than six months, and only one death was attributed to relapse in each group.

Overall, the proportion of participants who died was higher in the cohorts treated for longer than six months, but most deaths occurred during the first six months regardless of treatment duration. This difference is not due to the treatment duration, but rather indicates that there is likely to be substantial clinical heterogeneity between the six months cohorts and the longer treatment cohorts. The disease severity is unlikely to be the main cause of this difference in the mortality rate in these cohorts, as the proportion of participants with severe tuberculous meningitis (TBM) (grade III) was higher in the cohorts treated for six months. The reason for the higher mortality rate in the group of cohorts treated for longer than six months is likely multifactorial. Delay in starting antituberculous treatment (ATT), drug resistance, drug-induced hepatitis, adherence to ATT, quality of supportive care, HIV status, and drug regimens could all contribute to this difference between the groups of cohorts.

As there was a higher proportion of deaths during ATT in the longer treatment cohorts, the proportion of participants that achieved clinical cure was higher in the group of cohorts treated for six months.

Few participants defaulted from treatment in both groups of cohorts, and adherence was poorly reported.

Most of the study authors reported on adverse events, but the level of detail in reporting varied significantly, and we were unable to draw any clear conclusions about rates of adverse events between the two groups of cohorts.

The main difference between the Alvarez-Uria 2012 cohort and the rest of the included cohorts was that all participants in the Alvarez-Uria 2012 trial were HIV-positive, and that they were managed in a "real-world" setting, contrary to the other cohorts in which participants were under trial or study conditions. The relapse rate was higher, with no cases among the 18 survivors who completed six months of ATT, and seven cases among the 71 survivors treated for longer than six months. In this cohort, it would be misleading to compare participants treated for six and more than six months, as we do not know whether the baseline characteristics of the participants were comparable. The mortality rate was high (131/217, 60.4%), and 71.8% of the deaths occurred during the first six months of treatment, similarly to the rest of the cohorts included in the review. The proportion of defaulters was higher than in the rest of the included studies (13.8%). This could represent a more accurate picture of the real proportion of defaulters among HIV-positive people in an operational setting who must take a high number of prescribed drugs.

Overall completeness and applicability of evidence

This Cochrane review includes adults and children from a variety of geographical settings, including countries in South-East Asia and Africa with a high tuberculosis (TB) burden (WHO 2015).

Only one cohort in the group of studies treating for six months reported the HIV status of the participants, and in this study HIV-positive people were all treated for nine months (van Toorn 2014). Five cohorts where participants received more than six months mentioned HIV status: two cohorts explicitly excluded HIV-positive people (Iype 2014; Sharma 2013a), and three cohorts included 122/376 HIV-positive people (Lau 2005; Török 2011a; van Toorn 2014). In addition, the cohort from Alvarez-Uria 2012 reported 217 participants co-infected with HIV. Further evidence relating to the duration of ATT in HIV-positive people with TBM is needed.

Six of the seven cohorts treated for six months and 11 of the 12 cohorts treated for longer than six months presented the three stages of clinical severity, with around half of participants in stage II in all cohorts. Results from this review are therefore applicable for all stages of clinical severity of the disease at presentation.

In this review, we have restricted the inclusion of studies to those that included ATT regimens that contained rifampicin. All six months course regimens contained at least isoniazid, rifampicin, and pyrazinamide during the intensive phase, and 1250/1423 participants treated for longer also received these three drugs, which reflect the current first-line regimens. The range of single daily doses used is mostly concordant with current recommendations.

We also restricted study inclusion to studies that reported participants with drug-sensitive TBM. van Toorn 2014 excluded children with multidrug-resistant TBM. However, this study included those with isoniazid-monoresistance. For these participants, the planned treatment consisted in a fluoroquinolone and terizidone in addition to the standard ATT for nine months. We decided to include this study as data on isoniazid-monoresistant cases (three children) were disaggregated. Across all studies, most cases did not have a *M. tuberculosis*-positive culture. Thus, the drug-sensitivity pattern was unavailable and we cannot be sure that some cases were not caused by drug-resistant strains. However, if any, this would have affected few cases, as prevalence of drug-resistant strains was lower in the period when most of the studies were conducted. Hence, results from this review are not applicable to drug-resistant TBM.

Adjunctive treatment with corticosteroids is currently recommended in all cases of TBM to reduce death (Prasad 2016). Most of the recruited participants received corticosteroids, which means that applicability of the results is unlikely to be affected by this co-intervention.

Quality of the evidence

We derived the results from single-arm studies and not direct randomized comparisons, although some were arms within randomized controlled trials (RCTs) performed for other purposes. As such, participant characteristics, comorbidities, the severity of the disease, differences in ATT regimens, drug resistance, drug-related adverse events, quality of supportive care, and method of follow-up could be different between the two groups, and making causal inferences on the basis of potentially confounded cohorts is problematic. Because of this substantial clinical and methodological heterogeneity between the studies, we did not attempt to perform a meta-analysis or perform a Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessment. Nevertheless, relapse rates were low after treatment completion in both groups.

Potential biases in the review process

We attempted to limit bias by following the rigorous methods provided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The Cochrane Infectious Diseases Group Information Specialist performed the literature search without language restrictions, and as such it is unlikely that we missed any large studies. We attempted to identify unpublished studies by contacting relevant researchers in this area, but only one study author replied. Thus, we cannot rule out the possibility that we missed some unpublished data. Also, we were unable to assess publication bias because no study directly compares six versus longer than six months of ATT. We attempted to limit bias in the selection process, data extraction, and assessment of the quality of the included studies by conducting these processes independently and by comparing results between at least two review authors.

Agreements and disagreements with other studies or reviews

The findings of this Cochrane Review are similar to those of a systematic review conducted by van Loenhout-Rooyackers 2001, who concluded, based on the results of 11 included studies, that six months regimens with at least isoniazid, rifampicin, and pyrazinamide were sufficient for participants with fully drug sensitive TBM. This review was similar to our review in that the included studies were all non-randomized observational studies. Completion of treatment was 81% in participants that received six months regimens and 85% in those that received longer regimens. There were 2/131 and 0/591 participants with relapse in the six months regimen group and longer ATT group respectively. Another systematic review, which belongs to a series that addressed the scientific evidence behind the World Health Organization (WHO)'s recommendations, reviewed the most appropriate ATT for TBM and drew similar conclusions regarding length of treatment, based on four prospective and retrospective observational cohorts (Woodfield 2008).

AUTHORS' CONCLUSIONS

Implications for practice

Despite potential confounding, there is no evidence of higher relapse in people treated for only six months: relapse was an uncommon event regardless of the duration of treatment, and there was no higher proportion of deaths among those treated for six months. These data are almost all from participants who are HIV-negative, and thus it is inappropriate to make inferences from these data about the safety and efficacy of the six month regimen to HIV-positive people. The quality of the evidence is limited by a lack of studies including a direct comparison between six months and more than six months regimens.

Implications for research

Notably, no randomized controlled trials (RCTs) have compared six months standard first-line ATT with longer regimens, despite the significant uncertainty around best practice and the consequent variations in practice and guidelines. This could be because of resource constraints and competing research priorities, but it might also be due to prevailing perceptions that six months ATT is simply inadequate in this life-threatening form of TB disease.

We originally conducted this review to inform a guideline development process in India on extrapulmonary TB, the Indian Extra-Pulmonary TB (INDEX-TB) Guidelines (INDEX-TB 2016). During the guideline development process, several experts commented that they were concerned about the ethics of conducting a RCT that compared six months ATT with longer regimens in people with TBM, citing their experiences of patients treated for six months who have relapsed. They felt it would be unsafe and unethical to randomize patients to receive six months of ATT.

The results of this Cochrane review suggest that relapse is an uncommon event whether participants are treated for six months or longer, and so randomization of participants to a six months regimen would not be unethical in a well-conducted trial. An adequately powered, multicentre RCT conducted in low- and middle-income countries where TB prevalence is high, that compares six versus nine or 12-month regimens using the same first-line drugs in standardized doses would help answer this question. Such trials should involve HIV-positive and HIV-negative adults and children, and should be powered to allow subgroup analyses between age group, HIV status, nutritional status, and disease severity at presentation. An alternative to conducting an RCT would be to set up large, prospective cohort studies that compare six months and prolonged treatment regimens, where duration of treatment is clearly decided at initiation of ATT. This would have the advantage of more closely reflecting the outcomes that are achievable in everyday practice, rather in the carefully controlled conditions of a trial, and may be more feasible than an RCT. RCTs have the advantage of being better equipped to deal with the problems of confounding and bias in patient selection that we have identified in the studies included in this review than cohort designs.

On the other hand, shortening the overall duration of TBM treatment to achieve outcomes at least as good as the 12 months regimens may be possible through different regimens, such as increasing the length of the intensive phase, changing the doses, or the frequency of administration of the first-line drugs currently used, or adding or substituting second-line drugs. These different options need to be addressed. Few trials have been conducted evaluating high doses of rifampicin and use of fluoroquinolones for TBM (Heemskerk 2016; Ruslami 2013; Thwaites 2011). However, these trials assessed survival as main outcome and did not follow-up participants after completion of ATT for relapse. Whether these new regimens would allow shortening of the overall treatment duration is unknown. Most research focuses on pulmonary TB. Several trials assessing new regimens are being developed or are in progress (Zumla 2015). For drug-sensitive pulmonary TB, a systematic review assessed fluoroquinolones as substitute or additional agents in ATT regimens, and concluded that there is insufficient evidence on whether this would reduce death or relapse (Ziganshina 2013). When extrapolation of results is contemplated from pulmonary TB to TBM, pharmacodynamics of the antituberculous regimen should be taken into account, to ensure adequate effects of antituberculous agents in the site of infection. Analyses on cerebrospinal (CSF) concentrations of drugs may be required. Thus, additional studies are needed to elucidate the role of fluoroquinolones in TBM treatment, and to further address alternative regimens that would allow shortening of the overall length of ATT.

Finally, we noted that there was a lack of homogeneity in the included studies when reporting outcomes and follow-up. Efforts towards using standardized definitions for relapse and default, at least 12 months follow-up after completing ATT and better reporting on outcomes including adverse events should be encouraged for future studies to facilitate comparability between them and allow meta-analysis.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Alarcón 1990

Methods	Study objective: to review the clinical and therapeutic characteristics of the short course of antituberculous treatment (ATT) in tuberculous meningitis (TBM). Study design: prospective observational study.

Alarcón 1990 *(Continued)*

	Length of follow-up: 24 to 36 months from start of ATT in survivors. Follow-up method: after hospital discharge, programmed visit in their neurological department once a month for receiving antituberculous drugs, detailed neurological examination and cerebrospinal fluid (CSF) examination if indicated. CSF examination was performed at the beginning of the treatment, 48 h later, and 15, 30, 60, 90, 180, 360 and 720 days after initiating the treatment. Neurological sequelae were assessed 18 months after concluding the treatment. Losses to follow-up: none.
Participants	Number: 28; mean age 29.1 years (range 11 months to 70 years); 75% male. Target treatment groups: children and adults with TBM. Inclusion criteria: CSF analysis (differential cell count, protein and glucose levels, acid-fast bacilli (AFB), culture in Lowenstein-Jensen medium, adenosine deaminase (ADA), enzyme-linked immunosorbent assay (ELISA) for Bacillus Calmette–Guérin (BCG) antibodies). Participants were classified into the following groups. • Definite TBM: diagnosis based on an autopsy finding, or on positive CSF AFB smear and culture, or on both. • Probable TBM: negative CSF AFB smear and culture, but at least 1 of a positive AFB smear or positive culture of *M. tuberculosis* from another tissue or body fluids, positive ELISA, or positive ADA in CSF; and at least two of the following tests positive: purified protein derivative (PPD) test, chest X-ray, computerized tomography (CT) scan, and a history of previous tuberculosis (TB) or contact with someone with TB. Exclusion criteria: participants who received a treatment with isoniazid previously and had followed an adequate course of the drug. Bacteriologically confirmed TBM cases: 22/28. Site of TB other than central nervous system (CNS): 17 with abnormal chest X-ray including 7 miliary pattern. 5 positive smear/cultures from urine, 3 positive smear/cultures from sputum, 2 positive smear/cultures from gastric aspirate, 1 positive culture from perirenal abscess, and 1 positive culture from lymph node biopsy. Other clinical features: none described. Clinical severity of the disease: 4 in stage I; 10 in stage II; 14 in stage III. HIV status: not reported Duration of symptoms for less than 3 weeks prior to admission in 18/28; time to treatment initiation between 1 hour and 7 days after admission.
Interventions	Short-course ATT: 6 months - 2 months isoniazid, rifampicin and pyrazinamide, followed by 4 months isoniazid and rifampicin (2HRZ/4HR), daily dosage, orally. • Isoniazid: 10 mg/kg (6 months). • Rifampicin: 15 mg/kg (6 months). • Pyrazinamide: 30 mg/kg (2 months). Prolonged-course ATT: none. Other interventions • Prednisone (1 to 3 mg/kg/day) given to 19 cases (indicated for participants with impairment of consciousness, focal neurology abnormalities, and a CSF pressure greater than 300 mmH_2O). • Pyridoxine (50 to 100 mg/day) given to all participants. • Ventriculoperitoneal shunting in 3 participants.
Outcomes	Outcomes included in this review (directly reported or deductible from reported data)

Alarcón 1990 *(Continued)*

- Relapse.
- Death from any cause.
- Death after 6 months of ATT.
- Clinical cure.
- Default.
- All adverse effects related to the ATT.
- Drug toxicity leading to discontinuation of regimen.

Outcomes not included in this review

- Neurological sequelae.

Notes	Country: Ecuador. Setting: Department of Neurology in one Hospital of the capital (Eugenio Espejo Hospital, Quito). Study dates: from March 1986 to January 1989. Study sponsor: none reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Detection bias Relapse	Low risk	The trial followed up participants at specific points during the follow-up period, with physical and CSF examinations, although no details are given if participants did not attend the planned visits. All 19 survivors had CSF examination at 18 months after completing ATT.
Detection bias Clinical cure and default	Low risk	After hospital discharge, participants had visits programmed once a month for receiving antituberculous drugs, detailed neurological examination and CSF examination if indicated.
Attrition bias Relapse	Low risk	No losses of follow-up during the follow-up period of 18 to 30 months.
Attrition bias Clinical cure and default	Low risk	No losses of follow-up during the treatment duration.
Performance bias	Low risk	All participants received 6 months ATT.
Confounding bias	Unclear risk	Adherence to treatment is not reported. Prednisolone was given to 19/29 participants on the basis of disease severity but it is unclear how this would affect the results.

Alvarez-Uria 2012

Methods	We contacted the first author for disaggregated data for TBM and to clarify how long participants were followed-up. Instead, the study author provided us access to a larger database of cohort of participants with TBM. Some of these participants were included in Alvarez-Uria 2012, which describes the setting. Some of the participants included in our analysis have also been presented in Alvarez-Uria 2013 and Alvarez-Uria 2015. However, all the data we present in this review come from the larger database provided by the study author, which is of an ongoing study for which some results are available (Alvarez-Uria 2012; NCT02454569). Study objective: Rural Development Trust (RDT) is a non-governmental organization that provides free medical care to HIV-positive participants in a resource-poor rural setting of India (district of Ananta-

Alvarez-Uria 2012 *(Continued)*

	pur). The Vicente Ferrer HIV Cohort Study (VFHCS) is a long-term prospective cohort study of all HIV-infected participants who have attended RDT hospitals. Data are collected prospectively since September 2009 to describe the epidemiology of HIV and its related conditions in the investigators area, and to study the effectiveness of health interventions in a 'real-world' setting (implementation and operational research). Study design: prospective observational study. Length of follow-up among survivors who completed ATT: mean 28.8 months after completing ATT (range 2.8 to 51.3 months). Follow-up method: participants are followed up monthly during the duration of ATT, and every month or 2 months after completing ATT. Losses to follow-up: 2 participants were lost to follow-up right after completing ATT (1 participant in the 6 months group, 1 in the 8 months group)
Participants	Number: 217; mean age 38 years (3 children of 8, 9, and 13 years, otherwise range 18 to 70 years); 72% male. Target treatment groups: HIV-positive participants with TBM co-infection. Inclusion criteria: participants were diagnosed with TBM following the criteria defined in Marais 2010. Exclusion criteria: other CSF infection identified by positive cryptococcal antigen in CSF or positive culture for pyogenic bacteria. Bacteriologically confirmed TBM cases: not reported. Site of TB other than CNS: not reported. Other clinical features: not reported. Clinical severity of the disease: not reported. HIV status: all participants were HIV-positive. Duration of symptoms and time to treatment initiation: not reported.
Interventions	Short-course ATT: 6 months to participants without previous TB. From 23 December 2010 until 28 January 2012: standard regimen (category I) of 2HRZE/4HR, oral, once daily • Isoniazid: 300 mg (6 months). • Rifampicin: 450 mg (6 months). • Pyrazinamide: 1500 mg/kg (2 months). • Ethambutol: 800 mg (2 months). From 29 January 2012: new ATT regimen during admission, oral, once daily • Isoniazid: 600 mg. • Rifampicin: 900 mg. • Pyrazinamide: 1500 mg/kg. • Levofloxacin: 750 mg. • Ethionamide: 750 mg. After discharge, participants were treated with standard regimen (category I). Prolonged-course ATT: 8 months to participants previously exposed to ATT. From 23 December 2010 until 28 January 2012: standard regimen (category II) 2HRZES/1HRZE/5HRE, oral, once daily

Alvarez-Uria 2012 *(Continued)*

- Isoniazid: 300 mg (8 months).
- Rifampicin: 450 mg (8 months).
- Ethambutol: 800 mg (8 months).
- Pyrazinamide: 1500 mg/kg (3 months).
- Streptomcin: 750 mg (2 months).

From 29 January 2012: new ATT regimen during admission, oral, once daily

- Isoniazid: 600 mg.
- Rifampicin: 900 mg.
- Pyrazinamide: 1500 mg/kg.
- Levofloxacin: 750 mg.
- Ethionamide: 750 mg.

After discharge, participants were treated with standard regimen (category II).

The participants who relapsed were given category II regimen.

Other interventions

- Corticoids: the typical regimen given to all participants consisted of intravenous dexamethasone (16 mg every 6 hours for 3 to 4 days, then 8 mg every 8 hours for 3 to 4 days), followed by oral prednisolone (40 mg once daily) before hospital discharge. After discharge, prednisolone was reduced 10 mg every 2 weeks, so corticosteroids were stopped after 8 weeks of hospital discharge.
- Pyridoxine 50 mg/day to all participants.
- Sodium heparin (5000 IU subcutaneous every 12 hours) to all participants during the hospital admission.
- Valproate acid to participants with seizures.

Outcomes

Outcomes included in this review

- Relapse.
- Death from any cause.
- Death after 6 months of ATT.
- Default.
- Clinical cure (defined as treatment completed by the investigators).

Outcomes not included in this review: none.

Notes

Country: India.

Setting: RDT hospitals in the district of Anantapur.

Study dates: cases of TBM diagnosed from 23 December 2010 to 30 September 2014. Execution of the search from the database: 2 February 2016.

Study sponsor: none.

All the study data comes from the larger database provided by the study author, which is of an ongoing study for which some results are available (Alvarez-Uria 2012; NCT02454569).

Risk of bias

Bias	Authors' judgement	Support for judgement
Detection bias Relapse	High risk	After completing ATT, participants visited the clinic every 1 or 2 months, as part of the follow-up of the large HIV cohort. The length of follow-up in survivors who completed ATT ranges from 1 to 51 months.
Detection bias	Low risk	Participants were followed-up monthly during ATT.

Alvarez-Uria 2012 *(Continued)*
Clinical cure and default

Attrition bias Relapse	Unclear risk	Among the survivors who completed ATT, there were 5/94 participants with no day of follow-up after completing the therapy (5.3%).
Attrition bias Clinical cure and default	Low risk	No participant was reported lost of follow-up during the duration of the treatment.
Performance bias	High risk	According to local guidelines, participants without previous TB would be treated for 6 months and those with previous TB for 8 months. However, participants were treated up to 16.7 months according to clinician decision, with considerable variation in duration of treatment within the cohort.
Confounding bias	Unclear risk	Adherence to treatment is not reported. All participants received corticosteroids. All participants are HIV-positive. We do not know the antiretroviral treatment given and how this may have interacted with the outcomes.

