INDEX-TB GUIDELINES

Evidence Summaries and Guideline Panel Decision Tables
Core Group Guideline Meeting
14-18 July 2015

This document contains

- The systematic reviews and GRADE assessments used at the Index-TB Guideline Panel in July 2015
- The Evidence to Decision tables that record the Panel's assessment and recommendations from this meeting

The main guidelines are documented in:

Ministry of Health and Family Welfare. Index-TB Guidelines: guidelines on extra-pulmonary tuberculosis for India. Central TB Division: World Health Organization Country Office for India, 2016.

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INDEX-TB

Evidence Summaries and Guideline Panel Decision Tables

Contents

Background and methods

This annex contains the evidence summaries commissioned for the INDEX-TB Guidelines in 2015 and the evidence to decision tables summarising the INDEX-TB Guideline Group discussion on each recommendation.

The evidence summaries are derived from existing systematic reviews updated for the meeting, and other new reviews prepared rapidly to meet the needs of the guideline development process. Where appropriate, formal Cochrane reviews, which are lengthy pieces of research, have subsequently been initiated to address some of the objectives identified during this process, and will be available via the Cochrane Library upon completion.

The topics covered are:

- Use of Xpert MTB/RIF
    - For the diagnosis of LNTB
    - For the diagnosis of TB meningitis
    - For the diagnosis of pleural TB
- Use of corticosteroids
    - To treat TB meningitis
    - To treat TB pericarditis
    - To treat TB pleurisy
- Duration of anti-tuberculous treatment
    - For LNTB
    - For abdominal TB
    - For TB meningitis

For each of these topics, we present the evidence summary and GRADE table, and the evidence to decision sheet for the recommendation agreed by the INDEX-TB Guidelines panel in July 2015.

Synthesis methods outline

For the systematic reviews conducted for this guideline we followed rigorous and transparent methods in line with the Cochrane Handbook for Systematic Reviews of Interventions (Higgins, 2011). If there were existing Cochrane reviews, we updated them.

Criteria for including studies

For each systematic review, we specified the types of studies, participants, interventions and comparisons, outcome measures and adverse events for studies to be included in the review.

Search methods for identification of studies

We attempted to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and in progress). We specified which databases were searched for relevant studies, with the date of the search. The search strategies combined both text words and MeSH/EMTREE terms for each record identified.

The search terms and strategies used in each systematic review are outlined in boxes or tables.

Data collection and analysis

Selecting studies for inclusion

Two investigators each independently evaluated the studies identified by the search for eligibility for inclusion using a form based on the inclusion criteria.

Excluded studies, together with the reasons for exclusion, are summarized in tables at the end of the document.

Data extraction and analysis

Two investigators independently extracted data from the included studies according to an agreed data extraction tool.

Assessment of risk of bias

Each study was assessed for risk of bias using the Cochrane Risk of Bias Tool (Higgins, 2011). This tool assesses random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). The results of the assessment were summarized in risk of bias tables, with supporting evidence from the study reports, and are summarized in figures for each systematic review.

Assessment of heterogeneity

We assessed heterogeneity by visually inspecting the forest plots. We used the Chi^2 test with a P value of 0.10 to indicate statistically significant heterogeneity, and the I^2 statistic to quantify heterogeneity with a value of 50% taken to indicate substantial statistical heterogeneity.

Data synthesis

We summarized data extracted from each study in tables. We used Review Manager 5 to analyze the data, using risk ratio and risk difference when appropriate to assess the effect of estimates, with 95% confidence interval (Review Manager 5, 2014). Meta-analysis was conducted if appropriate. We assessed the quality of the evidence using the GRADE approach (Guyatt, 2011).

Presentation of results

For each systematic review:

- The results of the search and screening are shown in a flow diagram.
- The studies included are described in tables – characteristics of included studies.
- The risk of bias assessment for included studies.
- The forest plots are presented with the results of the meta-analysis if conducted.
- The summary of findings table shows the relative effects estimates, and the outcome of the GRADE assessment.

Evidence to decision making methods

These followed GRADE procedures of transparency and good guideline development. After presentation of the review results and a full discussion about values and preferences, the evidence to decision tables were used to facilitate consensus and record the decision of the guideline panel. Recommendations were made where possible, and graded as “strong” or “conditional” using the criteria outlined in the main guidelines document.

Xpert MTB/RIF for EPTB

Background

At the first meeting of the INDEX-TB guidelines group at AIIMS in March 2015, all the technical advisory committees identified the Xpert MTB/RIF test as a priority topic for evidence review.

Xpert MTB/RIF is a commercially available diagnostic test for MTB that uses polymerase chain reaction (PCR) to test specimens for genetic material specific to MTB, and simultaneously detects a gene that confers resistance to rifampicin, *rpoB* (Blakemore, 2010). Unlike other commercial PCR-based tests, it is a fully automated test using the GeneXpert® platform. The specimen is loaded into a cartridge and all the steps in the assay are then fully automated and contained within the unit. One of the reagents is powerfully tuberculocidal, making the used test cartridges safe to handle outside of a specialist laboratory environment. This allows the test to be brought closer to the clinical setting.

Xpert MTB/RIF was originally designed to test sputum samples from patients with active pulmonary tuberculosis, and has been shown to have high accuracy for diagnosing TB in these patients (Steingart, 2014). Since its introduction to research settings in 2010, several investigators have tested the accuracy of this test in non-respiratory samples for the diagnosis of various forms of EPTB. There are several *a priori* reasons the Xpert MTB/RIF may perform differently with non-sputum samples: Xpert MTB/RIF has a specimen treatment step which is designed to liquefy sputum but this may not be optimum pre-test processing for non-sputum samples; although the test has a limit of detection of 131 colony forming units per mL, it has been shown to perform less well in paucibacillary disease; as many forms of EPTB require invasive sampling methods, the size and quality of the specimens may affect the sensitivity of the test.

The Ministry of Health and Family Welfare has engaged with international partners to roll out Xpert MTB/RIF for the diagnosis of pulmonary TB as part of the RNTCP. Members of the INDEX-TB technical advisory subcommittees have recognised the need for evidence-informed guidance on the use of Xpert MTB/RIF for the diagnosis of EPTB in the country, to promote prudent use of the test for improved patient outcomes. The following evidence summary is intended for the consideration of the INDEX-TB guideline panel for the purpose of making recommendations that are evidence-informed, practical and appropriate.

Objectives

To present summary estimates of diagnostic accuracy of Xpert MTB/RIF for various forms of EPTB by specimen type compared with conventional culture methods and with a composite reference standard.

To appraise the quality of this evidence, and its applicability to clinical settings in India.

Methods

A new systematic review with meta-analysis was not feasible within the timescale dictated by the guideline process, therefore the methodology support team reviewed the literature for the most recent systematic reviews addressing the diagnostic accuracy of Xpert MTB/RIF in EPTB. We then performed a new search using the search strategy outlined in Box 1 to find new diagnostic test accuracy studies of Xpert MTB/RIF for EPTB, and screened them using the same criteria as the chosen systematic review (Denkinger, 2014).

Box 1. Detailed search strategy for Xpert MTB/RIF in EPTB

A search of Medline and Embase was performed using the terms below October 2013 to April 2015:

(extrapulmonary OR pleur* OR mening* OR pericard* OR lymph* OR extra-pulmon*)

AND

(tuberculosis OR TB OR mycobacter*)

AND

Xpert MTB* OR GeneXpert OR Cepheid

Results

We found three systematic reviews published reviewing the evidence for the diagnostic accuracy of Xpert MTB/RIF in EPTB: (Denkinger, 2014), (Maynard-Smith, 2014), (Penz, 2015). Of the three, only one (Denkinger, 2014) included only extrapulmonary specimens, with data disaggregated for specimen type and condition of interest. Assessment of this review using the AMSTAR tool (Shea, 2007) showed it to be a high-quality systematic review. We therefore used the results of the meta-analysis from this review to supply pooled estimates for the sensitivity and specificity for Xpert MTB/RIF for three important forms of EPTB: lymph node TB (LNTB), TB meningitis and pleural TB.

A search covering October 2013 to April 2015 found 68 results after removal of duplicates. These were screened and categorised as per Figure 1. The panel looked through these results when considering the Summary of Findings table. When reviewed qualitatively, the results of the new studies did not appear to substantially deviate from findings of the meta-analysis, so the panel felt confident in considering the meta-analysis data from Denkinger 2014 formally when making recommendations for each test.

The results of the original systematic review are presented in Figures 2, 3 and 4 with the summary estimates of sensitivity and specificity presented against both culture and a combined reference standard in Table 1 for LNTB, Table 4 for TB meningitis Table 7 for pleural TB (Denkinger, 2014).

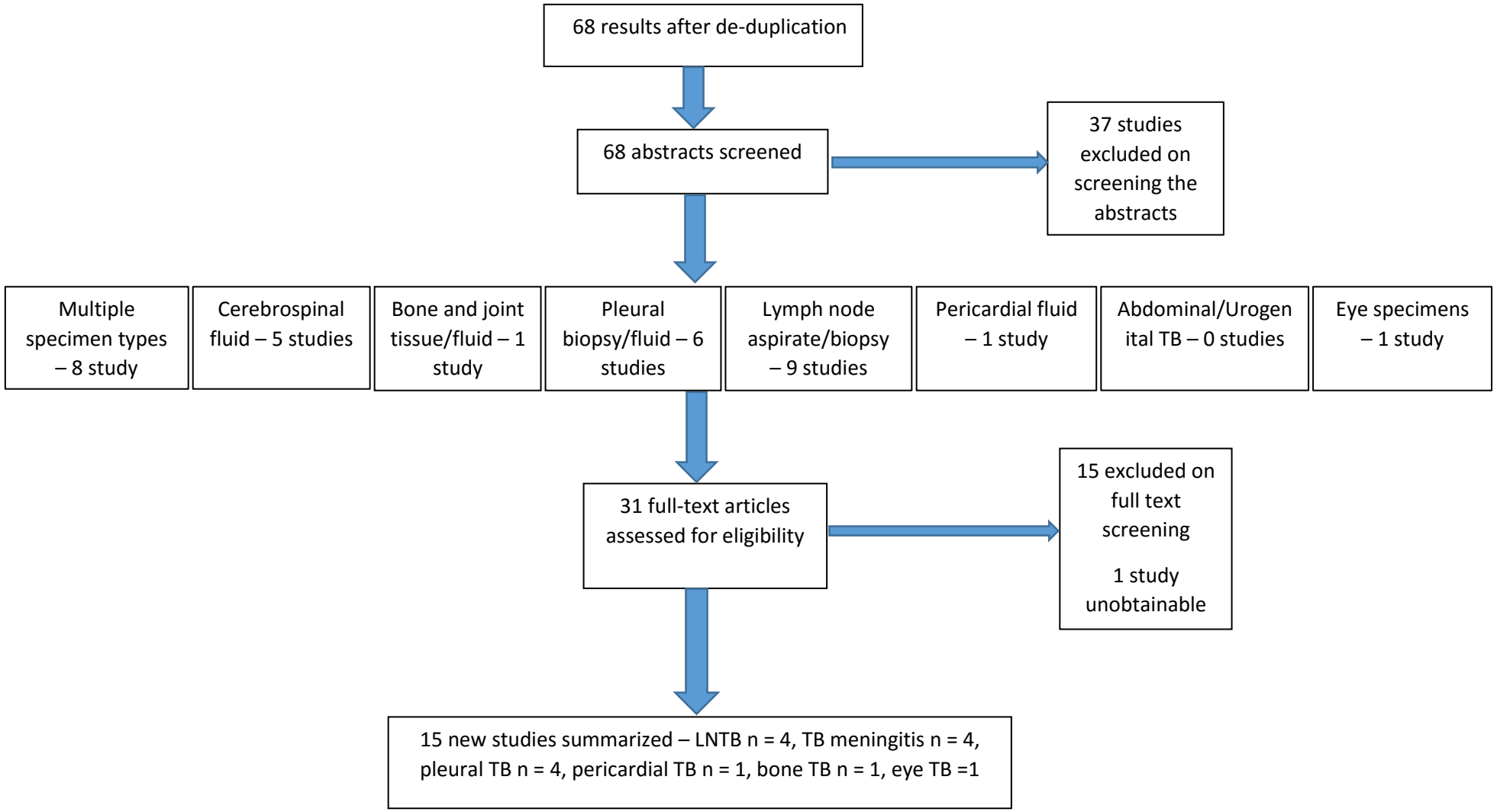
The summary of findings table with our GRADE assessments of the results from Denkinger 2014 is presented in Table 2 for LNTB, Table 5 for TB meningitis and Table 8 for pleural TB.

The results of the updated search, including brief description of studies and estimates of sensitivity and specificity, is presented in Table 3 for LNTB, Table 6 for TB meningitis and Table 9 for pleural TB.

Imperfect Reference Standard

An important problem in considering the evidence for estimates of sensitivity and specificity in EPTB diagnostics is the lack of a reference test which is reliably of high diagnostic test accuracy. Culture is the most frequently used reference test, but the low sensitivity of culture in paucibacillary TB disease may lead to misclassification of results. For example, if Xpert MTB/RIF correctly identifies a specimen as positive for TB, but the culture is negative, this will be classified as a false positive result. If this occurs frequently, an underestimation of Xpert MTB/RIF's specificity is expected. To mitigate this, Xpert MTB/RIF has been compared with a combined reference standard (CRS) in some studies. However, when compared with a CRS, which is more sensitive for detecting EPTB but less specific, Xpert may correctly identify a specimen as negative for TB which is wrongly classified as positive by the CRS, leading to a misclassified false negative result. If this occurs frequently, an underestimation of Xpert MTB/RIF's sensitivity could result. The panel considered both estimates, and the GRADE judgements for those estimates, when making the recommendations for the use of Xpert MTB/RIF in each form of EPTB.

Figure 1: Flow diagram illustrating the results of search and screening for Xpert MTB/RIF.



Xpert MTB/RIF for the diagnosis of LNTB

Figure 2: Forest plot demonstrating the sensitivity and specificity for Xpert MTB/RIF for the diagnosis of LNTB across all included studies a) against culture as a reference standard; b) against a combined reference standard. Blue squares represent point estimates of sensitivity and specificity, and lines represent 95% confidence intervals.

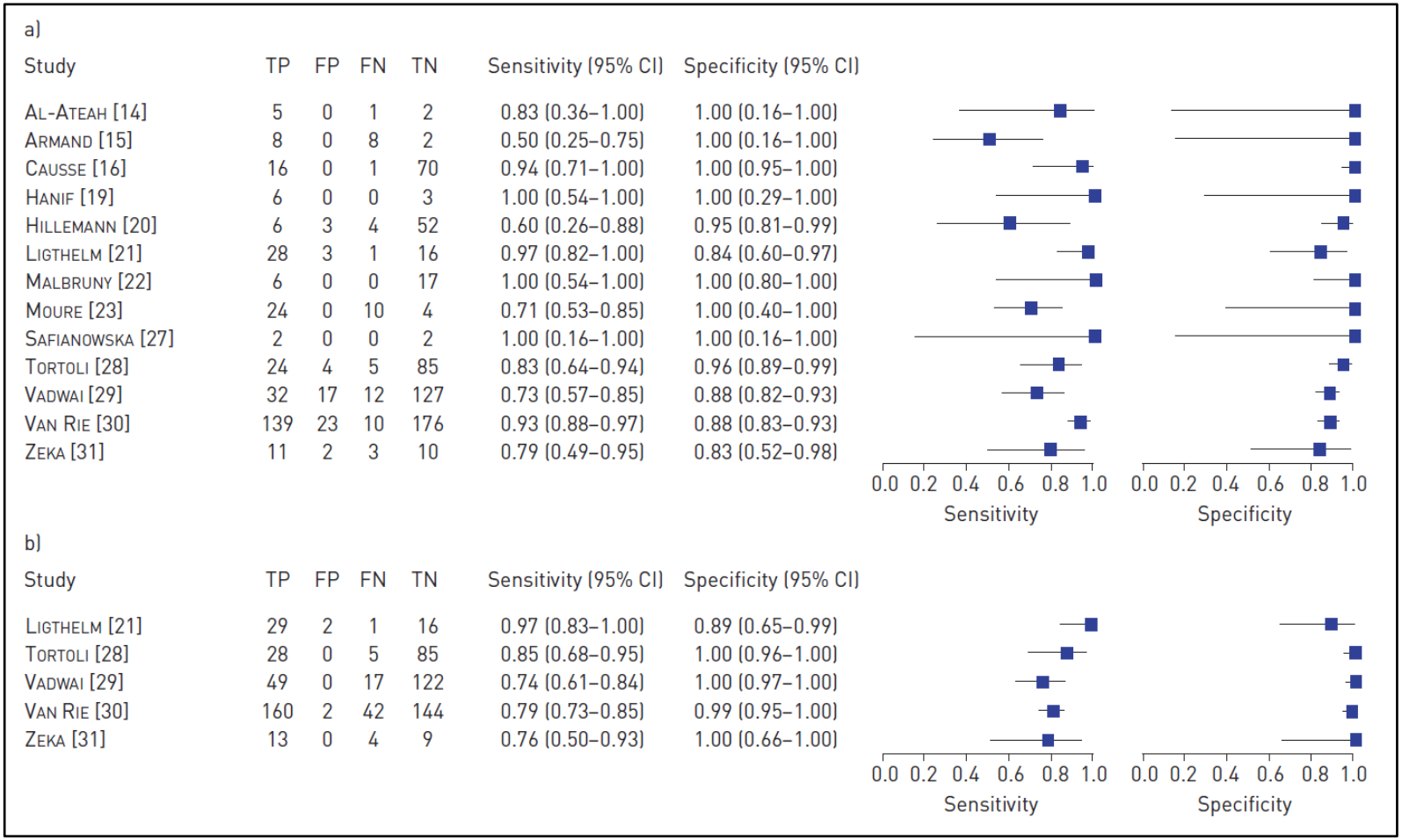


Table 1: Pooled sensitivity and specificity estimates for Xpert MTB/RIF for the diagnosis of LNTB against culture and against a combined reference standard.

	Pooled Sensitivity (95% CI)	Pooled Specificity (95% CI)
Against culture	83.1% (71.4–90.7)	93.6% (87.9–96.8)
Against CRS	81.2% (72.4–87.7)	99.1% (94.5–99.9)

Table 2: Should Xpert MTB/RIF be used to diagnose LNTB in patients suspected of LNTB?

Specimen: Lymph node aspirate and/or biopsy

Reference test: Culture

Sensitivity	0.83 (95% CI: 0.71 to 0.91)
Specificity	0.94 (95% CI: 0.88 to 0.97)

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients/year		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 20%	Pre-test probability of 45%	
True positives (patients with LNTB)	13 studies (362 patients)	Cohort & case-control type studies	Not serious [1]	Not serious [2]	Serious [3]	Serious [4]	Not serious	166 (142 to 182)	374 (320 to 410)	⊕⊕◯◯ LOW
False negatives (patients incorrectly classified as not having LNTB)								34 (58 to 18)	76 (130 to 40)	
True negatives (patients without LNTB)	13 studies (618 patients)	Cross-sectional (cohort type accuracy study)	Not serious [1]	Not serious	Not serious	Not serious	Not serious	752 (704 to 776)	517 (484 to 534)	⊕⊕⊕⊕ HIGH
False positives (patients incorrectly classified as having LNTB)								48 (96 to 24)	33 (66 to 16)	

1. Not downgraded for risk of bias: most studies were prospective cohort studies; only four of the thirteen studies were assessed as high risk of bias because patients were selected by convenience.
2. Not downgraded for indirectness: the studies were done in a variety of countries, mainly in secondary or tertiary centres and associated laboratories. The studies included mainly adults, but also children; HIV positive and negative people were included. The studies did not include specimens from patients being investigated for failed TB treatment/MDR TB.
3. Downgraded by one for inconsistency: unexplained heterogeneity may arise from differences between studies in specimen condition (fresh or frozen specimens), specimen processing and study population (e.g. prevalence of TB and HIV
4. Downgraded by one for imprecision: confidence intervals are wide partly due to the unexplained heterogeneity, and partly due to verification bias introduced by the imperfect reference standard.

Table 3: Characteristics of additional studies assessing Xpert MTB/RIF to make a diagnosis of LNTB published since 2013.

Study	Country, setting	Design	Participants	Specimens	Reference test	TP	FP	TN	FN	Sensitivity % (95% CI)	Specificity % (95% CI)
(Ablanedo-Terrazas Y, 2014)	Mexico, Tertiary referral hospital	Prospective cohort	Consecutive HIV positive patients with cervical lymphadenopathy	Excision biopsy or FNA. Decontaminated and homogenized.	Solid culture with L-J medium, liquid culture with BACTEC MGIT 960	15	0	53	0	100 (74.7 to 100)	100 (91.6 to 100)
(Biadglegne F, 2014)	Ethiopia, four main hospitals, one clinic	Cross-sectional	231 patients suspected of LNTB Children 15% HIV status not reported	FNA Decontaminated, concentrated, fresh	Culture (BacT/AlerT, LJ and Gottsacker)	30	55	126	2	93.75 (78.3 to 98.9)	69.61 (66.6 to 70.1)
(Coetzee L, 2014)	South Africa, Two tertiary referral hospitals	Prospective cohort	110 children <13 years suspected of LNTB HIV 8.3% pos,64% untested	FNA, no decontamination/concentration steps, diluted 2:1 in PBS, fresh	Culture (BACTEC MGIT 960 System)	21	13	34	4	84.0 (69.6 to 98.4)	72.24 (59.6 to 85.1)
					CRS (Cytology suggestive of TB + AFBs seen +/- culture)	32	2	30	8	80.0 (67.6 to 92.4)	93.8 (85.4 to 100)
(Kim YW, 2015)	South Korea, tertiary referral hospital	Retrospective cohort study	All non-respiratory specimens sent for Xpert testing. 0.8% HIV positive 6.8% children	Pus/tissue Decontaminated with NALC-NaOH 1% Concentrated by centrifugation. Solid samples frozen.	Culture (BACTEC MGIT and Ogawa medium)	27	22	343	5	84.4 (68.3 to 93.1)	94 (91.0 to 96.0)
					Culture pos OR probable TB (clinical features/ radiographic features and/or histology suggestive of TB) OR possible TB (clinical features but no tests suggestive of TB, good response to ATT)	49	0	330	18	73.1 (61.5 to 82.3)	100 (98.9 to 100)
(Van Rie A, 2013)	South Africa, tertiary referral hospital	Prospective cohort	Consecutive patients with suspected LNTB All HIV positive, aged >18	FNA aspirates Nodecontamination/ concentration steps	Culture (MGIT)	139	23	172	10	93.3 (87.6 to 96.6)	88.2 (82.6 to 96.1)

Question: Should Xpert MTB/RIF be used to make a diagnosis of LNTB in addition to FNAC at district level?

Balance of desirable and undesirable effects

Desirable	Undesirable
Quicker diagnosis	Patients with false negative Xpert results may have ATT withheld or stopped inappropriately
May have fewer patients treated with ATT when they do not have LNTB	False negatives may go on to develop disseminated disease
Reduced stigma from reduction in overtreatment	False positives exposed to ATT unnecessarily
May identify rifampicin resistance (evidence unclear)	May falsely diagnose rifampicin resistance – harm to patient from SEs of 2nd line drugs, high cost of 2nd line drugs
	Cost implications of managing missed cases (repeat diagnostic sampling, repeat hospital/clinic visits)
	Stigma for patients given a false positive diagnosis
	Litigation for misdiagnosis

Overall quality of evidence across all critical outcomes

High	Moderate	Low	Very low
Specificity		Sensitivity	

Values and preference statement

LNTB is common and usually diagnosed and treated at primary/secondary care level. Needs rapid, accurate test to improve case detection and facilitate rapid initiation of treatment.

Draft recommendation

Xpert MTB/RIF should be used at district level as an additional test to FNAC in the diagnosis of LNTB.

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
X				

Remarks

The group recognised that there are variations in diagnostic practice in private settings, but that current RNTCP guidance stipulates the use of FNAC for the diagnosis of LNTB.

The group felt that relying on Xpert alone for the diagnosis of LNTB would be inappropriate considering the sensitivity estimate of 82% (which implies around one in five patients are missed by this test). Rather, the group agreed that Xpert can be useful in confirming a diagnosis in patients suspected of LNTB when considered alongside the results of FNAC. A negative Xpert test does not reliably rule out LNTB.

Xpert MTB/RIF for the diagnosis of TB meningitis

Figure 3: Forest plot demonstrating the sensitivity and specificity for Xpert MTB/RIF for the diagnosis of TB meningitis across all included studies a) against culture as a reference standard; b) against a combined reference standard. Blue squares represent point estimates of sensitivity and specificity, and lines represent 95% confidence intervals.