Anastasatu 1993

Methods	Study objective: to review the results of 9 months ATT in children with severe forms of TB, 5 years after completing ATT. Study design: randomized controlled trial (RCT) that compared 9 months versus 12 months ATT regimens. Length of follow-up: 5 years after completing ATT. Follow-up method: periodic follow-up in the paediatric department of the Institute of Pneumo-physiology "M.Nasta". Losses to follow-up: 5/44
Participants	Number: 44 TBM; age and gender not reported. Target treatment groups: children between 0 and 14 years with severe forms of TB, including TBM, granulomas, and caseous forms (pneumonia and bronchopneumonia). Inclusion criteria: no further details provided. Exclusion criteria: none reported. Bacteriologically confirmed TBM cases: positive culture in 30/60 cases of severe forms of TB, without disaggregated data for TBM. Site of TB other than CNS in participants with TBM: no abnormal findings in chest X-ray, no other details reported. Other clinical features: none reported. Clinical severity of the disease: not reported. HIV status: not reported. Duration of symptoms prior to admission and time to treatment initiation: not reported.
Interventions	Short-course ATT: none. Prolonged-course ATT • Experimental group: 9 months – 3HRZ/6HR$_2$ (given to 19 participants with TBM).

Anastasatu 1993 *(Continued)*

- Control group: 12 months - 3HR/3HR$_2$/6H$_2$ (given to 25 participants with TBM).
- Drug dosages:
  - in the first 3 months:
    - isoniazid: 10 mg/kg/day (both groups);
    - rifampicin: 10 mg/kg/day (both groups);
    - pyrazinamide: 20 to 25 mg/kg/day (experimental groups);
    - streptomycin twice weekly is included in the administered drugs for both groups. However, this drug is not described earlier in the methods;
  - Thereafter, twice weekly:
    - isoniazid: 15 mg/kg (6 months in experimental group, 9 months in control group);
    - rifampicin: 15 mg/kg (6 months in experimental group, 3 months in control group).

Other interventions: none reported.

Outcomes	Outcomes included in this review (directly reported or deductible from reported data) • Relapse. • Death from any cause. • Death after 6 months of ATT. • Clinical cure. Outcomes not included in this review • Neurological sequelae at 5 years of follow-up. • Radiologic aspect at 5 years of follow-up. • Bacteriological status at 5 years of follow-up.
Notes	Country: Romania. Setting: Paediatric Department of the Institute of Pneumo-physiology Institute "M.Nasta". Study dates: not reported. Study sponsor: none reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Detection bias Relapse	Low risk	The study gave outcomes at 5 years of follow-up for all participants not lost to follow-up, with findings reported in radiological and bacteriological outcomes.
Detection bias Clinical cure and default	Unclear risk	The study authors reported that participants were followed-up periodically. However, the follow-up methods during ATT are unclear.
Attrition bias Relapse	Unclear risk	It is unclear when the 5/44 participants lost to follow-up left the trial and what their outcomes were.
Attrition bias Clinical cure and default	Unclear risk	It is unclear when the 5/44 participants lost to follow-up left the trial and what their outcomes were.
Performance bias	Low risk	Investigators did not report whether or not participants received prolonged ATT. However, this is unlikely, as the aim of this RCT was to compare 9 versus 12 months of treatment.
Confounding bias	Unclear risk	Adherence to treatment and co-intervention are not reported.

Biddulph 1990

Methods	Study objective: to review the results of 6 months ATT in childhood TB. Study design: prospective observational study. Length of follow-up: up to 24 months after completing ATT. Follow-up method • During ATT: all participants were managed in hospital for the first 2 months of chemotherapy, then discharged to an outpatient clinic for the last 4 months of treatment. They attended the clinic twice weekly to receive chemotherapy under supervision and were checked once monthly at the hospital paediatric TB follow-up clinic. A paediatric TB sister attempted to track down defaulters. • After completing ATT: visit every 3 months for the following 2 years, in the paediatric TB follow-up clinic. Losses to follow-up: no disaggregated data for TBM.
Participants	Number: 639 children with TB, including 43 children with CNS TB. 58% of the 639 TB participants were less than 5 years old and 54% were male, without disaggregated data provided for the CNS TB cases. Target treatment groups: children with TB. Inclusion criteria: TB diagnosis was made on clinical, bacteriologic or histologic evidence. • Clinical diagnosis required suggestive history and clinical findings, supported by either a significant Mantoux response or a confirmed household contact of TB, or characteristic findings on chest X-ray, CSF, pleural fluid, or ultrasound of the abdomen and a good response to ATT, in the absence of a more likely diagnosis. • Suggestive features of CNS TB were one or more of the following: meningeal signs, impaired state of consciousness, cranial nerve palsies, hemiparesis, ataxia, or papilledema in the absence of a more likely diagnosis (e.g. purulent or cryptococcal meningitis). Children with neurological signs who had gross papilledema did not have lumbar puncture performed, hence the use of the term CNS TB by the investigators rather than TBM. In a number of these children, it was not possible to distinguish between TBM, tuberculoma or TB encephalopathy. Thus, among the 43 children with CNS TB, there were as follows. • 31 TBM, with predominance of lymphocytes, reduced glucose and raised protein concentrations in CSF. • 11 children with gross papilloedema and thus without lumbar puncture. • 1 child with spinal subarachnoiditis, with high CSF protein concentration and partial block shown on myelography. Exclusion criteria: none reported. Bacteriologically confirmed TBM cases: 5. Site of TB other than CNS: 14 abnormal chest X-ray among the 43 children with CNS TB. Other clinical features: 1 spinal arachnoiditis. Clinical severity of the disease: not reported. HIV status: not reported. Duration of symptoms prior to admission and time to treatment initiation: not reported.
Interventions	Short-course ATT: 6 months - 2HRZS/4(HR)$_2$.

Biddulph 1990 *(Continued)*

- First 2 months: single daily dosages:
  - isoniazid: 10 to 15 mg/kg, max 300 mg;
  - rifampicin: 10 to 15 mg/kg, max 600 mg;
  - pyrazinamide: 25 to 35 mg/kg, max 1500 mg;
  - streptomycin: 20 to 30 mg/kg, max 750 mg.
- Following 4 months: twice a week:
  - isoniazid: 15 to 20 mg/kg, max 900 mg;
  - rifampicin: 10 to 15 mg/kg, max 600 mg.

Children who lived to far from an outpatient clinic were given 3 months HRZS, followed by 3 months of daily Isoniazid 10 to 15 mg/kg. Follow-up of these children was not possible.

Prolonged-course ATT: none.

Other interventions

- Corticosteroids to all children with CNS TB.
- Pyridoxine (25 mg) if isoniazid dose was more than 300 mg.
- Ventriculo-peritoneal shunt.

Outcomes	Outcomes included in this review (directly reported or deductible from reported data) • Relapse. • Death from any cause. • Death after 6 months of ATT. • Default (no disaggregated data for TBM). • All adverse effects related to ATT (no disaggregated data for TBM). • Drug toxicity leading to discontinuation of regimen (no disaggregated data for TBM). Outcomes not included in this review: none.
Notes	Country: Papua New Guinea. Setting: Port Moresby General Hospital. Study dates: from November 1984 to November 1986. Study sponsor: none reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Detection bias Relapse	Low risk	Survivors had programmed visits every 3 months for the following 2 years.
Detection bias Clinical cure and default	Low risk	All participants were managed in hospital for the first 2 months of treatment, then discharged to an outpatient clinic for the last 4 months of treatment. They attended the clinic twice weekly to receive chemotherapy under supervision and were checked once monthly at the hospital paediatric TB follow-up clinic. A paediatric TB nurse attempted to track down defaulters.
Attrition bias Relapse	High risk	There are no disaggregated data for TBM. However, 70/373 attended the full 24-month follow-up.
Attrition bias Clinical cure and default	Unclear risk	There are no disaggregated data for TBM.

Biddulph 1990 *(Continued)*

Performance bias	Unclear risk	Whether participants received ATT longer than the planned 6 months is not reported.
Confounding bias	Unclear risk	Study authors did not report on adherence to treatment. All participants received corticosteroids.

Chotmongkol 1991

Methods	Study objective: to review the results of 6 months ATT in adults with TBM. Study design: prospective observational study. Length of follow-up: mean 16.3 months after completion of therapy (range 4 to 33). Follow-up method: unclear. Correspondance by letters described in 4 participants. Losses to follow-up: the study authors reported 4 participants were lost to follow-up and excluded them from the results. However, the study authors reported that these participants received 2, 2, 3, and 4 months of ATT respectively, and correspondence via letter after a mean period of 16.5 months after treatment indicated that all fully recovered.
Participants	Number: 29; mean age 35 years (range 16 to 61); gender not reported. Target treatment groups: adults with TBM. Inclusion criteria: based on the characteristic clinical features and typical CSF findings (lymphocytic meningitis with low glucose and elevation of protein content). Exclusion criteria: none mentioned. Bacteriologically confirmed TBM cases: 6/29 Site of TB other than CNS: 10 participants with abnormal chest X-ray, 1 peritonitis, 1 osteomyelitis, 1 laryngitis. Other clinical features: 4 participants with tuberculoma, 7 with communicating hydrocephalus, 3 with spinal arachnoiditis. Clinical severity of the disease: 7 in stage I; 12 in stage II; 10 in stage III (Gordon and Parsons classification, Gordon 1972). HIV status: not reported. Duration of symptoms prior to admission and time to treatment initiation: not reported.
Interventions	Short-course ATT: 6 months - 2HRZS/4HR, single daily dosage • Isoniazid: 300 mg orally (6 months). • Rifampicin: 600 mg orally (450 mg if participant weight < 45 kg) (6 months). • Pyrazinamide: 1500 mg orally (2 months). • Streptomycin 750 mg intramuscular (2 months) (26 cases). • Ethambutol 800 mg was used as a replacement if streptomycin could not be taken. One participant had severe hepatitis due to isoniazid; treatment was continued with rifampicin and ethambutol for 18 months. Prolonged-course ATT: none Other interventions

Chotmongkol 1991 *(Continued)*

	• Prednisolone (45 to 60 mg/day, gradually tapered off over 2 to 4 weeks) given to 9 participants with mental change, high CSF protein content or spinal arachnoiditis. • Repeated lumbar puncture for participants with CSF pressure over 200 mmH_2O. • Ventriculo-peritoneal shunt for participants with persistent high CSF pressure after 3 to 4 weeks of daily lumbar puncture (8 participants). • Immediate ventriculostomy to participants who had severe mental change with hydrocephalus.
Outcomes	Outcomes included in this review (directly reported or deductible from reported data) • Relapse. • Death from any cause. • Death after 6 months of ATT. • Clinical cure. • Default. • Drug toxicity leading to discontinuation of regimen. Outcomes not included in this review • Neurological sequelae.
Notes	Country: Thailand. Setting: Department of Medicine, Srinagarind Hospital, Khon Kaen. Study dates: from January 1988 to June 1990. Study sponsor: none reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Detection bias Relapse	High risk	The study authors reported correspondence by letters for 4 participants. However, they did not describe the methods of follow-up for the rest of participants. Participants were followed-up for a mean of 16.3 months after completion of ATT, ranging from 4 to 33.
Detection bias Clinical cure and default	Unclear risk	The study authors did not describe the methods of follow-up during ATT.
Attrition bias Relapse	Low risk	No losses of follow-up during the follow-up period.
Attrition bias Clinical cure and default	Low risk	No losses of follow-up during the duration of the treatment.
Performance bias	Low risk	1/25 (4%) participant received more than 6 months ATT, due to modified treatment for adverse events.
Confounding bias	Unclear risk	The study authors did not report on adherence to treatment. Prednisolone was given to 9/29 participants on the basis of disease severity but it is unclear how this would affect the results.

Chotmongkol 1996

Methods	Study objective: to determine whether corticosteroid is beneficial to participants with TBM.

Chotmongkol 1996 *(Continued)*

	Study design: randomized double-blind controlled trial of antituberculous therapy with corticoids versus antituberculous therapy with placebo. Treated as prospective observational data for the purposes of this review. Length of follow-up: mean 30 months after completion of therapy (range 16 to 45). Follow-up method: assessment and record of physical examination and adverse events every week during hospitalization, every 1 or 2 months until the 6 months study period was completed, and at 3rd, 6th, 9th, and 12th months after completing antitubercular therapy. Losses to follow-up: 0/59.
Participants	Number: 59; mean age 42 and 39 years in the prednisolone and placebo groups respectively (range 16 to 86); 54.2% male. Target treatment groups: adults over 15 years with TBM. Inclusion criteria: diagnosis of TBM was based on the following • Characteristic clinical features. • Typical CSF findings: lymphocytic meningitis with low glucose level, elevation of protein content, sterile routine bacterial and fungal culture, a negative latex agglutination test for bacterial and cryptococcal antigen and a negative cytologic study for malignancy. Exclusion criteria: positive serologic test for syphilis or HIV. Bacteriologically confirmed TBM cases: 5 positive culture and 1 positive AFB stain (unclear whether specimen with positive stain was also culture positive). Site of TB other than CNS: 23 lung (including 4 miliary patter), 3 lymph node, 1 spine, 1 larynx, 1 peritoneum, and 1 intestine. Other clinical features: 26 hydrocephalus (including 3 with tuberculoma), 2 tuberculoma alone, 7 spinal arachnoiditis, 1 TB spondylitis. Clinical severity of the disease: 9 in stage I; 40 in stage II; 10 in stage III. HIV status: HIV-positive people excluded. Duration of symptoms prior to admission and time to treatment initiation: not reported.
Interventions	Short-course ATT: 6 months - 2HRZS/4HR, single daily dosage • Isoniazid: 300 mg orally (6 months). • Rifampicin: 600 mg orally (450 mg if participant weight < 50 kg) (6 months). • Pyrazinamide: 1500 mg orally (2 months). • Streptomycin 750 mg intramuscular (2 months). Prolonged-course ATT: none. Other interventions • Steroid therapy: participants were randomized to receive placebo (30 participants) or prednisolone (29 participants; 60 mg/day orally during 2 weeks, then dose gradually tapered off over 5 weeks). • Repeated lumbar puncture for participants with CSF pressure over 200 mmH_2O. • Ventriculo-peritoneal shunt for participants with persistent high CSF pressure after 4 weeks of daily lumbar puncture (9 participants). • Immediate ventriculostomy to participants who had severe mental change with hydrocephalus.
Outcomes	Outcomes included in this review (directly reported or deductible from reported data) • Relapse.

Chotmongkol 1996 *(Continued)*

- Death from any cause.
- Death after 6 months of ATT.
- Clinical cure.
- Default.

Outcomes not included in this review

- Neurological sequelae.
- Ventricular shunting.
- Time until disappearance of headache after treatment.
- Time until normal body temperature after treatment.

Notes	Country: Thailand. Setting: Srinagarind Hospital in Khon Kaen. Study dates: from July 1990 to December 1992. Study sponsor: none reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Detection bias Relapse	Unclear risk	The study aimed to follow participants every 3 months after completing ATT during the first year. Participants were, in reality, followed for a mean of 30 months after completion of therapy (range 16 to 45).
Detection bias Clinical cure and default	Low risk	Close follow-up of participants during ATT, under trial conditions.
Attrition bias Relapse	Low risk	No losses of follow-up during the follow-up period.
Attrition bias Clinical cure and default	Low risk	No losses of follow-up during the duration of the treatment.
Performance bias	Low risk	Investigators reported that no participants received prolonged treatment.
Confounding bias	Unclear risk	Adherence to treatment is not reported. 29/59 participants were randomized to receive either prednisolone or placebo, but it is unclear how this would affect the results.

Donald 1998

Methods	Study objective: to describe the results of 6 months intensive ATT in children with complicated forms of TBM. Study design: prospective observational study. Length of follow-up: 12 months after completion of therapy. Follow-up method: after the first month of treatment, children were transferred to a regional TB hospital for completion of 6 months of treatment under direct supervision. After completion of chemotherapy, parents were requested to take the child to the relevant clinic once monthly for the first year. Clinic personnel then reported the child's clinical condition to the study authors in writing following this monthly visit. When children failed to attend, a home visit was undertaken.

Donald 1998 *(Continued)*

	Losses to follow-up: 12/95 • 5 children, because they moved to a rural remote area immediately after discharge. • 7 children moved during the follow-up period.
Participants	Number: 95; median age 17 months for 39 participants in stage III, 38 months for 52 participants in stage II and 37 months for 4 participants in stage I. Gender not reported. Target treatment groups: children with TBM. Inclusion criteria: "the children were evaluated according to a long-standing protocol, and the majority were entered in studies evaluating different methods of managing the various complications of TBM". Exclusion criteria: not reported. Bacteriologically confirmed TBM cases: 18 positive culture of *M. tuberculosis* from CSF; 31 positive culture of *M. tuberculosis* from gastric aspirate (7 of them also had positive culture from CSF). Site of TB other than CNS: 41 abnormal chest X-ray, other sites not reported. Other clinical features: 6 children with 1 or more tuberculomata, 82 hydrocephalus. Clinical severity of the disease: 4 in stage I; 52 in stage II; 39 in stage III. HIV status: not reported. Duration of symptoms prior to admission and time to treatment initiation: not reported.
Interventions	Short-course ATT: 6 months - 6HRZEth, single daily dosage, which were increased appropriately as the children gained in weight. • Isoniazid: 20 mg/kg (6 months). • Rifampicin: 20 mg/kg (6 months). • Pyrazinamide: 40 mg/kg (6 months). • Ethionamide: 20 mg/kg (6 months). 3 children were inadvertently started again on ATT by regional medical staff after completing 6 months ATT. Prolonged-course ATT: none. Other interventions • Prednisone (4 mg/kg/day) in 40 or 44 (unclear as both numbers are stated in the text) children as part of a randomized prospective evaluation of the use of steroids in TBM. • Daily acetazolamide and furosemide during the first month of ATT. • Ventriculo-peritoneal shunt to 27 children (21 with non-communicating hydrocephalus and 6 with unsatisfactory response to medical management).
Outcomes	Outcomes included in this review (directly reported or deductible from reported data) • Relapse. • Death from any cause. • Death after 6 months of ATT. • Clinical cure. • Default. • All adverse effects related to ATT. • Drug toxicity leading to discontinuation of regimen. Outcomes not included in this review

Donald 1998 *(Continued)*

- Neurological sequelae.

Notes	Country: South Africa. Setting: Department of Paediatrics and Child Health of a tertiary care institution (Tygerberg Hospital) in the Western Cape Province. Study dates: from 1 January 1991 to 31 August 1994. Study sponsor: none reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Detection bias Relapse	Unclear risk	Methods of follow-up are clear, with monthly visits to the clinic during the first year after completing ATT. A home visit was undertaken when children failed to attend. Follow-up was planned for 1 year after completing ATT, with no details given on the real follow-up of the participants.
Detection bias Clinical cure and default	Low risk	Children received ATT in the study hospital after the first month of treatment, and were transferred afterwards to a regional TB hospital for completion of 6 months treatment under direct supervision.
Attrition bias Relapse	High risk	12/82 (14.6%) participants were lost to follow-up after completing ATT.
Attrition bias Clinical cure and default	Low risk	No losses of follow-up during the duration of the treatment.
Performance bias	Low risk	3/82 (3.7%) survivors were inadvertently started again on ATT by regional medical staff after completing 6 months ATT.
Confounding bias	Unclear risk	Adherence to treatment not reported. 40 or 44 (unclear as both numbers are stated in the text) children received prednisone as part of a randomized prospective evaluation of the use of steroids in TBM. Ventriculo-peritoneal shunt to 27 children. It is unclear how these co-interventions would affect the results.