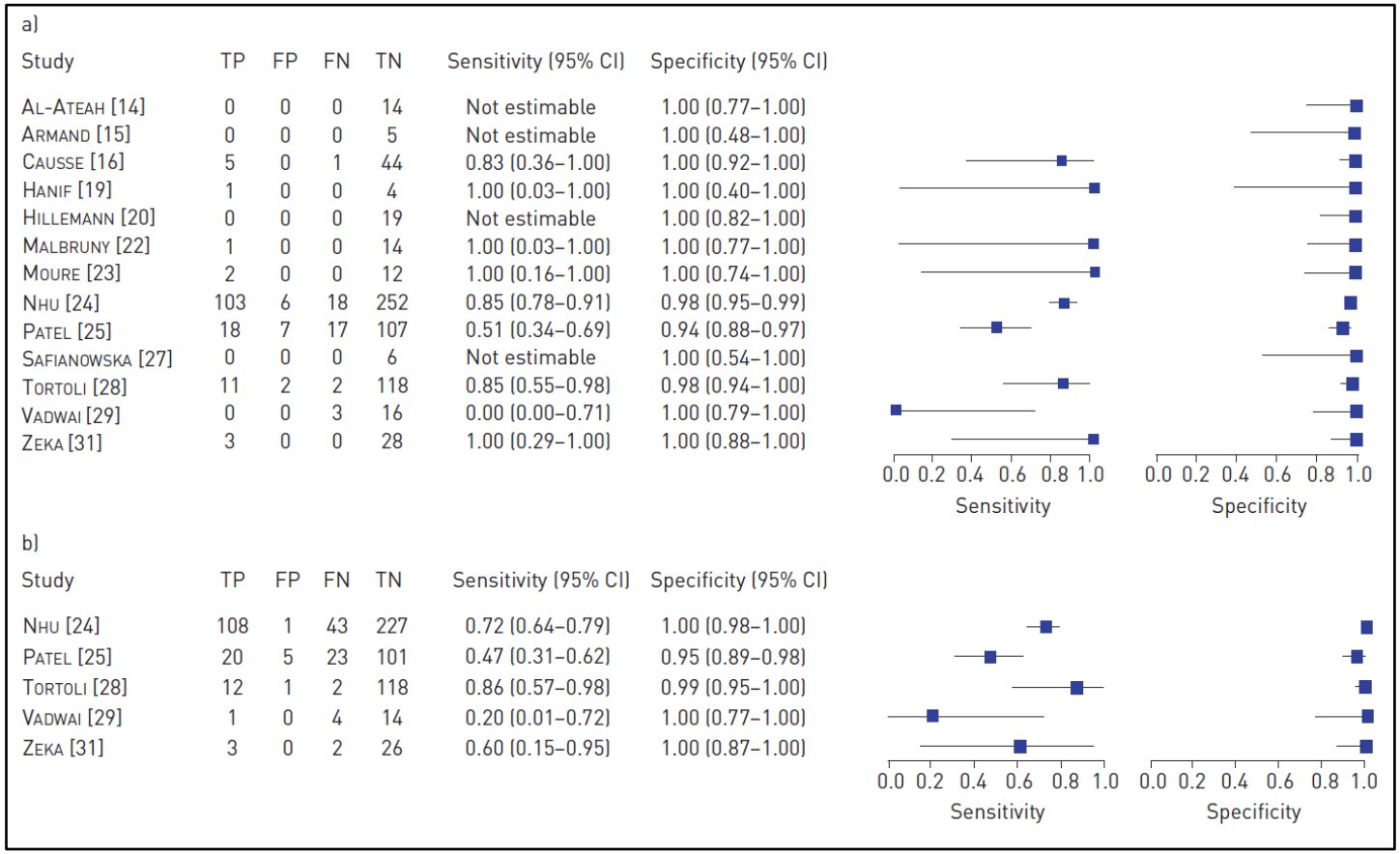


Table 4: Pooled sensitivity and specificity estimates for Xpert MTB/RIF for the diagnosis of TB meningitis against culture and against a combined reference standard.

	Pooled Sensitivity (95% CI)	**Pooled Specificity (95% CI)**
Against culture	80.5% (59.0–92.2)	97.8% (95.2–99.0)
Against CRS	62.8% (47.7–75.8)	98.8 (95.7–100)

Table 5: Should Xpert MTB/RIF be used to diagnose TB meningitis in patients suspected of TB meningitis?

Specimen: Cerebrospinal fluid

Reference test: Culture

Sensitivity	0.81 (95% CI: 0.59 to 0.92)
Specificity	0.98 (95% CI: 0.95 to 0.99)

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients/year		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 2%	Pre-test probability of 10%	
True positives (patients with TB meningitis)	13 studies (185 patients)	Cohort & case-control type studies	Not serious [1]	Not serious [2]	Serious [3]	Serious [4]	Not serious	16 (12 to 18)	81 (59 to 92)	⊕⊕◯◯ LOW
False negatives (patients incorrectly classified as not having TB meningitis)								4 (8 to 2)	19 (41 to 8)	
True negatives (patients without TB meningitis)	13 studies (654 patients)	Cohort & case-control type studies	Not serious	Not serious	Not serious	Not serious	Not serious	960 (931 to 970)	882 (855 to 891)	⊕⊕⊕⊕ HIGH
False positives (patients incorrectly classified as having TB meningitis)								20 (49 to 10)	18 (45 to 9)	

1. Downgraded by one for risk of bias: although there were concerns about the method of patient selection in two of the largest studies, most studies recruited consecutive patients. Reference test and index test were interpreted in a blinded fashion in most studies.
2. Not downgraded for indirectness: the studies included were from high and low TB prevalence settings, included HIV positive and negative participants, and included adults and children. The studies did not include participants who were being retested for TB after recent treatment failure.
3. Downgraded by one for inconsistency: unexplained heterogeneity may arise from differences between studies in specimen condition (fresh or frozen specimens), specimen processing, and varying populations (e.g. high or low HIV prevalence).
4. Downgraded by one for imprecision: there was wide variation in the estimates of sensitivity between studies due to the low number of participants.

Table 6: Characteristics of additional studies assessing Xpert MTB/Rif to make a diagnosis of TB meningitis published since 2013

Study	Country	Design	Participants	Specimens	TP	FP	TN	FN	Sensitivity % (95% CI)	Specificity % (95% CI)
(Kim YW, 2015)	South Korea, tertiary referral hospital	Retrospective cohort study	All non-respiratory specimens sent for Xpert testing. 0.8% HIV positive 6.8% children	CSF Decon. Fresh	3	0	250	1	75 (19.4–99.4)	100 (98.5–100)
(Nhu NT, 2014)	Vietnam, tertiary referral hospital	Prospective cohort	Consecutive patients suspected of TBM Aged >18 HIV pos 20.8% Untested 50.7%	Concentrated by centrifugation, frozen	103	--	--	18	85.1 (77.5 to 90.9)	
				Against clinical diagnosis	108	--	--	74	59.3 (51.8 to 66.5)	99.5 (97.2 to 100)
(Patel VB, 2014)	South Africa, tertiary referral hospital	Prospective cohort	Consecutive patients suspected of TBM	Against liquid culture/microscopy	18	3	50	18	50	94
(Solomons RS, 2015)	South Africa, tertiary referral hospital	Prospective cohort	Consecutive paediatric patients suspected of TBM	No centrifugation or decon. Fresh.	5	0	46	8	0.92 (0.64–1.00)	0.98 (0.89–1.00)

Guideline Panel's Judgement

Question: Should Xpert MTB/RIF be used in addition to conventional diagnosis tests to diagnose TB meningitis?

Balance of desirable and undesirable effects

Desirable	Undesirable
If Xpert is positive its highly likely to be TBM – this could increase access to a diagnosis	High number of false negatives – significant concern that this could lead to missed or delayed diagnosis
Quick result	Delayed diagnosis leads to worse outcomes (death)
Already widely available	Additional costs

Overall quality of evidence across all critical outcomes

High	Moderate	Low	Very low
Specificity		Sensitivity	

Values and preference statement

TBM is a significant cause of death and disability in India, and early diagnosis saves lives. A rapid test that is reliable and does not miss cases is needed. Survival is related to early diagnosis and treatment.

Draft recommendation

A negative Xpert result does not rule out TBM.

Xpert may be used as an adjunctive test for TBM.

(Conditional recommendation)

Decision to give ATT should be based on clinical features and CSF profile.

Remarks

- The group noted that the stakes are high in the diagnosis of TBM because it has a high associated mortality
- The group felt that this test was not sufficiently sensitive to be considered a ‘gold standard’, and there are diagnostic tools to guide diagnosis which incorporate multiple tests.
- There was concern about harm to patients from relying on negative Xpert results.
- The sensitivity of AFB smear is extremely low, and Xpert is more sensitive than this conventional rapid test. Sensitivity of culture varies widely, and Xpert is not likely to be more sensitive than culture, but culture results take several weeks to come back.
- Xpert is not sensitive for TBM so a decision to give ATT should not be based on a negative Xpert result. Xpert has high specificity so a positive result may be reassuring in the context of this disease where no diagnostic tests are very reliable.

Xpert MTB/RIF for the diagnosis of pleural TB

Figure 4: Forest plot demonstrating the sensitivity and specificity for Xpert MTB/RIF for the diagnosis of pleural TB across all included studies a) against culture as a reference standard; b) against a combined reference standard. Blue squares represent point estimates of sensitivity and specificity, and lines represent 95% confidence intervals.

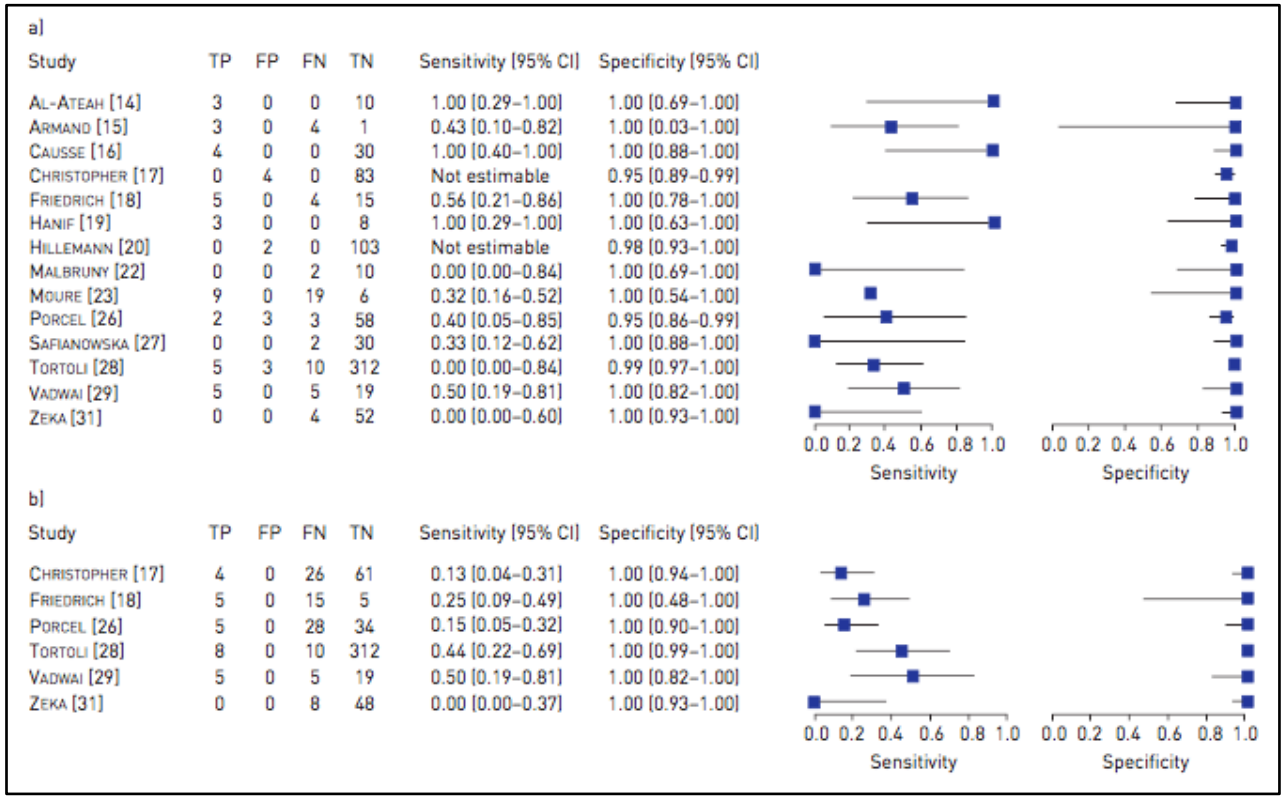


Table 7: Pooled sensitivity and specificity estimates for Xpert MTB/RIF for the diagnosis of pleural TB against culture and against a combined reference standard

	Pooled Sensitivity (95% CI)	**Pooled Specificity (95% CI)**
Against culture	46.4% (26.3–67.8)	99.1% (95.2–99.8)
Against CRS	21.4% (8.8–33.9%)	100% (99.4–100)

Table 8: Should Xpert MTB/RIF be used to diagnose pleural TB in people with suspected pleural TB?

Specimen: Pleural fluid

Reference test: Culture of pleural biopsy

Sensitivity	0.46 (95% CI: 0.26 to 0.68)
Specificity	0.99 (95% CI: 0.95 to 1.00)

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients/year		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 5%	Pre-test probability of 20%	
True positives (patients with pleural TB)	14 studies (776 patients)	Cohort & case-control type studies	Not serious [1]	Not serious [2]	Serious [3]	Serious [4]	Not serious	23 (13 to 34)	92 (52 to 136)	⊕⊕◯◯ LOW
False negatives (patients incorrectly classified as not having pleural TB)								27 (37 to 16)	108 (148 to 64)	
True negatives (patients without pleural TB)	14 studies (65 patients)	Cohort & case-control type studies	Not serious [1]	Not serious	Not serious	Not serious	Not serious	941 (903 to 950)	792 (760 to 800)	⊕⊕⊕⊕ HIGH
False positives (patients incorrectly classified as having pleural TB)								9 (47 to 0)	8 (40 to 0)	

1. Not downgraded for risk of bias: although there were concerns about the method of patient selection in two of the largest studies, most studies recruited consecutive patients. Reference test and index test were interpreted in a blinded fashion in most studies.
2. Not downgraded for indirectness: the studies included were from high and low TB prevalence settings, included HIV positive and negative participants, and included adults and children. The studies did not include participants who were being retested for TB after recent treatment failure.
3. Downgraded by one for inconsistency: unexplained heterogeneity may arise from differences between studies in specimen condition (fresh or frozen specimens), specimen processing, and varying populations (e.g. high or low HIV prevalence). Four of the studies with lowest estimates of sensitivity were conducted in low TB prevalence settings and two of these had over 10% prevalence of HIV.
4. Downgraded by one for imprecision: there was wide variation in the estimates of sensitivity between studies due to the low number of participants.

Table 9: Characteristics of additional studies assessing Xpert MTB/Rif to make a diagnosis of pleural TB published since 2013

Study	Country	Design	Participants	Specimens	Reference test	TP	FP	TN	FN	Sensitivity % (95% CI)	Specificity % (95% CI)
(Du J, 2015)	China, Four tertiary referral hospitals	Prospective cohort	Patients suspected of pleural TB with negative sputum cultures. Patient selection unclear.	Pleural biopsy	Pleural biopsy culture	47	2	69	8	85.5	97.2
				Pleural fluid	Pleural biopsy culture	24	1	70	1	43.6	98.6
(Lusiba JK, 2014)	Uganda, tertiary referral hospital	Prospective cohort	Patients suspected of pleural TB, no recent ATT. Consecutively recruited. n = 116 44.8% HIV pos	Pleural fluid	Pleural biopsy culture and/or histology	25	1	28	62	28.7	96.6
(Meldau R, 2014)	South Africa, two secondary hospitals	Prospective cohort	Patients suspected of pleural TB, no recent ATT. Adults, 10% HIV positive. Consecutively recruited. n=93	Pleural fluid, centrifuged and uncentrifuged	Pleural biopsy/sputum culture, or pleural biopsy histology	9	1	47	31	22.5 (12.4 to 37.6)	97.9% (89.2 to 99.7)
(Trajman A, 2014)	Brazil, tertiary referral hospital	Specimens collected prospectively, subjected to Xpert testing retrospectively	Patients requiring thoracocentesis. Adults, 5% HIV positive, 26.9% unknown HIV status N=65	Pleural fluid (previously frozen)	Confirmed TB (positive culture/smear in any specimen, granulomata on histology of pleural biopsy) OR probable TB (symptoms consistent with pleural TB and response to ATT)	1	0	26	32	3 (0 to 17)	100 (89 to 100)

Guideline Panel's Judgement

Question: Should Xpert MTB/RIF be used in addition to conventional tests to diagnose TB pleurisy?

Setting: district level health system

Balance of desirable and undesirable effects

Desirable	Undesirable
Quick result	50% of TB pleurisy patients are missed by this test
Easy to do compared with pleural biopsy (which is painful, requires expertise and carries risks)	Cost
	Does not help rule out other diagnoses such as malignancy

Overall quality of evidence across all critical outcomes

High	Moderate	Low	Very low
Spec		Sens	

Values and preference statement

A rapid, accurate test is needed to identify patients with pleural TB and start them on ATT appropriately. Pleural fluid rather than pleural biopsy is preferred, as it is easier to sample in most cases and is less risky and invasive for the patient.

Draft recommendation

Xpert should not be used to diagnose pleural TB.

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
				X

Remarks

The group had concerns about dual pathology in older patients – if Xpert is positive, the patient may be given ATT when in fact further investigation would have revealed malignancy. Some clinicians had experienced this happening.

A paediatrician in the group noted that this is much less of a concern for children, where the pre-test probability of TB is high in India.

The group felt that sometimes Xpert could help (if positive) if the diagnosis was unclear, and noted the advantage of having a rapid test. The group considered that a positive Xpert result may help in avoiding more invasive procedures in some patients, for example those with low adenosine deaminase activity in pleural fluid.

However, the sensitivity estimates against culture of pleural biopsy and against CRS are very low, and given the possibility that the misleading results of this test could lead to harm to patients in some circumstances, the group decided not to recommend the use of Xpert for pleural TB.

Should steroids be used to treat TB meningitis?

This evidence summary is based on the draft of the latest update of the Cochrane Review *Corticosteroids for managing tuberculous meningitis* (Prasad, 2016)

Authors

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Declaration of interests from review authors

K. Prasad is a co-author of two of the included trials (Kumarvelu, 1994) and (Prasad, 2006). H. Ryan extracted data and assessed risk of bias for these two trials with the Cochrane Infectious Disease Group co-ordinating editor, Paul Garner.

H. Ryan is part of the Cochrane Infectious Diseases Group, which is principally funded by the Department for International Development, Government of the United Kingdom.

Background

TB meningitis is a life-threatening condition affecting adults and children, which can leave survivors with a range of neurological disabilities. The pathophysiology of TB meningitis involves the inflammation of blood vessels in the subarachnoid space which can lead to loss of blood flow to brain tissue, leading to stroke. Steroids are thought to reduce this inflammation, improving blood flow and reducing cerebral oedema and intracranial pressure. However, the risks associated with steroids include immunosuppression, which is a major concern in the context of an infectious disease, gastrointestinal bleeding, hyperglycaemia and hypertension, amongst others.

Several randomized controlled trials have been conducted on the effect of corticosteroids in managing TB meningitis. The conclusions from these trials, seen individually, appear inconsistent. One trial (Thwaites, 2004) showed that dexamethasone increases survival rate, but it also raised two questions − do patients who survive because of dexamethasone therapy tend to be left with severe disability, and are there differential effects among subgroups of patients with different degrees of disease severity?

Objective

To evaluate the effects of corticosteroids as an adjunct to ATT on death and severe disability in people with TB meningitis.

Methods

Criteria for considering studies for this review

Types of studies - Randomized controlled trials.

Types of participants - People of any age with clinically diagnosed TB meningitis.

Types of interventions

Intervention - Corticosteroid (hydrocortisone, prednisolone, or dexamethasone) given orally, intramuscularly, or intravenously *plus* ATT.

Control **-** ATT (same as intervention) with or without placebo.

Types of outcome measures

Primary outcomes

- Death.
- Persisting disabling neurological deficit at the end of follow up.

Adverse events

Adverse events, including upper gastrointestinal bleeding, invasive bacterial or fungal infections, and hyperglycaemia.

Search methods for identification of studies

We searched the following databases using the search terms and strategy described below: Cochrane Infectious Diseases Group Specialized Register (February 2015); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library*; MEDLINE (1966 to February 2015); EMBASE (1974 to February 2015); and LILACS (1982 to February 2015). We also searched Current Controlled Trials (www.controlled-trials.com; accessed February 2015) using 'tuberculosis' and 'meningitis' as search terms.

Table 10: Detailed search strategy for steroids in TB meningitis

Search set	CIDG SR[1]	CENTRAL	MEDLINE[2]	EMBASE[2]	LILACS[2]
1	tuberculosis	tuberculosis	tuberculosis	TUBERCULOSIS-MENINGITIS	tuberculosis
2	TB	steroid*	tuberculosis	tuberculosis	TB
3	steroids	corticosteroid*	TB	TB	1 or 2
4	corticosteroids	glucocorticoid*	1 or 2 or 3	1 or 2 or 3	steroid*
5	dexamethasone	hydrocortisone	steroid*	steroid$	hydrocortisone
6	hydrocortisone	prednisolone	STEROIDS	STEROIDS	dexamethasone
7	prednisolone	dexamethasone	corticosteroid*	corticosteroid$	prednisolone
8	1 or 2	2 or 3 or 4 or 5 or 6 or 7	glucocorticoid*	glucocorticoid$	4 or 5 or 6 or 7
9	3 or 4 or 5 or 6 or 7	1 and 8	hydrocortisone	hydrocortisone	3 and 8
10	8 and 9	—	dexamethasone	dexamethasone	—
11	—	—	prednisolone	prednisolone	—
12	—	—	prednisone	methylprednisone	—
13	—	—	methylprednisone	5-12/or	—
14	—	—	5-13/or	4 and 13	—
15	—	—	4 and 14	Limit 14 to human	—
16	—	—	Limit 15 to human	—	—

[1] Cochrane Infectious Diseases Group Specialized Register.
[2] Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration; (Lefebvre, 2011) upper case: MeSH or EMTREE heading; lower case: free text term.

Data collection and analysis

We analyzed the outcome data based on an intention-to-treat analysis.

Results

Figure 5: Flow diagram illustrating the results of search and screening for steroids to treat TB meningitis

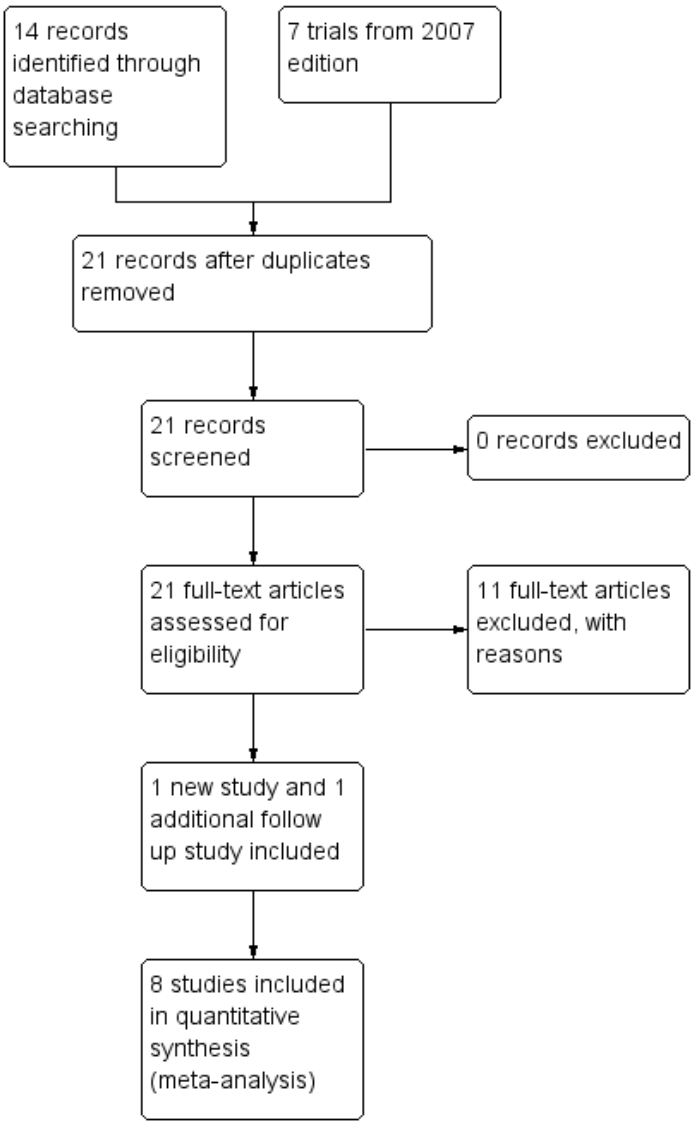

Table 11: Characteristics of the included studies assessing steroids in the treatment of TB meningitis

Study ID	Country	Year	Setting	Age	MRC Grade	HIV status reported	TB treatment regimen	Steroid	Route	Starting dose	Duration
(O'Toole, 1969)	India	1966-67	Tertiary	All	II and III	No	HS (duration not specified)	Dexamethasone	IV/IM	Adults: 9 mg/day Children: unclear	4 weeks
(Girgis NI, 1983)	Egypt	1982-87	Research	All	All	No	24HE1.5S	Dexamethasone	IM	Adults: 12 mg/day Children: 8 mg/day	6 weeks
(Chotmongkol V, 1996)	Thailand	1990-92	Tertiary	>15 years	All	Yes, HIV positive patients excluded	2HRZS+4HR	Prednisolone	Oral	60 mg/day	5 weeks
(Kumarvelu, 1994)	India	1991-92	Tertiary	>12 years	All	No	12HRZ	Dexamethasone	IV	16 mg/day	4 weeks
(Lardizabal, 1998)	Phillipines	1996-97	Tertiary	>18 years	II and III	No	2HRZE+10HR	Dexamethasone	IV	16 mg/day	7 weeks
(Schoeman, 1997)	South Africa	Unclear	Tertiary	Children	II and III	No	6HRZE	Prednisolone	Oral	2-4 mg/kg/day	4 weeks
(Thwaites, 2004)	Vietnam	2001-03	Tertiary	>14 years	All	Yes, HIV patients included	3HRZE (or S) +6HRZ	Dexamethasone	IV	Grade II & III: 0.4 mg/kg/day Grade I: 0.3 mg/kg/day	8 weeks
(Malhotra, 2009)	India	2006-07	Tertiary	>14 years	All	Yes, HIV positive patients excluded	2HRZE (or S) +7H	Dexamethasone	IV	0.4 mg/kg/day	8 weeks
								Methylprednisolone	IV	20 mg/kg/day	5 days

Risk of Bias Assessment

Figure 6. Risk of bias summary for steroids to treat TB meningitis: review authors' judgements about each risk of bias item for each included study. Green indicates low risk of bias, yellow indicates unclear risk of bias, and red indicates high risk of bias.