Doğanay 1995

Methods	Study objective: to evaluate the results of therapy in participants with TBM at 4 centres in Turkey. Study design: prospective comparative study between 2 ATT regimens (8 months treatment in 3 centres, 12 to 16 months treatment in 1 centre), with data collected during the same period of time. Length of follow-up: median 10 (range 6 to 24) and 13 (range 4 to 36) months after completion of therapy in 48 participants in the 8 months and the 12 to 16 months treatment groups respectively. Follow-up method: not reported. Losses to follow-up: 10 participants during ATT, 7 additional participants after completing ATT.
Participants	Number: 72; mean age 30.4 years (range 16 to 65 years); 55.6% male. Target treatment group: adults over 15 years with TBM. Inclusion criteria: the diagnosis of TBM was based on

Doğanay 1995 *(Continued)*

- Clinical findings of subacute and chronic meningitis (meningeal symptoms lasting for > 4 days).
- CSF findings (clear or xanthochromatic, elevated cell count with predominance of lymphocytes, glucose level < 400 mg/L, protein level > 1 g/L).
- Demonstration of AFB in CSF by microscopy examination,or culture, or both.
- Evidence of any associated extrameningeal tuberculous lesion.

Exclusion criteria: participants dying in the first 5 days of admission. Exclusion criteria for receiving 8 months therapy: if participants were given a different ATT regimen for > 1 week; if therapy lapsed for 10 days during treatment period; participants treated for TB in the previous 2 years.

Bacteriologically confirmed TBM cases: not reported.

Site of TB other than CNS: 22 pulmonary TB (PTB), 5 miliary TB, 4 spondylitis, 1 TB lymphadenitis.

Other clinical features: 1 intracerebral tuberculoma, 3 hydrocephalus.

Clinical severity of the disease: 7 in stage I; 34 in stage II; 31 in stage III.

HIV status: not reported.

Duration of symptoms prior to admission and time to treatment initiation: not reported.

Interventions	Short-course ATT: none.
	
	Prolonged-course ATT:
	
	• 8 months - 2HRZS/6HR. 37 participants:
	  ◦ isoniazid: 300 mg/day (8 months);
	  ◦ rifampicin: 600 mg/day (8 months);
	  ◦ pyrazinamide: 1500 mg/day (2 months);
	  ◦ streptomycin: 1 g/day (1 month, thereafter on alternate days, to a total of 45 g).
	
	Duration of therapy was prolonged in 1 participant until 9 months and in 1 participant until 10 months. Treatment was modified in 1 participant because of inadequate clinical response.
	
	• 12 to 16 months: 4 drugs for 4 to 6 months, followed by 2 to 3 drugs until overall duration of treatment of 12 to 16 months. 35 participants:
	  ◦ regimens used: 19 participants: HRZE; 6 participants: HRES; 6 participants: HRZS; 3 participants: HRZES; 1 participant: HRE; protainamide was also given to 3 participants;
	  ◦ duration of treatment: 25 participants for 12 months; 2 participants for 15 months; 3 participants for 16 months.
	
	Other interventions:
	
	• Steroid therapy in 48 participants:
	  ◦ 8 months group: prednisolone given to participants in stage III;
	  ◦ 12 to 16 months group: prednisolone or dexamethasone given if papilloedema, cranial nerve palsies, clouding of consciousness or coma, or both.
	• Pyridoxine (100 mg/day) to all participants.
	• Ventriculo-peritoneal shunt in the 3 participants who developed hydrocephalus.

Outcomes	Outcomes included in this review (directly reported or deductible from reported data) • Relapse. • Death from any cause. • Death after 6 months of ATT. • Clinical cure. • Default. • All adverse effects related to the ATT. • Drug toxicity leading to discontinuation of regimen.

Doğanay 1995 *(Continued)*

	Outcomes not included in this review • Treatment failure. • Residual sequelae (including neurological sequelae).
Notes	Country: Turkey. Setting: 4 university clinics (Kayseri, Sivas, Diyarbakir, and Istanbul). Study dates: from January 1989 to April 1993. Study sponsor: none reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Detection bias Relapse	High risk	The study authors followed-up the participants for between 4 and 36 months, but did not report the method of follow-up.
Detection bias Clinical cure and default	Unclear risk	The study authors did not report the methods of follow-up during treatment.
Attrition bias Relapse	High risk	7/55 (12.7%) participants were lost to follow-up after completing ATT.
Attrition bias Clinical cure and default	High risk	10/72 (13.9%) participants were lost to follow-up during ATT.
Performance bias	High risk	In the 8 months regimen group, treatment was prolonged in 2 participants up to 9 and 10 months respectively, with no reasons given. Treatment was modified in another participant due to inadequate clinical response. Overall in the 8 months group, 3/25 (12%) survivors had their treatment modified. In the long course therapy group, there was no strict upper definition; participants were treated for between 12 and 16 months.
Confounding bias	Unclear risk	Adherence to treatment not reported. Prednisolone was given to some participants on the basis of disease severity but it is unclear how this would affect the results.

Iype 2014

Methods	Study objective: to assess all-cause mortality and 9-months morbidity of participants with TBM on intermittent thrice-a-week directly observed ATT. Study design: prospective observational study. Length of follow-up from start of ATT: median of 396 days (interquartile interval 274 to 544) for the whole cohort; 425 days (interquartile interval 373 to 565) among survivors. Follow-up method: participants came to the Revised National TB Control Programme (RNTCP) clinic (opened 6 days/week) once a month during the duration of treatment and thereafter once every 3 months until the 31st of December 2012 (12 months after the end of the recruitment period). In addition to this caregivers were encouraged to contact the principal investigator by cell phone in case of any medical illness or life events. Losses to follow-up: 2 participants (both excluded for analysis).

Iype 2014 *(Continued)*

Participants	Number: 47 recruited, 43 analysed (2 deaths within 5 days and 2 losses to follow-up); median age 36 years (range 14 to 61); 51% males. Target treatment group: adults with TBM. Inclusion criteria: TBM diagnosis was based on consensus TBM criteria, and categorized into definite, probable and possible TBM. Exclusion criteria: patients below the age of 13 years; with Thwaites index of above 4; with a setting for bacterial meningitis like bacterial sinusitis, otitis media, CSF, rhinorrhoea; with history of head injury and nasal or aural bleeding; with pre-existing renal or liver disease; immunocompromised including those with retroviral positive status; with premorbid visual impairment, deafness and mental retardation since it would affect the morbidity assessment; and patients who died within 5 days of initiation of RNTCP regimen. Bacteriologically confirmed TBM cases: 2/43. Site of TB other than CNS: 11 with abnormal chest X-ray, 1 with TB pyelonephritis, and 1 with lymph nodes TB. Other clinical features: 5 tuberculoma, 9 hydrocephalus, 3 spinal arachnoiditis. Clinical severity of the disease: 15 in stage I; 24 in stage II; 4 in stage III. HIV status: HIV status tested for all participants; HIV-positive people excluded. Duration of symptoms prior to admission: median 17 days (interquartile interval 8 to 62); time to treatment initiation: median 25 days (interquartile interval 15 to 65).
Interventions	Short-course ATT: none. Prolonged-course ATT: all drugs were given thrice weekly under directly observed therapy (DOTS). Category I: 9 months - $2(HRZS)_3$ /$7(HR)_3$ for 41 participants • Isoniazid: 10 mg/kg (9 months). • Rifampicin: 10 mg/kg (9 months). • Pyrazinamide: 35 mg/kg (2 months). • Streptomycin: 750 mg (2 months). Category II: 10 months - $2(HREZS)_3$ /$1(HREZ)_3$ /$7(HR)_3$ for 2 participants previously exposed to ATT. • Isoniazid: 10 mg/kg (9 months). • Rifampicin: 10 mg/kg (9 months). • Pyrazinamide: 35 mg/kg (2 months). • Streptomycin: 750 mg (2 months). Treatment was stopped at 4 months in 1 participant, at 6 months in 3 participants, and at 7 months in 2 participants (5 due to the RNTCP DOTS providers, 1 after 124 days due to induced drug hepatitis). 1 participant received 12 months for tuberculoma; 1 participant received 15 months for spinal arachnoiditis. Other interventions: steroids during the 4 first weeks to all participants.
Outcomes	Outcomes included in this review (directly reported or deductible from reported data) • Relapse. • Death from any cause. • Clinical cure. • Default. • All adverse effects related to ATT.

Iype 2014 *(Continued)*

	• Drug toxicity leading to discontinuation of regimen. Reported outcomes not included in this review • Treatment failure. • Neurological sequelae.
Notes	Country: India. Setting: Departments of Community Medicine and Neurology, Government Medical College Hospital, Thiruvananthapuram, Kerala, a tertiary care referral centre in South India. Study dates: from 1 January 2010 to 31 December 2011. Study sponsor: the State Board of Medical Research, Government of Kerala.

Risk of bias

Bias	Authors' judgement	Support for judgement
Detection bias Relapse	High risk	Participants were followed-up once every 3 months in the RNTCP clinic until up to 12 months after the end of the recruitment period. Participants were therefore followed-up for a median of 5.2 months after completing ATT, with an interquartile range from 3.4 to 9.8 months.
Detection bias Clinical cure and default	Low risk	Participants received ATT under DOT and were visited monthly in the RNTCP clinic during the duration of treatment.
Attrition bias Relapse	Low risk	No losses of follow-up after completing ATT.
Attrition bias Clinical cure and default	Low risk	2/47 (4.2%) participants were lost to follow-up during ATT.
Performance bias	Unclear risk	2/35 (5.7%) participants received prolonged ATT: 12 months in a participant for the complete disappearance of tuberculoma, and 15 months in another participant with spinal arachnoiditis.
Confounding bias	Unclear risk	Adherence to treatment not reported. Corticosteroids given to all participants.

Jacobs 1992

Methods	Study objective: to evaluate the outcomes of participants with TBM treated with 12, 9 and 6 months ATT regimens. Study design: prospective comparative study. Data are reported for 3 successive cohorts in the same centre over time. The first cohort received a 12-month regimen with 2/4 participants receiving rifampicin, the second a 9 months regimen with all participants receiving rifampicin, and the third received a 6 months regimen with all participants receiving rifampicin and pyrazinamide. Length of follow-up: only reported for children receiving the 6 months regimen; at least 6 months after treatment in 27/38 survivors, less than six months after treatment in 7/38. Follow-up method: not reported. Losses to follow-up: unclear. Authors first mentioned that 2 participants were lost of follow-up, it is unclear which treatment group they were in but it seems they were excluded from the analysis. Four children were lost to follow-up after completion of ATT.

Jacobs 1992 *(Continued)*

Participants	Number: 53; 8 cases aged 0 to 6 months, 21 cases aged 7 to 24 months, 7 cases aged 2 to 5 years, and 17 cases aged more than 5 years; 51% male.
	
	Target treatment groups: children with TBM.
	
	Inclusion criteria
	
	• Characteristic CSF findings (pleocytosis with mononuclear predominance, decrease in glucose content initially or during the course of disease, elevated protein content), and 2 or more of the following:
	  • positive tuberculin skin test (≥ 10 mm induration);
	  • radiographic evidence of PTB that included parenchymal or hilar lymph node involvement;
	  • history of contact with a known TB patient;
	  • presence of *M. tuberculosis* in CSF.
	
	Exclusion criteria: none reported.
	
	Bacteriologically confirmed TBM cases: 5 positive CSF cultures and 2 positive CSF acid-fast stains (unknown whether specimen with positive stain was also culture positive).
	
	Site of TB other than CNS: "positive" chest X-ray in 35/53 participants; other sites not reported.
	
	Other clinical features: 7 hydrocephalus
	
	Clinical severity of the disease: 8 in stage I; 29 in stage II; 16 in stage III.
	
	HIV status: not reported.
	
	Duration of symptoms prior to admission and time to treatment initiation: not reported.

Interventions	Short-course ATT
	
	• 6 months - 2HRZS/4HR. 45 participants. Daily dosage:
	  ○ isoniazid: 15 mg/kg (6 months);
	  ○ rifampicin: 20 mg/kg (6 months);
	  ○ pyrazinamide: 30 mg/kg (2 months);
	  ○ streptomycin: 40 mg/kg (2 months).
	
	Prolonged-course ATT
	
	• 9 months - 2HRS/7HR. 4 participants. Daily dosage:
	  ○ isoniazid: 15 mg/kg (9 months);
	  ○ rifampicin: 20 mg/kg (9 months);
	  ○ streptomycin: 40 mg/kg (2 months).
	• 12 months - 2HSE/10HE or 2RSE/10RE. 4 participants. Daily dosage:
	  ○ isoniazid: 15 mg/kg;
	  ○ rifampicin: 20 mg/kg;
	  ○ streptomycin: 40 mg/kg;
	  ○ ethambutol: 25 mg/kg.
	
	Other interventions
	
	• Dexamethasone (0.3 to 0.5 mg/kg/day) for 1 week, then prednisolone (2 mg/kg/day) for 3 to 4 weeks with tapering dosages to all children with stage II and III (45 children).
	• Ventriculostomy to children who had CSF pressure > 200 mmH_2O and whose condition was severe or progressed rapidly.
	• Ventriculo-peritoneal shunt to children with obstructive or persistent hydrocephalus.

Outcomes	Outcomes included in this review (directly reported or deductible from reported data) • Relapse.

Jacobs 1992 *(Continued)*

- Death from any cause.
- Clinical cure.
- Default.
- Drug toxicity leading to discontinuation of regimen.

Outcomes not included in this review

- Neurological sequelae.

Notes	Country: Thailand. Setting: Bangkok Children's Hospital. Study dates: from 1984 to 1990. Study sponsor: none reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Detection bias Relapse	High risk	The study authors did not report the follow-up methods. 27/38 survivors were followed-up for at least 6 months, and 7/38 were followed-up for less than 6 months after completing ATT. For the 4 survivors who received more than 6 months treatment, the study authors did not describe the length of follow-up after completing ATT.
Detection bias Clinical cure and default	Unclear risk	The study authors did not report the follow-up methods.
Attrition bias Relapse	High risk	4/38 (10.5%) participants were lost to follow-up after completing ATT.
Attrition bias Clinical cure and default	Unclear risk	There were 2 participants lost to follow-up, it is unclear which treatment group they were in but it seems they were excluded from the analysis.
Performance bias	Unclear risk	The study authors did not report whether participants received prolonged ATT.
Confounding bias	Unclear risk	The study authors did not report on adherence to treatment. Corticosteroids were given to 45/53 participants on the basis of disease severity but it is unclear how this would affect the results.

Lau 2005

Methods	Study objective: to investigate the presentation, diagnosis, treatment, and outcome of TBM, and to evaluate predictors of poor outcome. Study design: prospective observational study. Length of follow-up: at least 3 years from the date of diagnosis. Follow-up method: once the participants were discharged, follow-up in the outpatient clinics of the general hospitals, or in the Department of Health chest clinics. The Death Registry for occurrence of deaths, and causes of death were also checked and recorded. Losses to follow-up: 10 participants who moved from Hong Kong.
Participants	Number: 166; mean age 42.9 years (range 3 to 100); 51.2% male.

Lau 2005 *(Continued)*

	Target treatment group: all TBM participants within the catchment area of the hospitals participating in the Hong Kong Tuberculous Meningitis Study Group (HKTBMSG). Inclusion criteria: 3 degrees of certainty of diagnosis of TBM were used. • Definite: positive culture of *M. tuberculosis* from CSF. • Presumptive: positive smear of acid-fast bacilli from CSF. • Probable: low CSF sugar of < 2.8 mmol/L and/or high CSF protein of > 0.45 g/L, plus a clinical response to ATT reflected by defervescence associated with clinical improvement 5 to 7 days after initiation of treatment. Exclusion criteria: none mentioned. Bacteriologically confirmed TBM cases: 68/166. Site of TB other than CNS: 12 disseminated TB, 21 co-existing PTB. Other clinical features: 15 cerebral tuberculoma, 25 hydrocephalus. Clinical severity of the disease: 94 in stage I; 68 in stage II; 4 in stage III at admission; 91 in stage I; 69 in stage II; 6 in stage III when starting ATT. HIV status: 2 HIV-positive. Duration of symptoms (fever, malaise, or headache) prior to admission: mean 11.26 days; time to treatment initiation: mean 5.22 days.
Interventions	Short-course ATT: no disaggregated data. Prolonged-course ATT • Different regimens were used: HRZES in 66 participants; HRZE in 63; HRZS in 24; HRZ in 8; HRE in 2; SHRE in 1; HZE in 1; and HR 1. • Duration of ATT: mean 11.53 months; at least 12 months in 114/166 participants. One participant received 36 months due to brainstem tuberculoma. Other interventions: steroids were prescribed according to the decisions of the clinicians, and were given to 105/166 participants mainly due to routine/usual practice and deteriorating clinical condition.
Outcomes	Outcomes included in this review (directly reported or deductible from reported data) • Relapse. • Death from any cause. • Clinical cure. • Poor adherence. • Default. • All adverse effects related to ATT. • Drug toxicity leading to discontinuation of regimen ("no severe drug reaction"). Outcomes not included in this review • Survival with disability, classified as mild, moderate, and severe.
Notes	Country: China (Hong Kong at the time of the trial). Setting: the catchment area of the hospitals participating in the HKTBMSG: 9 general hospitals until 31 March 1995; 9 additional regional hospitals and the chest clinics of the Department of Health from 31 March 1995. Study dates: from 1 April 1993 to 31 March 2000. Study sponsor: none mentioned.

Lau 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Detection bias Relapse	Unclear risk	All participants were followed-up for at least 3 years from the date of diagnosis, until death, or until they left the study site, in the outpatient clinics of the general hospitals or chest clinics. However, because we don't know how long each participant was treated for, it is unclear how many participants could be followed for at least 18 months.
Detection bias Clinical cure and default	Low risk	All participants were followed-up in outpatient chest clinics under DOT.
Attrition bias Relapse	Low risk	No losses of follow-up during the follow-up period.
Attrition bias Clinical cure and default	Unclear risk	10/166 (6.0%) were lost to follow-up during ATT.
Performance bias	High risk	Participants received individualized treatment regimens according to the decisions of the clinicians.
Confounding bias	Unclear risk	Adherence to treatment is reported. Corticosteroids were prescribed to 105/166 participants according to the decisions of the clinicians, but it is unclear how this would affect the results.

Phuapradit 1987

Methods	Study objective: to review the results of 9-month ATT in adults with TBM. Study design: prospective observational study. Length of follow-up: mean 19.8 months after completion of ATT (range 12 to 29 months) in the 21 survivors who completed the follow-up period. Follow-up method • During ATT: after discharge, observed monthly until completion of ATT. • After ATT: assessed every 3 to 6 months. Losses to follow-up: during ATT, 4 cases dropped out during the early stage of treatment (1/4 stage I, 2/18 stage II, 1/6 stage III), out of whom 3 presented poor compliance and one presented erythema multiforme from pyrazinamide. After completing ATT, 1 additional case lost to follow-up.
Participants	Number: 28; mean age 32 years (range 17 to 76 years); gender not reported. Target treatment groups: adults with TBM. Inclusion criteria: adults with TBM, diagnostic algorithm not described. Exclusion criteria: none reported. Bacteriologically confirmed TBM cases: 12/28. Site of TB other than CNS: 18 active PTB including 8 miliary TB, 4 caseating cervical lymphadenitis, 2 otitis media, and 1 epididymoorchitis. Other clinical features: 1 tuberculoma, 1 spinal arachnoiditis, 1 optochiasmic arachnoiditis, 10 communicating hydrocephalus.