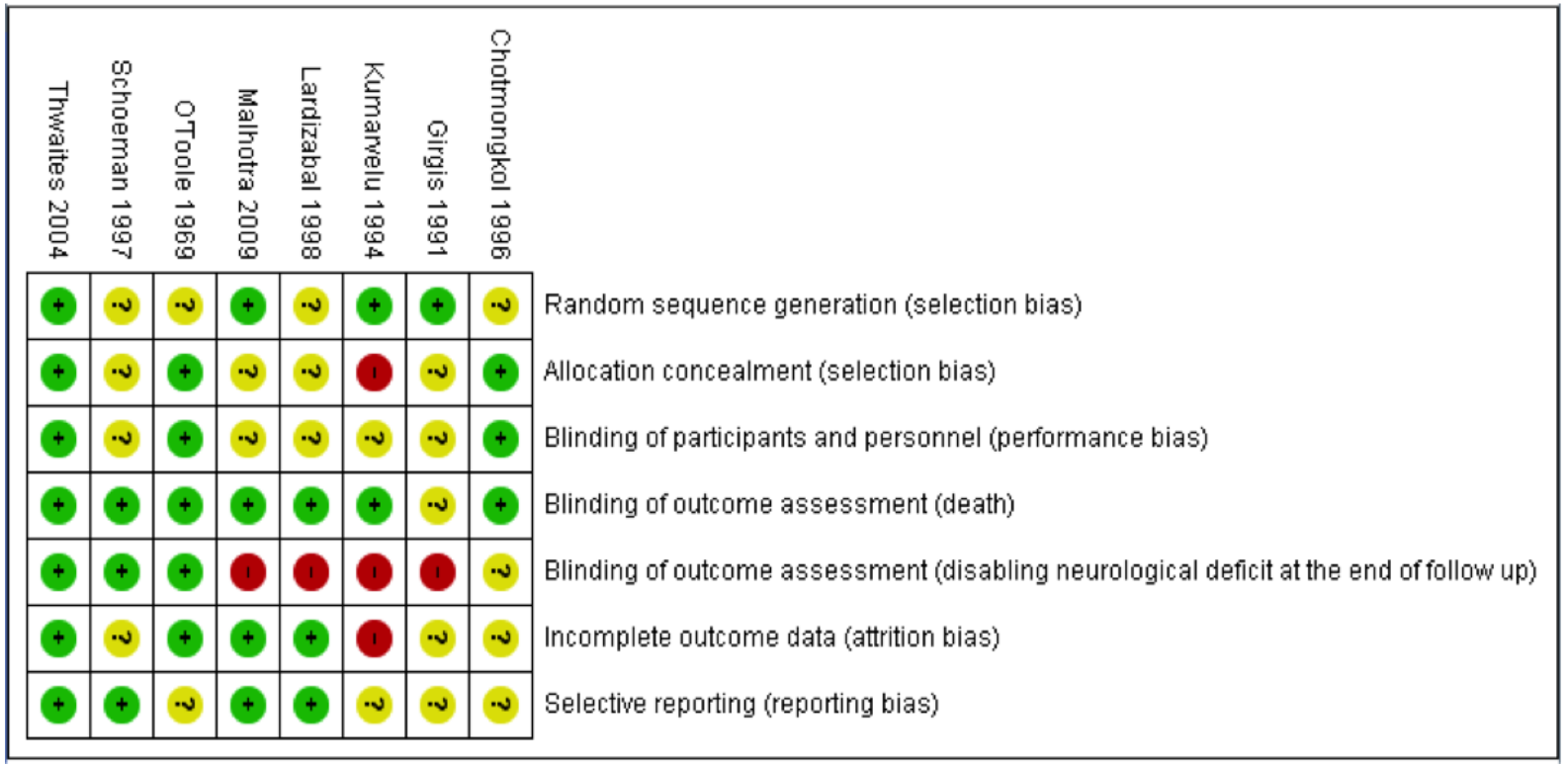

Figure 7. Forest plot demonstrating the effect of steroids in patients with TB meningitis on death at three points of follow up. Blue squares represent the risk ratio and study weighting; the black lines represent confidence intervals. The black diamond represents the pooled estimate of effect. Green indicates low risk of bias, yellow indicates unclear risk of bias, and red indicates high risk of bias.

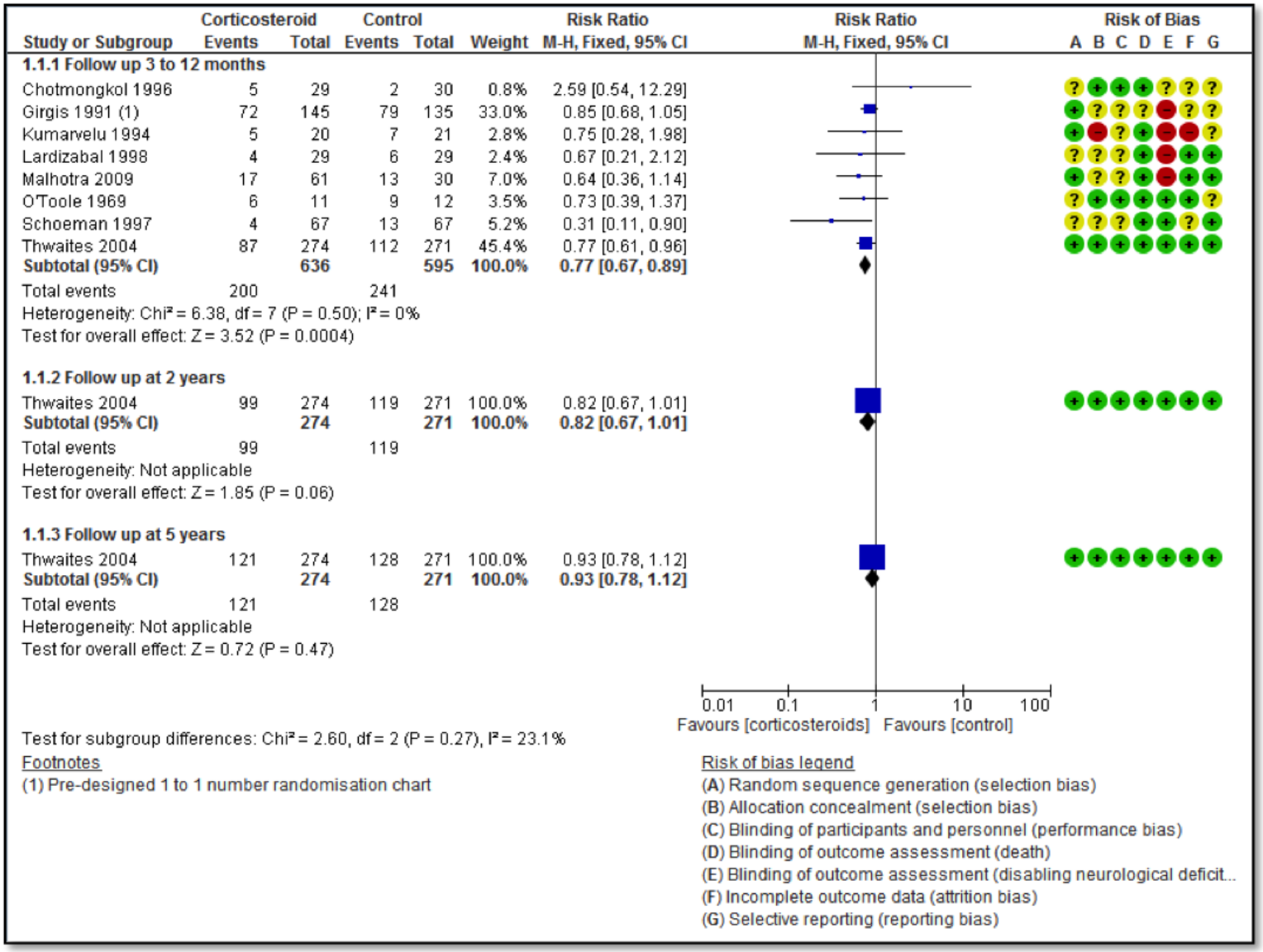

Table 12: Summary of findings for the use of corticosteroids to treat TB meningitis

Participants: Adults or children with tuberculous meningitis on tuberculosis (TB) chemotherapy
Settings: Hospital care
Intervention: Any corticosteroid
Comparison: Placebo or no corticosteroid

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Quality of the evidence (GRADE)
	Placebo	Corticosteroid			
Follow-up to 2 to 24 months					
Death	41 per 100	**31 per 100** (27 to 36)	RR 0.76 (0.66 to 0.87)	1318 (9 trials)	⨁⨁⨁⨁ **high**[1, 2, 3, 4, 5]
Disabling neurological deficit	8 per 100	**7 per 100** (6 to 10)	RR 0.92 (0.71 to 1.20)	1295 (8 trials)	⨁⨁⨀⨀[6, 7, 8] **low**
Follow-up to 5 years					
Death	47 per 100	44 per 100 (37 to 53)	RR 0.93 (0.78 to 1.12)	545 participants (1 trial)	⨁⨁⨁⨀[9,10] moderate
Disabling neurological deficit	15 per 100	14 per 100 (7 to 25)	RR 0.91 (0.49 to 1.69)	244 (1 trial)	⨁⨀⨀⨀[10, 11, 12] very low

*The **assumed risk** is from the median control group risk across studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio; **TB:** tuberculosis.

GRADE Working Group grades of evidence.
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

Footnotes

[1]Not downgraded for risk of bias. There are few uncertainties regarding allocation concealment or sequence generation in one of the two largest studies, but the largest trial was high quality and effects between these two trials were consistent.
[2]Not downgraded for inconsistency: low statistical heterogeneity, and the forest plot shows a consistent benefit.
[3]Not downgraded for indirectness in relation to age: all the participants in Schoeman 1997 and 59% of the participants in Girgis 1991 were children, and the effect is consistent with the other large trial, Thwaites 2004, which included participants aged 14 and over.
[4]Not downgraded for indirectness for HIV status: one trial included 98 HIV-positive participants, with no obvious qualitative heterogeneity when compared to HIV-negative participants (Thwaites 2004). If making recommendations for HIV-positive participants only, a guidelines panel may wish to downgrade on indirectness.
[5]Not downgraded for serious imprecision: the overall meta-analysis is adequately powered to detect this effect, but is only adequately powered when the trials at unclear or high risk of bias are included. The effect is clinically important.
[6]Downgraded by one for risk of bias: four of the eight trials were at high risk of bias due to lack of blinding of outcome assessors, which could impact on the interpretation of assessments of disability.
[7]Not downgraded for indirectness: trials included children, adults, some HIV-positive people, and people from different continents.
[8]Downgraded by one for imprecision: effects range from clinically important benefits of 29% reduction to 20% increase in disability.
[9]Not downgraded on risk of bias: number of participants followed up was high: 91% at five years, or imprecision.
[10]Downgraded by one for indirectness. This was a single trial conducted in a high quality health care unit in a population with high levels of infectious diseases endemicity and poverty. The attenuation of the effect may be less marked in populations with lower exposure to infectious diseases and other causes of reduced life expectancy associated with poverty. The authors were not able to establish the cause of death in most of the people who died after 9 months' follow-up, and so it is not possible to assess whether these deaths were related to TBM or other causes.
[11]Not downgraded on risk of bias. Although the assessors were not blind to the allocation, and some assessments were conducted by telephone, the numbers of disabled participants in the two groups were the same, and it is unlikely that systematic bias in the observers is present.
[12]Downgraded by two for imprecision. There were few events, and the confidence interval ranges from substantive harms to substantive benefits.

Guideline Panel's Judgement

Question: Should steroids be routinely prescribed for TB meningitis in people that are HIV negative?

Balance of desirable and undesirable effects

Desirable	Undesirable
Reduced mortality Reduced disability	Adverse effects of steroids

Overall quality of evidence across all critical outcomes

High	Moderate	Low	Very low
X			

Values and preference statement

TBM is a devastating disease with high mortality, and preventing mortality is a priority in this condition.

Draft recommendation

Steroids are recommended for TB meningitis in HIV negative people. Duration of steroid treatment should be for at least four weeks with tapering as appropriate.

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
X				

Remarks

The group noted that the effects may be greater in MRC Stage I and II, but the recommendation should stand for TB meningitis patients of any MRC stage.

Duration of corticosteroids was discussed. The group agreed that there is no clear evidence for any one regimen of steroids and debated what the best option would be.

Guideline Panel's Judgement

Question: Should steroids be routinely prescribed for TB meningitis in people that are HIV positive?

Balance of desirable and undesirable effects

Desirable	Undesirable
Reduced mortality	Relapse of TB meningitis
Reduced disability	HIV-associated adverse events
	Steroid-associated adverse events

Overall quality of evidence across all critical outcomes

High	Moderate	Low	Very low
		X	

Values and preference statement

HIV positive people are at increased risk of multiple opportunistic infections and cancer. Steroids could theoretically increase this risk, particularly in patients with advanced HIV disease (very low CD4 counts).

Draft recommendation

Steroids may be used for TB meningitis in HIV positive people, where other life-threatening opportunistic infections are absent.

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
	X			

Remarks

The group was concerned about the lack of evidence for the use of steroids people with HIV and TB meningitis. There are circumstances where steroids are clearly indicated (raised intracranial pressure, mass effect from a tuberculoma, for example).

Steroids are associated with increased risk of serious, life-threatening opportunistic infections in patients with advanced HIV disease. The criteria to be taken into account are stage of TB meningitis disease, evidence of raised intracranial pressure or mass effect, CD4 count, presence or absence of other opportunistic infections. Giving long courses of steroids in patients with HIV may be undesirable, especially in patients with advanced HIV disease. Specialist advice in managing such cases is warranted.

Should corticosteroids be prescribed routinely for TB pericarditis?

This evidence summary is based on the draft update for the Cochrane Review *Interventions for treating tuberculous pericarditis* (Wiysonge, unpublished).

Authors

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Declaration of interests from review authors

BM Mayosi, M Ntsekhe, L Thabane and S Pandie are co-authors of a new study included in the current review update (Mayosi BM, 2014). However, data were independently extracted and verified by an additional author who was not involved with this trial (CS Wiysonge) and a research assistant. CS Wiyonge, BM Mayosi, and M Ntsekhe were co-authors of a study assessed and excluded from this update (Wiysonge, 2008). Although the study is indexed in electronic databases as a trial, it was actually an observational cohort study.

Background

TB infection of the membrane round the heart (the pericardium), causes inflammation and fluid accumulation, which can lead to cardiac tamponade, a life-threatening medical emergency. In the long term fibrosis caused by the inflammation can cause the pericardium to thicken, and lead to heart failure, disability and death. Apart from anti-tuberculous therapy, treatments include corticosteroids, drainage of the fluid around the heart (pericardiocentesis), and surgery (including pericardectomy).

Objective

To evaluate the effects of corticosteroids for treating TB pericarditis in HIV negative and HIV positive patients.

Methods

Criteria for considering studies for this review

Types of studies - Randomised and quasi-randomised controlled trials.

Types of participants - People of all ages requiring treatment for clinically diagnosed TB pericarditis (effusive, constrictive, or effusive-constrictive), whether HIV negative or positive.

Types of interventions

Corticosteroids versus no corticosteroids.

The review addressing this intervention on corticosteroids for treating TB pericarditis also looked at other interventions used in TB pericarditis: immune modulators versus no immune modulators; and surgical procedures versus conservative management.

Types of outcome measures

Primary outcomes

- Deaths from all causes.

Secondary outcomes

- Death or disabled at 1 to 2 years follow up. 'Disabled' is defined as a history of restricted physical activity, combined with signs of cardiac compromise pre-specified in the protocol (such as clinical, radiographic, and electrocardiogram evidence of persisting pericardial disease).
- Death from pericarditis.
- Occurrence of tamponade requiring drainage of the pericardium (pericardiocentesis).
- Need for excision of the pericardium (pericardectomy).

Adverse events

- Opportunistic infections.
- HIV-associated cancer.

Search methods for identification of studies?

We searched the following databases using the search terms and strategy described below: Cochrane Infectious Diseases Group Specialized Register (06 May 2015); Cochrane Central Register of Controlled Trials (CENTRAL), published in The Cochrane Library (2015, Issue 5); MEDLINE (1966 to 06 May 2015); EMBASE (1974 to 06 May 2015); and LILACS (1982 to 06 May 2015).

Table 13: Detailed search strategy for corticosteroids in TB pericarditis

Search set	CIDG SR[1]	CENTRAL	MEDLINE[2]	EMBASE[2]	LILACS[2]
1	tuberculosis	Tuberculosis [MeSH]	Tuberculosis [MeSH]	Tuberculosis [MeSH]	tuberculosis
2	Pericard*	Tuberculosis ti, ab	Tuberculosis ti, ab	Tuberculosis ti, ab	Pericard*
3	heart	1 or 2	1 or 2	1 or 2	heart
4	2 or 3	heart or cardi* or pericard* ti, ab	heart or cardi* or pericard* ti, ab	heart or cardi* or pericard* ti, ab	2 or 3
5	1 and 4	3 and 4	3 and 4	3 and 4	1 and 4
6		"Pericarditis, Tuberculous"[Mesh]	"Pericarditis, Tuberculous"[Mesh]	tuberculous pericarditis [Emtree]	
7		5 or 6	5 or 6	5 or 6	

[1] Cochrane Infectious Diseases Group Specialized Register.
[2] Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Lefebvre C, 2011).

Data collection and analysis

Subgroup analyses

We stratified the analyses by HIV status. HIV testing was not done in three studies conducted in South Africa before the onset of the HIV epidemic in the country and we have assumed in the analyses that the participants in these studies were HIV-negative (Schrire 1959; Strang 1987; Strang 1988). One study enrolled only HIV-positive people (Hakim 2000) and two recruited both HIV-positive and HIV-negative

people (Reuter 2006; Mayosi 2014). We obtained data by HIV status for the Mayosi 2014 trial. Data were not available by HIV status in the Reuter 2006 trial in which one-third of participants were HIV positive. We therefore included two studies in the HIV positive subgroup (Hakim 2000; Mayosi 2014), four studies in the HIV negative subgroup (Schrire 1959; Strang 1987; Strang 1988; Mayosi 2014), and one study a subgroup "mixed HIV status".

Results

Figure 8: Flow diagram illustrating the results of search and screening for corticosteroids in TB pericarditis.

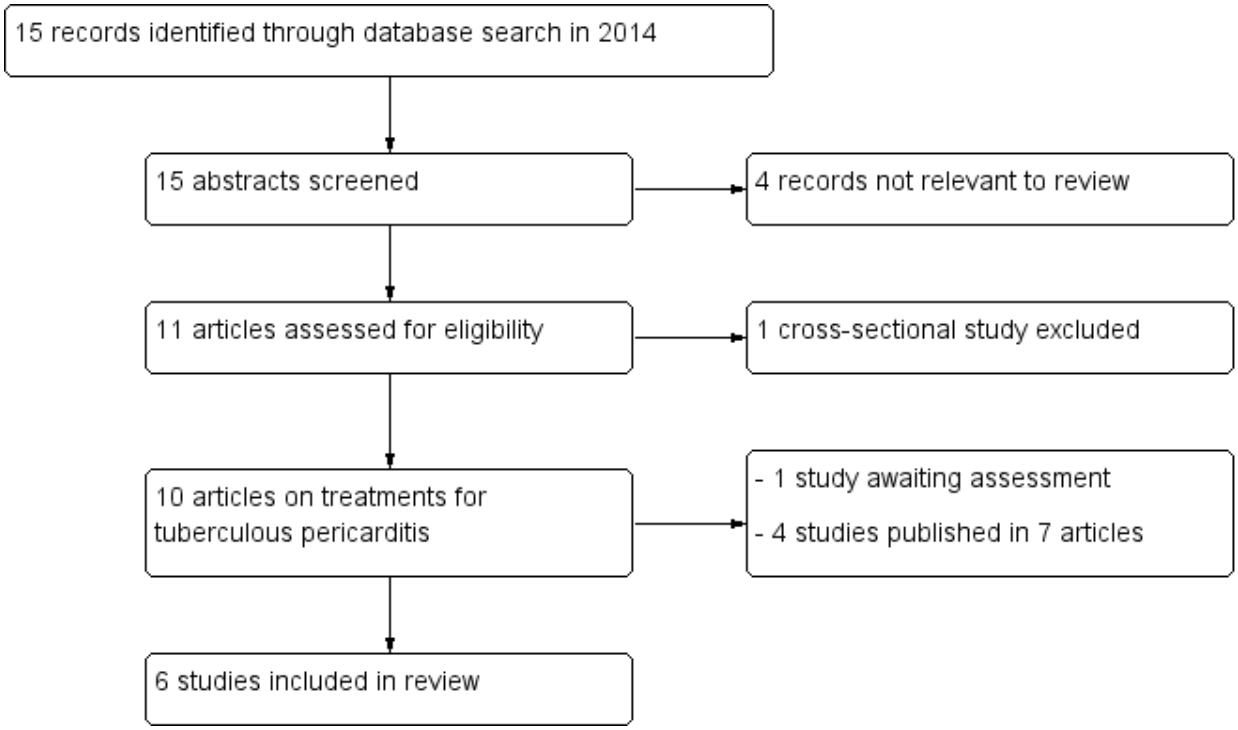

Table 14: Characteristics of the included studies assessing corticosteroids to treat TB pericarditis.

Study ID	Location	Participants				Intervention	Outcome
		Sample size	Age (years)	HIV (+)	ARVs	Definite TB [1]		
(Hakim 2000)	Zimbabwe	58 people with pericardial effusion	18 to 55	100%	0%	38%	Prednisolone for 6 weeks vs placebo	All deaths Constriction
(Mayosi 2014)	SSA	1440 with pericardial effusion (83%) or constriction (17%)	18 or older	67%	21%	17%	Prednisolone for 6 weeks. Factorial design with *M. indicus pranii*	All deaths PC deaths Constriction Hospitalisation Infection HIV cancer
(Strang 1987)	South Africa	143 with constrictive pericarditis	5 or older	Assume none	N/A	10%	Prednisolone first 11 weeks vs placebo	All death PC death PCY
(Strang 1988)	South Africa	240 with pericardial effusion	5 or older	Assume none	N/A	60%	Prednisolone for 11 weeks vs placebo. Also open surgical drainage vs no drainage.	All death PC death Repeat PCT PCY
(Schrire 1959)	South Africa	28 people with pericardial effusion	Adults	None	N/A	Not reported	Cortisone for several weeks vs no steroids	PCY
(Reuter 2006)	South Africa	57 people with pericardial effusion	17 to 66	37%	0%	Not reported	Intrapericardial triamcinolone vs prednisone for 4 weeks vs placebo	Repeat PCT PCY Constriction Infection

Constriction, constrictive pericarditis; PC deaths, deaths from pericarditis; PCY, pericardiectomy; Repeat PCT, repeat pericardiocentesis; SSA, sub-Saharan Africa (South Africa, Mozambique, Malawi, Uganda, Sierra Leone, Zimbabwe, Kenya, and Nigeria).

[1] Positive microbiological diagnosis, as defined by study authors.

Risk of Bias Assessment

Figure 9: Risk of bias summary for corticosteroids to treat TB pericarditis: review authors' judgements about each risk of bias item for each included study. Green indicates low risk of bias, yellow indicates unclear risk of bias, and red indicates high risk of bias.

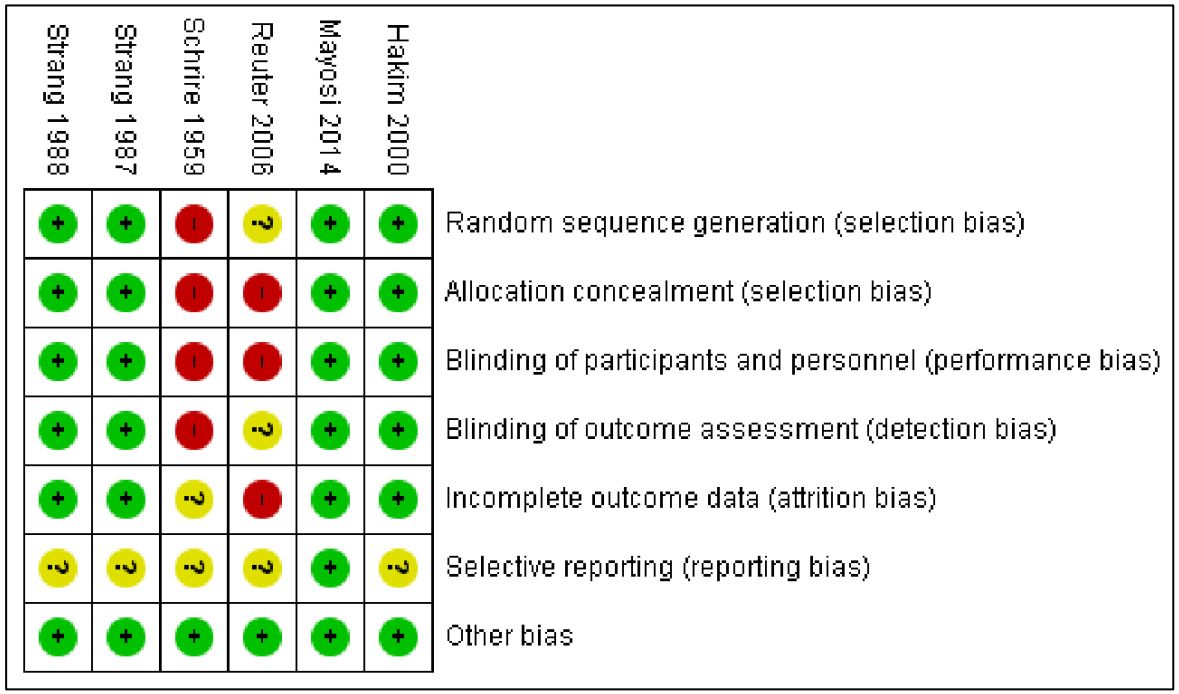

Figure 10: Forest plot demonstrating the effects of steroids in patients with TB pericarditis on death from all causes. Blue squares represent the risk ratio and study weighting, the black lines represent confidence intervals. The black diamond represents the pooled estimate of effect. Green indicates low risk of bias, yellow indicates unclear risk of bias, and red indicates high risk of bias.