Phuapradit 1987 *(Continued)*

	Clinical severity of the disease: 4 in stage I; 18 in stage II; 6 in stage III. HIV status: not reported. Duration of symptoms prior to admission: range 3 days to 3 months; time to treatment initiation: study authors reported "all patients were treated immediately".
Interventions	Short-course ATT: none. Prolonged-course ATT: 9 months - 2HRZS/7HR, single daily dosage • Isoniazid: 300 mg orally (9 months). • Rifampicin: 600 mg orally (450 mg if < 45 kg) (9 months). • Pyrazinamide: 1500 mg orally (2 months). • Streptomycin 750 to 1000 mg intramuscular (2 months). Other interventions • Prednisolone (60 mg/day) to 10 participants with hydrocephalus, arteritis, spinal and optochiasmic arachnoiditis. • Repeated lumbar puncture in 7 participants with hydrocephalus. • Ventriculo-peritoneal shunting in the 3 participants (grade III) with hydrocephalus who were comatose with decerebrate rigidity.
Outcomes	Outcomes included in this review (directly reported or deductible from reported data) • Relapse. • Death from any cause. • Death after 6 months of ATT. • Clinical cure. • Default. • Poor adherence. • All adverse effects related to the ATT. • Drug toxicity leading to discontinuation of regimen. Outcomes not included in this review • Treatment failure. • Neurological sequelae.
Notes	Country: Thailand. Setting: Department of Medicine, Ramathibodi Hospital, Bangkok. Study dates: 1983 and 1984. Study sponsor: none reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Detection bias Relapse	Unclear risk	Participants were assessed every 3 to 6 months for a mean duration of follow-up of 19.8 months after completion of ATT, ranging from 12 to 29 months.
Detection bias Clinical cure and default	Low risk	After discharge, participants were followed-up monthly until completion of ATT.
Attrition bias	Low risk	1/23 (4.3%) participant was lost to follow-up after completing ATT.

Phuapradit 1987 *(Continued)*

Relapse		
Attrition bias Clinical cure and default	High risk	3/28 (10.7%) participants were lost to follow-up during ATT.
Performance bias	Low risk	1/23 (4.3%) participant received longer ATT due to adverse event.
Confounding bias	Unclear risk	Adherence to treatment not reported. Prednisolone was given to 10/28 participants, but it is unclear how this would affect the results.

Ramachandran 1989

Methods	Study objective: to evolve suitable regimens for the treatment of TBM in children. Study design: series of 3 consecutive prospective observational studies. Length of follow-up: between 4.5 and 8 years from start of ATT Follow-up method: "patients were hospitalised for the first 2 months of treatment. Those who were discharged during the first 2 months attended as outpatients daily for chemotherapy until they completed 2 months. After 2 months, the participants attended twice or once a week (or once in 15 days if they lived outside Madras) to collect a supply of drugs. Their medication was fully supervised on the days they attended. Progress was assessed mainly by monthly clinical examination including a detailed neurological examination and, if indicated, a CSF examination." In the long-term follow-up study (1989), participants were called back to be seen in clinic (98/119), or completed a questionnaire that was posted to them (2/119). Losses to follow-up: 6 at 12 months. 2 additional cases in the long-term follow-up study.
Participants	Number: 180 recruited; mean age 2.8 years (range 1 to 10 years); 53% male. Target treatment groups: children aged between 1 and 12 years with TBM. Inclusion criteria: the diagnosis of TBM was based on clinical symptoms and signs (notably fever, vomiting, irritability, apathy, refusal to play, anorexia, constipation, well-marked meningeal signs, impaired consciousness, coma, and widespread paralysis) and on the CSF findings. Exclusion criteria: children who had received more than 4 weeks of ATT, and evidence of renal or liver disease. Bacteriologically confirmed TBM cases: 83/180. All cultures were sensitive to rifampicin. Resistance to streptomycin (1), isoniazid (3), ethambutol (1), and streptomycin and isoniazid (9). Site of TB other than CNS: 99 abnormal chest X-ray suggestive of PTB, 2 spinal TB. Other clinical features: 14 hydrocephalus, 28 optic disc pallor or optic atrophy, 4 cortical blindness. Clinical severity of the disease: 24 in stage I; 139 in stage II; 17 in stage III. HIV status: not reported. Severe malnutrition: 34% according to the growth standards from the Indian Council of Medical Research. Duration of symptoms prior to admission and time to treatment initiation: not reported.
Interventions	Short-course ATT: none. Prolonged-course ATT: 12 months Regimen I: 2SHR/4S$_2$EH/6EH; 77 participants

Ramachandran 1989 *(Continued)*

- Isoniazid, 12 months, daily.
- Rifampicin, 2 month, daily.
- Streptomycin, daily the first 2 months; then twice a week for 4 additional months.
- Ethambutol, from the 3rd month until end of treatment, daily.

Regimen II: 2SHRZ/10 EH; 29 participants

- Isoniazid, 12 months, daily.
- Rifampicin, 2 months, daily.
- Streptomycin, 2 months, daily.
- Pyrazinamide, 2 months, daily.
- Ethambutol, from the 3rd month until the end of treatment, daily.

Regimen III: $2R_2$SHZ/10EH; 74 participants

- Isoniazid, 12 months, daily.
- Rifampicin, twice a week for 2 months.
- Streptomycin, 2 months, daily.
- Pyrazinamide, 2 months, daily.
- Ethambutol, from the 3rd month until the end of treatment, daily.

Longer treatment than 12 months in 23 participants

- 13 to 18 months in 12 participants.
- 19 to 24 months in 10 participants.
- 36 months in 1 participant.

Reasons for longer treatment

- CSF abnormality, surgery, or neurological complications.
- Persistence of abnormality on chest radiography.
- Spinal TB.
- Severe respiratory infection in 1 participant with severe sequelae (the participant died in the twenty-first month).
- Detection of PTB in one of the parents of 1 participant.

Doses of anti-tubercular drugs

- Isoniazid: 20 mg/kg in daily dosage in the first 20 participants. Then reduced to 12 mg/kg due to a substantial number of jaundice.
- Rifampicin: 12 mg/kg.
- Pyrazinamide: 30 mg/kg.
- Streptomycin: 40 mg/kg.
- Ethambutol: 17.5 mg/kg.

Other interventions

- Steroids to all participants. For those in stage II and III, intramuscular dexamethasone (2 to 4 mg/6 to 8 hours) for the first 3 or 4 days followed by oral prednisolone (1 to 2 mg/kg).
- Supportive therapy (intravenous fluids, anti-oedema measures, anti-convulsants and vitamins).
- Ventriculo-peritoneal shunt in 7 cases for hydrocephalus.

Outcomes	Outcomes included in this review (directly reported or deductible from reported data) • Relapse. • Death from any cause. • Death after 6 months of ATT. • Clinical cure.

Ramachandran 1989 *(Continued)*

- All adverse effects related to ATT.
- Drug toxicity leading to discontinuation of regimen.

Outcomes not included in this review

- Complete recovery without sequelae.
- Neurological sequelae.

Notes	Country: India. Setting: Tuberculosis Research Centre, Institute of Child Health and Hospital for Children, Chennai. Study dates: from October 1977 to April 1981. Study sponsor: none reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Detection bias Relapse	Low risk	All survivors who completed 12-month ATT were assessed monthly up to 24 months. The follow-up assessments included neurological examination, CSF examination, and chest X-ray. Afterwards, survivors were called back to be seen in clinic (98/119), or completed a questionnaire that was posted to them (2/119). They were followed-up for between 42 to 84 months after completing ATT.
Detection bias Clinical cure and default	Low risk	Participants were hospitalized for the first 2 months of treatment and those who were discharged during the first 2 months attended as outpatients daily for chemotherapy until they completed 2 months. After 2 months, the participants attended twice or once a week (or once in 15 days if they lived outside Madras) to collect a supply of drugs. Progress was assessed mainly by monthly clinical examination including a detailed neurological examination and, if indicated, a CSF examination.
Attrition bias Relapse	Low risk	2/119 (1.7%) participants were lost to follow-up after completing treatment.
Attrition bias Clinical cure and default	Unclear risk	14/180 (7.8%) participants were lost to follow-up during ATT.
Performance bias	High risk	23/119 (19.3%) received prolonged ATT for various reasons: CSF abnormality, surgery. or neurological complications; persistence of abnormality on chest radiography; spinal TB; severe respiratory infection in 1 participant with severe sequelae; and detection of PTB in one of the parents of 1 participant.
Confounding bias	Unclear risk	Adherence to treatment was not assessed or reported. Corticosteroids were given to all participants, and 7 participants had ventriculo-peritoneal shunt for hydrocephalus. Three different regimens were used. It is unclear how this would affect the results.

Ramachandran 1997

Methods	Study objective: to assess the results of two 9 months intensive regimens with 5 drugs in the initial phase followed by 2 bactericidal drugs during the follow-up phase in children with TBM. Study design: RCT that compared 2 ATT regimens of 9 months duration. Treated as prospective observational data for the purposes of this review.

Ramachandran 1997 *(Continued)*

Length of follow-up: 60 months from start of ATT.

Follow-up method: participants were hospitalized for a minimum period of 2 months or more, if necessary. However, those who showed very good improvement were discharged at request before completing the intensive phase of 2 months treatment and asked to attend daily until they completed 2 months of treatment. After 2 months, the participants attended twice or once a week (or once in 15 days if they lived outside Chennai city) to collect drugs. They were given the drugs under supervision on the days they attended. The progress was assessed by monthly examination until completion of ATT. In the long-term follow-up study, participants were followed-up once a month till 24 months, once in 3 months till 36 months, and thereafter once in 6 weeks till 60 months.

Losses to follow-up

- 29 participants were discharged against medical advice. Among them, 10 died within 4 days of discharge and the study authors included them in the analysis as they assumed they had died of TBM; 10 died at a later point and were not included in the analysis; and 9 were alive at the end of ATT, but not followed-up during the long-term follow-up study.
- 10 participants received modified treatment and were not followed-up during the long-term follow-up study.
- No losses to follow-up among the 128 participants who completed the 9-month ATT and 5-year follow-up.

Participants	Number: 215; 56% aged less than 3 years (2 years in abstract) and 75% less than 5 years (range 1 to 12 years); "approximately" 50% male. Target treatment groups: children aged 1 to 12 years with TBM. Inclusion criteria: the diagnosis of TBM was based on clinical symptoms and signs (like fever, vomiting, irritability, apathy, anorexia, constipation, refusal to play, in the initial stages followed by presence of meningeal signs and impaired consciousness, coma, and widespread paralysis) and the CSF findings (CSF protein value of more than 40 mg/dL plus cell count more than 10/mm^3 (predominantly lymphocytes) was taken as confirmatory). Exclusion criteria: children who had received more than 4 weeks of ATT, evidence of renal or liver disease, and children with optic atrophy or pallor of optic discs. Bacteriologically confirmed TBM cases: 101/215 Site of TB other than CNS: 111 abnormal chest X-ray suggestive of PTB. Other clinical features: 74 suspected hydrocephalus (68 confirmed with CT scan), 5 mild pallor of optic disc, and 7 optic atrophy with blindness. Clinical severity of the disease on admission: 45 in stage I; 160 in stage II; 10 in stage III. HIV status: not reported. Severe malnutrition: 40% according to the growth standards from the Indian Council of Medical research Duration of symptoms prior to admission: 1 to 14 days in 53 participants, 2 to 4 weeks in 108 participants, 1 to 3 months in 24 participants. Time to treatment initiation not reported.
Interventions	Short-course ATT: none. Prolonged-course ATT: 9 months 1. Regimen I: $2S_7H_7E_7R_3Z_3$ /$7R_2H_2$; 89/185 participants for analysis First 2 months • Streptomycin, isoniazid and ethambutol, daily. • Rifampicin and pyrazinamide thrice a week.

Ramachandran 1997 *(Continued)*

	Following 7 months • Rifampicin and isoniazid thrice a week. 2. Regimen II: $2S_7H_7E_7R_2Z_2$ /$7R_2H_2$; 96/185 participants for analysis First 2 months • Streptomycin, isoniazid, and ethambutol, daily. • Rifampicin and pyrazinamide twice a week. Following 7 months • Rifampicin and isoniazid thrice a week. Treatment was modified in 10 participants (unknown reason; excluded from analysis). Doses of antituberculous drugs • Isoniazid: 12 mg/kg. • Rifampicin: 12 mg/kg. • Pyrazinamide: 30 mg/kg in the thrice weekly regimen; 40 mg/kg in the twice weekly regimen. • Streptomycin: 40 mg/kg. • Ethambutol: 20 mg/kg for 2 weeks, followed by 15 mg/kg for the next 6 weeks. 20 mg/kg in daily dosage in the first 20 participants. Then reduced to 12 mg/kg due to a substantial number of jaundice. Other interventions • Steroids to all participants. For those seriously ill, intramuscular dexamethasone (2 to 4 mg/6 to 8 hours) for the first 3 or 4 days followed by oral prednisolone (1 to 2 mg/kg). • Supportive therapy (intravenous fluids, anti-oedema measures, anti-convulsants and vitamins). • Ventriculo-peritoneal shunt in 38 cases for hydrocephalus.
Outcomes	Outcomes included in this review (directly reported or deductible from reported data) • Relapse. • Death from any cause. • Death after 6 months of ATT. • Clinical cure. • All adverse effects related to ATT. • Drug toxicity leading to discontinuation of regimen. Outcomes not included in this review • Complete recovery without sequelae. • Neurological sequelae.
Notes	Country: India. Setting: The Tuberculosis Research Centre in collaboration with the Institute of Child Health and Hospital for Children, Chennai. Study dates: not reported. Study sponsor: none reported.

Risk of bias

Bias	Authors' judgement	Support for judgement

Ramachandran 1997 *(Continued)*

Detection bias Relapse	Low risk	All the participants who completed 9-month ATT were followed-up once a month until 24 months, once in 3 months until 36 months and thereafter once in 6 weeks until 60 months. AT all these visits, a complete neurological examination was done, and CSF examination repeated until normal.
Detection bias Clinical cure and default	Low risk	Participants were hospitalized for a minimum period of 2 months or more, if necessary. After 2 months, they attended twice or once a week (or once in 15 days if they lived outside Chennai city) to collect drugs, given under supervision. The progress was assessed by monthly examination until completion of ATT.
Attrition bias Relapse	Low risk	None of the 137 survivors after completing ATT were lost to follow-up during the follow-up period.
Attrition bias Clinical cure and default	High risk	29/215 (13.5%) participants were lost to follow-up during treatment.
Performance bias	Unclear risk	10 participants received modified treatment for unknown reason. It is unclear whether this was prolonged, shortened or stopped. The study authors excluded these 10 participants from the analysis.
Confounding bias	Unclear risk	Adherence to treatment was not assessed or reported. Corticosteroids were given to all participants, and 38 participants had ventriculo-peritoneal shunt for hydrocephalus. Two different regimens were used. It is unclear how this would affect the results.

Sharma 2013a

Methods	Study objective: to assess effectiveness of Revised National TB Control Program (RNTCP-DOTS) regimes among TBM participants. Study design: prospective observational study. Length of follow-up: 6 months after completing ATT. Follow-up method: participants were followed-up monthly. No data are given on the way they were followed-up. Losses to follow-up: 0/42.
Participants	Number: 42; range age 16 to 78 years; 54.8% males. Target treatment group: adults with TBM. Inclusion criteria: the diagnosis of TBM was made when participants with meningitis (CSF pleocytosis) were admitted with symptoms lasting 1 week or more, with negative CSF Gram's and India ink stains, negative CSF culture for pyogenic bacteria, plus one or more of the following. • CT scan consistent with TBM (hydrocephalus, basal meningeal enhancement, ring enhancing lesion). • Chest X-ray consistent with active pulmonary TB. • Good response to antituberculous chemotherapy. Exclusion criteria: children, participants with HIV, and participants with bacterial meningitis. Bacteriologically confirmed TBM cases: 4/42 Site of TB other than CNS: 9 with abnormal chest X-ray and 2 axillary lymph node TB. Other clinical features: cases of hydrocephalus with no disaggregated data.

Sharma 2013a *(Continued)*

	Clinical severity of the disease: 21 in stage III with no disaggregated data between stage I and II. HIV status: HIV positive people were excluded. Duration of symptoms prior to admission: less than 10 days; time to treatment initiation: not reported.
Interventions	Short-course ATT: none. Prolonged-course ATT: 9 months - $2(HREZ)_3$ /$7(HR)_3$ All drugs were given thrice weekly under DOTS (all participants started with DOTS; 78% actually received DOTS). Dosages not reported. Other interventions: steroids during the 6 first weeks to all participants.
Outcomes	Outcomes included in this review (directly reported or deductible from reported data) • Relapse. • Death from any cause. • Clinical cure. • Default. • All adverse effects related to ATT. Reported outcomes not included in this review • Neurological sequelae.
Notes	Country: India. Setting: Department of Neurology, NEIGRIHMS, North Eastern Indira Gandhi Regional Institute of Medical Sciences (An Autonomous Institute, Ministry of Health and Family Welfare, Govt of India, Shillong, India). Study dates: from September 2008 to March 2011. Study sponsor: none.

Risk of bias

Bias	Authors' judgement	Support for judgement
Detection bias Relapse	Unclear risk	Participants were followed-up monthly for 6 months. Methods of follow-up are not described.
Detection bias Clinical cure and default	Unclear risk	All drugs were given thrice weekly under DOTS, but "finally 78% received actual DOTS".
Attrition bias Relapse	Unclear risk	No losses of follow-up are described during the follow-up period, but the study authors did not specifically state that all participants were followed for the full period.
Attrition bias Clinical cure and default	Low risk	The study authors stated that 35 participants completed ATT, and 7 died. No losses of follow-up during were reported the duration of the treatment, but the study authors did not specifically state that none occurred.
Performance bias	Unclear risk	It was not reported whether participants received longer ATT than the planned treatment.

Sharma 2013a *(Continued)*

Confounding bias	Unclear risk	Adherence to treatment was not reported. All participants received corticosteroids.

Török 2011a

Methods	Study objective: to determine whether adjunctive dexamethasone was associated with reduced mortality or neurological disability 5 years after entry into the original RCT. Study design: randomized double-blind placebo-controlled trial of antitubercular therapy with dexamethasone versus antitubercular therapy with placebo. Treated as prospective observational data for the purposes of this review. Length of follow-up: median of 5.2 years (interquartile range 4.7 to 5.5 years) after randomization. Follow-up method: during ATT, participants were assessed at 1, 2, 6, and 9 months after randomization. At each point, disability was assessed and scored. Participants were contacted by letter or telephone, or both, and attended clinic for assessment 5 years after randomization into the original study. If the participant had died prior to the follow-up assessment, the date and cause of death was requested from the relatives. Participants were assessed using a standard questionnaire and neurological examination. Four survivors who were unable to attend the hospital gave verbal consent and were assessed by telephone interview. Losses to follow-up: 50 participants. 5 were lost to follow-up after 1 month, 3 after 2 months, 1 after 3 months, 1 after 4 months, and 40 were lost during the follow-up period between 9 months and 5 years.
Participants	Number: 545 participants randomized in the original study and 495 followed up to 5 years; median age 35 years (range 15 to 88); 61% male. Target treatment groups: adults and adolescents over 14 years with TBM. Inclusion criteria • Clinical evidence of meningitis was defined as the combination of nuchal rigidity and CSF abnormalities. TBM was defined as follows. • Definite: acid-fast bacilli on CSF smear. • Probable: one or more of the following: suspected active PTB on chest radiography, acid-fast bacilli found in any specimen other than the CSF, and clinical evidence of other extra-pulmonary TB (EPTB). • Possible: at least 4 of the following: a history of TB, predominance of lymphocytes in the CSF, a duration of illness of more than 5 days, a ratio of CSF glucose to plasma glucose of less than 0.5, altered consciousness, yellow CSF, or focal neurologic signs. Participants were reclassified on discharge as having definite TBM if acid-fast bacilli were seen or *M. tuberculosis* was cultured from the CSF, or as not having TBM if another diagnosis was confirmed by microbiological or histopathological evaluation. Exclusion criteria • Corticosteroids contraindicated. • Patients who received more than 1 dose of any corticosteroid or more than 30 days of ATT immediately before study entry. • Consent withheld. Bacteriologically confirmed TBM cases: 187/545 with positive culture from CSF or another site. Site of TB other than CNS: 214 active non-miliary PTB on chest radiography, 155 miliary TB, 114 at another site (other than lung or CNS).