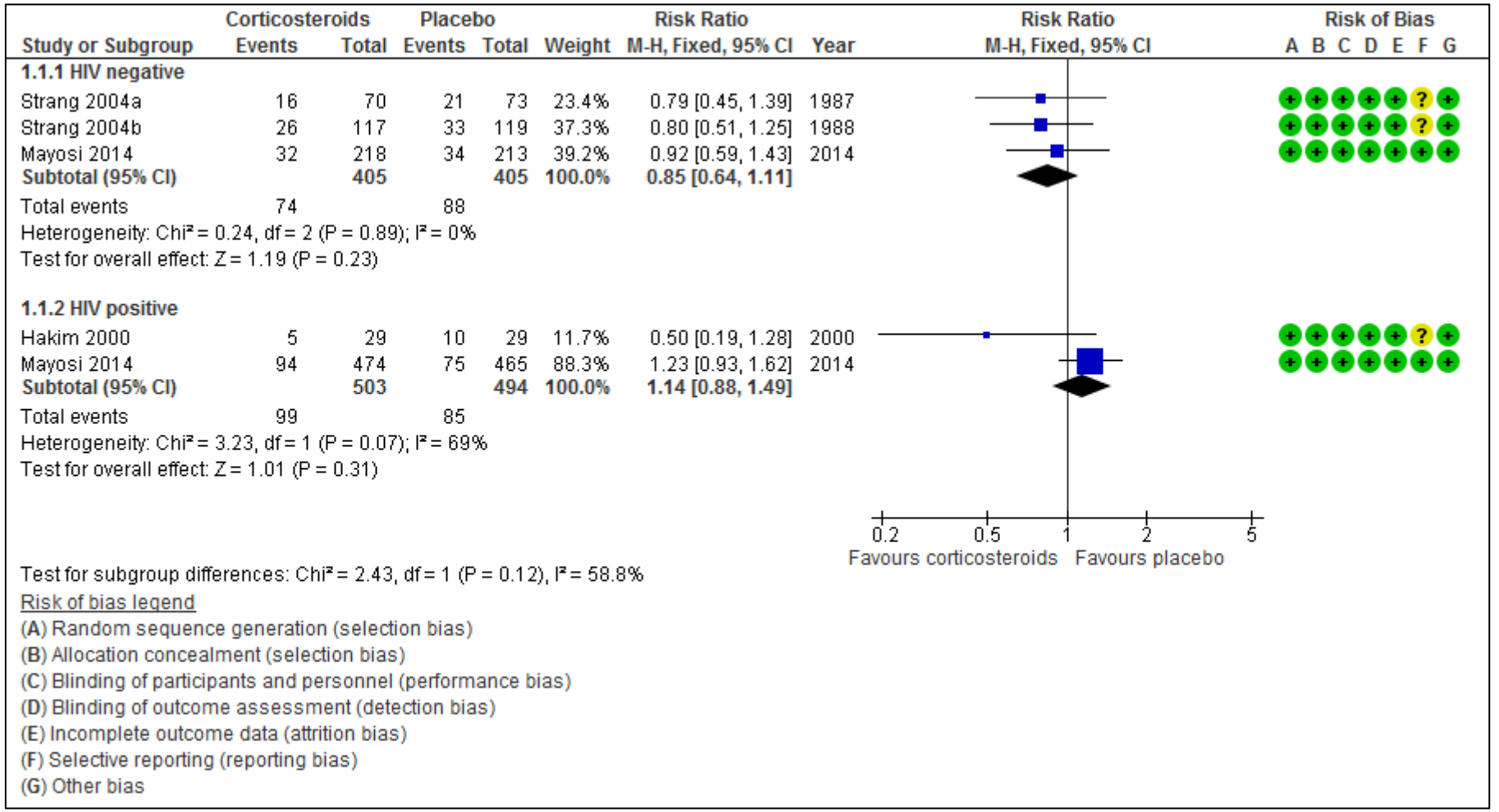

Figure 11: Forest plot demonstrating the effects of steroids in patients with TB pericarditis on risk of constrictive pericarditis. Blue squares represent the risk ratio and study weighting, the black lines represent confidence intervals. The black diamond represents the pooled estimate of effect. Green indicates low risk of bias, yellow indicates unclear risk of bias, and red indicates high risk of bias.

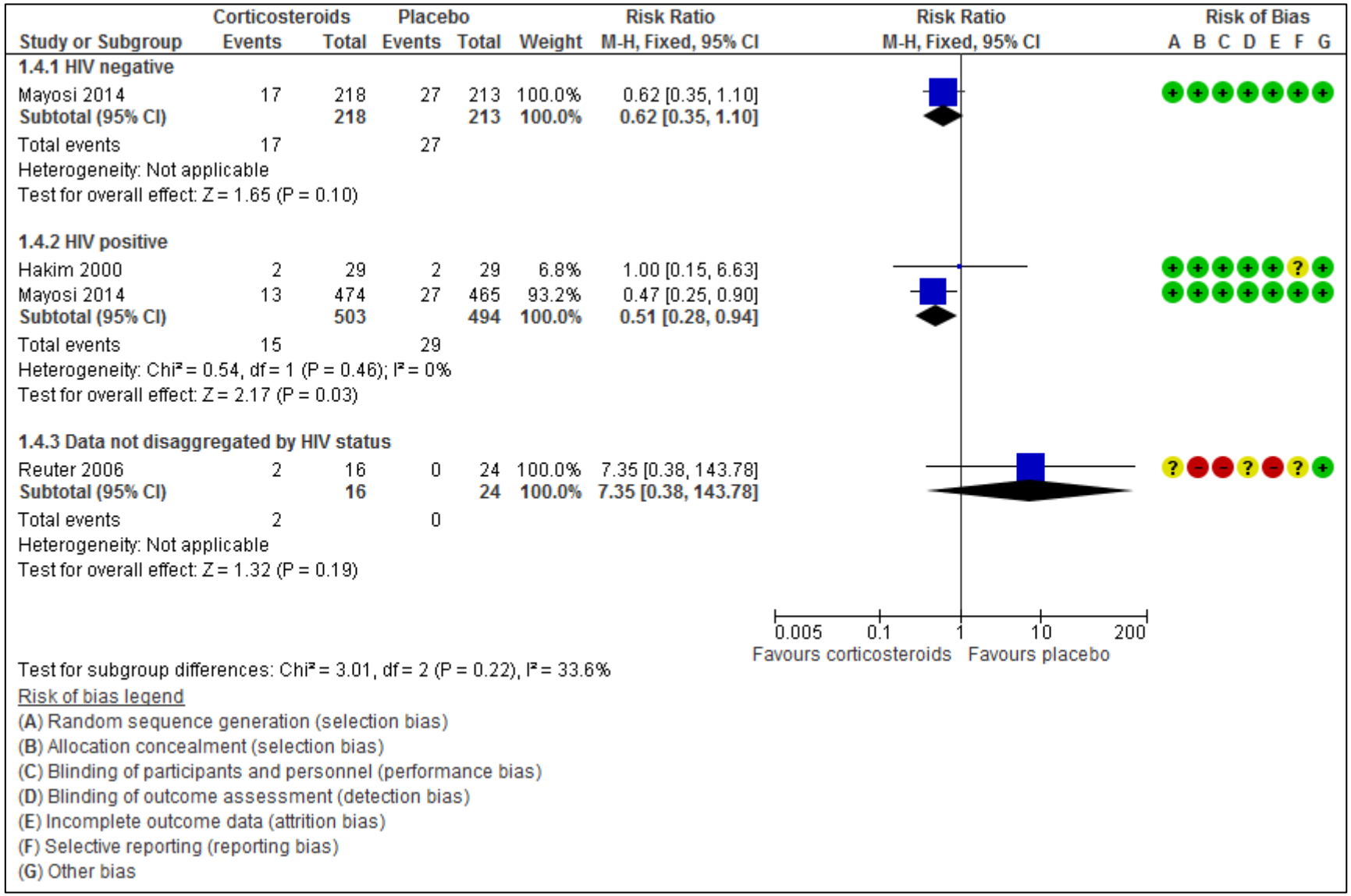

Table 15: Summary of findings on corticosteroids to treat TB pericarditis in people with HIV infection

Population: HIV positive people with tuberculous pericarditis
Settings: Sub-Saharan Africa
Intervention: Corticosteroids
Comparison: Placebo

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)
	Placebo	Corticosteroids			
Deaths from all causes Follow-up: 1.5-2 years	**172 per 1000**	**196 per 1000** (151 to 256)	**RR 1.14** (0.88 to 1.49)	997 (2 studies)	⨁⨁⊖⊖ **low**[1]
Deaths from pericarditis Follow-up: 2-10 years	**30 per 1000**	**40 per 1000** (20 to 79)	**RR 1.33** (0.68 to 2.62)	939 (1 study)	⨁⨁⊖⊖ **low**[1]
Repeat pericardiocentesis Follow-up: mean 2 years	**37 per 1000**	**32 per 1000** (16 to 63)	**RR 0.87** (0.44 to 1.71)	939 (1 study)	⨁⨁⊖⊖ **low**[1]
Constrictive pericarditis Follow-up: 1.5-2 years	**59 per 1000**	**30 per 1000** (16 to 55)	**RR 0.51** (0.28 to 0.94)	997 (2 studies)	⨁⨁⨁⊖ **moderate**[2]
Hospitalisation Follow-up: mean 2 years	**280 per 1000**	**224 per 1000** (179 to 280)	**RR 0.80** (0.64 to 1.0)	939 (1 study)	⨁⨁⊖⊖ **low**[1]
Opportunistic infections Follow-up: mean 2 years	**135 per 1000**	**152 per 1000** (111 to 207)	**RR 1.12** (0.82 to 1.53)	939 (1 study)	⨁⨁⊖⊖ **low**[1]
HIV-associated cancer[3] Follow-up: mean 2 years	**2 per 1000**	**19 per 1000** (2 to 149)	**RR 8.83** (1.12 to 69.41)	939 (1 study)	⨁⨁⊖⊖ **low**[1]

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: We are very uncertain about the estimate.

Footnotes

[1] We downgraded by 2 for imprecision, given the wide confidence intervals, which sometimes range from clinically important benefits to clinically important harms.

[2] We downgraded by 1 for selective reporting; data were only reported from one of three studies that recruited people living with HIV

[3] These data assume no interaction between *M. Indicus pranii* and corticosteroids in relation to this outcome. Most HIV cancers occurred in the group that received both *M. Indicus pranii* and corticosteroids, and this possibility was raised by the authors in the New England Journal of Medicine paper. The review team as of February 2016 is clarifying whether this potential interaction will require these data to be expressed differently. In the meantime, this relative risk should be treated as provisional.

Table 16: Summary of findings on corticosteroids to treat TB pericarditis in people without HIV infection

Population: HIV negative people with tuberculous pericarditis
Settings: Sub-Saharan Africa
Intervention: Corticosteroids
Comparison: Placebo

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)
	Placebo	Corticosteroids			
Deaths from all causes Follow-up: 2-10 years	**217 per 1000**	**185 per 1000** (139 to 241)	**RR 0.85** (0.64 to 1.11)	810 (3 studies)	⊕⊕⊖⊖ **low**[1,2]
Deaths from pericarditis Follow-up: 2-10 years	**77 per 1000**	**42 per 1000** (24 to 75)	**RR 0.55** (0.31 to 0.98)	810 (3 studies)	⊕⊕⊕⊖ **moderate**[1,3]
Repeat pericardiocentesis Follow-up: 2-10 years	**99 per 1000**	**49 per 1000** (27 to 85)	**RR 0.49** (0.27 to 0.86)	667 (2 studies)	⊕⊕⊕⊖ **moderate**[4]
Constrictive pericarditis Follow-up: mean 2 years	**127 per 1000**	**79 per 1000** (44 to 139)	**RR 0.62** (0.35 to 1.1)	431 (1 study)	⊕⊕⊖⊖ **low**[2]
Pericardiectomy Follow-up: 2-10 years	**160 per 1000**	**146 per 1000** (93 to 226)	**RR 0.91** (0.58 to 1.41)	407 (3 studies)	⊕⊕⊖⊖ **low**[2,5]
Hospitalisation Follow-up: mean 2 years	**197 per 1000**	**174 per 1000** (116 to 258)	**RR 0.88** (0.59 to 1.31)	431 (1 study)	⊕⊕⊖⊖ **low**[2]
Opportunistic infections Follow-up: mean 2 years	**23 per 1000**	**27 per 1000** (8 to 89)	**RR 1.17** (0.36 to 3.78)	431 (1 study)	⊕⊕⊖⊖ **low**[2]

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: We are very uncertain about the estimate.

Footnotes

The data in this table are what the panel used in July 2015 apart for some minor corrections to absolute estimates so the data correspond to the final version of the Cochrane review

[1] Two trials with 45% of participants in this meta-analysis were done in South Africa at a time when HIV prevalence was below 1%. HIV test not done, but we assume that participants in the trials were HIV negative. The trials report outcome data for a 10-year period which extends into the time when there was already a generalised HIV epidemic in South Africa, but we do not downgrade because of this.

[2] Downgraded by 2 for imprecision: the confidence intervals range from clinically important benefits to clinically important harms.

[3] Downgraded by 1 for imprecision (although a significant effect, the confidence intervals are too wide).

[4]Downgraded by 1 for selective reporting; data were only reported from two of four studies that recruited HIV negative people with pericardial effusion.

[5] Downgraded by 1 because two of the three studies had a high risk of selection bias.

Guideline Panel's Judgement

Question: Should steroids be routinely prescribed for TB pericarditis with pericardial effusion in people without HIV infection?

Balance of desirable and undesirable effects

Desirable	Undesirable
Increased survival	Steroid-associated adverse events
Reduced constrictive pericarditis	
Reduced need for pericardectomy	
Reduction of ATT-associated adverse effects	

Overall quality of evidence across all critical outcomes

High	Moderate	Low	Very low
			X

Values and preference statement

Use of steroids in TB pericarditis is widely established practice in India. Constrictive pericarditis is an important cause of morbidity and mortality in survivors of TB pericarditis. As the only definitive treatment is pericardectomy, a risky and expensive operation, prevention of constrictive pericarditis is an important outcome.

Draft recommendation

Steroids are recommended for HIV-negative patients with TB pericarditis with pericardial effusion.

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
	X			

Remarks

Steroids are associated with multiple adverse effects.

The effects estimates in the review suggest that steroids have little or no effect on all-cause mortality and pericarditis-associated mortality, however the largest study (which had one third HIV negative participants) showed a reduction in the number of participants with constrictive pericarditis at the end of treatment.

The group felt that future trials would be unlikely to show a reduction in mortality with the use of steroids, but risk of constrictive pericarditis and associated morbidity was the most important outcome.

Guideline Panel's Judgement

Question: Should steroids be routinely prescribed for TB pericarditis with pericardial effusion in people with HIV infection?

Balance of desirable and undesirable effects

Desirable	Undesirable
Increased survival	HIV opportunistic infections
Reduced constrictive pericarditis	HIV associated cancer
Reduced need for pericardectomy	Steroid-associated adverse events
Reduction of ATT-associated adverse effects	

Overall quality of evidence across all critical outcomes

High	Moderate	Low	Very low
		X	

Values and preference statement

Constrictive pericarditis must be treated surgically – there may be harms associated with surgery and there may be low access/high cost for many people in India.

Draft recommendation

Steroids are recommended for HIV-positive patients with TB pericarditis with pericardial effusion.

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
	X			

Remarks

Steroids may be safer in patients with CD counts above 200, and less safe in patients with CD counts below 200.

The guideline group recognised that there was uncertainty about whether steroids reduced all-cause mortality and the need for pericardectomy.

The review evidence showed an increase in HIV-associated cancers with steroid treatment, this was low quality evidence. The group noted that rates of Kaposi's sarcoma (the most commonly reported cancer in the largest trial) are low in India.

The group felt that reducing rates of constrictive pericarditis was important for patients and also for reducing resource use (cost of hospitalisation, pericardectomy etc.), and so steroids are recommended based on the evidence that risk of constrictive pericarditis is probably reduced with corticosteroids (moderate quality evidence).

Should corticosteroids be used to treat TB pleurisy?

This evidence summary is based on the draft update of the Cochrane Review *Corticosteroids for TB Pleurisy* (Ryan, unpublished)

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Declaration of interests from review authors

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H. Ryan is part of the Cochrane Infectious Diseases Group, which is principally funded by the Department for International Development, Government of the United Kingdom.

Background

Pleural TB (or TB pleurisy) is one of the most common forms of TB, with an incidence of 3-25% of TB patients depending on geographical location (Light, 2010). Incidence is higher in high TB prevalence settings (Doosoo, 2014). Immune compromise is an important risk factor for all forms of TB, and there is evidence suggesting that pleural TB is more common in people living with HIV (Batungwanayo , 1993) (Frye, 1997), but less frequent in people with solid organ transplants (Queipo, 2003). Pleural TB can arise post primary MTB infection or as a reactivation of TB.

Clinically, pleural TB presents as an acute illness consisting of cough, fever, chest pain, and shortness of breath (Morehead, 1998) and usually a pleural effusion is demonstrated on chest X-ray. Pleural TB usually resolves without treatment of any kind, but untreated patients may experience longer duration of the acute symptoms and risk recurrence of active TB at a later point in time (Light, 2010). Pleural TB can be complicated by massive effusion leading to respiratory compromise in the short term; pleural thickening, fibrosis and pleural adhesions causing impaired respiratory function in the medium to long term.

Pleural TB is thought to be caused by a delayed-type (type IV) hypersensitivity reaction following mycobacterial infection of the pleura (Rossi, 1987), as a result of rupture of a subpleural focus of infection in the lung. This explains the tendency towards resolution of the effusion and associated symptoms with or without treatment of the TB infection. There appears to be a spectrum of disease in pleural TB in terms of the extent of the underlying lung infection, which could be important in terms of patient outcomes and the potential for corticosteroids to be effective. One cohort study reported evidence of pulmonary TB infection on chest X-ray in 20% of 254 patients (Valdés, 1998). Pulmonary involvement rises to 86% in another cohort where computed tomography (CT) scanning was used (Kim, 2006). Shu et al. (2011) demonstrated that pulmonary involvement (as defined by positive sputum culture and/or chest X-ray appearances) was an important predictor of mortality in hospitalised pleural TB patients in Korea, and was associated with a longer hospital stay.

This review was conducted originally because there was uncertainty about the efficacy of corticosteroids in reducing the short-term and long-term effects on the acute symptoms of pleural TB and the long-term

sequelae. Steroids are associated with several adverse effects, especially in people with HIV, and administering them in the absence of evidence of efficacy may be exposing patients to unnecessary risk.

Objective

To evaluate the effects of adding corticosteroids to drug regimens for TB pleural effusion.

Methods

Criteria for considering studies for this review

Types of studies - Randomized and quasi-randomized controlled trials.

Types of participants - People diagnosed with TB pleurisy by chest X-ray (as defined by trial authors) *plus* any of the following: pleural biopsy for histology; staining and microscopy for acid-fast bacilli and/or culture of sputum; pleural fluid; or pleural biopsy.

Types of interventions

Intervention - Any corticosteroid at any dose.

Control - Placebo or no adjunctive treatment.

Both groups should receive the same anti-tubercular drug regimen.

Types of outcome measures

Short term (under six months)

- Time to resolution of clinical symptoms (as defined by the authors, including fever and pain).
- Change in respiratory function.
- Time to resolution of pleural effusion.

Long term (six months or more)

- Development of pleural thickening.
- Development of pleural adhesions.
- Deaths from any cause.

We will also report on other outcomes of resolution as defined by the author.

Adverse events

- Corticosteroid-associated adverse events.
- HIV-associated adverse events.

Search methods for identification of studies

We searched the following databases using the search terms and strategy described in the table below: Cochrane Infectious Diseases Group Specialized Register (January 2015); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2015); MEDLINE (1966 to March 2015); EMBASE (1974 to March 2015) and LILACS (1982 to March 2015). We also searched Current Controlled Trials (March 2015) using 'tuberculosis' and 'pleur*' as search terms. We also checked the reference lists of all studies identified with the above methods.

Table 17: Detailed search strategy for steroids in TB pleurisy

Search set	CIDG SR[1]	CENTRAL	MEDLINE[2]	EMBASE[2]	LILACS[2]
1	tuberculosis	tuberculosis	TUBERCULOSIS	TUBERCULOSIS	tuberculosis
2	TB	steroids	tuberculosis	tuberculosis	TB
3	steroids	corticosteroids	TB	TB	1 or 2
4	corticosteroids	glucocorticoids	1 or 2 or 3	1 or 2 or 3	steroids
5	dexamethasone	hydrocortisone	steroid*	steroids	hydrocortisone
6	hydrocortisone	prednisolone	STEROIDS	STEROIDS	dexamethasone
7	prednisolone	dexamethasone	corticosteroids	corticosteroids	prednisolone
8	—	2 or 3 or 4 or 5 or 6 or 7	glucocorticoids	glucocorticoids	4 or 5 or 6 or 7
9	—	1 and 8	hydrocortisone	hydrocortisone	3 and 8
10	—	—	dexamethasone	dexamethasone	—
11	—	—	prednisolone	prednisolone	—
12	—	—	prednisone	methylprednisone	—
13	—	—	methylprednisone	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	—
14	—	—	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	4 and 13	—
15	—	—	4 and 14	Limit 13 to human	—
16	—	—	Limit 15 to human	—	—

[1] Cochrane Infectious Diseases Group Specialized Register.
[2] Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Lefebvre C, 2011); upper case: MeSH or EMTREE heading; lower case: free text term.

Data collection and analysis

We analyzed the outcome data based on an intention-to-treat analysis.

Results

Figure 12: Flow diagram illustrating the results of search and screening for steroids to treat TB pleurisy

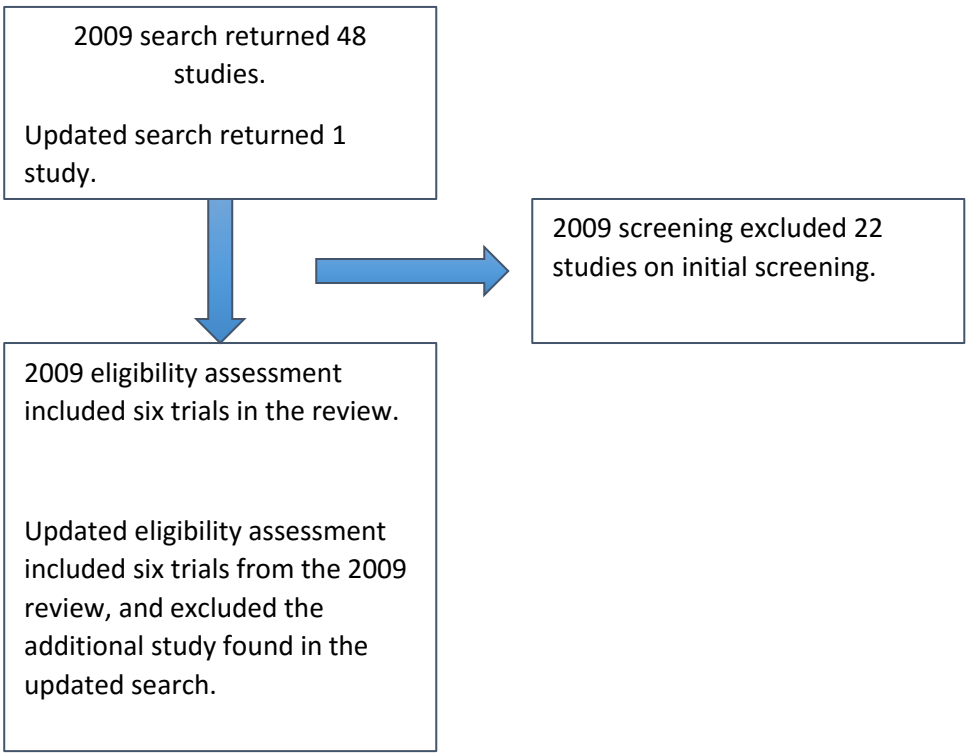

Table 18: Characteristics of the included studies assessing steroids to treat TB pleurisy

Study	Setting	Dates	Design	Participants	HIV status	ATT Regimen	Steroid regimen	Outcomes assessed
(Bang 1997)	Inha University hospital, Sungnam, Korea	June 1991 to Sept 1994	Prospective randomized study	n= 118 Age over 18, mean age 34, No contraindications to steroids, no heart disease Diagnosis – culture of pleural biopsy/fluid	HIV positive people excluded	2RHZE, 7RHE	Prednisolone 1 mg/kg twice weekly (period not stated) thereafter tapered off by 10 mg/week)	Mean duration to relief from symptoms, rate of reabsorption of pleural fluid, pleural adhesions and thickening, adverse effects
(Elliott 2004)	Mulago Hospital, Kampala, Uganda	Nov 1998 to July 2002	RCT, double-blind placebo-controlled	n=197 Over 18 years old, no previous ATT, no recent steroids Diagnosis – pleural biopsy culture/histology	HIV positive patients only	4RHZE, 2RH	Prednisolone 50mg/day - 14days, 40mg/day – 14 days, 25 mg/day 14 days, 15 mg/day -14 days. Stop	Mortality, time to resolution of symptoms, time to resolution of pleural effusion, CD4 count and viral load during treatment, adverse events
(Galarza 1995)	Hospital Universitari de Bellvitge, Barcelona, Spain	Jan1985 and Dec1992	RCT, double-blind placebo-controlled	n=117 Age 11-53 years.	HIV positive people excluded	6RH	Prednisolone 1 mg/kg/day for 15 days, then 0.5 mg/kg/day for 5 days, then 0.25mg/kg/day for 5 days, then 0.1 mg/kg/day for 5 days	Time to resolution of symptoms, change in PFTs, time to resolution of pleural effusion, development of pleural thickening
(Lee 1988)	Chang Gung Hospital, Taipei, Taiwan	Oct 1983 to June 1987	RCT, double-blind placebo-controlled	n=40 Aged 18-45 (mean 28.7), no previous ATT, no history of PTB, no contraindication to steroids. Diagnosis – pleural biopsy demonstrating TB or chronic granulomatous inflammation	Not reported	3RHE, 6-9RH	Prednisolone 0.75 mg/kg daily, reduced by two-thirds when the CXR improved, then gradually tapered	Time to resolution of pleural effusion (based on CXR taken on day 4, day 7 and then weekly during hospitalisation, then monthly during follow up), development of pleural adhesions at end of follow up, adverse events
(Lee 1999)	South Korea	Feb 1990 to Feb 1997	Randomized trial, blinding not specified	n=82 Mean age 32 years No contraindications to steroids, no heart disease Diagnosis – culture of pleural biopsy/fluid	HIV positive people excluded	6RHZE or 2RHZS/4RHZ	Prednisolone single dose per injection of 30 mg/day for 30 days, followed by a tapering off over a further 30 days	Rate of reabsorption of pleural fluid, pleural adhesions and thickening, adverse effects
(Wyser 1996)	Tygerberg Hospital, Cape Town, South Africa	April 1994 to Jan 1995	RCT, double-blind placebo-controlled	n= 74 Adults, mean age 32.9. Diagnosis - pleural biopsy microscopy/histo/culture All patients had thoracoscopy with thoracocentesis.	HIV positive people excluded	6RHZ	Prednisolone 0.75 mg/kg/day reduced after 2-4 weeks according to response by 5 mg/day.	Time to resolution of symptoms (patient reported outcome using visual analogue scale), change in PFTs, development of pleural thickening (CXR and HRCT)

Risk of Bias Assessment

Figure 13: Risk of bias summary for steroids to treat TB pleurisy: review authors' judgments about each risk of bias item for each included study. Green indicates low risk of bias, yellow indicates unclear risk of bias, and red indicates high risk of bias.