Török 2011a *(Continued)*

	Other clinical features: not reported. Clinical severity of the disease: 176 in stage I; 247 in stage II; 122 in stage III. HIV status: 436 HIV-negative; 98 HIV-positive; 11 not tested. Duration of symptoms prior to admission: median 15 days; time to treatment initiation not reported.
Interventions	Short-course ATT: none. Prolonged-course ATT: 9 months. • 3RHZS/6RHZ (HIV-negative participants; 399). • 3RHZE/6RHZ (HIV-positive participants; 98). • 3RHZES/6RHZ (previously treated participants; 43). • HZE (2 participants). • SE (1 participant). Daily doses • Isoniazid: 5 mg/kg, oral (9 months). • Rifampicin: 10 mg/kg, oral (9 months). • Pyrazinamide: 25 mg/kg (maximum dose 2g), oral (9 months). • Streptomycin: 20 mg/kg (maximum dose 1g), intramuscular (3 months). • Ethambutol: 20 mg/kg (maximum dose 1.2 g), oral (3 months). Drugs were administered by nasogastric tube to participants who were unable to swallow. Other interventions • Participants were randomized to receive dexamethasone (0.3 to 0.4 mg/kg/day, intravenous, according to TBM grade at presentation and tapered over 6 to 8 weeks; 274 participants) or placebo (271 participants). • Mannitol was given in 199 participants. • None of the participants received antiretroviral drugs.
Outcomes	Outcomes included in this review (directly reported or deductible from reported data) • Relapse (defined by the study authors as re-treatment for TB). • Death from any cause. • Clinical cure. • All adverse effects related to ATT. • Drug toxicity leading to discontinuation of regimen. Outcomes not included in this review • Coma-clearance time. • Fever-clearance time. • Time to discharge from the hospital. • Treatment failure and time to treatment failure (the term "relapse" is used in the article instead of treatment failure, defined by the onset of new focal neurological signs or a fall in the Glasgow coma score of 2 points or more for 2 or more days after more than 7 days of clinical stability or improvement at any time after randomization). • Presence of focal neurologic deficit 9 months after randomization. • Disability status at 5 years of follow-up.
Notes	Country: Vietnam.

Török 2011a *(Continued)*

	Setting: Pham Ngoc Thach Hospital (tertiary referral centre for patients with severe TB) and the Hospital for Tropical Diseases (tertiary referral centre for patients with infectious diseases) in Ho Chi Minh City. Study dates: from 4 April 2001 to 29 March 2003. Study sponsor: the Wellcome Trust, UK.

Risk of bias

Bias	Authors' judgement	Support for judgement
Detection bias Relapse	Low risk	Participants were contacted by letter or telephone, or both, and attended clinic for assessment 5 years after randomization into the original study. If the participant had died prior to the follow-up assessment, the date and cause of death was requested from the relatives. Participants were assessed using a standard questionnaire and neurological examination. Four survivors who were unable to attend the hospital gave verbal consent and were assessed by telephone interview. The accomplished length of follow-up was 5.2 years (median) with an interquartile range of 4.7 to 5.5 years after randomization.
Detection bias Clinical cure and default	Low risk	During ATT, participants were assessed at 1, 2, 6, and 9 months after randomization. At each point, disability was assessed and scored.
Attrition bias Relapse	High risk	40/336 (11.9%) participants were lost to follow-up during the follow-up period.
Attrition bias Clinical cure and default	Low risk	10/545 (1.8%) participants were lost to follow-up during ATT.
Performance bias	Unclear risk	143 participants received altered ATT regimen due to adverse events. It is not stated whether the regimen was prolonged for these participants.
Confounding bias	Unclear risk	Adherence to treatment is not reported. 274/545 participants were randomized to receive either corticosteroids or placebo, but it is unclear how this would affect the results.

van Toorn 2014

Methods	Study objective: to demonstrate non-inferiority of a 6-month intensive ATT regimen compared with other published ATT regimens for TBM. Study design: prospective observational study. Length of follow-up: at least 2 years after completing ATT. Follow-up method: during ATT, home-based participants were reviewed monthly; relapse rate was determined by telephonic contact with the child's caregiver at least 2 years after therapy completion or if the participant was reviewed in our neurology outpatient clinic after this time. Losses to follow-up: 29 children after completing ATT (they completed treatment in hospital but caregivers could not be traced).
Participants	Number: 184; median age 58 months (range 3 to 156 months); 49% male. Target treatment groups: children from 0 to 13 years.

van Toorn 2014 *(Continued)*

	Inclusion criteria: TBM was classified as follows. • Definite TBM: when *M. tuberculosis* was cultured from CSF or polymerase chain reaction (PCR), or both, for *M. tuberculosis* tested positive in CSF. • Probable TBM: based on clinical signs of meningitis in the presence of characteristic CSF findings (macroscopically clear, pleocytosis usually with lymphocyte predominance, elevated protein, and reduced glucose). In addition, 2 of the following criteria were required: other clinical specimens culture positive for *M. tuberculosis* or positive TB histology or both, a positive tuberculin skin test, a chest radiograph compatible with TB, a cranial CT or magnetic resonance imaging (MRI) compatible with TBM, growth failure with crossing of weight-for-age percentiles or finally, household contact with sputum smear-positive PTB. Exclusion criteria: multidrug-resistant TB (defined as resistance to at least isoniazid and rifampicin) Bacteriologically confirmed TBM cases: 16/184. Site of TB other than CNS: not reported. Other clinical features: 12 TB mass lesion which refers to either large tuberculoma(s) or TB abscesses; 72 communicating hydrocephalus, 37 non-communicating hydrocephalus. Clinical severity of the disease: 22 in stage I; 98 in stage II; 64 in stage III. HIV status: 128 HIV-negative, 22 HIV-positive, 5 exposed HIV-negative, 29 not tested. Duration of symptoms prior to admission and time to treatment initiation: not reported.
Interventions	Short-course ATT: 6 months - 6HRZEth, single daily dosage • Isoniazid: 20 mg/kg, maximum 400 mg (6 months). • Rifampicin: 20 mg/kg, maximum 600 mg (6 months). • Pyrazinamide: 40 mg/kg, maximum 2g (6 months). • Ethionamide 20 mg/kg, maximum 750 mg (6 months). 24 children received prolonged ATT up to 18 months for different reasons (antituberculous drug-induced hepatotoxicity, poor adherence, TB mass lesions, TB-immune reconstitution inflammatory syndrome). Prolonged-course ATT: 9 months • 22 HIV-infected children were treated for 9 months because of perceived slower response to treatment. • 3 additional children with isoniazid-monoresistant TB were treated with the addition of a fluoroquinolone and terizidone for 9 months. Other interventions • Prednisone (2 mg/kg/day, maximum 60 mg/day) given to all children for the first month of treatment and gradually discontinued over the next 2 weeks. • Ventriculo-peritoneal shunt to 34 children and endoscopic third ventriculostomy to 3 children to treat non-communicating hydrocephalus. • Acetazolamide (50 mg/kg/day) and furosemide (1 mg/kg/day) for communicating hydrocephalus. • Combination antiretroviral therapy consisting of stavudine, lamivudine and efavirenz initiated as soon after HIV diagnosis as possible.
Outcomes	Outcomes included in this review (directly reported or deductible from reported data) • Relapse. • Death from any cause. • Death after 6 months of ATT. • Clinical cure.

van Toorn 2014 *(Continued)*

- Default.
- Poor adherence.
- All adverse effects related to the ATT.
- Drug toxicity leading to discontinuation of regimen.

Outcomes not included in this review

- Neurological sequelae.

Notes	Country: South Africa. Setting: Tygerberg Children's Hospital, a referral hospital in the Western Cape province. Study dates: from 1 January 2006 to 31 December 2009. Study sponsor: none.

Risk of bias

Bias	Authors' judgement	Support for judgement
Detection bias Relapse	Low risk	Relapse rate was determined by telephonic contact with the child's caregiver at least 2 years after therapy completion.
Detection bias Clinical cure and default	Low risk	During the duration of the treatment, 1 group of participants was hospital-based. The other group of participants was home-based and were reviewed monthly.
Attrition bias Relapse	High risk	29/184 (15.8%) children were lost to follow-up.
Attrition bias Clinical cure and default	Low risk	No losses of follow-up during the duration of the treatment.
Performance bias	High risk	28/177 (15.8%) children received prolonged ATT up to 18 months for different reasons (antituberculous drug-induced hepatotoxicity, poor adherence, TB mass lesions, TB-immune reconstitution inflammatory syndrome).
Confounding bias	Unclear risk	All children received prednisone. 3 children are reported to poorly adhere to treatment, but it is unclear how this would affect the results.

Visudhiphan 1989

Methods	Study objective: to evaluate the results of treating TBM with isoniazid and rifampicin. Study design: prospective observational study. Length of follow-up: 1½ to 7 years after finishing the course of ATT. Follow-up method: not described. Losses to follow-up: 4 participants lost during ATT, none after completing ATT.
Participants	Number: 51; 26/51 children were less than 4 years (range 7 months to 14 years); 47% male. Target treatment groups: children with TBM.

Visudhiphan 1989 *(Continued)*

	Inclusion criteria: all TBM cases were diagnosed according to the characteristic clinical features and typical CSF findings (that is, lymphocytic pleocytosis, decreased glucose level, and elevation of protein content). At least 3 of the following supporting criteria had to be present. • A history of contact with a known TB patient. • A positive skin test result. • Radiological evidence of PTB. • The characteristic change of large intracranial vessels, as seen in a cerebral angiogram. • Typical basal arachnoiditis and dilation of the ventricles, as seen in CT of the brain. Participants who had characteristic clinical features with the presence of *M. tuberculosis* in the CSF but without typical CSF findings were also included in this study. Exclusion criteria: none mentioned. Bacteriologically-confirmed TBM cases: 13/51. Partial resistance to H in 2 participants, and to R in 2 other participants. Site of TB other than CNS: not reported. Other clinical features: 1 non-communicating hydrocephalus, 43 increased intracranial pressure. Clinical severity of the disease: 5 in stage I; 25 in stage II; 21 in stage III. HIV status: not reported. Duration of symptoms prior to admission and time to treatment initiation: not reported.
Interventions	Short-course ATT: none. Prolonged-course ATT: 12 months - 12 HR. Daily, 1 to 2 hours before breakfast, either orally or by nasogastric tube: • Isoniazid 10 to 15 mg/kg. • Rifampicin 15 mg/kg. Other interventions • Dexamethasone 0.3 to 0.5 mg/kg/day in the first week of ATT, then prednisolone 2 mg/kg/day for 2 to 3 weeks, followed by gradually tapered dose, to all participants. • Ventriculostomy to 3 participants who had a high CSF pressure (> 200 mmH_20) and whose condition deteriorated rapidly after the initial lumbar puncture. • Ventriculoperitoneal shunt to 1 participant with obstructive hydrocephalus. • Acetazolamide (25 to 50 mg/kg/day in 3 or 4 divided doses) and repetitive lumbar puncture for management of increased intracranial pressure to 41 participants.
Outcomes	Outcomes included in this review, directly reported (directly reported or deductible from reported data) • Relapse. • Death from any cause. • Clinical cure. • All adverse effects related to ATT. • Drug toxicity leading to discontinuation of regimen. Outcomes not included in this review • Neurological sequelae.
Notes	Country: Thailand.

Visudhiphan 1989 *(Continued)*

Setting: Department of Pediatrics, Ramathibodi Hospital, Mahidol University, Bangkok.

Study dates: from January 1979 to December 1985.

Study sponsor: none mentioned.

Risk of bias

Bias	Authors' judgement	Support for judgement
Detection bias Relapse	Unclear risk	Survivors were followed-up for a period ranging from 1.5 to 7 years after finishing the course of ATT. No details are given on the methods of follow-up.
Detection bias Clinical cure and default	Unclear risk	It is not stated how participants were given antituberculous drugs and the way they were followed-up during the 12-month treatment.
Attrition bias Relapse	Low risk	No participants were lost to follow-up after completing treatment for at least 1.5 years.
Attrition bias Clinical cure and default	Unclear risk	4/51 (7.8%) participants were lost to follow-up during ATT.
Performance bias	Low risk	There were 44 survivors at the time of completing ATT. The study authors stated that "44 patients who received the full course of treatment with isoniazid and rifampicin for 12 months were followed for 1.5 to 7 years after finishing the course of treatment." No extended treatment is described.
Confounding bias	Unclear risk	Adherence to treatment was not assessed or reported. All participants received corticosteroids.

ADA: adenosine deaminase activity; AFB: acid-fast bacilli; ATT: antituberculous treatment, BCG: Bacillus Calmette–Guérin; CNS: central nervous system; CSF: cerebrospinal fluid; CT: computerized tomography; DOT: directly observed therapy; E: ethambutol; ELISA: enzyme-linked immunosorbent assay; EPTB: extra-pulmonary tuberculosis; Eth: ethionamide; H: isoniazid; HIV: human immunodeficiency virus; PCR: polymerase chain reaction; PPD: purified protein derivative; PTB: pulmonary tuberculosis; R: rifampicin; RCT: randomized controlled trial; RDT: Rural Development Trust; RNTCP: Revised National Tuberculois Control Programme; S: streptomycin; TB: tuberculosis; TBM: tuberculous meningitis; UK: United Kingdom; VFHCS: Vicente Ferrer HIV Cohort Study; Z: pyrazinamide.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Acharya 1985	There was no data on relapse.
Agrawal 1989	There was no data on length of antituberculous treatment (ATT), it is unlikely that there was follow-up of participants after completing ATT and there was no data on relapse.
Alarcón 2013	There was no follow-up of participants after completing ATT.
Alvarez-Uria 2013	There was no follow-up of participants after completing ATT.
Anuradha 2010	There was no follow-up of participants after completing ATT.
Bandyopadhyay 2009	There was no follow-up of participants after completing ATT.
Bhagwati 1986	There was no data on length of ATT, and no follow-up of participants after completing ATT.

Study	Reason for exclusion
Bokade 2014	There was no data on length of ATT, and no follow-up of participants after completing ATT.
Cardozo 1976	Retrospective collection of data.
Chan 1988	Study examined prolonged therapeutic external ventricular drainage, and included four participants with TBM.
Chan 2005	No follow-up of participants after completing ATT.
Chandra 1976	There was no data on length of ATT, and no follow-up of participants after completing ATT.
Chugh 2009	There was no data on length of ATT, and no follow-up of participants after completing ATT.
Cotton 1991	There was no data on follow-up of participants after completing ATT.
Cotton 1993	There was no data on length of ATT, and no follow-up of participants after completing ATT.
de March-Ayuela 1994	There was no data on length of ATT and no data on relapse.
Degefie 2003	There was no data on relapse.
Dikshit 1976	The ATT regimen did not include rifampicin.
Donald 1986	There was no data on length of ATT, and no follow-up of participants after completing ATT.
Donald 1996	There was no data on length of ATT, and no follow-up of participants after completing ATT.
Doğanay 1989	There was no follow-up of participants after completing ATT.
Eintracht 2000	Diagnostic test accuracy study, and there was no data on length of ATT and outcomes.
Elliott 1993	We contacted the authors: there was no disaggregated data for tuberculous meningitis (TBM).
Elliott 1995a	Duplicated cohort of participants from Elliott 1993.
Elliott 1995b	Duplicated cohort of patients from Elliott 1993.
Erdös 1974	Retrospective study.
Escobar 1975	The ATT regimen did not include rifampicin.
Ganiem 2009	There was no data on length of ATT, and no follow-up of participants after completing ATT.
Garg 2010	There was no follow-up of participants after completing ATT.
Girgis 1978	There was no follow-up of participants after completing ATT.
Girgis 1991	The ATT regimen did not include rifampicin.
Girgis 1993	Retrospective analysis of records.
Goyal 2014	There was no data on length of ATT not reported, and no follow-up of participants after completing ATT.
Guillen 1993	Retrospective analysis of hospital records.

Study	Reason for exclusion
Gujjar 2009	This study examined the efficacy of hypervolemia-hypertension-hemodilution (HHH) regime in participants with TBM with arteritis. The study authors reported outcomes during ATT but there was no follow-up after completing ATT.
Gupta 2013	There was no follow-up of participants after completing ATT.
Gupta 2015	There was no follow-up of participants after completing ATT.
Heemskerk 2016	There was no follow-up of participants after completing ATT.
Hoose 1990	Retrospective cohort.
Immanuel 1990	There was no data on relapse.
Irfan 1995	It is unclear whether this is a prospective or retrospective analysis. The study authors did not describe the ATT regimen, and did not report relapse outcome.
Jain 2011	There was no follow-up of participants after completing ATT.
Jain 2013	We contacted the study authors: there was unknown duration of ATT and no follow-up after completing treatment.
Jakka 2005	Study looking at prognostic implication of cerebrospinal fluid (CSF) adenosine deaminase activity (ADA); there was no data on relapse.
Jubelt 2006	Duplicate cohort of patients from Török 2011a.
Julka 1998	There was no data on length of ATT, and no data on relapse.
Kalita 1999	There was no data on length of ATT, and no follow-up of participants after completing ATT.
Kalita 2001	Duplicate cohort of patients from Kalita 1999.
Kalita 2007	There was no follow-up of participants after completing ATT.
Kalita 2009	There was no follow-up of participants after completing ATT.
Kalita 2014	There was no follow-up of participants after completing ATT.
Karande 2005a	There was no follow-up of participants after completing ATT.
Karande 2005b	There was no follow-up of participants after completing ATT.
Kingkaew 2009	There was no follow-up of participants after completing ATT.
Koh 2007	There was no follow-up of participants after completing ATT.
Kumarvelu 1994	There was no data on length of ATT, and no follow-up of participants after completing ATT.
Lamprecht 2001	Retrospective study.
Lardizabal 1998	There was no follow-up of participants after completing ATT.
Malhotra 2009	There was no data on relapse, and maximum 1 month of follow-up of participants after completing ATT.

Study	Reason for exclusion
Marais 2006	There was no data on relapse.
Marais 2013	There was no follow-up of participants after completing ATT.
Maree 2007	There was no follow-up of participants after completing ATT.
Mathew 1998	This study assessed the predictive value of the response to external ventricular drainage on long term outcome in the poor grade patients with TBM and hydrocephalus. We contacted the study authors: there was no data on relapse during the follow-up period.
Misra 1996	There was no follow-up of participants after completing ATT.
Misra 2000	There was no follow-up of participants after completing ATT.
Misra 2010	There was no follow-up of participants after completing ATT.
Moreira 2008	There was no follow-up of participants after completing ATT.
Nadvi 2000	There was no follow-up of participants after completing ATT.
Narayanan 1982	The ATT regimen did not include rifampicin.
Panigatti 2014	There was no follow-up of participants after completing ATT.
Pardasani 2008	There was no data on length of ATT and no data on relapse.
Park 2014	There was no data on length of ATT and no data on relapse.
Patwari 1996	We contacted the study authors contacted: there was no data on relapse.
Pepper 2009	There was no follow-up of participants after completing ATT.
Phuapradit 1990	There was no data on relapse.
Porkert 1997	Retrospective analysis from hospital records.
Radhakrishnan 1990	There was no data on length of ATT, and no follow-up of participants after completing ATT.
Raghu Raman 1997	Prospective study that recruited non-consecutive cases of tuberculosis (TB) in children, and looked at the pattern of TB in children vaccinated with Bacillus Calmette–Guérin (BCG). There was no data on relapse.
Rahajoe 1979	There was no follow-up of participants after completing ATT.
Rai 2014	There was no follow-up of participants after completing ATT.
Ramzan 2013	There was no follow-up of participants after completing ATT.
Ranjan 2003	There was no follow-up of participants after completing ATT.
Rao 1982	Retrospective study.
Rao 2013	There was no follow-up of participants after completing ATT.

Study	Reason for exclusion
Raut 2013	There was no data on relapse.
Rojas-Echeverri 1996	There was no data on relapse.
Ruslami 2013	There was no follow-up of participants after completing ATT.
Saleem 2011	There was no data on length of ATT, and no data on relapse.
Saleem 2015	Duplicated cohort of patients from Saleem 2011 with no data on relapse.
Salekeen 2013	We contacted the study authors: no follow-up of participants after completing ATT.
Savula 1975	Retrospective study.
Schoeman 1990	Duplicated cohort of patients from Schoeman 1997a.
Schoeman 1991	There was no follow-up of participants after completing ATT.
Schoeman 1997a	The aim of this study was to evaluate cognitive and motor impairment of children surviving TBM. The study reported findings on 19 children from a cohort of 75 participants, with no details on eligible criteria.
Schoeman 1997b	There was no follow-up of participants after completing ATT.
Schoeman 2000a	There was no follow-up of participants after completing ATT.
Schoeman 2000b	There was no follow-up of participants after completing ATT.
Schoeman 2002	Retrospective study.
Schoeman 2004	There was no follow-up of participants after completing ATT.
Schoeman 2011	There was no follow-up of participants after completing ATT.
Shah 2014	We contacted the study authors: there were 7 participants with TBM followed-up for more than 6 months after completing ATT (other participants had shorter length of follow-up). The study authors identified these 7 participants as treatment failure with multidrug resistant (MDR) TB or extensively drug resistant (XDR) TB (according to our outcome definitions).
Shahbaz 2011	There was no follow-up of participants after completing ATT.
Sharma 2013b	There was no data on length of ATT, and no follow-up of participants after completing ATT.
Shor 1973	Retrospective study.
Simmons 2006	Duplicated cohort of patients from Török 2011a.
Singh 1994	There was no data on length of ATT, and no follow-up of participants after completing ATT.
Singh 1998	There was no follow-up of participants after completing ATT.
Springer 2009	There was no data on length of ATT, and no follow-up of participants after completing ATT.
Swamy 1987	This paper presented findings from three studies (no study identifiers) with no data on relapse.

Study	Reason for exclusion
Te Brake 2015	There was no follow-up of participants after completing ATT.
Thwaites 2002	There was no follow-up of participants after completing ATT.
Thwaites 2003a	We contacted the author of this PhD thesis: findings on the cohort of participants have been published elsewhere (duplicated data), such as Thwaites 2003b.
Thwaites 2003b	There was no follow-up of participants after completing ATT.
Thwaites 2005b	Duplicated cohort of patients from Török 2011b.
Thwaites 2005c	Duplicated cohort of patients from Török 2011b.
Thwaites 2007	Duplicated cohort of patients from Török 2011b.
Thwaites 2011	There was no follow-up of participants after completing ATT.
Torok 2008	There was no follow-up of participants after completing ATT.
Török 2011b	The trial reported outcomes at time of completing ATT and three months after completing ATT.
van der Merwe 2009	Retrospective study.
van Toorn 2012	There was no follow-up of participants after completing ATT.
Wait 2010	Duplicated cohort of patients from Schoeman 2002.

ADA: adenosine deaminase activity; ATT: antituberculous treatment; BCG: Bacillus Calmette–Guérin; CSF: cerebrospinal fluid; MDR: multidrug resistant; TB: tuberculosis; TBM: tuberculous meningitis; XDR: extensively drug resistant.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Caliman-Sturdza 2010

Methods	Study objective: to investigate the particularities of the clinical manifestation and evolution of tuberculous meningitis (TBM) in children. Study design: prospective observational study.
Participants	169 children with TBM.
Interventions	Antituberculous treatment (ATT) regimen not mentioned in abstract.
Outcomes	Socioeconomic conditions, clinical presentation, time of initiating ATT, and evolution under ATT including neurological complications and deaths. There are no data in the abstract about follow-up of the participants after ATT completion and, if so, whether relapse was reported.
Notes	Country: Romania. Setting: Clinical infectious diseases Iasi and Emergency County Hospital 'Sf. Ioan cel Nou'. Study dates: from January 2000 to December 2008. Reason for awaiting classification: no access to full-text paper.

Carrasco 1988

Methods	Unknown.
Participants	Unknown.
Interventions	Unknown.
Outcomes	Unknown.
Notes	We did not have access to the abstract and the full-text paper.

Das Gupta 2005

Methods	Unknown.
Participants	Unknown.
Interventions	Unknown.
Outcomes	Unknown.
Notes	We did not have access to the abstract and the full-text paper.

Gunawardhana 2013

Methods	Study objective: to describe the demographic profile, clinical features, laboratory, and imaging results of a cohort of adults with TBM. Study design: prospective observational study.
Participants	89 adults with TBM.
Interventions	ATT consisted of rifampicin, isoniazid, pyrazinamide, ethambutol, and streptomycin in 62 participants and without streptomycin in 17 participants. Duration of ATT is not reported.
Outcomes	It is unclear whether there is any follow-up after completing ATT.
Notes	Country: Sri Lanka. Study dates: from 1 January 2010 to 31 December 2011. We attempted to contact the study author, and await a reply.

Kilincoglu 2009

Methods	Study objective: to evaluate the results of shunt function in cases having high concentrations of cerebrospinal fluid (CSF) proteins. Study design: prospective observational study. Mean follow-up period: 45 months.

Kilincoglu 2009 *(Continued)*

Participants	32 children with TBM hydrocephalous.
Interventions	ATT regimen unknown.
Outcomes	There was no data on relapse.
Notes	Country: Turkey. Study dates: from January 1995 to January 2001. We attempted to contact the study author for data on relapse during the 45 month follow-up period; we await a reply.

Mahadevan 2002

Methods	Study objective: to identify the various factors that affect the outcome in childhood TBM. Study design: prospective observational study. Follow-up period: from 9 to 18 months, but it is unclear whether it is from starting or after completing ATT.
Participants	50 children with TBM.
Interventions	ATT consisted of rifampicin, isoniazid, pyrazinamide, and either ethambutol or streptomycin, for unknown duration.
Outcomes	There was no data on relapse.
Notes	Country: India. Study dates: from May 1999 to July 2000. We attempted to contact the study author for clarification of the length of follow-up and whether they have data on relapse during this follow-up period; we await a reply.

Mahajan 2005

Methods	Unknown.
Participants	Unknown.
Interventions	Unknown.
Outcomes	Unknown.
Notes	We did not have access to the abstract and the full-text paper.

Nair 2005

Methods	Unknown.

Nair 2005 *(Continued)*

Participants	Unknown.
Interventions	Unknown.
Outcomes	Unknown.
Notes	We did not have access to the abstract and the full-text paper.

Rahman 2009

Methods	Study objective: to assess whether corticosteroids improve the clinical outcome in patients with CNS TB. Study design: prospective observational study.
Participants	13 participants with central nervous system tuberculosis (CNS TB) (7 TBM and 6 tuberculoma).
Interventions	ATT regimen unknown.
Outcomes	There was no data on death, recovery, and residual neurological deficits in the abstract.
Notes	Country: Bangladesh. Reason for awaiting classification: no access to full-text paper to determine duration of follow-up and relapse.

Yadav 2004

Methods	Study objective: to evaluate the lumboperitoneal shunt procedure. Study design: prospective observational study. Follow-up period: 45.34 months in average, but it is unclear whether it is from starting or after completing ATT.
Participants	285 participants with TBM-related hydrocephalus.
Interventions	ATT not described. Co-intervention: lumboperitoneal shunt.
Outcomes	There was no data on relapse in the abstract.
Notes	Country: India. Study dates: from March 1992 to February 2002. Reason for awaiting classification: no access to full-text paper to obtain data on ATT regimens administered and whether data on relapse were collected.

Yadav 2011

Methods	Study objective: to evaluate the role of endoscopic third ventriculostomy in TBM hydrocephalus.

Yadav 2011 *(Continued)*	Study design: prospective observational study. Follow-up period: not stated.
Participants	59 participants with TBM and obstructive hydrocephalus.
Interventions	ATT not described. Co-intervention: endoscopic third ventriculostomy.
Outcomes	There was no data on relapse in the abstract.
Notes	Country: India. Study dates: not reported. Reason for awaiting classification: no access to full-text paper to inquire data on ATT regimens administered, duration of follow-up, and data on relapse.

ATT: antituberculous treatment; CNS TB: central nervous system tuberculosis; CSF: cerebrospinal fluid; TBM: tuberculous meningitis.

Characteristics of ongoing studies *[ordered by study ID]*

NCT02454569

Trial name or title	Vicente Ferrer HIV Cohort Study (VFHCS)
Methods	Long-term prospective cohort study of all HIV-positive patients who have attended Bathalapalli RDT Hospital. Routine clinical data from patients are collected prospectively since September 2009 and entered in a SQL-server database using C# as front end. Details of route of transmission, HIV-associated risk factors, and sociodemographic data are collected at enrolment. Data collected include medical treatment (antiretroviral treatment and other medications), laboratory investigations (haemogram, renal function tests, liver function tests, CD4 lymphocyte count, bacterial infections), and standardized diagnoses.
Participants	HIV-positive patients of any age or gender who have attended Bathalapalli RDT Hospital. Participants must have positive serology for HIV and those who refuse consent will be excluded.
Interventions	Routine clinical care
Outcomes	Primary outcome measure: mortality (time frame: time to event methods will be used. Participants will be followed from HIV diagnosis until death, assessed up to 30 years)
Starting date	Study start date: September 2009 This study is currently recruiting participants (last updated 30 December 2016)
Contact information	Gerardo Alvarez Uria, MD PhD; hivbtp@gmail.com
Notes	Sponsor: Rural Development Trust Hospital Target follow-up duration: 30 years This is an ongoing study for which some results are available (Alvarez-Uria 2012)

ADDITIONAL TABLES

Table 1. Description of cohort studies that administered six months ATT

Study	Setting		Participants				ATT regimens	Duration of FU after ATT, in months
	Country	Centre	Number	Adults/children	HIV status	MRC stages of the disease		Mean (range)
Alarcón 1990	Ecuador	Tertiary centre	28	Adults and adolescents	NR	I: 4/28 II: 10/28 III: 14/28	2HRZ/4HR	(18 to 30)
Biddulph 1990	Papua New Guinea	Tertiary centre	43	Children	NR	NR	2HRZS/4(HR)$_2$	(up to 24)
Chotmongkol 1991	Thailand	Tertiary centre	29	Adults	NR	I: 7/29 II: 12/29 III: 10/29	2HRZS/4HR	16.3 (4 to 33)
Chotmongkol 1996	Thailand	Tertiary centre	59	Adults	NR	I: 9/59 II: 40/59 III: 10/59	2HRZS/4HR	30 (16 to 45)
Donald 1998	South Africa	Tertiary centre	95	Children	NR	I: 4/95 II: 52/95 III: 39/95	6HRZEth	12
Jacobs 1992 [a]	Thailand	Tertiary centre	45	Children	NR	I: 8/45 II: 25/45 III: 12/45	2HRZS/4HR	At least 6 months: 27/38 Less than 6 months: 7/38
van Toorn 2014 [b]	South Africa	Tertiary centre	159	Children	HIV-negative or unknown	I: 22/184[c] II: 98/184 III: 84/184	6HRZEth	At least 24

Abbreviations: ATT: antituberculous treatment, E: ethambutol; Eth: ethionamide; FU: follow-up; H: isoniazid; HIV: human immunodeficiency virus; MRC: Medical Research Council; NR: not reported; R: rifampicin; Z: pyrazinamide.

[a]In this prospective cohort study, data are reported for three successive cohorts in the same centre over time. The first cohort received a 12-month regimen with 2/4 participants receiving rifampicin, the second a 9-month regimen with all participants receiving rifampicin, and the third received a 6-month regimen with all participants receiving rifampicin and pyrazinamide.

[b]HIV-positive children were treated with a 9-month regimen due to a perceived slower response to treatment.

[c]There were no diaggregated data for clinical severity of the disease between the cohort of HIV-negative participants receiving 6 months of treatment and the cohort of HIV-positive participants receiving 9-month ATT.

Table 2. Diagnosis of TBM: clinical and radiological characteristics in cohorts that received six months ATT

Study	Previous history of TB	Known contact with TB patient	PPD skin test positive	Neuroimaging	Abnormal chest X-ray
Alarcón 1990	5/28	9/28	8/28	Done in all participants. Abnormal findings in 19/28.	17/28
Biddulph 1990	NR	5/38	25/38 (≥ 15 mm or ≥ 10 mm with BCG scar)	Myelogram in participants with partial spinal block.	14/43
Chotmongkol 1991	NR	NR	NR	CT scan in 18 participants.	10/29
Chotmongkol 1996	NR	NR	NR	CT scan: abnormal findings in 31/37. Myelogram for participants with paraparesis	23/59
Donald 1998	NR	55/95	2/95 between 10 mm and 15 mm, 84/95 ≥ 15 mm	CT scan	41/95
Jacobs 1992 [a]	NR	45/53	25/53	NR	35/53
van Toorn 2014 [a]	NR	NR	NR	CT scan on admission: bilateral basal ganglia infarction in all 7 cases who died before completing ATT.	Done, NR

Abbreviations: ATT: antituberculous treatment; BCG: Bacillus Calmette–Guérin; CT: computed tomography; NR: not reported; PPD: purified protein derivative.
[a] Jacobs 1992 and van Toorn 2014 also reported cohorts of participants treated for longer than 6 months, but no disaggregated data are provided on clinical features between both cohorts.

Table 3. Diagnosis of TBM: microbiological and other diagnostic characteristics in cohorts that received six months ATT

Study	CSF				Other diagnostic methods for TB	Diagnostic classification	
	Cell count, protein and glucose content	Positive AFB smear	Positive culture	Other tests performed in CSF		Bacteriologically confirmed	Clinically diagnosed
Alarcón 1990	Reported	15/28	16/28	ELISA for BCG antibodies, ADA	Bacteriological analyses of sputum, gastric aspirate, and urine. 1 lymph node biopsy, 1 culture from abscess drainage. Autopsy findings.	22/28	6/28
Biddulph 1990	Reported	Done but NR	5/36	None	Sputum specimens, fasting gastric aspirates, and pleural fluid for microscopy and culture. Lymph node biopsy for histology and culture. Abdominal ultrasound. BCG vaccine scar.	5/43	38/43
Chotmongkol 1991	Reported	NR	6/29	None	None	6/29	23/29
Chotmongkol 1996	Reported	1/59	5/59	Pyogenic bacterial and fungal culture, latex agglutination test for bacterial and cryptococcal Ag and cytologic study for malignancy; results NR	None	5 or 6/59[a]	53 or 54/59[a]
Donald 1998	Reported	NR	18/95	DST Air encephalogram	Gastric aspirate for microscopy and culture	18/95	77/95
Jacobs 1992 [b]	NR	2/33	5/35	None	Presence of a BCG vaccine scar in 28/53	7/53	46/53
van Toorn 2014 [b]	NR	NR	16/136	PCR for MTB in CSF 2 specimens[c]	Culture of gastric washings: 43/155	16/184	168/184

Abbreviations: ADA: adenosine deaminase activity; AFB: acid-fast bacillus; Ag: antigen; BCG: Bacillus Calmette–Guérin; CSF: cerebrospinal fluid; DST: drug sensitivity tests; ELISA: enzyme-linked immunosorbent assay; NR: not reported; MTB: *Mycobacterium tuberculosis*; PCR: polymerase chain reaction; PPD: purified protein derivative.

[a]Unclear whether the specimens with positive stain were also culture positive.

[b] Jacobs 1992 and van Toorn 2014 also reported cohorts of participants treated for longer than 6 months, but no disaggregated data are provided on CSF characteristics and diagnosis classification between the cohorts.

[c]The study authors stated that PCR was not done routinely, but did not report how many specimens were tested this way. The 2 positive PCR specimens were also culture positive.

Table 4. Description of cohort studies that administered more than six months ATT

Study	Setting		Participants				ATT regimens	Duration of ATT (months)	Duration of FU after ATT, in months Mean (range)
	Country	Centre	Number	Adults/children	HIV status	Severity of the disease			
Anastasatu 1993	Romania	Tertiary centre	44	Children	NR	NR	$3HRZ/6HR_2$ (19 cases)[a]	9	51
							$3HR/3HR_2/6H_2$ (25 cases)[a]	12	
Doğanay 1995	Turkey	Multicentre; university hospitals	72	Adults	NR	I: 7/72 II: 34/72 III: 31/72	2HRZS/6HR (37 cases)	8	Median 10 (6 to 24)
							HRZE (19 cases) HRES (6 cases) HRZS (6 cases) HRZES (3 cases) HRE (1 case)	12 to16	Median 13 (4 to 36)
Iype 2014	India	Tertiary centre	47	Adults	HIV positive excluded	I: 15/43 II: 24/43 III: 4/43	$2(HRZS)_3/7(HR)_3$ (41 cases)	9	Median 5.2 (IQ 3.4 to 9.8)

Table 4. Description of cohort studies that administered more than six months ATT *(Continued)*

							$2(HREZS)_3/1(HREZ)_3/7(HR)_3$ (2 cases)	10	
Jacobs 1992 [b]	Thailand	Tertiary centre	8	Children	NR	I: 0/8 II: 4/8 III: 4/8	2HRS/7HR (4 cases)	9	NR
							2HSE/10HE (2 cases) 2RSE/10RE (2 cases)	12	NR
Lau 2005	China (Hong Kong)	Multicentre; tertiary and secondary hospitals	166	Adults and children	2 HIV positive	I: 91/166 II: 69/166 III: 6/166	HRZES (66 cases) HRZE (63 cases) HRZS (24 cases) HRZ (8 cases) HRE (2 cases) SHRE (1 case) HZE (1 case) HR (1 case)	11.53 (mean)	24
Phuapradit 1987	Thailand	Tertiary centre	28	Adults	NR	I: 4/28 II: 18/28 III: 6/28	2HRZS/7HR	9	19.8 (12 to 29)
Ramachandran 1989	India	Multicentre; tertiary hospitals	180	Children	NR	I: 24/180 II: 139/180	2SHR/4S_2EH/6EH (77 cases) 2SHRZ/10EH	12	(42 to 84)

Table 4. Description of cohort studies that administered more than six months ATT *(Continued)*

						III: 17/180	(29 cases) 2R_2 SHZ/10EH (74 cases)		
Ramachandran 1997	India	Multicentre; tertiary hospitals	215	Children	NR	I: 45/215 II: 160/215 III: 10/215	2SHE$(RZ)_3$/7$(RH)_2$ (89 cases) 2SHE$(RZ)_2$/7$(RH)_2$ (96 cases)	9	51
Sharma 2013a	India	Tertiary centre	42	Adults	HIV positive excluded	I: NDD II: NDD III: 21/42	2$(HREZ)_3$/7$(HR)_3$	9	6
Török 2011a	Vietnam	Multicentre; tertiary hospitals	545	Adults and adolescents	436 HIV negative 98 HIV positive 11 unknown	I: 176/545 II: 247/545 III: 122/545	3RHZS/6RHZ (399 HIV negative) 3RHZE/6RHZ (98 HIV positive) 3RHZES/6RHZ (43 previously treated) HZE (2 cases) SE (1 case)	9	Median 53.4 (IQ 47.4 to 57)
van Toorn 2014	South Africa	Tertiary centre	25	Children	22 HIV positive; 3 unknown	I: 22/184 [c] II: 98/184 III: 84/184	9HRZEth[d]	9	At least 24
Visudhiphan 1989	Thailand	Tertiary centre	51	Children	NR	I: 5/51 II: 25/51 III: 21/51	12HR	12	(18 to 84)

Abbreviations: ATT: antituberculous treatment, E: ethambutol; Eth: ethionamide; FU: follow-up; H: isoniazid; HIV: human immunodeficiency virus; IQ: interquartile range; MRC: Medical Research Council; NR: not reported; R: rifampicin; Z: pyrazinamide

[a]It is unclear whether streptomycin twice weekly was also administered in both regimens in the first 3 months.
[b]In this prospective cohort study, data are reported for 3 successive cohorts in the same centre over time. The first cohort received a 12-month regimen with 2/4 participants receiving rifampicin, the second a 9-month regimen with all participants receiving rifampicin, and the third received a 6-month regimen with all participants receiving rifampicin and pyrazinamide.

[c]There were no diaggregated data for clinical severity of the disease between the cohort of HIV-negative participants receiving 6 months of treatment and the cohort of HIV-positive participants receiving 9-month ATT.
[d]The 22 HIV-positive children were treated with a 9-month regimen due to a perceived slower response to treatment, as well as the 3 children with *M. tuberculosis* isoniazid-monoresistance.