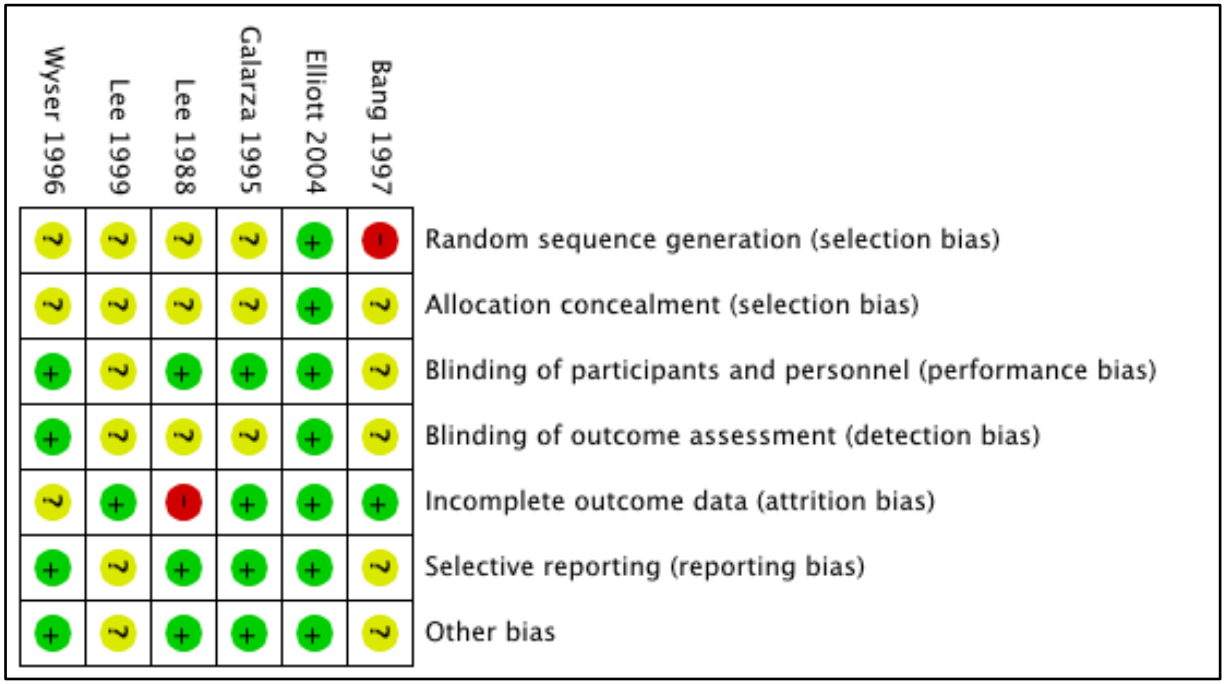

Figure 14: Forest plot demonstrating the effect of steroids in patients with TB pleural on residual pleural effusion at 4 weeks. Blue squares represent the risk ratio and study weighting, the black lines represent confidence intervals. The black diamond represents the pooled estimate of effect.

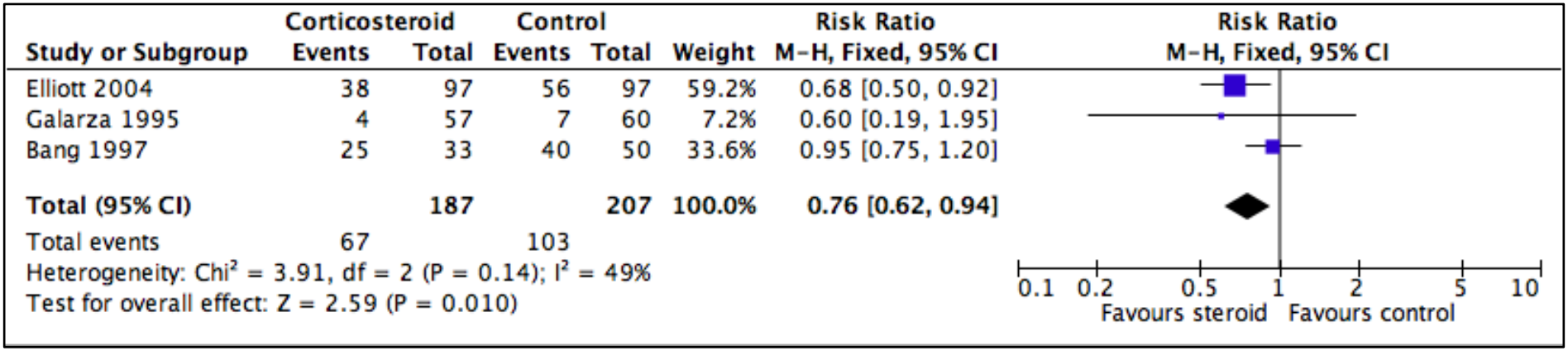

Figure 15: Forest plot demonstrating the effect of steroids in patients with TB pleura on residual pleural effusion at 8 weeks. Blue squares represent the risk ratio and study weighting, the black lines represent confidence intervals. The black diamond represents the pooled estimate of effect.

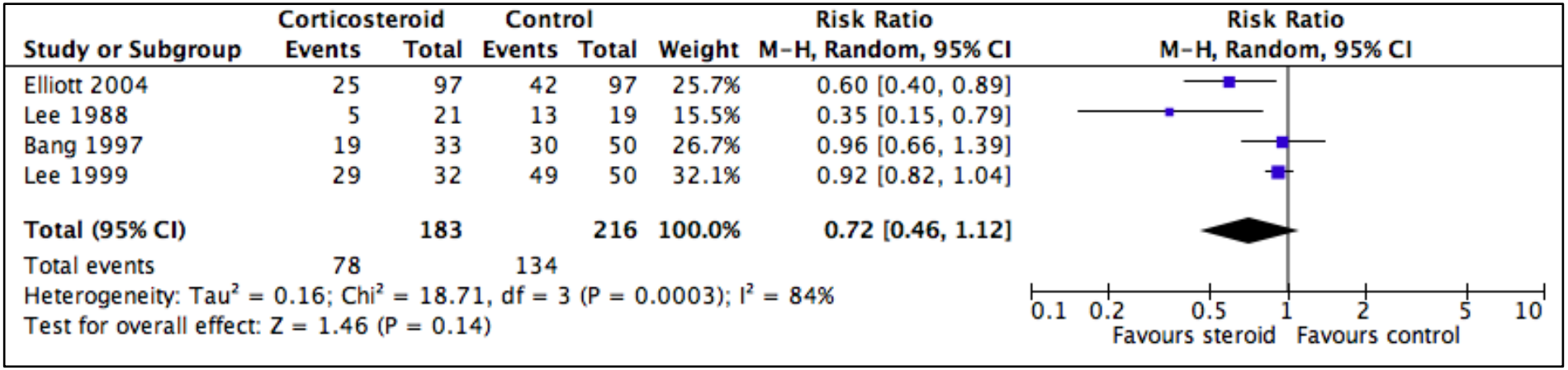

Figure 16: Forest plot demonstrating the effect of steroids in patients with TB pleura on pleural thickening at the end of follow up. Blue squares represent the risk ratio and study weighting, the black lines represent confidence intervals. The black diamond represents the pooled estimate of effect.

Study or Subgroup	Corticosteroid Events	Corticosteroid Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Galarza 1995	1	57	5	60	9.0%	0.21 [0.03, 1.75]
Lee 1988	1	21	3	19	5.8%	0.30 [0.03, 2.66]
Lee 1999	15	32	37	50	53.1%	0.63 [0.42, 0.95]
Wyser 1996	17	34	18	36	32.2%	1.00 [0.63, 1.60]
Total (95% CI)		**144**		**165**	**100.0%**	**0.69 [0.51, 0.94]**
Total events	34		63			

Heterogeneity: $Chi^2 = 4.31$, df = 3 (P = 0.23); $I^2 = 30\%$

Test for overall effect: Z = 2.35 (P = 0.02)

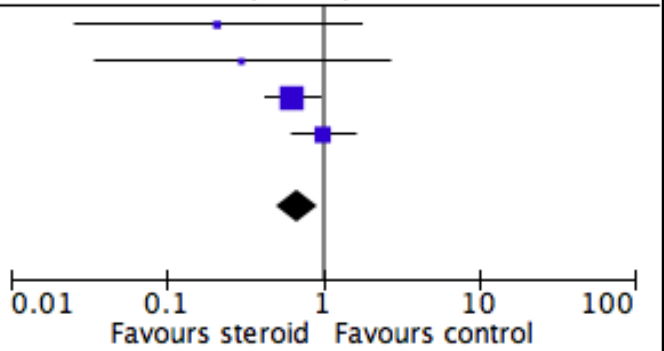

Figure 17: Forest plot demonstrating the effect of steroids in patients with TB pleura on adverse events leading to discontinuation of treatment. Blue squares represent the risk ratio and study weighting, the black lines represent confidence intervals. The black diamond represents the pooled estimate of effect.

Study or Subgroup	Corticosteroid Events	Corticosteroid Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bang 1997	1	33	0	50	6.9%	4.50 [0.19, 107.25]
Elliott 2004	9	97	2	97	34.3%	4.50 [1.00, 20.29]
Galarza 1995	0	57	0	60		Not estimable
Lee 1988	1	21	0	19	9.0%	2.73 [0.12, 63.19]
Lee 1999	0	32	0	50		Not estimable
Wyser 1996	4	34	3	36	49.9%	1.41 [0.34, 5.85]
Total (95% CI)		**274**		**312**	**100.0%**	**2.80 [1.12, 6.98]**
Total events	15		5			

Heterogeneity: $Chi^2 = 1.36$, df = 3 (P = 0.72); $I^2 = 0\%$

Test for overall effect: Z = 2.21 (P = 0.03)

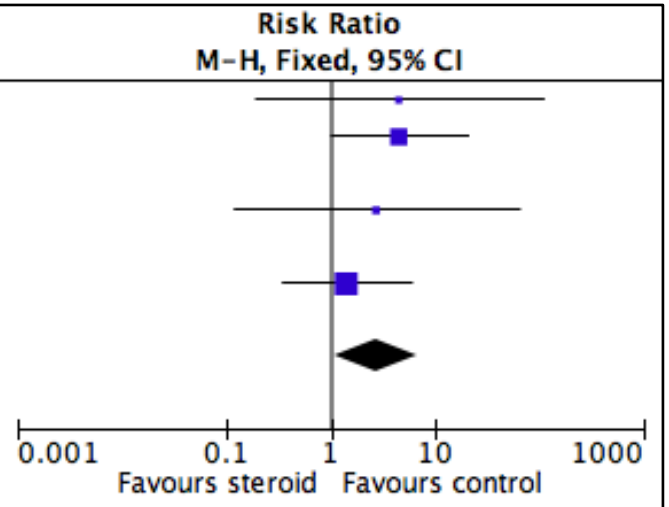

Figure 18: Forest plot demonstrating the effect of steroids in patients with TB pleura on HIV-associated adverse events. Blue squares represent the risk ratio and study weighting, the black lines represent confidence intervals. The black diamond represents the pooled estimate of effect.

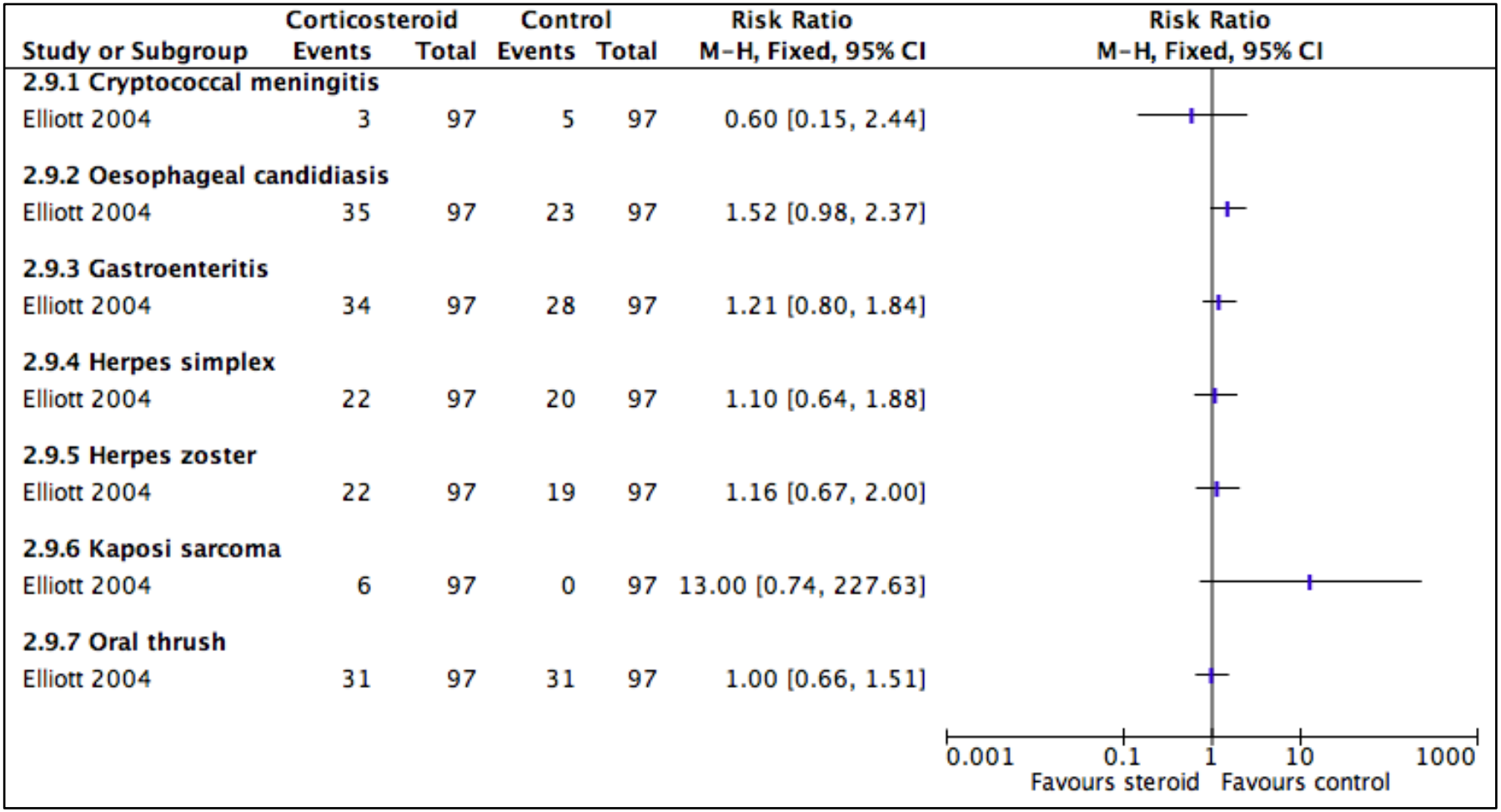

Table 19: Summary of findings table for the effect of corticosteroids in the treatment of pleural TB

Steroids compared with placebo for pleural TB					
Patient or population: Adults with pleural TB **Settings:** Hospital and outpatient **Intervention**: Steroids **Comparison**: Placebo					
Outcomes	**Illustrative comparative risks (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Certainty of the evidence (GRADE)**
	Placebo	**Corticosteroids**			
Residual fluid at 4 weeks	**58 per 100**	**44 per 100** (36 to 55)	**RR** 0.76 (0.62 to 0.94)	394 (3 studies)	⨁⨁⊖⊖[1, 2] **low**
Residual fluid at 8 weeks	**64 per 100**	**46 per 100** (29 to 72)	**RR** 0.72 (0.46 to 1.12)	399 (4 studies)	⨁⊖⊖⊖[3, 4, 5] **very low**
Presence of pleural thickening	**33 per 100**	**23 per 100** (17 to 31)	**RR** 0.69 (0.51 to 0.94)	309 (4 studies)	⨁⨁⊖⊖[6, 7] **low**
Adverse events leading to study drug discontinuation	**5 per 100**	**14 per 100** (6 to 35)	**RR** 2.80 (1.12 to 6.98)	586 (6 studies)	⨁⨁⊖⊖[7, 8] **low**
CI: Confidence interval; **RR:** Risk ratio					
GRADE Working Group grades of evidence **High certainty:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate certainty:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low certainty:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low certainty:** We are very uncertain about the estimate.					

Footnotes

[1]Downgraded by one for risk of bias: one of the three studies (Bang 1997) was assessed as high risk of bias for random sequence generation, and both Bang 1997 and Galarza 1995 were at unclear risk of bias for allocation concealment.

[2] Downgraded by one for inconsistency: the two smaller studies in the meta-analysis (Bang 1997, Galarza 1995) have 95% CI that cross the line of no effect, while the study with the largest weighting (Elliott 2004) shows an effect in favour of steroids, and this contributes the most to the summary estimate.

[3] Downgraded by one for ROB: three of the four studies (Bang 1997, Lee 1988, Lee 1999) were at high or unclear risk of bias for randomization or allocation concealment.

[4]Downgraded by one on inconsistency: two studies showed no effect of steroids, two studies showed steroids reduced the number of patients with pleural effusion at 8 weeks.

[5]Downgraded by one for imprecision: the summary estimate of effect has a broad 95% CI going from a large effect in favour of steroids to a small effect in favour of no steroids.

[6] Downgraded by one for ROB: All four studies (Galarza 1995, Lee 1988, Lee 1999, Wyser 1996) had unclear risk of bias for randomization and allocation concealment.

[7] Downgraded by one for imprecision: small numbers of participants and events led to broad 95% CI.

[8] Downgraded by one for ROB: several studies have unclear or high risk of bias for randomization and allocation concealment.

Guideline Panel's Judgement

Question: Should steroids be routinely prescribed for TB pleura, irrespective of HIV status?

Balance of desirable and undesirable effects

Desirable	Undesirable
Quick recovery	Steroid-associated adverse events
No X-ray changes at the end of treatment	HIV-associated opportunistic infections HIV-associated cancer in people living with HIV
Return to baseline lung function	

Overall quality of evidence across all critical outcomes

High	Moderate	Low	Very low
		X	

Values and preference statement

Patients want to recover quickly, and have quick resolution of radiological evidence of pleural disease. Reducing the risk of long-term disability related to impaired lung function from fibrothorax is the most important outcome.

Draft recommendation

Steroids are not routinely recommended in TB pleura.

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
	X			

Remarks

- The group felt that therapeutic thoracocentesis was a preferred treatment in patients with large pleural effusions.
- The group recognised that there was evidence of an effect in reducing pleural thickening, low quality evidence, but there was no clear evidence that this translated into an effect on lung function or long-term disability.
- The group noted that the outcomes reported in the studies in this review are all proxy measures for long-term morbidity, rather than direct measures. The most important outcomes are long-term lung function and disability.

How long should we treat lymph node TB (LNTB) with ATT?

Background

LNTB can present with involvement of peripheral, mediastinal and/or abdominal lymph nodes. As well as enlarged lymph nodes perceivable clinically or visualized on chest X-ray, abdominal ultrasound scan or CT, and clinical features sometimes include weight loss, fever and night sweats. Most recommendations for the treatment of LNTB have evolved alongside PTB. The problem of persistently enlarged lymph nodes at the end of treatment has vexed clinicians and some practitioners extend treatment duration in such patients, fearing relapse of active TB disease in this group.

This systematic review aims to evaluate the efficacy of rifampicin-based ATT given for six months versus longer duration of therapy. Further, it looks into the outcome of patients with partial clinical response (resolution of clinical signs and symptoms, decrease in lymph node size but residual LN size >1 cm) versus patients with complete clinical cure (resolution of clinical signs and symptoms and residual lymph node size <1cm) at the end of treatment.

This rapid review was prepared specifically for the INDEX-TB Guidelines. A formal Cochrane review is underway at the time of publication.

Objectives

Primary objective:

To compare the efficacy of rifampicin-based 6 months versus 9 months ATT at standard doses in patients with isolated LNTB.

Secondary objective:

To find out the rates of relapse at 12 months or more among cured patients of LNTB in general and among the fraction of partial responders (residual lymph node size >1cm) to treatment.

Methods

Criteria for considering studies for this review

Types of studies - Randomized or quasi-randomized controlled trials, and prospective cohort studies.

Types of participants - Adults and children with a diagnosis of presumed drug sensitive peripheral LNTB.

Types of intervention

Intervention - Six months of rifampicin-based ATT.

Comparator - Nine months or more of rifampicin-based therapy ATT.

Types of outcome measure

Primary outcomes

- Relapse rate in cured patients – defined as increase in size of affected lymph nodes or appearance of new nodes or other forms of TB proven by culture positivity or presence of granulomata on histopathological examination.
- Successful treatment at end of follow up - resolution of constitutional signs and symptoms with decrease in size of lymph nodes.

Secondary outcomes

- Relapse rate in cured patients with partial response (residual lymph node size >1cm).

Search methods for identification of studies

The following databases were searched for relevant studies up to 3rdJune 2015: PubMed (including MEDLINE), EMBASE (accessed via OvidSP), and the Cochrane Central Register of Controlled Trials (CENTRAL), and LILACS. The search terms used are outlined in Box 2.

Box 2 – Detailed search strategy for duration of treatment for LNTB

lymph node, lymphad*, mtb, mycobact*, tuberculosis, lymph node [MeSH term], mycobacterium tuberculosis [MeSH term]

AND

Treatment, therapy, drug*, regimen

Data collection and analysis

We intended to conduct subgroup analyses for children, HIV positive people, malnutrition and other types of immunosuppression, but this was not possible due to lack of reporting on most of these subgroups, and small numbers of participants in the studies.

Results

Figure 19: Flow diagram illustrating the results of search and screening for length of treatment for LNTB

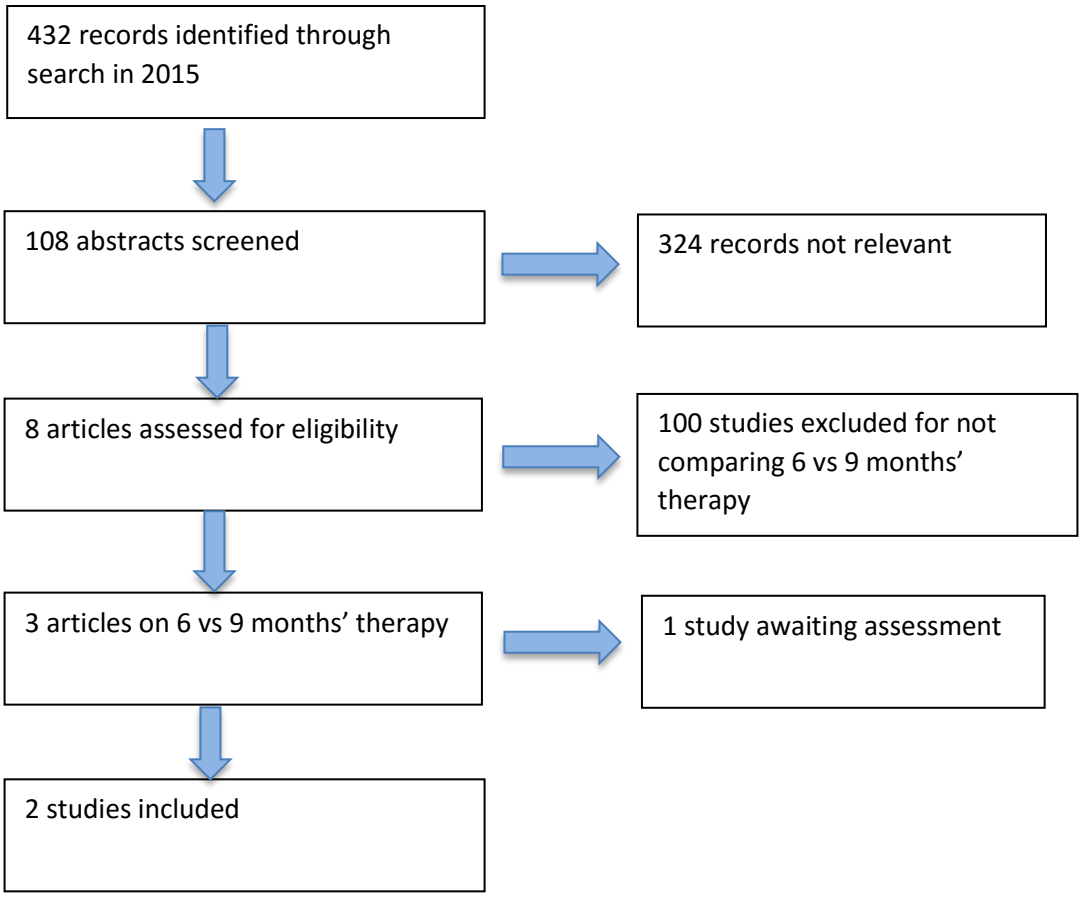

Table 20: Characteristics and outcomes of the included studies comparing 9 months ATT versus 6 months ATT to treat LNTB.

Study	Setting and Study design	Length of follow up after treatment completion (months)	Participants	Regimen
(Yuen 1997)	Hong-Kong Single tertiary care hospital: Department of ENT Surgery, University of Hong Kong, Queen Mary Hospital RCT	Median: 21 (up to 55)	Newly diagnosed, biopsy proven cervical LNTB patients Mean age in years (SD): 6-month group: 28 (10); 9-month group: 32 (14) HIV status not reported	4RHZS/5RH Thrice weekly treatment
				4RHZS/2RH Thrice weekly treatment
(Campbell 1993)	UK Multiple secondary care hospitals: British Thoracic Society Research Committee RCT	30	Newly diagnosed peripheral and mediastinal LNTB patients Age: 16-80 years HIV status not reported	2RHE/7RH Daily treatment
				2RHZ/7RH Daily treatment
				2RHZ/4RH Daily treatment

Table 21. Results of the included studies comparing 9 months ATT versus 6 months ATT to treat LNTB

Study	Total duration (months)	Participants (n)	Lost to follow-up	Treatment modified[1]	Completed treatment	Primary treatment failure at the end of ATT	Successful treatment at end of follow up[2]	Relapse (%)[3]
(Yuen 1997)	9	64	3	13	48	1	42/64	5/47 (10.6%)
	6	49	2	4	42	2	36/49	5/41 (12.2%)
(Campbell 1993)	9	63	14	7	50	0	45/63	4/49 (8.2%)
	9	70	12	10	56	0	56/70	2/58 (3.4%)
	6	66	8	11	51	0	55/66	3/58 (5.2%)

[1]In Yuen 1997, 17 participants required modification of ATT due to a drug-related adverse event – 11 drug-induced hepatitis, 3 gastrointestinal upset, 1 gastrointestinal upset with skin rash, 1 tinnitus, and 1 thrombocytopenia). In BTS 1993, 28 participants had their treatment modified; 8 due to drug toxicity (5 in 9 month arms, 5 in 6 month arm), other reasons for treatment modification reported were drug resistance (5 in 9 month arms, 5 in 6 month arm), non-compliance (1 in 9 month arm), and clinician judgement.

[2] Intention-to-treat analysis, includes participants who received modified treatment

[3] Complete case analysis

Figure 20: Forest plot demonstrating relative risk of relapse in cured patients treated with 6 months ATT compared to 9 months ATT.

This is a complete case analysis, with the denominator in each group consisting of the total number of participants who completed treatment with clinical remission at the end of ATT. Participants who were lost to follow up, had treatment discontinued due to drug-related adverse events, failed to improve on treatment or had their treatment modified were excluded from this analysis. For Yuen 1997, the number of relapses are estimated from the data provided; in the 6-month group, 41 out of 49 participants randomized completed treatment with clinical remission, and the remission rate at five years was 89%; in the 9-month group 47 out of 64 participants randomized completed treatment with clinical remission, and the remission rate at five years was 90%. We cannot be certain of the exact number of relapses in each group as this is not reported, and neither are losses to follow up.

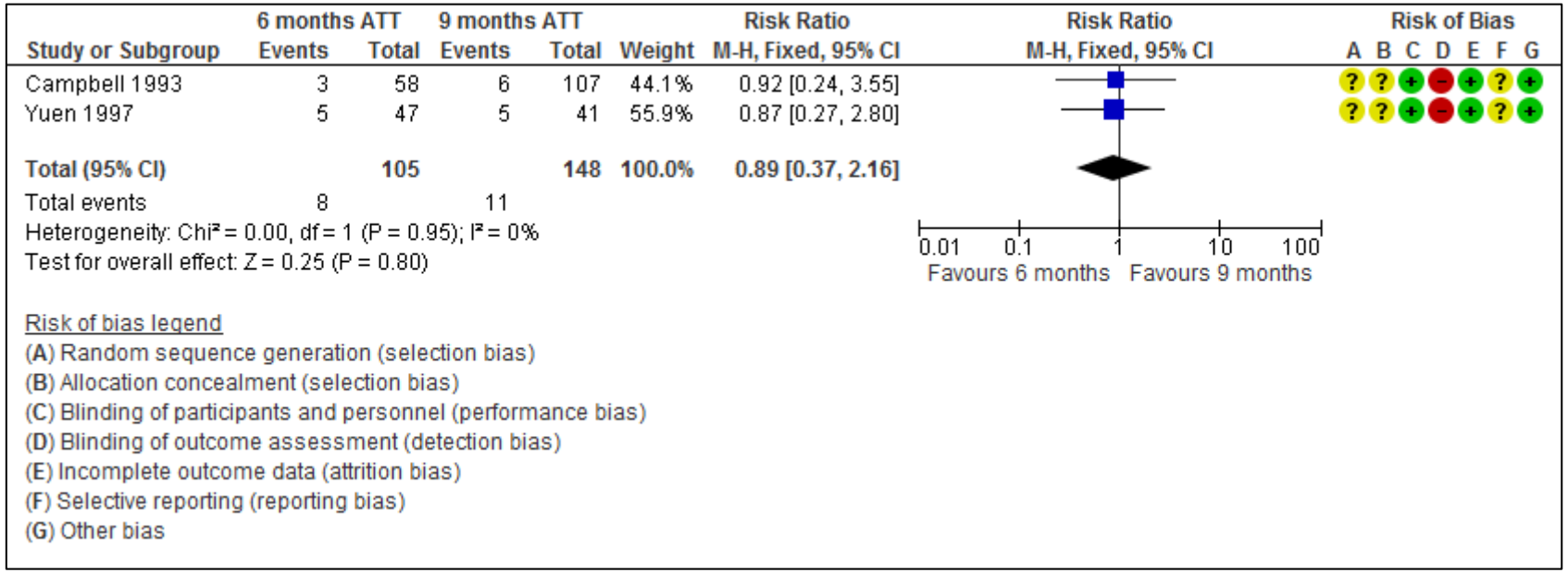

Figure 21: Forest plot demonstrating relative risk of successful treatment at the end of follow up with 6 months ATT compared to 9 months ATT.

This is an intention-to-treat analysis, including all randomized participants. Participants were described as having had successful treatment at the end of follow up if they had completed the course of ATT without primary treatment failure, and had not required further treatment for relapse by the end of follow up. Participants who had residual lymphadenopathy at the end of follow up but who were not deemed to have active TB disease and who had not received retreatment for TB were counted as having had successful treatment.

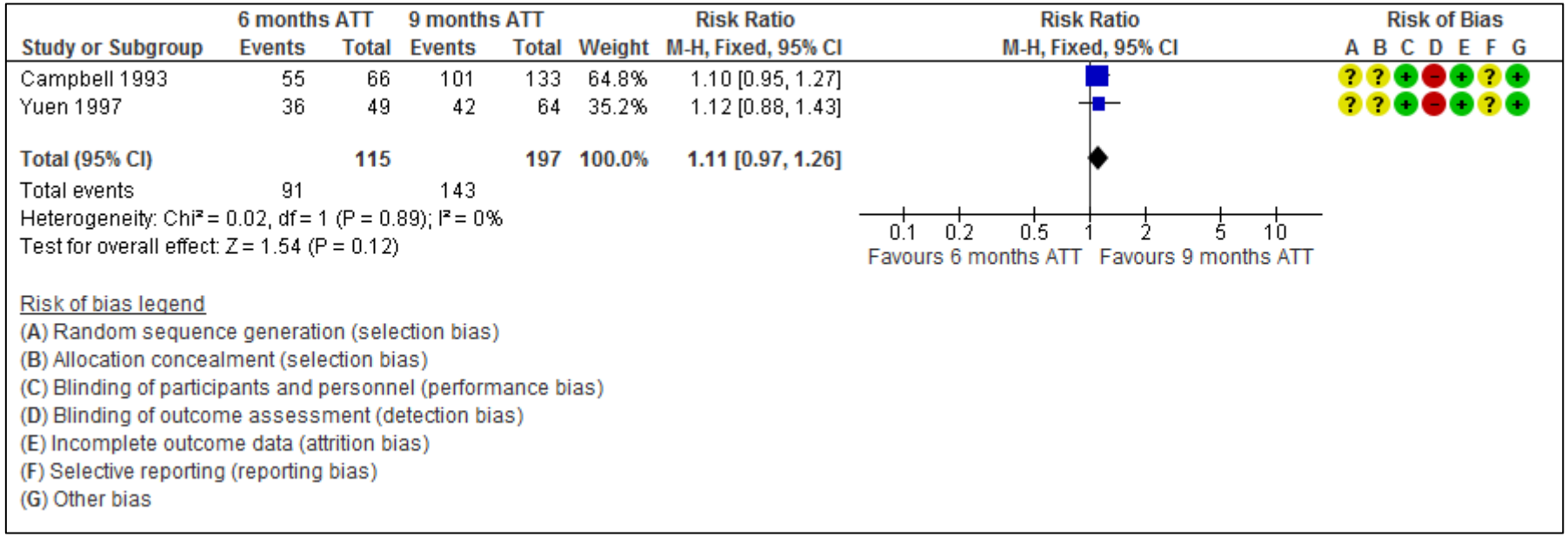

Table 22: Summary of findings on duration of treatment for LNTB

9 months ATT compared to 6 months Rifampicin-based ATT for LNTB					
Patient population: Adults with newly diagnosed LNTB Settings: Hospitals and outpatient clinics Intervention: 9 months ATT Comparison: 6 months ATT					
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**
	Assumed risk	Corresponding risk			
	9 months ATT	**6 months ATT**			
Relapse in cured patients Follow-up: median 21 months, up to 55 months	**89 per 1000**	**79 per 1000** (33 to 192)	**RR 0.89** (0.37 to 2.16)	253 (2 studies)	⊕⊕⊖⊖ **Low**[1,2]
Successful treatment at end of follow up	**708 per 1000**	**786 per 1000** (687 to 893)	**RR** 1.11 (0.97 to 1.26)	312 (2 studies)	⊕⊕⊕⊖ **Moderate**[1]
The **assumed risk** is the median risk in the nine month group between studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (6 months ATT), and its 95% CI. **CI:** Confidence interval; **RR:** Risk ratio					
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.					

Footnotes

[1]Downgraded by one for risk of bias: both of the included studies had inadequately reported methods of randomization and allocation concealment.

[2]Downgraded by one for imprecision: the lower bound of the 95% CI of the relative effect estimate implies that there are less than half as many relapses in patients treated for 6 months compared to patients treated for 9 months, whereas the upper bound implies there are over twice as many relapses in patients treated for 6 months compared to patients treated for 9 months.

Relapse Rate among partial responders in LNTB

It was not possible to disaggregate data about the rate of relapse in patients who completed treatment but had residual lymphadenopathy >1 cm (partial responders) from the two included randomised controlled trials.

In the preliminary paper to Campbell 1993 (British Thoracic Society Research Committee, 1992) the authors report residual lymphadenopathy at the end of ATT in 41% in the six-month arm, 28% in the nine-month arm with ethambutol and 17% in the nine-month arm with pyrazinamide. The absolute numbers are not reported, and no data are provided about whether any of these patients went on to have a relapse. At the end of the 30-month post-treatment follow up period, 10 out of the 58 participants available for follow-up in the six-month group had residual lymphadenopathy, 6 out of 49 in the nine-month ethambutol group, and 10 out of 58 in the nine-month pyrazinamide group.

In Yuen 1997, participants were considered to be in remission if they had complete resolution of lymphadenopathy, or the size of the affected lymph nodes was decreasing or smaller than 0.5cm. Again, it is not clear from the reported data how many partial responders there were, and whether any of these went on to relapse.

Five additional studies returned by the search but excluded from the meta-analysis because they did not compare 6 months versus 9 months ATT gave disaggregated data on outcomes for patients with residual lymphadenopathy at the end of ATT. The Table 23 shows the numbers of partial responders, and the number of these who went on to relapse. These studies included adults and children with peripheral LNTB patients only, except Ayed AK 2001 which included mediastinal LNTB patients only. None of the studies included people with HIV.

Table 23: Characteristics and outcomes of single-arm studies returned in the search that reported data on outcomes for patients with residual lymphadenopathy at the end of ATT (partial responders).

Study	No. of participants	Drug Regimen	Total treatment duration (months)	Partial Responders (%)	Follow up after completion of ATT (months)	Relapse among partial responders (%)
(British Thoracic Society Research Committee, 1985)	56	2HRE/7HR	9	7/56 (12.5%)	27	0
	57	2HRE/16HR	18	3/ 57 (14%)	18	0
(Jawahar 1990)	168	2HRZS (thrice weekly/4HS (twice weekly)	6	50 (30.4%)	33-36	4 (2.4%)
(Jawahar 2005)	134	2HRZ/4RH (twice weekly under DOT)	6	14/134 (10.4%)	36	1 (1.3%)
	134	6RH (daily)	6	17/134 (12.68%)	36	1 (1.3%)
(Ayed 2001) [1]	34	2HRZ/4-7HR	6-9	6 (17.6%)	6-19	0
(Cheung WL 1990)	123	6HRZE	6	18(14.6%)	36	0

[1]Ayed 2001 was a prospective cohort study looking at patients with mediastinal LNTB diagnosed via mediastinoscopy. They report 28/34 complete response to ATT at the end of 6 months. Six patients had further enlargement of affected nodes, new nodes or wound-related sinuses at the end of 6 months ATT. These patients received an additional 3 months RH. All participants had complete resolution of disease at follow up 6-19 months after completing ATT.

Guideline Panel's Judgement

Question: What duration of treatment should be used to treat peripheral LNTB?

Balance of desirable and undesirable effects

Desirable	Undesirable
Cure rates are similar in the data collected for 6 months and 9 months (moderate quality evidence Relapse rates are similar in the data collected for 6 months and 9 months (low quality evidence) Patients more likely to complete shorter regimens Less exposure to adverse effects of ATT	Drug-related adverse events such as drug-induced hepatitis Poor adherence to treatment increasing the risk of acquired drug resistance Relapse of LNTB or of more life-threatening form of TB

Overall quality of evidence across all critical outcomes

High	Moderate	Low	Very low
		X	

Values and preference statement

Relapse of LNTB is not serious or life-threatening, but may contribute to chronic morbidity.

Draft recommendation

Six months ATT standard first-line regimen is recommended for peripheral LNTB.

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
X				

Remarks

- The group considered that the available evidence for peripheral LNTB did not demonstrate any significant harm associated with 6 months' treatment compared with 9 months (low quality evidence).
- There was very little evidence available for abdominal and mediastinal LNTB, and the group noted that the optimal duration of treatment may be different for these patients. A specific recommendation was not made.
- There is little evidence in patients who are found to have disseminated TB or TB in multiple lymph node groups.
- There is some evidence that partial responders (patients with persisting lymphadenopathy >1cm at the end of 6 months' treatment) do not relapse. These patients do not generally require extension of treatment.

How long should we treat abdominal TB with ATT?

Background

Abdominal TB can present with isolated involvement of any of the following sites: peritoneal, intestinal, upper gastrointestinal (oesophageal, gastroduodenal), hepatobiliary, pancreatic and perianal. The clinical features as well as diagnostic modalities depend on the site of involvement. Internationally, most guidelines recommend to treat all types of abdominal TB with the same regimen as for pulmonary TB – a two-month intensive phase with four drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) followed by a four-month continuation phase with isoniazid and rifampicin. Adding pyrazinamide to a regimen containing isoniazid and rifampicin for treating pulmonary TB has allowed shortening treatment duration from nine to six months. However, evidence supporting this could be extrapolated to abdominal TB is unclear.

Shorter duration of treatment may increase compliance, leading to reduced numbers of relapses as well as the emergence of drug-resistance strains. Furthermore, shorter regimens decrease the risk of anti-tubercular drug toxicity. Whether six-month regimen achieves successful treatment rates as good as with nine-month regimen without significantly increasing the number of relapse is the key concern for accepting a shorter ATT regimen. The present review aim to evaluate the effects of treatment with the six-month regimen compared to the nine-month regimen for abdominal TB.

Objective

To compare the effects of treatment with the six-month first line regimen 2RHZE/4RH versus the nine-month regimen 2RHZE/7RH for abdominal TB.

Methods

Criteria for considering studies for this review

Types of studies - Randomized or quasi-randomized controlled trials.

Types of participants - Adults and children with a diagnosis of presumed drug sensitive abdominal tuberculosis as defined by the authors.

Types of intervention

Intervention - 2RHZE/4RH.

Control - 2RHZE/7RH.

Types of outcome measures

Primary outcomes

- Relapse - new symptoms and signs of abdominal TB after completion of ATT[1].
- Successful treatment - resolution of signs and symptoms at the end of follow up.

Secondary outcomes

- All cause death.
- Treatment failure – failure to improve with ATT, or deterioration following initial improvement while on ATT.
- Default – patients who discontinue ATT before the end of treatment, or patients whose treatment is interrupted for 8 weeks or more consecutively.

[1] Used interchangeably with “recurrence”

Adverse events

- Adverse effects relating to the ATT.
- Drug toxicity (including hepatic toxicity) leading to discontinuation of regimen.

Search methods

The following databases were searched for relevant studies up to 3rd June 2015: PubMed (including MEDLINE), EMBASE (accessed via OvidSP), and the Cochrane Central Register of Controlled Trials (CENTRAL), and LILACS. The search terms used are outlined in Table 24.

Table 24: Detailed search strategy for duration of treatment for abdominal TB

1	abdominal tuberculosis.mp. or abdominal tuberculosis/ or tuberculous peritonitis/
2	limit 1 to human
3	gastrointestinal tuberculosis.mp.
4	splenic tuberculosis.mp.
5	2 or 3 or 4
6	randomized controlled trial/
7	drug comparison/ or controlled clinical trial.mp. or controlled clinical trial/
8	cohort study.mp. or cohort analysis/
9	6 or 7 or 8
10	5 and 9

Data collection and analysis

We analyzed the outcome data based on an intention-to-treat analysis.

We intended to conduct subgroup analyses for children, HIV positive people, malnutrition and other types of immunosuppression, but this was not possible due to lack of reporting on most of these subgroups, and small numbers of participants in the studies.

Results

Search results

Figure 22: Flow diagram illustrating the results of search and screening for length of treatment for abdominal TB

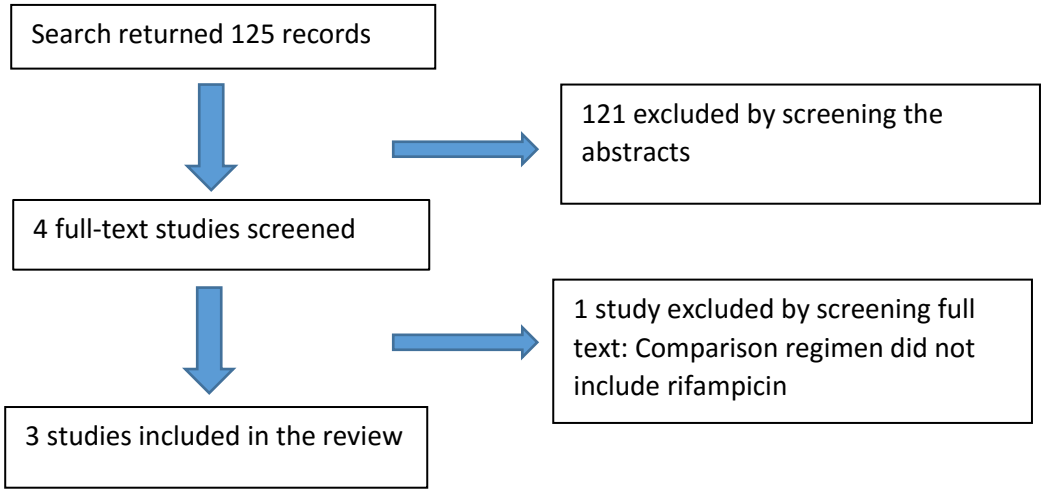

Table 25: Characteristics of the included studies comparing 9 months ATT versus 6 months ATT to treat abdominal TB.

Study	Study design	Setting	Drug regimen	Participants	Site of TB	Duration of follow in months	Relapse	Successful treatment
(Makharia GK, 2015)	RCT	India Three tertiary centres	$2(HRZE)_3/4(HR)_3$	n = 100 Mean age, years (SD): 34 (14.2)	Peritoneum: 23 participants GIT: 77 participants	12	1/100	75/100
			$2(HRZE)_3,7(HR)_3$	n = 91 Mean age, years (SD): 34.9 (13.9)	Peritoneum: 18 participants GIT: 73 participants	12	0/91	69/91
(Park SH, 2009)	RCT	South Korea SIngle university hospital	2HRZE/4HRE	n = 45 Median age, years (range): 36 (18-71)	Ileocaecal area: 38 Ascending colon: 25 Transverse colon: 10 Rectum and sigmoid colon: 5 Descending colon: 4	Median: 39	1/45	42/45
			2HRZE/7HRE	n = 45 Median age, years (range): 42 (20-71)	Ileocaecal area: 41 Ascending colon: 28 Transverse colon: 15 Rectum and sigmoid colon: 10 Descending colon: 5	Median: 32	0/45	41/45
(Tony J, 2008)	RCT	India One medical college	$2(HRZE)_3/4(HR)_3$	n = 23 Mean age, years (SD): 39.9 (13.5)	Ileocecal area, colon or both sites	Median: 27 (range 3-55)	0/23	23/23
			2HRZE/7HR	n = 24 Mean age, years (SD): 37.8 (11.6)	Ileocecal area, colon or both sites	Median: 26 (range 3-52)	0/24	24/24

GIT: gastrointestinal tract

Risk of bias assessment

Figure 23: Risk of bias summary for duration of treatment for abdominal TB: review authors' judgements about each risk of bias item for each included study.

Figure 24: Forest plot demonstrating the risk difference of relapse across studies. Blue squares represent the risk ratio and study weighting, the black lines represent confidence intervals. The black diamond represents the pooled estimate of effect.

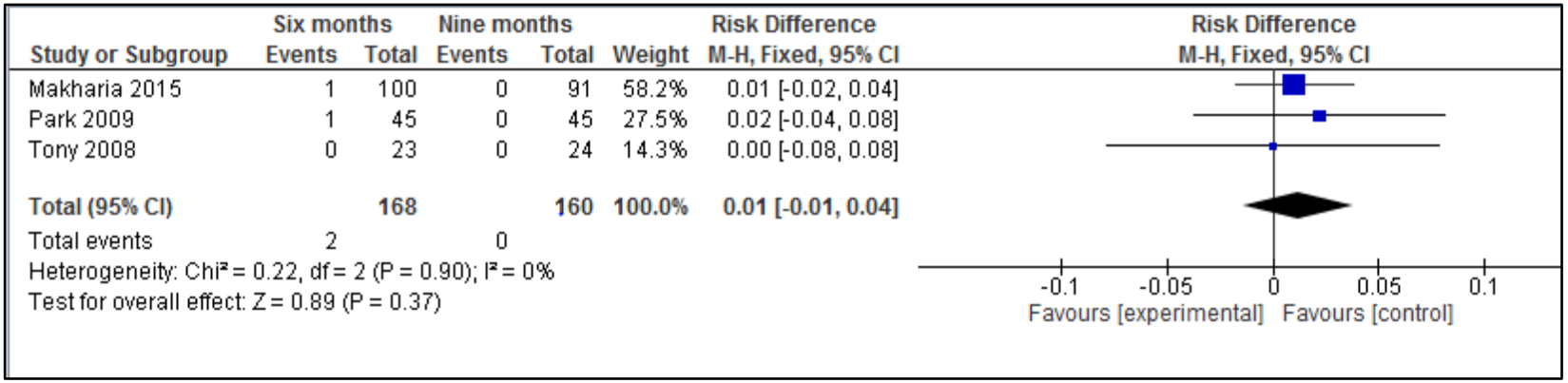

Figure 25: Forest plot demonstrating the risk ratio of death across studies. Blue squares represent the risk ratio and study weighting, the black lines represent confidence intervals. The black diamond represents the pooled estimate of effect.

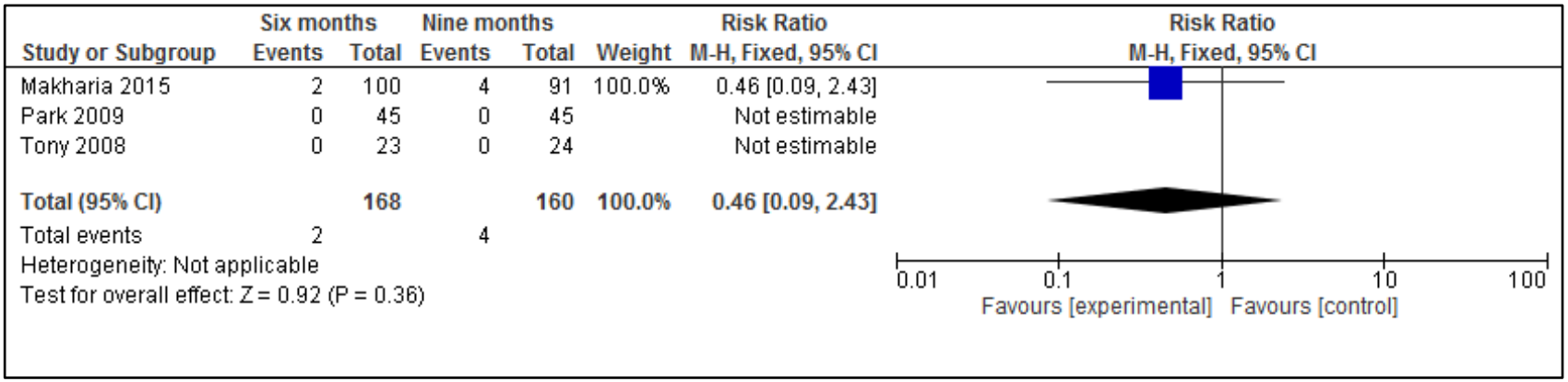

Figure 26: Forest plot demonstrating the risk ratio of treatment failure across studies. Blue squares represent the risk ratio and study weighting, the black lines represent confidence intervals. The black diamond represents the pooled estimate of effect.