Table 5. Diagnosis of TBM: clinical and radiological characteristics in cohorts receiving more than six months ATT

Study	Previous history of TB	Known contact with TB patient	PPD skin test positive	Neuro-imaging	Abnormal chest X-ray
Anastasatu 1993	NR	NR	NR	NR	0/39
Doğanay 1995	3/72	NR	NR	NR (although 1 intracerebral tuberculoma is reported)	NR (although 22 PTB are reported)
Iype 2014	NR	14/43	NR	Done in all participants. 5 tuberculoma, 9 hydrocephalus, 14 arteritis, 3 spinal arachnoiditis.	11/43
Jacobs 1992 [a]	NR	45/53	25/53	NR	35/53
Lau 2005	NR	50/166	NR	50/155 had meningeal enhancement, ventricular dilatation, tuberculoma or space occupying lesion.	63/158
Phuapradit 1987	NR	NR	NR	CT scan in 21 participants with increased intracranial pressure: 10 communicating hydrocephalus 3 diffuse cerebral oedema with small lateral ventricles 1 associated tuberculoma	18/28
Ramachandran 1989	NR	84/180	90/180 (≥10mm)	NR	99/180
Ramachandran 1997	NR	137/215	73/215 (≥10mm)	CT scans to 68 participants with suspected hydrocephalus	111/215
Sharma 2013a	NR	NR	NR	CT scan in 30 participants (14 with multiple lacunar infarct, hydrocephalus, basal meningeal enhancement). MRI performed in 11 participants.	9/42
Török 2011a	NR	NR	NR	NR	Active non-miliary TB: 214/545 Miliary TB: 155/545
van Toorn 2014 [a]	NR	NR	NR	CT scan on admission: bilateral basal ganglia infarction in all 7 cases who died before completing ATT.	Done, NR

Table 5. Diagnosis of TBM: clinical and radiological characteristics in cohorts receiving more than six months ATT *(Continued)*

Visudhiphan 1989	NR	NR	NR	NR	NR

Abbreviations: ATT: antituberculous treatment; CT: computed tomography; MRI: magnetic resonance imaging; NR: not reported; PPD: purified protein derivative; PTB: pulmonary tuberculosis.

[a] Jacobs 1992 and van Toorn 2014 also reported cohorts of participants treated for 6 months, but did not provide disaggregated data on clinical features between both cohorts.

Table 6. Diagnosis of TBM: microbiological and other diagnostic characteristics in cohorts receiving more than six months ATT

Study	CSF				Other diagnostic methods for TB	Diagnostic classification	
	Cell count, protein and glucose content	Positive AFB smear	Positive culture	Other tests performed in CSF		Bacteriologically confirmed	Clinically diagnosed
Anastasatu 1993	NR	NR	NDD[a]	None	None	NDD[a]	NDD[a]
Doğanay 1995	NR	NR	NR	None	None	NR	NR
Iype 2014	NR	0/43	0/43	PCR: 2/4	Abdominal ultrasound, sputum smear microscopy. Findings not reported.	2/43	41/43 23 probable, 18 possible
Jacobs 1992 [b]	NR	2/33	5/35	None	Presence of a BCG vaccine scar in 28/53	7/53	46/53
Lau 2005	Reported	82/166 had AFB smear or culture positive	68/166	None	None	68/166	98/166 14 presumptive, 84 probable
Phuapradit 1987	Reported	NR	12/28	None	Discharge of otitis media with AFB	12/28	16/28
Ramachandran 1989	Reported	36/180	59/180	DST	None	83/180	97/180
Ramachandran 1997	NR	74/215[c]	88/215[c]	DST	None	101/215	114/215
Sharma 2013a	Reported	4/42	NR	ADA in 29 cases; PCR in 2 samples	Histology of 2 axillary lymph nodes	4/42	38/42
Török 2011a	Reported	65/545	166/545	DST	187 positive cultures of samples other than CSF	187/545	352/545 261 probable, 91 possible

Table 6. Diagnosis of TBM: microbiological and other diagnostic characteristics in cohorts receiving more than six months ATT *(Continued)*

van Toorn 2014 [b]	NR	NR	16/136	PCR for MTB in CSF 2 specimens[d]	Culture of gastric washings: 43/155	16/184	168/184
Visudhiphan 1989	NR	NR	13/40	DST	None	13/51	38/51

Abbreviations: ADA: adenosine deaminase activity; AFB: acid-fast bacillus; BCG: Bacillus Calmette–Guérin; CSF: cerebrospinal fluid; DST: drug sensitivity tests; NDD: no disaggregated data; NR: not reported; MTB: *Mycobacterium tuberculosis*; PCR: polymerase chain reaction; PPD: purified protein derivative; TBM: tuberculous meningitis.

[a]There were 30 positive cultures among 60 participants with severe forms of TB, with no disaggregated data for the 44 TBM cases.

[b] Jacobs 1992 and van Toorn 2014 also reported cohorts of participants treated for 6 months, but did not provide disaggregated data on CSF characteristics and diagnosis classification between the cohorts.

[c]Numbers of smear- and culture-positive participants seem to be incorrectly reported.

[d]The study authors stated that PCR was not done routinely, but did not report how many specimens were tested this way. The 2 positive PCR specimens were also culture positive.

Table 7. Findings from the Alvarez-Uria 2012 cohort

Duration of ATT	All	< 6 months	6 months[a]	> 6 months
Participant characteristics				
Number of participants	217	122	20	75
Mean age (years)	38.0	37.7	37.3	38.6
HIV-positive	217	122	20	75
Previous TB	45	25	1	19
Real duration of ATT received	In those who received 6 months or more: 8.6 months (259 days)	1.2 months (34.9 days)	6 months (196 days)	9.2 months (276 days) Range from 212 to 501 days
Outcomes at the end of ATT				
Cure	94 (43.3%)	0 (0%)	19 (95%)	75 (100%)
Default	30 (13.8%)	29 (23.8%)	1[b] (5%)	0 (0%)
Death	94 (43.3%)	93 (76%)	1 (5%)	0 (0%)
FU in survivors (from end of ATT)				
Lost to FU (0 days of FU after completing ATT)	7/123 (5.7%)	2/29 (6.9%)	1/19 (5.3%)	4/75 (5.3%)
Length of FU among survivors, mean (range)	22.9 months 687 days (9 to 1539 days)	12.4 months 372 days (9 to 1272 days)	30.5 months 915 days (66 to 1539 days)	25 months 750 days (30 to 1511 days)
Relapse	7/89 (7.9%)	NA[c]	0/18 (0%)	7/71[d] (9.9%)
Death	37/116 (31.6%)	18/27 (66.7%)	3/18 (16.7%)	16/71 (22.5%)
Total number of deaths	131/217 (60.4%)	111/122 (91%)	4/20 (20%)	16/75 (21.3%)

Note: we have presented the results based on complete-case analysis.
Abbreviations: ATT: antituberculous treatment; FU: follow-up; HIV: human immunodeficiency virus; NA: not applicable; TB: tuberculosis; TBM: tuberculous meningitis.
[a]We considered those participants treated between 180 and 209 days.
[b]One participant had previous TB, thus the planned ATT was 8-month regimen. The investigators classified this participant as a defaulter as he stopped ATT at 6 months.
[c]Relapse is defined as the number of participants who have new symptoms and signs of TBM after resolution of disease and completion of ATT. None of the participants receiving less than 6-month ATT completed their treatment. Therefore, we could not apply the term relapse to these participants. However, 5/27 participants who were defaulters and could be followed-up, presented new symptoms and signs of TBM after stopping ATT, and were retreated.
[d]We have presented the profile of these participants in Table 12.

Table 8. Six months ATT: relapse, death, and clinical cure

Study	Number of participants	Prolonged ATT	Losses to FU		Length of FU after ATT, in months	Relapse		Death from any cause	Death after 6 months ATT	Clinical cure
			During ATT	After ATT	Mean (range)	Number	Outcome			
Alarcón 1990	28	0/20	0/28	0/20	(18 to 30)	1/20	Death	9/28 (32.1%)	1/28 (3.6%)	20/28 (71.4%)
Biddulph 1990	43	NR	NDD	NDD	(up to 24)	1/38	Recovery	7/43 (16.3%)	2/43 (4.7%)	38/43 (88.4%)
Chotmongkol 1991	29	1/25	0/29[a]	0/29	16.3 (4 to 33)	0/25	NA	4/29 (13.8%)	0/29 (0%)	25/29 (86%)
Chotmongkol 1996	59	0/52	0/59	0/59	30 (16 to 45)	0/52	NA	7/59 (11.9%)	0/59 (0%)	52/59 (88.1%)
Donald 1998	95	3/82	0/95	12/82	12[b]	1/70	Recovery	15/95 (15.8%)	2/95 (2.1%)	82/95 (86.3%)
Jacobs 1992	45	NR	0/45	4/38	NDD[c]	0/34	NA	7/45 (15.6%)	0/45 (0%)	38/45 (84.4%)
van Toorn 2014	159	24/153	0/159	23/153	At least 24	0/130	NA	9/159 (5.7%)	3/159 (1.9%)	153/159 (96%)
Total	**458**	**28/332** (8.4%)	**0/415** (0%)	**39/381** (10.2%)	**Range 4 to 45**	**3/369** (0.8%)	**1 death 2 recoveries**	**58/458** (12.7%)	**8/458** (1.7%)	**408/458** (89.1%)

Abbreviations: ATT: antituberculous treatment; FU: follow-up; NA: not applicable; NDD: no disaggregated data; NR: not reported.
Note: we have presented these results based on complete-case analysis.
[a]The study authors reported 4 participants lost to follow-up and excluded them from their analyses. However, the study authors reported that these participants received 2, 2, 3, and 4 months of ATT respectively, and correspondence via letter after a mean period of 16.5 months indicated that all had fully recovery.
[b]Attempted length of follow-up. No data reported on the real follow-up of the survivors.
[c]Follow-up was available for at least 6 months after completion of ATT in 27/38 survivors, and for less than 6 months in 7/38.

Table 9. Six months ATT: default, poor adherence, treatment failure, and adverse effects

Study	Number of participants	Prolonged ATT	Losses to FU during ATT	Default	Poor adherence	Treatment failure	All adverse effects (number of events)	Drug toxicity leading to ATT discontinuation or modification
Alarcón 1990	28	0/28	0/28	0/28	NR	0/28	24	6/28
Biddulph 1990	43	NR	NDD	NDD	NR	NR	NDD	NDD
Chotmongkol 1991	29	0/25	0/29[a]	4/29[a]	NR	NR	1	1/29
Chotmongkol 1996	59	0/52	0/59	0/59	NR	NR	NR	NR
Donald 1998	95	3/82	0/95	0/95	NR	NR	32	6/95
Jacobs 1992	45	NR	0/45	NR	NR	NR	NR	0/45
van Toorn 2014	159	24/153	0/159	0/159	3/159	NR	NDD[b]	NDD[c]
Total	**458**	**28/332** (8.4%)	**0/415** (0%)	**4/370** (1.1%)	**3/159** (1.9%)	**0/28** (0%)	**57**	**13/197** (6.6%)

Abbreviations: ATT: antituberculous treatment; FU: follow-up; NDD: no disaggregated data; NR: not reported.
Note: we have presented these results based on complete-case analysis.
[a]The study authors reported that 4 participants were lost to follow-up and excluded them from their analyses. However, the study authors reported that these participants received 2, 2, 3, and 4 months of ATT respectively, and correspondence via letter after a mean period of 16.5 months indicated that all had fully recovered. All four participants fit the definition of defaulter.
[b]51 adverse effects were reported among the 184 participants recruited, without disaggregated data between those receiving 6 and 9 months of ATT.
[c]ATT was discontinued in 17/184 participants, without disaggregated data between participants receiving 6 or 9 months of ATT.

Table 10. More than six months ATT: relapse, death, and clinical cure

Study	Duration of ATT (months)	Number of participants	Prolonged ATT	Losses to FU		Length of FU after ATT, in months	Relapse		Death from any cause	Death after 6 months ATT	Clinical cure
				During ATT	After ATT	Mean (range)	Number	Outcome			

Table 10. More than six months ATT: relapse, death, and clinical cure *(Continued)*

Anastasatu 1993	9	19	NR	2/19[a]	0/17[a]	60[b]	0/17	NA	0/19 (0%)	0/19 (0%)	17/17 (100%)
	12	25	NR	3/25[a]	0/22[a]	60[b]	0/22	NA	0/25 (0%)	0/25 (0%)	22/22 (100%)
Doğanay 1995	8	37	2/25	7/37	7/55	Median 10 (6 to 24)	0/48	NA	5/37 (13.5%)	0/37 (0%)	25/30 (83.3%)
	12 to 16	35	0/30	3/35		Median 13 (4 to 36)			2/35 (5.7%)	0/35 (0%)	30/32 (93.8%)
Iype 2014	9	47	2/35	2/47	0/35	Median 5.2 (3.4 to 9.8)	1/35	Recovery	10/47 (21.3%)	1/47 (2.1%)	35/45 (77.8%)
Jacobs 1992	9	4	NR	0/4	NR	NR	NR	NA	2/4 (50%)	NDD[c]	2/4 (50%)
	12	4	NR	0/4	NR	NR	NR	NA	2/4 (50%)	NDD[c]	2/4 (50%)
Lau 2005	Mean 11.53	166	Individualised for all	10/166	0/133	At least 24	0/133	NA	26/166 (15.7%)	NDD[d]	133/156 (85.3%)
Phuapradit 1987	9	28	1/23	3/28[e]	1/23	19.8 (12 to 29)	0/22	NA	2/28 (7.1%)	2/28 (7.1%)	23/25 (92%)
Ramachandran 1989	12	180	23/119	14/180	2/119	(42 to 84)	0/117	NA	64/180 (35.6%)	19/180 (10.6%)	119/166 (71.7%)
Ramachandran 1997	9	215	9/137	29/215[f]	0/137	51[b]	3/128	1 death 2 recoveries	69/215 (32%)	12/215[g] (5.6%)	137/186 (73.7%)

Table 10. More than six months ATT: relapse, death, and clinical cure *(Continued)*

Sharma 2013a	9	42	0/35	0/42	0/35	6[b]	0/35	NA	7/42 (16.7%)	NR	35/42 (83%)
Török 2011a	9	545	NR[h]	10/545	40/336	Median 53.4 (IQR 47.4 to 57)	3/296[i]	3 recoveries	249/545 (45.7%)	NDD[j]	336/535 (62.8%)
van Toorn 2014	9	25 HIV-positive and isoniazid-resistant	4/24	0/25	6/24	At least 24	0/18	NA	6/25 (24%)	5/25 (20%)	24/25 (96%)
Visudhiphan 1989	12	51	0/44	4/51	0/44	(18 to 84)	0/44	NA	3/51 (5.9%)	0/51 (0%)	44/47 (93.6%)
Total	**8 to 16**	**1423**	**32/472 and 166 individualized ATT**	**87/1423** (6.1%)	**56/985** (5.7%)	**Range 6 to 84**	**7/915** (0.8%)	**1 death 6 recoveries**	**447/1423** (31.4%)	**39/662** (5.9%)	**984/1336** (73.7%)

Abbreviations: ATT: antituberculous treatment; FU: follow-up; HIV: human immunodeficiency virus; IQR: interquartile range; NA: not applicable; NDD: no disaggregated data; NR: not reported.

Note: we have presented these results based on complete-case analysis.

[a]There were 5 participants (2 in the 9-month group, 3 in the 12-month group) lost to follow-up at the end of the 5 years follow-up. No results were reported for these 5 participants, and it is unclear when they left the trial and what their outcomes were.

[b]Attempted length of follow-up. No data reported on the real follow-up of the survivors.

[c]Data could not be disaggregated by time until death. There were 7 deaths in the 6-month group, 2 in the 9-month group, and 2 in the 12-month group; the study authors stated that over 90% of deaths occurred within the first 3 months of treatment in this study.

[d]There were at least 3 deaths after six months of ATT. Indeed, three participants died in the second year from the start of ATT, due to nasopharyngeal carcinoma, acquired immune deficiency syndrome and chronic obstructive pulmonary disease. There were no disaggregated data among the deaths occuring within the first 12 months to report those occuring between the sixth and twelfth months from the start of ATT.

[e]Three participants with poor compliance dropped out during the early stage of ATT and could not be followed-up. One participant developed erythema multiform and had treatment suspended, then restarted with RHS. Another participant completed ATT but was lost to follow-up afterwards.

[f]Ten out of these 29 participants received modified ATT regimens with unknown reason, and the study authors excluded them from analysis.

[g]Ten participants discharged against medical advice died.

[h]143 participants received altered ATT regimen due to adverse events. It is unknown whether these participants received prolonged ATT.

[i]These 3 participants were re-treated for TB. It is unclear whether they were re-treated because of TBM relapse or because of presenting another form of TB.

jThere were 50 deaths reported among the 296 survivors who completed the 9-month treatment. We do not know if there were additional number of death between the sixth and ninth month of ATT, due to a lack of data reporting. The study authors could not determine how many of these deaths could be attributed to relapse.

Table 11. More than six months ATT: default, poor adherence, treatment failure, and adverse effects

Study	Duration of ATT (months)	Number of participants	Prolonged ATT	Losses to FU during ATT	Default	Poor adherence	Treatment failure	All adverse effects (number of events)	Drug toxicity leading to ATT discontinuation or modification
Anastasatu 1993	9	19	NR	2/19[a]	NR	NR	0/17	NR	NR
	12	25	NR	3/25	NR	NR	0/22	NR	NR
Doğanay 1995	8	37	2/25	7/37	0/30	NR	1/30[b]	6	12/62
	12 to 16	35	0/30	3/35	2/32	NR	1/32	8	
Iype 2014	9	47	2/35	2/47	2/45	NR	4/45[c]	4	1/45
Jacobs 1992	9	4	NR	0/4	NR	NR	NR	NR	0/4
	12	4	NR	0/4	NR	NR	NR	NR	0/4
Lau 2005	Mean 11.53	166	Individualised for all	10/166	0/156	0/156	NR	58	0/156
Phuapradit 1987	9	28	1/23	3/28[d]	4/25	NR	NR	21	1/25
Ramachandran 1989	12	180	23/119	14/180	NR	NR	NR	37	37/174
Ramachandran 1997	9	215	0/137	29/215[e]	NR	NR	NR	18	18/205
Sharma 2013a	9	42	0/35	0/42	0/42[f]	NR	NR	3	0/42
Török 2011a	9	545	NR[g]	10/545	NR	NR	89/535	400	143/535
van Toorn 2014	9	25 HIV-pos and H-resistant	4/24	0/25	0/25	0/25	NR	NDD[h]	NDD[i]

Table 11. More than six months ATT: default, poor adherence, treatment failure, and adverse effects *(Continued)*

Visudhiphan 1989	12	51	0/44	4/51	NR	NR	NR	12	4/47
Total	**8 to 16**	**1423**	**32/472 and 166 individualized ATT**	**87/1423** (6.1%)	**8/355** (2.3%)	**0/181** (0%)	**95/681** (14.0%)	**567**	**216/1299** (16.6%)

Abbreviations: ATT: antituberculous treatment; FU: follow-up; H: isoniazid; HIV: human immunodeficiency virus; mo: months; NDD: no disaggregated data; NR: not reported.
Note: we have presented these results based on complete-case analysis.

[a]There were 5 participants (2 in the 9-month group, 3 in the 12-month group) lost to follow-up at the end of the 5 years follow-up. No results were reported for these five participants, and it is unclear when they left the trial and what their outcomes were.

[b]This study described 1 participant in the 8-month ATT group as having treatment modified due to "inadequate clinical response", and 1 participant in the 12- to 16-month ATT group as dying in the fifth month of treatment due to "therapeutic failure".

[c]Four participants developed treatment failure, 3 during the fourth month of ATT, and 1 during the ninth month (who had concurrent pulmonary TB with proven isoniazid resistance). Three of these 4 participants died.

[d]Three participants with poor compliance dropped out during the early stage of ATT and could not be followed-up. One participant developed erythema multiform and had treatment suspended, then restarted with RHS. Another participant completed ATT but was lost to follow-up afterwards.

[e]Ten out of these 29 participants received modified ATT regimens with unknown reason, and the study authors excluded them from analysis.

[f]The study authors stated that out of the 42 participants, 35 completed ATT, and 7 died. It is very likely that there was no defaulters, although this outcome was not clearly stated.

[g]143 participants received altered ATT regimen due to adverse events. It is unknown whether these participants received prolonged ATT.

[h]51 adverse effects are reported among the 184 participants, without disaggregated data between participants receiving 6 or 9 months of ATT.