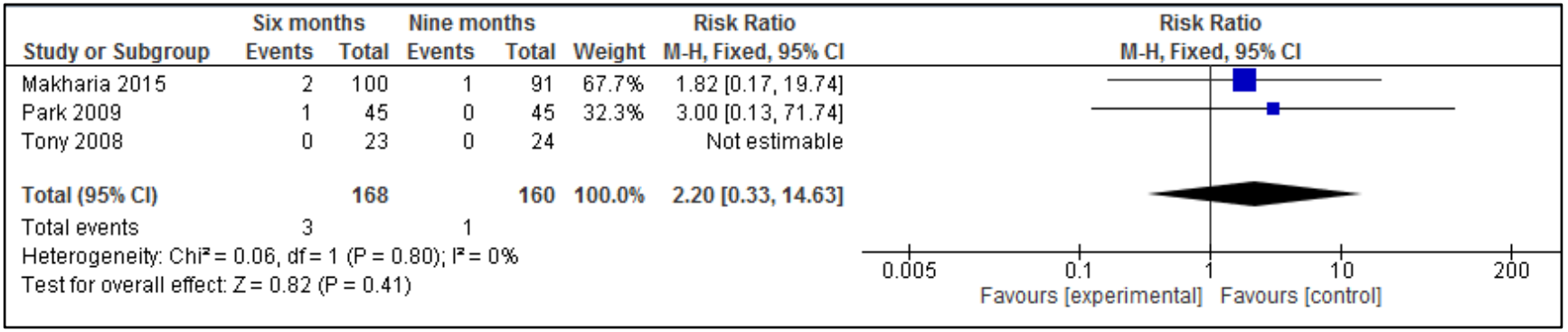

Figure 27: Forest plot demonstrating the risk ratio of adverse events leading to discontinuation of ATT across studies. Blue squares represent the risk ratio and study weighting, the black lines represent confidence intervals. The black diamond represents the pooled estimate of effect.

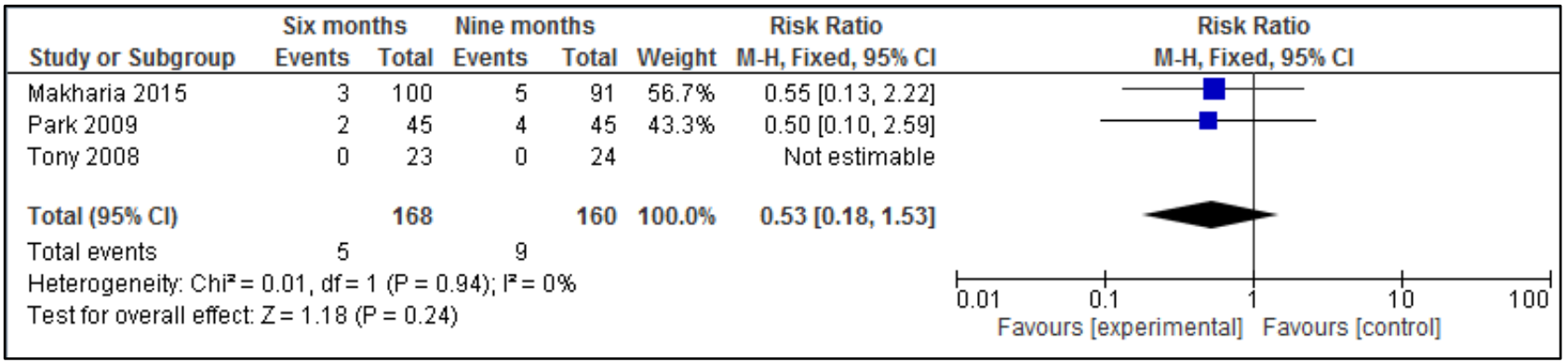

Table 26: Summary of findings on duration of treatment for abdominal TB

Is treatment with six months' ATT as effective as treatment with nine months ATT?

Patient or population: 328 people with abdominal tuberculosis
Settings: specialist hospitals, India, South Korea
Intervention: 6 months ATT - 2RHZE/4RH[1]
Comparison: 9 months ATT - 2RHZE/7RH[1]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risks	Corresponding risk			
	9 months	6 months			
Relapse (from 3 to 12 months)	**0 per 1000**	10 per 1000 (0 to 40)	**RD** 0.01 (-0.01 to 0.04)	328 (3 studies)	⊕⊖⊖⊖ **Very Low**[2,3,4]
Treatment failure at end of treatment	**6 per 1000**	13 per 1000 (2 to 88)	**RR** 2.20 (0.33 to 14.63)	328 (3 studies)	⊕⊖⊖⊖ **Very Low**[2,3,4]
Death	**40 per 1000**	18 per 1000 (4 to 970)	**RR** 0.46 (0.09 to 2.43)	328 (3 studies)	⊕⊖⊖⊖ **Very Low**[2,3,4,]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **RD**: Risk Difference

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Footnotes

[1]One study (Park 2009) used ethambutol in the continuation phase in both arms due to high rates of primary drug resistance in their population.

[2]Downgraded by one for risk of bias: two studies (Park 2009, Tony 2008) had problems with risk of bias in patient selection; definitions of outcome measures were vague in all studies.

[3]Downgraded by one for imprecision: very small numbers of events, as well as small numbers randomized to each group.

[4]Downgraded by one for indirectness: Park 2009 and Tony 2008 had highly restrictive inclusion criteria leading to a highly selected sample of patients; all studies excluded children under 11 years, HIV positive people, and people who were unlikely to comply with treatment.

Guideline Panel's Judgement

Question: What duration of treatment should be used to treat abdominal TB?

Balance of desirable and undesirable effects

Desirable	Undesirable
More patients complete treatment	Uncertainty about relapse rates from current evidence
Possibly fewer adverse events related to ATT	Longer regimens could increase the risk of default and drug toxicity
No evidence to show higher relapse rates from shorter regimen from efficacy data (very low quality evidence)	

Overall quality of evidence across all critical outcomes

High	Moderate	Low	Very low
			X

Values and preference statement

Patients with abdominal TB need treatment that will cure them of TB infection and reduce the risk of relapse. Longer treatment regimens are more difficult to adhere to, so the shortest effective regimen is preferred.

Draft recommendation

Six months ATT standard first-line regimen is recommended for abdominal TB.

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
X				

Remarks

- Six months' treatment was deemed to be appropriate for new patients with low risk of drug resistance.
- The group recognised the paucity of data to answer this question, but noted that the six-month groups did not have a marked number of relapses.
- The data refer to peritoneal and intestinal disease – the group had concerns about other forms of abdominal TB where there was very little evidence. Longer treatment may be required for other sites (hepatic, pancreatic, perianal, gastric), and further research is required to establish the optimum treatment duration in these forms of abdominal TB.
- Some patients may require extension of the continuation phase of ATT, and the group agreed that this must be assessed by the treating clinician.
- The gastroenterology group noted that some patients who are considered cured remain symptomatic due to adhesions/strictures. These patients do not benefit from continued ATT.

How long should we treat TB meningitis with ATT?

Background

TB meningitis constitutes a medical emergency, and it is essential to start ATT as soon as it is suspected in order to reduce rapidly progressing, life threatening outcomes. In contrast to pulmonary TB, there is a lack of standardised international recommendations for treating TB meningitis. This is partly due to the limited existing evidence regarding the optimal choice and dose of anti-tubercular drugs, as well as the most appropriate duration of treatment for this form of EPTB.

Two main arguments have led to the perception that longer treatment (than for PTB) is needed for TB meningitis to bring about microbiological cure and prevent relapse. The first one is that the blood-brain barrier hinders the penetration of anti-tubercular drugs to reach adequate drug concentration in the infected site. The second one concerns relapse rates. When assessing PTB regimens, relapse rates of 5% are generally considered acceptable (Donald, 2010). However relapse of TB meningitis is fearsome as it is a life-threatening condition and can lead to severe neuro-disability. Thus, whether any risk of relapse is tolerable for TB meningitis is to be considered when establishing TB meningitis regimens. However, longer anti-tubercular treatments are associated with reduced adherence, increased incidence of drug toxicity and increased costs (van Loenhout-Rooyackers, 2001).

The standard first-line regimen for drug sensitive TB meningitis, according to the WHO guidelines, is a 2-month intensive phase with isoniazid, rifampicin, pyrazinamide and ethambutol or streptomycin followed by a 10-month continuation phase with isoniazid and rifampicin – 2 HRZE or S / 10 HR (WHO, 2010). Several different regimens are used in current practice, with variations regarding doses, selection of the fourth drug and duration of treatment from 6 to more than 24 months. Variations regarding the number of drugs used in both the intensive and continuation phases are used. As an example, the South African regimen consists in 6-month intensive course with four drugs (isoniazid, rifampicin, pyrazinamide and ethionamide) with no continuation phase. A study reviewing the duration of treatment for TB meningitis by comparing case series of both adults and children, showed similar completion and relapse rates between 6-month treatment regimens including at least isoniazid, rifampicin and pyrazinamide and longer treatment (van Loenhout-Rooyackers, 2001).

Given the potentially devastating outcomes of relapse on the one hand, and the disadvantages of long therapy on the other hand, it is time to review the literature for establishing the most appropriate duration of treatment for TB meningitis.

Objective

To compare the effects of treatment regimens of nine months or less versus regimens given for twelve months or more for TB meningitis.

Methods

Criteria for including studies

Types of studies - Randomized or quasi-randomized controlled trials, and prospective cohort studies.

Types of participants - Adults and children with a diagnosis of presumed drug sensitive TB meningitis as defined by the authors.

Types of intervention

Intervention - ATT regimens of nine months or less which include rifampicin.

Comparator - ATT regimens of twelve months or longer which include rifampicin.

Types of outcome measure

Primary outcomes

- Relapse – patients who have new symptoms and signs of TBM after completion of ATT.

- Default - patients who discontinue ATT before the end of treatment, or patients whose treatment is interrupted for 8 weeks or more consecutively.

Secondary outcomes

- Successful treatment - sustained improvement in signs and symptoms at the end of follow up.
- Treatment failure - failure to improve with ATT, or deterioration following initial improvement while on ATT.
- Treatment completed.
- Neurological sequelae.
- Death.

Adverse events

- Adverse effects relating to the ATT.
- Drug toxicity (including hepatic toxicity) leading to discontinuation of regimen.

Search methods for identification of studies

The following databases were searched for relevant studies up to 21 May 2015: PubMed (including MEDLINE), EMBASE (accessed via OvidSP), the Cochrane Central Register of Controlled Trials (CENTRAL), and LILACS. The search terms used are outlined in Table 27. The references of all included studies were hand-searched.

Table 27: Detailed search strategy for length of treatment in TB meningitis

1	tuberculous meningitis/ or tuberculosis meningitis.mp.
2	brain tuberculosis.ab. or brain tuberculosis.ti.
3	1 or 2
4	randomized controlled trial/
5	controlled clinical trial.mp. or controlled clinical trial/
6	cohort study.mp. or cohort analysis/
7	4 or 5 or 6
8	3 and 7

Data collection and analysis

Each study was assessed for risk of bias according to the Downs and Black checklist for assessment of methodological quality. It provides an overall score by assessing the quality of reporting, external validity, internal validity (bias and confounding) and power.

Meta-analysis was not possible due to the heterogeneity of the studies and the lack of randomized controlled trials.

We intended to conduct subgroup analyses for adults/children, disease severity, HIV status, malnutrition and other types of immunosuppression, but this was not possible due to lack of reporting on most of these subgroups, and small numbers of participants in the studies.

Results

Figure 28: Flow diagram illustrating the results of search and screening for length of treatment for TB meningitis

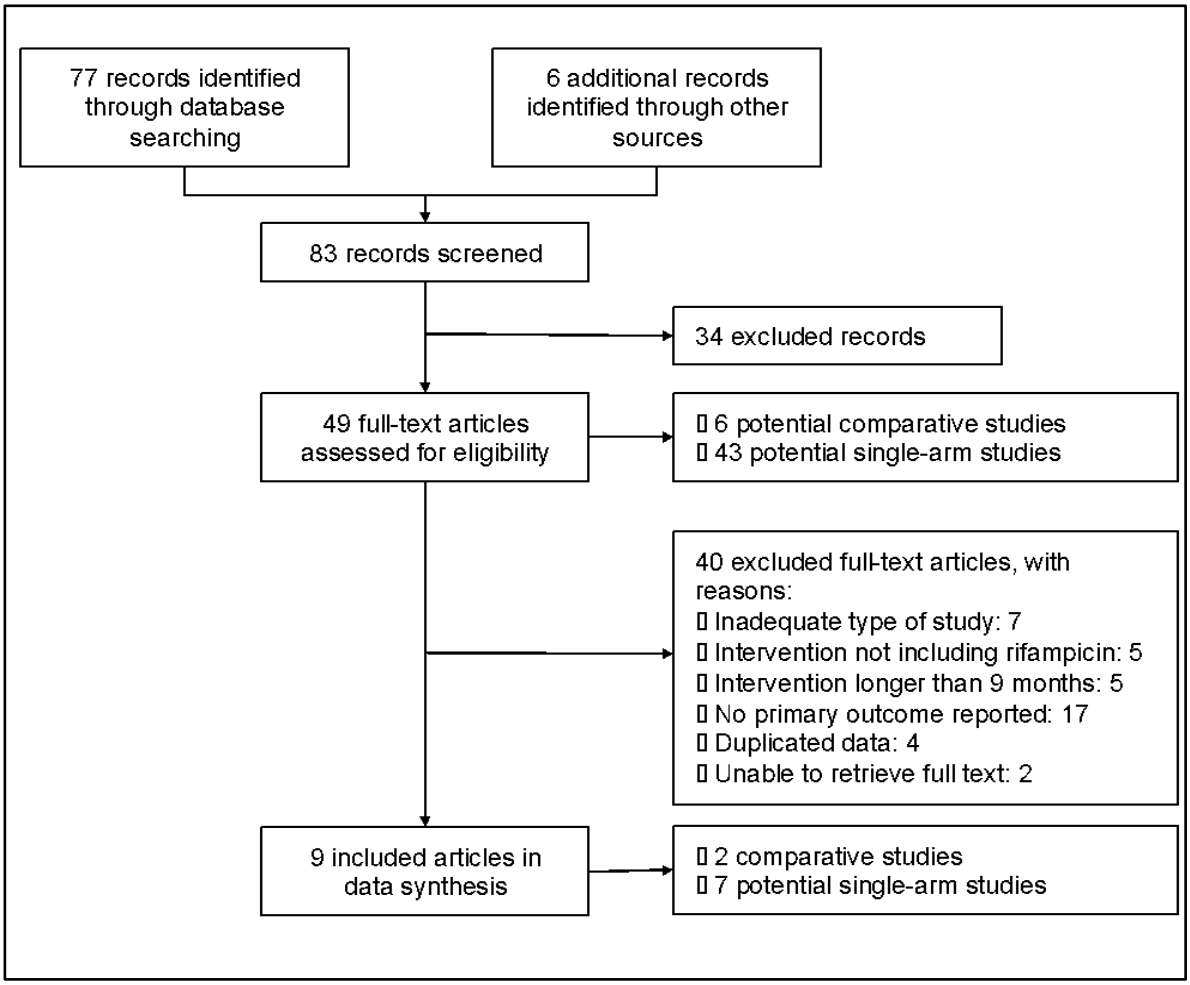

Table 28: Characteristics on the included studies on length of treatment for TB meningitis

Study	Type of Study	Setting	Participants			Drugs	Duration of treatment	Duration of follow up	Lost to follow up
			Number	Adults/ Children	HIV status				
(Doganay M, 1995)	Prospective comparative study – two regimens (short course in 3 centres, long course in 1 centre), data collected at the same time	Turkey	72	Adults	NR	2HRZS/6HR (37 cases)	8 mo	Median 10 mo (range 6 to 24 mo)	10/72
						HRZE (19 cases) HRES (6 cases) HRZS (6 cases) HRZES (3 cases) HRE (1 case)	12-16 mo	Median 13 mo (range 4 to 36 mo)	
(Jacobs RF, 1992)	Prospective comparative study[1] – successive cohorts in the same centre using different regimens over time	Thailand	53	Children	NR	2HRZS/4HR (45 cases)	6 mo	At least 12 mo: 27/38 Less than 12 mo: 7/38	4/38
						2HRS/7HR (4 cases)	9 mo	Not clear	NR
						2HSE/10HE (2 cases) 2RSE/10RE (2 cases)	12 mo	Not clear	NR
(Alarcón F, 1990)	Prospective observational study	Ecuador	28	Adults and adolescents	NR	2HRZ/4HR	6 mo	24 to 36 mo	0/28
(Biddulph, 1990)	Prospective observational study, one centre[2]	Papua New Guinea	43	Children	NR	2HRZS/4HR	6 mo	No disaggregated data for TBM (up to 24 mo)	No disaggregated data
(Chotmongkol, 1991)	Prospective observational study	Thailand	29	Adults	NR	2HRZS/4HR	6 mo	Mean 16.3 mo (range 4-33 mo)	4/29
(Chotmongkol V, 1996)	Prospective observational data[3]	Thailand	59	Adults	NR	2HRZS/4HR	6 mo	Mean 30 mo (range 16-45 mo)	NR
(Donald PR, 1998)	Prospective observational study	South Africa	95	Children	NR	6HRZEth	6 mo	12 mo	12/95
(Phuapradit P, 1987)	Prospective observational study	Thailand	28	Adults	NR	2HRZS/7HR	9 mo	Mean 19.8 (range 12-29)	5/28

(van Toorn R, 2014)	Prospective observational study	South Africa	184	Children	133/184 HIV- 22/184 HIV+	6HRZEth (135 cases) 9HRZEth (25 cases)[4] Prolonged HRZEth (24 cases)[5]	6 mo (HIV-) 9 mo (HIV+)	24 mo	29/184

E: ethambutol, Eth: ethionamide; H: isoniazid; R: rifampicin; S: streptomycin; Z: pyrazinamide; NR: not reported

[1] 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 patients receiving rifampicin, the second a 9 month regimen with all patients receiving rifampicin, and the third received a 6 month regimen with all patients receiving rifampicin and pyrazinamide.

[2] This study reported on a cohort of children in one centre with all forms of tuberculosis. The data for the subset of patients with CNS TB are presented here. It was not possible to disaggregate data for defaulters and adverse events in CNS TB patients in this cohort.

[3] This study was a randomized double-blind controlled trial of ATT with steroids versus ATT with placebo. Treated as prospective observational data for the purposes of this review.

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

[5] Prolonged ATT was given to 24 cases with adverse events and/or TB mass lesions.

Assessment of risk of bias in included studies

No RCT comparing directly short and long-course ATT regimens were found. All studies were observational studies with small numbers of participants. As these were non-randomized studies, we used the checklist for the assessment of methodological quality developed by Downs and Black (Downs SH, 1998). This checklist scores each study in five areas of methodological quality: reporting, external validity (how generalizable the results are), internal validity (the risk of bias and confounding), and power.

Figure 29: Bar chart showing the results of the quality assessment for each study included on length of treatment for TB meningitis using the Downs and Black checklist.

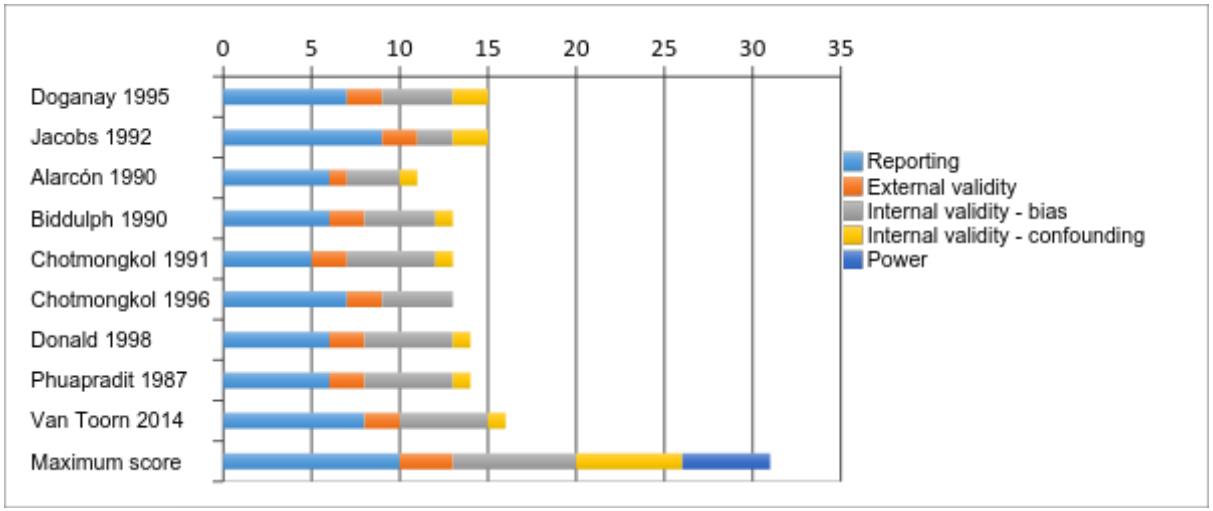

Table 29: Outcomes reported within the included studies for length of treatment for TB meningitis

Duration of Tx (months)	Studies	Primary outcomes		Secondary outcomes						Adverse events	
		Relapse	Default	All-cause deaths	Deaths after 6 mo Tx	Successful Tx	Tx failure	Tx completed	Neurological sequelae	Relating to ATT	Leading to discontinuation of ATT
6	**Jacobs 1992**	0/45	0/45	7/45	NDD[4]	38/45	NR	38/45	11/45	NR	0/45
	Alarcón 1990	1/28	NR	9/28	1/28	16/28	4/28	NR	3/28	20/28	6/28
	Biddulph 1990	1/43	NDD[2]	5/43	0/43	NR	NR	NDD[7]	NR	NR[8]	NR[8]
	Chotmongkol 1991	0/29	0/29	4/29	0/29	20/29	Unclear[6]	20/29	3/29	NR	1/29
	Chotmongkol 1996	0/59	0/59	7/59	0/59	52/59	0/59	52/59	6/59	NR[9]	NR
	Donald 1998	1/95	0/95	15/95	2/95	64/95	0/95	77/95	22/95	23/95	5/95
	Van Toorn 2014	0/184	Unclear[3]	15/184	8/184	140/184	0/184	177/184	98/184	51/184	17/184
8	**Doganay 1995**	0/37	0/37	5/37	0/37	58/72[5]	1/37	25/37	8/37	6/37	NR
9	**Phuapradit 1987**	0/28	0/28	2/28	2/28	23/28	0/28	23/28	3/28	21/28	1/28
	Jacobs 1992	0/4	0/4	2/4	NDD[4]	2/4	NR	2/4	2/4	NR	0/4
12	**Jacobs 1992**	0/4	0/4	2/4	NDD[4]	2/4	NR	2/4	2/4	NR	0/4
12-16	**Doganay 1995**	2/35[1]	2/35[1]	2/35	0/35	58/72[5]	1/35	30/35	10/35	8/35	NR

NDD: no disaggregated data; NR: not reported; Tx: treatment

[1] The two patients who presented relapse had interrupted treatment after three and five months of ATT and were therefore reported as defaulters.

[2] There were 145/639 defaulters among all participants with TB with no disaggregated data for TB meningitis.

[3] 3 patients were described to have poor adherence to treatment, with no further details to know whether they fulfil default definition.

[4] Data from Jacobs 1992 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 authors state that over 90% of deaths occurred within the first 3 months of treatment in this study.

[5] No disaggregated data on successful treatment between both arms in Doganay 195 study.

[6] Unclear whether 3 deaths from underlying disease were because of treatment failure.

[7] 373/639 TB cases had completed treatment and were available for follow-up.

[8] There were 15/639 TB cases with adverse events due to the ATT, with no disaggregated data for TBM. ATT was stopped and not restarted in 9 children and stopped but restarted in 5 children.

[9] Authors reported there were no complications secondary to prednisolone therapy such as gastrointestinal bleeding or hyperglycaemia. No other data were reported regarding other potential adverse effects related to ATT.