[i]ATT was discontinued in 17/184 participants, without disaggregated data between participants receiving 6 or 9 months of ATT.

Table 12. Profile of participants who relapsed after completing ATT

Studies	Gender, age (years)	Duration of ATT received (months)	Time between end of ATT and relapse	Outcome	Comments
Six months ATT					
Alarcón 1990	Female, 34	6	3 months	Death	Disease severity: stage III when first diagnosed
Biddulph 1990	Male, 1	6	2 months	Recovery	Disease severity: stage I at relapse It is unclear whether or not this participant missed doses in the continuation phase of treatment, but the study authors reported that missed doses were made up in all participants.
Donald 1998	Female, 11	6	3 weeks	Recovery	Disease severity: stage I when first diagnosed, and stage II at relapse During the first course of ATT, Eth was stopped and the dosage of H and R halved to 10 mg/kg and Z halved to 20 mg/kg due to poor appetite and nausea after 3 months of treatment.
More than six months ATT					
Iype 2014	Male, adult	9	3 months	Recovery	-
Ramachandran 1997	Child	9	3 months	Death	Positive CSF culture, fully sensitive on DST at initial diagnosis and relapse. Mild sequelae at the end of first course of ATT. Treated with 'intensive therapy' for 9 months, died 10 months after completing the second ATT regimen despite having normal CSF analysis and negative CSF cultures.
	Child	9	2 months	Recovery	Positive CSF culture, fully sensitive on DST at initial diagnosis and relapse. Mild sequelae at the end of first course of ATT.
	Child	9	13 months	Recovery	Abnormal CSF and positive CSF culture, resistant to H and S on DST at initial diagnosis and relapse. Moderate sequelae at the end of first course of ATT.
Török 2011a	Adult	9	NR	Recovery	At five-year follow-up, these three participants self-reported re-treatment for TB. It is unclear whether this was for TBM or another form of TB.
	Adult	9	NR	Recovery	
	Adult	9	NR	Recovery	

Table 12. Profile of participants who relapsed after completing ATT *(Continued)*

Additional cohort					
Alvarez-Uria 2012	Male, 32, HIV-positive	8.4	10 months	Recovery	This participant had previous TB
	Male, 65, HIV-positive	9.1	24 months	Death	-
	Male, 31, HIV-positive	9.6	8 months	Recovery	This participant was cure after completing ATT for relapse. However, he died 12 months after completing the second ATT regimen.
	Male, 32, HIV-positive	9.8	31 months	Recovery	This participant had previous TB
	Male, 32, HIV-positive	9.9	5 days	Recovery	This participant had previous TB
	Male, 45, HIV-positive	10	20 months	Death	-
	Male, 13, HIV-positive	10.9	16 months	Recovery	-

Abbreviations: ATT: antituberculous treatment; CSF: cerebrospinal fluid; DST: drug sensitivity tests; Eth: ethinamide; H: isoniazid; HIV: human immunodeficiency virus; R: rifampicin; TB: tuberculosis; Z: pyrazinamide.

Table 13. Causes of deaths after six months ATT

Study	Length of treatment (months)	Deaths after 6 months ATT	Number of these deaths attributed to:			
			Relapse	Complications of TBM[a]	Non TB causes	Unknown
Six months ATT						
Alarcón 1990	6	1	1	0	0	0
Biddulph 1990	6	2	0	2	0	0
Donald 1998	6	2	0	2	0	0
van Toorn 2014	6	3	0	2	0	1
More than six months ATT						
Iype 2014	9	1	0	0	0	1
Phuapradit 1987	9	2	0	2	0	0
Ramachandran 1997	9	12	1	6	4	1
Török 2011a	9	50[b]	0	0	0	50

Table 13. Causes of deaths after six months ATT *(Continued)*

van Toorn 2014	9	5	0	4 (HIV infection or post-TBM complications)		1
Lau 2005	11.53 (mean)	3[c]	0	0	3	0
Ramachandran 1989	12	19	0	12	7	0

Abbreviations: ATT: antituberculous treatment; HIV: human immunodeficiency virus; mo: months; TB: tuberculosis; TBM: tuberculous meningitis.
[a]Death due to TBM complications can occur at any point in the course of treatment regardless of treatment duration, even after microbiological cure has been achieved. The complications leading to deaths reported in the included studies were all related to severe neurological sequelae.
[b]There were 50 deaths reported among the 296 survivors who completed the nine-month treatment. We do not know if there were additional number of death between the sixth and ninth month of ATT, due to a lack of data reporting. Authors could not determine how many of these deaths could be attributed to relapse.
[c]Three participants died in the second year from the start of ATT, due to nasopharyngeal carcinoma, acquired immune deficiency syndrome, and chronic obstructive pulmonary disease. There were no disaggregated data among the deaths occuring within the first 12 months to report those occuring between the sixth and twelfth months from the start of ATT.

Table 14. Adverse events

Study ID	Number of adverse events		Description of adverse events
	Related to ATT (events)	Leading to ATT discontinuation (participants)	
Six months ATT			
Alarcón 1990	24	6/28	• Elevation in ALT/AST/alkaline phosphatase/bilirubin: 15, leading to discontinuation of treatment with H/R and substitution with S for 3 to 7 days in 4 participants. • Hyperuricaemia leading to 3-day suspension of Z in 2 participants. • Gastrointestinal symptoms 3 participants. • Arthralgia 2 participants. • Dizziness with nystagmus 1 participant. • Rash 1 participant.
Biddulph 1990	NDD	NDD	15/639 TB cases had problems with the drug prescribed, but NDD for TBM.
Chotmongkol 1991	1	1/29	• 1 severe hepatitis due to H. ATT was continued with R and E for 18 months with full recovery. • No other adverse events reported.
Chotmongkol 1996	NR	NR	• Gastrointestinal bleeding or hyperglycemia was not observed as complications of prednisolone therapy. • Adverse events were assessed and recorded; but results not reported.
Donald 1998	32	6/95	• Nausea and vomiting leading to stopping of Eth and reduction of RH doses. This case relapsed and was successfully re-treated with HRZEth at full doses.

Table 14. Adverse events *(Continued)*

			• Hepatotoxicity:
			  ○ 10 mild elevation of bilirubin leading to substitution of HRZEth with SE in 5 children, who were then re-started on HRZEth when liver function normalised in 2 to 3 weeks;
			  ○ 13 mild and transient elevation of ALT/AST, without treatment interruption.

Six and more than six months ATT			
Jacobs 1992	NR	0/45	NR
	NR	0/4	NR
	NR	0/4	NR

van Toorn 2014	51	17/184	• Anti-TB drug-induced hepatotoxicity (ADIH):
			  ○ Grade 1 (mild) ALT 51 to 125 U/L: 18/184;
			  ○ Grade 2 (mild) ALT 126 to 250 U/L: 6/184; ATT changed to liver-friendly regimens;
			  ○ Grade 3 (moderate) ALT 251 to 500 U/L: 6/184; ATT changed to liver-friendly regimens;
			  ○ Grade 4 (severe) ALT > 500 U/L: 2/184; ATT changed to liver-friendly regimens.
			
			In all ADIH cases from grade 2 severity, change to liver-friendly regimens resulted in normalization of liver enzymes (medium duration 7 days, range 3 to 16 days) and the original regimen was restarted (stepwise) without recurrence.
			
			• Significant nausea and vomiting: 19/184
			
			Eth was substituted with E in 3 cases, solving the problem. In the remaining 16 cases, administration of Eth at night solved the problem.
			
			Of these 19 participants, 8 had drug-induced hepatotoxicity and 11 had normal liver function. In these 11 either substituting Eth for E or giving Eth at night resolved the nausea and vomiting.

More than six months ATT			
Anastasatu 1993	NR	NR	NR
Doğanay 1995	6	12/72	• 2 nausea and vomiting. • 10 toxic hepatitis with a moderate increase in hepatic enzyme levels. HR were discontinued in these cases for a short time (3 to 5 days) and after recovery, reinstituted. • 2 hearing loss. S was stopped.
	8		
Iype 2014	12	1/43	• 8 paradoxical reactions (increased size of tuberculoma or development of new tuberculoma, 2 died) • 4 hepatitis: 1 at the end of 1st month; 2 at 4 months; 1 at 7 months. One case of hepatitis led to discontinuation of ATT at 124 days.
Lau 2005	58	0/166	Skin rash, hearing difficulty, impaired liver function with elevated ALT, and blurring of vision.

Table 14. Adverse events *(Continued)*

Phuapradit 1987	21	1/28	• 6 participants with 2 to 3-fold elevation of ALT/AST ± alkaline phosphatase level (no discontinuation of ATT) during the early weeks of treatment. • 14 participants with asymptomatic hyperuricemia (90 to 140 mg/L) during the first 2 months of ATT when Z was given, 8 received probenecid. • 1 erythema multiforme from Z. All drugs were discontinued. After rashes healed, ATT was continued with HRS with full recovery.
Ramachandran 1989	37 (36*)	37 (36*)/180	• 4 cases according to the 1989 publication (*3 cases according to the 1986 publication) with ocular complications: ethambutol was discontinued and PAS substituted, even though it was clear that the problem was unrelated to drugs. • 30 jaundice: R (first study) or both RZ (second and third studies) were discontinued while the other drugs were continued. • 2 skin reactions: R was stopped in 1 participant and the participant recovered completely; all anti-tuberculosis drugs were withheld for 1 week in the other participant and the participant recovered fully. The treatment was resumed uneventfully. • 1 arthralgia: Z was stopped and the swelling diminished during the next 3 weeks. He could not be followed up further as he died of TBM.
Ramachandran 1997	18	18/215	13 participants developed jaundice with abnormal liver function tests 5 participants had an increase in hepatic enzymes levels without clinical jaundice For these 15 participants: R and Z were terminated and other drugs were continued.
Sharma 2013a	3	0/42	• 1 drug-induced hepatitis causing death. • 2 participants with clinical jaundice and persistent vomiting who were converted to daily regimen. • No other adverse events reported.
Török 2011a	400	155/545	329 non-severe; 71 severe • Subclinical hepatitis: 92 non-severe; 0 severe. • Clinical hepatitis: 9 non-severe; 8 severe. • Gastrointestinal bleeding: 10 non-severe; 5 severe. • Bacterial sepsis: 12 non-severe; 7 severe. • Septic shock: 0 non-severe; 3 severe. • Brain herniation syndrome: 0 non-severe; 5 severe. • Decrease in visual acuity: 16 non-severe; 14 severe. • Hyponatremia: 11 non-severe; 7 severe. • Hyperglycaemia: 5 non-severe; 0 severe. • Hypertension: 5 non-severe; 0 severe. • Vertigo: 39 non-severe; 0 severe. • Deafness: 8 non-severe; 6 severe. • Cushing's features: 12 non-severe; 0 severe. • Pruritus: 12 non-severe; 0 severe. • Polyarthralgia: 5 non-severe; 0 severe.

Table 14. Adverse events *(Continued)*

			• Streptomycin reaction: 4 non-severe; 0 severe. • Rifampin flu: 7 non-severe; 0 severe. • Rash: 13 non-severe; 1 severe. • Other (other events that were reported fewer than 4 times): 76 non-severe; 15 severe. ATT was stopped or modified in 143 participants.
Visudhiphan 1989	12	4/51	• 4 participants: elevation of serum AST/ALT levels à rifampicin dose decreased to 10 mg/kg/day in 3 participants, and to 8 mg/kg/day in the 4th participant. • 8 participants with mild gastrointestinal disturbances.

Abbreviations: ALT: alanine transaminase; AST: aspartate transaminase; ATT: antituberculous treatment, E: ethambutol; Eth: ethionamide; H: isoniazid; HIV: human immunodeficiency virus; NDD: no disaggregated data; NR: not reported; R: rifampicin; Z: pyrazinamide

APPENDICES

Appendix 1. Recommendations of antitubercular regimens for TBM according to different guidelines

Guidelines and local practices	Intensive phase		Continuation phase	
	Drugs	Duration (months)	Drugs	Duration (months)
WHO Guidelines. Treatment of tuberculosis (WHO 2010a)	HRZS	2	HR	7 to 10
WHO Rapid advice. Treatment of tuberculosis for children (WHO 2010b)	HRZE	2	HR	10
TB CARE I 2014 [a]	HRZE	2	HR	4
European Union Standards for Tuberculosis Care (Migliori 2012)[a]	HRZE	2	HR	4
British Infectious Society Guidelines (Thwaites 2009)	HRZE	2	HR	10
NICE 2011	HRZ + 4th drug (for example, E)	2	HR	10
Clinical Practical Guideline on the Diagnosis, Treatment and Prevention of Tuberculosis. The Spanish Guideline (CPG 2009)	HRZE	2	HR	10
SEIP 2008	HRZE (or HRZS or HRZA)	2	HR	10
American Thoracic Society 2003	HRZE	2	HR	7 to 10

(Continued)

Technical and Operational Guidelines for Tuberculosis Control, India (RNTCP 2005)	HRZS	2	HR	6 to 7
National Guidelines on diagnosis and treatment of pediatric tuberculosis, India (RNTCP 2012)	HRZE	2	HR	7[b]
Department of Health South Africa 2014	HRZE	2	HR	7
Local official practice in Cape Town, South Africa (van Toorn 2014)	HRZEth	6	—	0
IUATLD 2010 [a]	HRZE	2	HR	4

Abbreviations: A: amikacin; E: ethambutol; Eth: ethionamide; H: isoniazid; R: rifampicin; S: streptomycin, Z: pyrazinamide; WHO: World Health Organization; TB: tuberculosis; TBM: tuberculous meningitis.
[a]General recommendations for TB treatment. There is no specific mention regarding TBM treatment.
[b]A further extension may be done for 3 more months on a case-to-case basis in case of delayed response and as per the discretion of the treating physician.

Appendix 2. Detailed search strategy

Medline (Pubmed)

Search	Query
#26	Search (#25) AND #12 Field: Title/Abstract
#12	Search (#11) OR #9 Field: Title/Abstract
#25	Search (#24) OR #23 Field: Title/Abstract
#23	Search "Prospective Studies"[mesh] Field: Title/Abstract
#24	Search ((((#20) OR #19) OR #18) OR #15) OR #14 Field: Title/Abstract
#14	Search "Cohort Studies"[Mesh] Field: Title/Abstract
#18	Search "Controlled Clinical Trial" [Publication Type] Field: Title/Abstract
#15	Search cohort Field: Title/Abstract
#19	Search "Randomized Controlled Trial" [Publication Type] Field: Title/Abstract
#20	Search Random* or placebo* or "single blind*" or "double blind*" or " triple blind* " Field: Title/Abstract
#22	Search "Prospective Studies"[Majr] Field: Title/Abstract
#9	Search (#8) AND #7 Field: Title/Abstract
#11	Search "Tuberculosis, Meningeal"[Majr] Field: Title/Abstract
#8	Search Brain OR mening* OR cerebral OR neurological Field: Title/Abstract

(Continued)

#7	Search (#6) OR "Tuberculosis"[Majr] Field: Title/Abstract
#6	Search tubercul* Field: Title/Abstract
#3	Search "Tuberculosis"[Majr]

Embase (OVID)

Search	Query
1	tuberculosis/
2	limit 1 to human
3	tubercul*.ab. or tubercul*.ti.
4	limit 3 to human
5	2 or 4
6	(Brain or mening* or cerebral or neurological).ab. or (Brain or mening* or cerebral or neurological).ti.
7	5 and 6
8	tuberculous meningitis/
9	limit 8 to human
10	7 or 9
11	cohort analysis/
12	prospective study/
13	controlled clinical trial/
14	randomized controlled trial/
15	11 or 12 or 13 or 14
16	(Random* or placebo* or single blind* or double blind* or triple blind*).ab. or (Random* or placebo* or single blind* or double blind* or triple blind*).ti.
17	15 or 16)
18	10 and 17

Cochrane library

ID Search Hits

Search	Query
#1	tubercul* ti,ab,kw (Word variations have been searched)
#2	MeSH descriptor: [Tuberculosis] explode all trees
#3	Brain or mening* or cerebral or neurological:ti,ab,kw (Word variations have been searched)
#4	#1 or #2
#5	#3 and #4
#6	MeSH descriptor: [Tuberculosis, Meningeal] explode all trees
#7	#5 or #6

LILACS, INDMED, South Asian Database of controlled trials, WHO ICTRP, Clinicaltrials.gov, ProQuest Dissertations and theses, openSigle:

Tuberculosis AND meningitis

Tuberculosis AND brain

Tuberculosis AND cerebral

FEEDBACK

Maria-Inti Metzendorf, 8 February 2017

Summary

I would like to draw your attention to an error in the abstract of a recently published review of your group ("Six months therapy for tuberculous meningitis", CD012091).

In the abstract 16 included studies are reported, but in the main results, COIS table and flowchart there are actually 18 included studies. And in the plain language summary 19 included studies are reported.

Reply

We appreciate these helpful and detailed comments. We have checked through these carefully, and responded to the key points. We clarified the number of included cohorts and studies throughout the review text, and added a reference to the ongoing studies section (NCT02454569). Included are 13 prospective cohorts, one unpublished ongoing study, and a total of 2098 participants. We have also clarified that there are actually 20 cohorts across the 18 studies.

The CIDG editorial team republished the review with all the corrected data as an amendment.

Contributors

Sophie Jullien, Hannah Ryan

WHAT'S NEW

Date	Event	Description
19 September 2017	Amended	We received comments on this review in February 2017. The review authors have responded to the queries in the appropriate 'Feedback' section of this review.

Date	Event	Description
19 September 2017	Feedback has been incorporated	Feedback received and responded to. This related to correcting the number of included studies and cohorts. Details are noted in the 'Feedback' section. The CIDG editorial team published the review with all the corrected data as an amendment.

CONTRIBUTIONS OF AUTHORS

SJ and HR assessed the eligibility of the studies, extracted the data and assessed the methodological quality of the included studies. SJ drafted the text with input from HR. RB and MM gave input to the final draft. All authors read and approved the final version of the review.

DECLARATIONS OF INTEREST

SJ and HR are employed by the CIDG, which is funded by a grant from the UK Government DFID.

SJ and HR conducted the preliminary work that contributed to the conception and design of this Cochrane Review as part of the evidence review process for the Indian Extra-Pulmonary TB (INDEX-TB) Guidelines, a guideline for extrapulmonary TB commissioned by the Ministry of Health and Family Welfare, Government of India. Global Health Advocates funded this guideline, and the All India Institute of Medical Sciences, New Delhi convened it.

RB and MM were part of the technical advisory group on central nervous system TB and took part in discussions that led to the recommendations in the INDEX-TB Guidelines.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.
- All India Institute of Medical Sciences, New Delhi, India.

External sources

- Department for International Development (DFID), UK.

  Grant: 5242

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We included studies when most of the participants were followed-up for at least six months after completing antituberculous treatment (ATT).

We reported on drug toxicity leading to discontinuation or modification of the treatment regimen rather than to discontinuation only.

We anticipated in our protocol that there would be no studies with a direct comparison between short and prolonged ATT, and that it would therefore be inadequate to assess the risk of bias of the included studies with the Cochrane 'Risk of bias' assessment tool (Higgins 2011), and the Downs and Black checklist for assessment of methodological quality (Downs 1998). We mentioned in the protocol that instead, to assess the risk of bias of the single-arm cohort studies, we would assess different items for each outcome: study design, how the participants were selected, the way the participants were selected, etc. In our review, we have devised a 'Risk of bias' assessment tool to appraise the reliability of the outcome data from each study, based on the domains included in the ACROBAT-NSRI tool (Sterne 2016). We believe that this was a more reliable way to assess risk of bias, and the used tool actually includes the items we mentioned in our protocol.

We stated in our protocol that we would calculate the risk ratio (RR) for dichotomous outcomes and the rate ratio for count data outcomes, and that we would present the effect estimates with 95% confidence intervals (CIs). This was not possible, as we did not find any trials that directly compared short versus prolonged course regimens. Therefore, we presented the findings separately from each group of cohorts.

We did not use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) principles to assess the quality of the evidence as originally planned, because this was not possible as already explained in the review. Instead, we assessed the quality of the evidence descriptively.