Table 30: Adverse events reported in studies included on length of treatment for TB meningitis

Studies	Duration of Tx (months)	Adverse events		Adverse events
		Relating to ATT	Leading to discontinuation of ATT	
Doganay 1995	8	6/37	NR	- Toxic hepatitis: 10 cases - Nausea and vomiting: 2 cases - Hearing loss: 2 cases
	12-16	8/35	NR	
Jacobs 1992	6	NR	0/45	NR
	9	NR	0/4	
	12	NR	0/4	
Alarcón 1990	6	20/28	6/28	- Elevation in hepatic enzymes/bilirubin: 11/28 (39.1%), leading to discontinuation of treatment with H/R and substitution with S for 3-7 days in 4/28. - Hyperuricaemia leading to 3-day suspension of Z 2/28. - Gastrointestinal symptoms 3/28 - Arthralgia 2/28 - Dizziness with nystagmus 1/28 - Rash 1/28
Biddulph 1990	6	NR	NR	No disaggregated data for TBM (15/639 TB cases had problems with the drugs prescribed).
Chotmongkol 1991	6	NR	1/29	- Severe hepatitis due to isoniazid. Treatment was continued with R and E for 18 months with full recovery.
Chotmongkol 1996	6	NR	NR	No gastrointestinal bleeding or hyperglycaemia secondary to prednisolone therapy.
Donald 1998	6	23/95	5/95	Hepatotoxicity: - Mild elevation of bilirubin: 10/95 leading to substitution of Eth by E for 2-3 weeks for 5 of them. - Mild and transient elevation of ALT/AST, without treatment interruption: 13/95.
Phuapradit 1987	9	21/28	1/28	- Erythema multiforme from pyrazinamide. All drugs were discontinued. After rashes healed, ATT was continued with HRS with full recovery.
Van Toorn 2014	6 (HIV -) 9 (HIV +)	51/184	17/184	- Anti-TB drug-induced hepatotoxicity (ADIH): *Grade 1 (mild) ALT 51–125 U/L: 18/184 *Grade 2 (mild) ALT 126–250 U/L: 6/184 *Grade 3 (moderate) ALT 251–500 U/L: 6/184

				*Grade 4 (severe) ALT> 500 U/L: 2/184 In all ADIH cases from grade 2 severity, change to liver-friendly regimens resulted in normalization of liver enzymes (medium duration 7 days, range 3–16 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.

Table 31: Summary table with main outcomes for length of treatment for TB meningitis

Duration	Study	Relapse	Deaths	Deaths after 6 mo treatment
6	Jacobs 1992	0/45	7/45	NR[7]
	Alarcón 1990	1/28	9/28	1/28
	Biddulph 1990	1/43	5/43	0/43
	Chotmongkol 1991	0/29	4/29	0/29
	Chotmongkol 1996	0/59	7/59	0/59
	Donald 1998	1/95	15/95	2/95
	Van Toorn 2014	0/184	15/184	8/184
8	Doganay 1995	0/37	5/37	0/37
9	Phuapradit 1987	0/28	2/28	2/28
	Jacobs 1992	0/4	2/4	NR[7]
12	Jacobs 1992	0/4	2/4	NR[7]
12-16	Doganay 1995	2/35[1]	2/35	0/35

Table 32: Summary of findings on length of treatment for TB meningitis

Is anti-tubercular treatment for TBM with 9 months or less inferior to treatment for 12 months or more?

Patient or population: Adults and children with tuberculous meningitis

Settings: Hospitals

Intervention: ATT for 9 months or less

Comparison: ATT for 12 months or more

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**9 mo or less**	**12 mo+**	**Relative (95% CI)**	**Absolute**		
Relapse												
9	Single arm cohort	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	None	3 relapses in 9 studies with 552 patients	2 relapses in 2 studies with 39 patients	Not evaluable	Not evaluable	Very low	Critical
Deaths after 6 months of treatment												
8	Single arm cohort	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	None	13 deaths in 8 studies with 503	0 death in 1 study with 35 patients	Not evaluable	Not evaluable	Very low	Important

[1] Prospective single arm studies, and no large effects evident. So downgrading by 2 remains in place.

[2] Downgraded by 1 for imprecision: underpowered with few event

Guideline Panel's Judgement

Question: What duration of treatment should be used to treat TB meningitis?

Balance of desirable and undesirable effects

Desirable	Undesirable
Low numbers of relapses – current understanding is that longer regimens are associated with lower risk of relapse Good cure rates – the best regimen would be associated with the best rates of cure in terms of low mortality, high treatment completion and low relapse rate	Longer ATT regimens are associated with poor compliance Longer regimens expose patients to increased risk of adverse effects of ATT

Overall quality of evidence across all critical outcomes

High	Moderate	Low	Very low
			X

Values and preference statement

TB meningitis is a serious life-threatening disease and treatment should be adequate to prevent relapse as this is a critical outcome.

Draft recommendation

TB meningitis should be treated with standard first-line ATT for at least 9 months.

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
	X			

Remarks

- The group recognised that there was very low quality evidence for using one treatment regimen over another.
- There was variation in practice between clinicians – some treat for 9 months, some for 12 or 18 months. The RNTCP recommendation is for 9 months treatment for adults and 12 months treatment for children.
- The neurologists present stated that there was clinical equipoise over this question.
- The key factors dictating mortality may be early treatment and use of steroids, and the role of duration of treatment is unclear.
- Extension of treatment is sometimes indicated, and this should be assessed by the treating clinician on a case-by-case basis.
- There was some disagreement about the optimum duration of treatment, and the recommendation made was the best consensus possible.

References

Ablanedo-Terrazas Y, A.-d. l.-J.-C.-T. (2014). Xpert MTB/RIF for diagnosis of tuberculous cervical lymphadenitis in HIV-infected patients. *Laryngoscope, 124* (6), 1382-1385.

Alarcón F, E. L. (1990). Tuberculous meningitis. Short course of chemotherapy. *Archives of Neurology*, *47* (12), 1313-1317.

Ayed AK, B. N. (2001). Diagnosis and treatment of isolated tuberculous mediastinal lymphadenopathy in adults. *European Journal of Surgery*, *167*, 334-338.

Bang JS, K. M. (1997). Evaluation of steroid therapy in tuberculous pleurisy - A prospective, randomized study. *Tuberculosis and Respiratory Disease*, *44* (1), 52-58.

Batungwanayo J, T. H. (1993). Pleural effusion, tuberculosis and HIV-1 infection in Kigali, Rwanda. *AIDS*, *7* (1), 73-79.

Biadglegne F, M. A. (2014). Diagnostic performance of the Xpert MTB/RIF assay for tuberculous lymphadenitis on fine needle aspirates from Ethiopia. *Tuberculosis*, *94*, 502-505.

Biddulph, J. (1990). Short course chemotherapy for childhood tuberculosis. *Pediatric Infectious Diseases Journal*, *9* (11), 794-801.

Blakemore R, S. E. (2010). Evaluation of the analytical performance of the Xpert MTB/RIF assay. *Journal of Clinical Microbiology*, *48* (7), 2495-2501.

British Thoracic Society Research Committee. (1985). Short course chemotherapy for tuberculosis of lymph nodes: a controlled trial. *British Medical Journal*, *290*, 1106-1108.

British Thoracic Society Research Committee. (1992). Six-months versus nine-months chemotherapy for tuberculosis of lymph nodes: preliminary results. *Respiratory Medicine*, *86*, 15-19.

Campbell IA, O. L. (1993). Six months versus nine months chemotherapy for tuberculosis of lymph nodes: final results. *Respiratory Medicine*, *87*, 621-623.

Cheung WL, S. K. (1990). Six-month combination chemotherapy for cervical tuberculous lymphadenitis. *Journal of the Royal College of Surgeons of Edinburgh*, *35* (5), 293-295.

Chotmongkol V, J. S. (1996). Corticosteroid in tuberculous meningitis. . *Journal of the Medical Association of Thailand*, *79* (2), 83-90.

Chotmongkol V, J. S. (1996). Corticosteroid in tuberculous meningitis. *Journal of the Medical Association of Thailand*, *79* (2), 83-90.

Chotmongkol, V. (1991). Treatment of tuberculous meningitis with 6-month course of chemotherapy. *The Southeast Asian Journal of Tropical Medicine and Public Health*, *22* (3), 372-374.

Coetzee L, N. M. (2014). Rapid diagnosis of pediatric mycobacterial lymphadenitis using fine needle aspiration biopsy. *Pediatric Infectious Diseases Journal*, *33*, 893-896.

Denkinger CM, S. S. (2014). Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. *European Respiratory Journal*, *44* (2), 435-446.

Doganay M, C. S. (1995). Treatment of tuberculous meningitis in Turkey. *Scandinavian Journal of Infectious Diseases*, *27*, 135-138.

Donald PR, S. J. (1998). Intensive short course chemotherapy in the management of tuberculous meningitis. *International Journal of Tuberculosis and Lung Disease*, *2* (9), 704-711.

Donald, P. (2010). The chemotherapy of tuberculosis meningitis in children and adults. *Tuberculosis*, *90* (6), 375-392.

Doosoo, J. (2014). Tuberculous Pleurisy: An Update. *Tuberculosis and Respiratory Diseases*, *76*, 153-159.

Downs SH, B. N. (1998). The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *Journal of Epidemiology and Community Health*, *52*, 377-384.

Du J, H. Z. (2015). Rapid diagnosis of pleural tuberculosis by Xpert MTB/RIF assay using pleural biopsy and pleural fluid specimens. *Journal of Research in Medical Sciences*, *20* (1), 26-31.

Elliott AM, L. H. (2004). A randomized, double-blind, placebo-controlled trial of the use of prednisolone as an adjunct to treatment in HIV-1-associated pleural tuberculosis. *Journal of Infectious Diseases*, *190* (5), 869-878.

Frye MD, P. C. (1997). Tuberculous pleurisy is more common in AIDS than in non-AIDS patients with tuberculosis. *Chest*, *112* (2), 393-397.

Galarza I, C. C. (1995). Randomised trial of corticosteroids in the treatment of tuberculous pleurisy. *Thorax*, *50* (12), 1305-1307.

Girgis NI, F. Z. (1983). The use of dexamethasone in preventing ocular complications in tuberculous meningitis. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *77* (5), 658-659.

Guyatt, G. O. (2011). GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology, 64*(4), 383-94.

Hakim J, T. I. (2000). Double blind randomised placebo controlled trial of adjuvant prednisolone in the treatment of effusive tuberculous pericarditis in HIV seropositive patients. *Heart*, *84*, 183-188.

Higgins JPT, A. D. (2011). Chapter 8: Assessing risk of bias in included studies. In G. S. Higgins JPT, *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.* The Cochrane Collaboration.

Jacobs RF, S. P. (1992). Intensive short course chemotherapy for tuberculous meningitis. *Pediatric Infectious Diseases*, *11* (3), 194-198.

Jawahar MS, R. K. (2005). Treatment of lymph node tuberculosis – a randomized clinical trial of two 6-month regimens. *Tropical Medicine and International Health*, *10* (11), 1090-1098.

Jawahar MS, S. S. (1990). Short course chemotherapy for tuberculous lymphadenitis in children. *British Medical Journal*, *301*, 359-362.

Kim HJ, L. H. (2006). The prevalence of pulmonary parenchymal tuberculosis in patients with tuberculous pleuritis. *Chest*, *129* (5), 1253-1258.

Kim YW, K. N.-W.-C.-G.-J. (2015). Accuracy of the XpertW MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis in South Korea. *International Journal of Tuberculosis and Lung Disease*, *19* (1), 81-86.

Kumarvelu S, P. K. (1994). Randomized controlled trial of dexamethasone in tuberculous meningitis. *Tubercle and Lung Disease*, *75* (3), 203-207.

Lardizabal DV, R. A. (1998). Dexamethasone as adjunctive therapy in adult patients with probable TB meningitis stage II and stage III: an open randomised controlled trial. *Philippines Journal of Neurology*, *4*, 4-10.

Lee BH, J. H. (1999). Therapeutic effect of prednisolone in tuberculous pleurisy - A prospective study for the prevention of the pleural adhesion. *Tuberculosis and Respiratory Disease*, *46* (4), 481-488.

Lee CH, W. W. (1988). Corticosteroids in the treatment of tuberculous pleurisy. A double-blind, placebo-controlled, randomized study. *Chest*, *94* (6), 1256-1259.

Lefebvre C, M. E. (2011). Chapter 6: Searching for Studies. In G. S. Higgins JPT, *Cochrane Handbook for Systematic Reviews of Interventions version 5.0.1.* The Cochrane Collaboration.

Light, R. (2010). Update on tuberculous pleural effusion. *Respirology*, *15* (3), 451-458.

Lusiba JK, N. L.-K. (2014). Evaluation of Cepheid's Xpert MTB/Rif test on pleural fluid in the diagnosis of pleural tuberculosis in a high prevalence HIV/TB setting. *PLoS One*, *9* (7), e102702.

Makharia GK, G. U. (2015). Intermittent Directly Observed Therapy for Abdominal Tuberculosis: A Multicenter Randomized Controlled Trial Comparing 6 Months Versus 9 Months of Therapy. *Clinical Infectious Diseases*, *61* (5), 750-757.

Malhotra HS, G. R. (2009). Corticosteroids (dexamethasone versus intravenous methylprednisolone) in patients with tuberculous meningitis. *Annals of Tropical Medicine and Parasitology*, *103* (7), 625-634.

Maynard-Smith L, L. N. (2014). Diagnostic accuracy of the Xpert MTB/RIF assay for extrapulmonary and pulmonary tuberculosis when testing non-respiratory samples: a systematic review. *BMC Infectious Diseases*, *14*, 709.

Mayosi BM, N. M. (2014). Prednisolone and Mycobacterium indicus pranii in tuberculous pericarditis. *New England Journal of Medicine*, *371*, 1121-1130.

Meldau R, P. J.-S. (2014). Comparison of same day diagnostic tools including Gene Xpert and unstimulated IFN-γ for the evaluation of pleural tuberculosis: a prospective cohort study. *BMC Pulmonary Medicine*, *14*, 58.

Morehead, R. (1998). Tuberculosis of the pleura. *Southern Medical Journal*, *91* (7), 630-636.

Nhu NT, H. D. (2014). Evaluation of GeneXpert MTB/RIF for diagnosis of tuberculous meningitis. *Journal of Clinical Microbiology*, *52* (1), 226-233.

O'Toole RD, T. G. (1969). Dexamethasone in tuberculous meningitis. Relationship of cerebrospinal fluid effects to therapeutic efficacy. *Annals of Internal Medicine*, *70* (1), 39-47.

Park SH, Y. S. (2009). Prospective randomized trial of six-month versus nine-month therapy for intestinal tuberculosis. *Antimicrobial Agents and Chemotherapy*, *53* (10), 4167-4171.

Patel VB, C. C. (2014). Comparison of amplicor and GeneXpert MTB/RIF tests for diagnosis of tuberculous meningitis. *Journal of Clinical Microbiology*, *52* (10), 3777-3780.

Penz E, B. J. (2015). Diagnostic accuracy of the XpertW MTB/RIF assay for extrapulmonary tuberculosis: a meta-analysis. *International Journal of Tuberculosis and Lung Disease*, *19* (3), 278-284.

Phuapradit P, V. A. (1987). Treatment of tuberculous meningitis: role of short-course chemotherapy. *Quarterly Journal of Medicine*, *62* (239), 249-258.

Prasad, K. (2006). A randomized controlled trial to study the effectiveness of dexamethasone as an adjunct to standard antituberculous treatment in patients with clinically presumed tuberculous meningitis: 10-year follow up study. *Unpublished study*, NA.

Prasad K, Singh MB, Ryan H. (2016) Corticosteroids for managing tuberculous meningitis. Cochrane Database of Systematic Reviews 2016, Issue 4. Art. No.: CD002244. DOI: 10.1002/14651858.CD002244.pub4.

Queipo JA, B. E.-P.-C. (2003). Mycobacterial infection in a series of 1261 renal transplant recipients. *Clinical Microbiology and Infection*, *9* (6), 518-525.

Reuter H, B. L. (2006). Experience with adjunctive corticosteroids in managing tuberculous pericarditis. *Cardiovascular Journal of South Africa*, *17*, 233-238.

Review Manager 5. (2014). Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre: The Cochrane Collaboration.

Rossi GA, B. B. (1987). Tuberculous pleural effusions. Evidence for selective presence of PPD-specific T-lymphocytes at site of inflammation in the early phase of the infection. *American Review of Respiratory Disease*, *136* (3), 575-579.

Ryan, H., Yoo, J., Darsini, P. Corticosteroids for TB pleurisy. Cochrane Database of Systematic Reviews, publication expected 2016.

Schoeman JF, V. Z. (1997). Effect of corticosteroids on intracranial pressure, computed tomographic findings, and clinical outcome in young children with tuberculous meningitis. *Pediatrics*, *99* (2), 226-231.

Schrire, V. (1959). Experience with pericarditis at Groote Schuur Hospital, Cape Town: An analysis of one hundred and sixty cases over a six-year period. *South African Medical Journal*, *33*, 810-817.

Shea BJ, G. J. (2007). Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology*, *7*, 10.

Shu CC, W. J.-T.-Y.-N.-J. (2011). In-hospital outcome of patients with culture-confirmed tuberculous pleurisy: clinical impact of pulmonary involvement. *BMC Infectious Diseases*, *11*, 46.

Solomons RS, V. D. (2015). Improved diagnosis of childhood tuberculous meningitis using more than one nucleic acid amplification test. *International Journal of Tuberculosis and Lung Disease*, *19* (1), 74-80.

Steingart KR, S. I. (2014). Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. *Cochrane Database Syst Rev*, *1* (CD009593).

Strang JIG, K. H. (1988). Controlled clinical trial of complete open surgical drainage and of prednisolone in treatment of tuberculous pericardial effusion in Transkei. *Lancet*, *2*, 759-764.

Strang JIG, K. H. (1987). Controlled trial of prednisolone as adjuvant in treatment of tuberculous constrictive pericarditis. *Lancet*, *ii*, 1418-1422.

The Nordic Cochrane Cenre. (2014). *Review Manager (RevMan) [Computer program]. Version 5.3*. (T. N. Cenre, Producer, & The Cochrane Collaboration)

Thwaites GE, N. D. (2004). Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *New England Journal of Medicine*, *351* (17), 1741-1751.

Tony J, S. K. (2008). Randomized controlled trial of DOTS versus conventional regime for ileocecal and colonic tuberculosis. *Indian Journal of Gastroenterology*, *27* (1), 19-21.

Trajman A, d. S. (2014). Accuracy of polimerase chain reaction for the diagnosis of pleural tuberculosis. *Respiratory Medicine*, *108* (6), 918-923.

Valdés L, A. D.-P. (1998). Tuberculous pleurisy: a study of 254 patients. *Archives of Internal Medicine*, *158* (18), 2017-2021.

van Loenhout-Rooyackers JH, K. A. (2001). Tuberculosis meningitis: is a 6-month treatment regimen sufficient? *The International Journal of Tuberculosis and Lung Disease*, *5*, 1028-1035.

Van Rie A, P.-S. L. (2013). Diagnostic accuracy and effectiveness of the Xpert MTB/RIF assay for the diagnosis of HIV-associated lymph node tuberculosis. *European Journal of Clinical Microbiology and Infectious Disease*, *32*, 1409-1415.

van Toorn R, S. H. (2014). Short intensified treatment in children with drug-susceptible tuberculous meningitis. *Pediatric Journal of Infectious Diseases*, *33* (3), 248-252.

WHO. (2010). *Treatment of tuberculosis guidelines.* (4th ed.). The World Health Organisation.

Wiysonge CS, N. M. (2008). Contemporary use of adjunctive corticosteroids in tuberculous pericarditis. *International Journal of Cardiology*, *124*, 388-390.

Wiysonge CS, Ntsekhe M, Thabane L, Volmink J, Majombozi D, Gumedze F, Pandie S, Mayosi BM. Interventions for treating tuberculous pericarditis. Cochrane Database of Systematic Reviews, publication expected 2016.

Wyser C, W. G. (1996). Corticosteroids in the treatment of tuberculous pleurisy. A double-blind, placebo-controlled, randomized study. *Chest*, *110* (2), 333-338.

Yuen AP, W. S. (1997). Prospective randomized study of thrice weekly six-month and nine-month chemotherapy for cervical tuberculous lymphadenopathy. *Otolaryngol Head Neck Surg. 116* (2), 189-192.

Excluded Studies

The tables below list all the studies excluded after full text screening for each of the reviews conducted or updated to produce the evidence summaries.

The principle evidence summary for the recommendations on the use of Xpert MTB/RIF was based on a systematic review published in 2014, the search for which was performed in September 2013. The 238 excluded studies for this review are not listed in the published article (Denkinger, 2014). We updated the literature search from October 2013 to April 2015, and screened the search results. Tables 32 to 34 below list the studies we excluded after abstract and full text review, with reasons for exclusion.

Table 33. Excluded studies for Xpert MTB/RIF for LNTB (October 2013 to April 2015)

Study	Reason for exclusion
(Biadglegne, 2013)	Xpert only used for culture negative specimens
(Blaich, 2014)	Participants not described, not possible to disaggregate data by specimen type.
(Dhasmana, 2014)	Not possible to extract TP FP TN FN. Sensitivity and specificity estimates based on selected subset of patients.
(Iram, 2015)	No disaggregated data for LN specimens
(Kwak, 2015)	Duplicate data from Kim 2015.
(Ozkutuk, 2014)	In Turkish
(Scott, 2014)	Not possible to extract TP FP TN FN.
(Sharma, 2014)	Not possible to extract TP FP TN FN.
(Razack, 2014)	Did not use Xpert MTB/RIF
(Salvador, 2015)	Not possible to extract TP FP TN FN.
(Zmak, 2013)	No disaggregated data for LN specimens

Table 34. Excluded studies for Xpert MTB/RIF for TBM (October 2013 to April 2015)

Study	Reason for exclusion
(Iram, 2015)	No disaggregated data for specimens by tissue type
(Ozkutuk, 2014)	In Turkish
(Scott, 2014)	Not possible to extract TP FP TN FN.
(Sharma, 2014)	Not possible to extract TP FP TN FN.
(Patel, 2013)	Comparator is culture or Amplicor, not possible to disaggregate data for culture alone
(Rajasingham, 2015)	Xpert not compared against culture/CRS

Table 35. Excluded studies for Xpert MTB/RIF for pleural TB (October 2013 to April 2015)

Study	Reason for exclusion
(Iram, 2015)	No disaggregated data for specimens by tissue type
(Ozkutuk, 2014)	In Turkish
(Scott, 2014)	Not possible to extract TP FP TN FN.
(Sharma, 2014)	Not possible to extract TP FP TN FN.
(Kim, 2015)	Data not disaggregated for pleural specimens
(Christopher, 2013)	Compared with CRS only
(Coleman, 2015)	Not possible to extract TP FP TN FN
(Zmak, 2013)	No disaggregated data for pleural specimens

Table 36. Excluded studies for steroids to treat TB meningitis

Study ID	Reason for exclusion
(Donald, 2004)	Perspective article with no original data.
(Escobar, 1975)	Not a randomized study. The report says that a pair of participants matched for age and neurological status was administered differential therapy in a double-blind fashion. However, it is unclear if this differential administration was random.
(Frieman, 1970)	Case series.
(Girgis, 1983)	Participants allocated to steroid or non-steroid group on alternate basis; unclear why there is a difference of 4 in the number of participants in the 2 groups (non-steroid 70 and steroid 66).
(Hockaday, 1966)	Case series.
(Kalita, 2001)	Study with historical controls, not a randomized study.
(Kapur, 1969)	Case series.
(Karak, 1998)	Commentary on an included trial (Schoeman 1997).
(Lepper, 1963)	Allocation was not truly randomized: the first half of the study was an alternate participant design, whereas in the last half, participants were randomized by using random numbers.
(Marras, 2005)	Letter to the editor with no original data.
(Quagliarello, 2004)	Editorial.
(Seligman, 2005)	Letter to the editor with no original data.
(Shah, 2014)	RCT comparing three different doses of prednisolone; no placebo arm.
(Vagenakis, 2005)	Letter to the editor with no original data.
(Volijavec, 1960)	Comparison cohort with historical controls.
(Wosz-Höckert, 1963)	Control trial using historical controls.
(Weiss, 1965)	Retrospective case series of 102 cases.

Table 37. Excluded studies for steroids to treat TB pericarditis

Study	Reason for exclusion
(Wiysonge, 2008)	The study is a cross-sectional analysis of the contemporary use of adjunctive steroids in the management of patients with tuberculous pericarditis in Africa. Despite being observational in nature, this study is indexed in electronic databases as a controlled trial.

Table 38. Excluded studies for steroids to treat TB pleurisy

Study ID	Reason for exclusion
(Aspin, 1958)	No randomization
(Bilaceroglu, 1999)	Participants did not have pleurisy - cases of pulmonary tuberculosis
(Cherednikova, 1973)	Case series
(Cisneros, 1996)	Review
(Damany, 1968)	Numbers of participants in each arm not clearly stated
(Filler, 1963)	No randomization
(Fleishman, 1960)	Diagnosis of tuberculosis not confirmed
(Grewal, 1969)	No randomization
(Khomenko, 1990)	Participants did not have pleurisy - cases of pulmonary tuberculosis
(Manresa, 1997)	Letter referring to included trial (Galarza 1995)
(Mansour, 2006)	No randomization
(Mathur, 1960)	No randomization
(Mathur, 1965)	No randomization
(Mayanja-Kizza, 2005)	Participants did not have pleurisy - cases of pulmonary tuberculosis
(Menon, 1964)	No randomization
(Pacheco, 1973)	Compared prednisolone to another steroid (cortivazol)
(Paley, 1959)	No randomization
(Porsio, 1966)	Participants did not have pleurisy - cases of pulmonary tuberculosis
(Singh, 1965)	No randomization
(Starostenko, 1989)	No randomization
(Tani, 1964)	No randomization
(Tanzj, 1965)	No randomization

Table 39. Excluded studies for comparison for duration of treatment for LNTB

Study ID	Reason for exclusion
BTS 1985	Longer duration of therapy in both arms
Jawahar 2001	Single arm cohort
Jindal 2013	Outcomes reported different from intended
McCarthy 2000	Single arm cohort
Cheug WL 1990	Single arm cohort
Kumar 1990	Compared only twice weekly vs daily arms for 6 months each
Ayed 2001	Single arm cohort
Jacob 2001	Single arm retrospective cohort

Table 40. Excluded studies for duration of treatment for abdominal TB

Study ID	Reason for exclusion
(Balasubramanian, 1997)	Comparison regimen did not include rifampicin

Table 41. Excluded studies for duration of treatment for TBM

Study	Reason for exclusion
Comparative studies	
Acharya 1985	No primary outcome measure reported
Alvarez-Uria 2013	Retrospective cohort study
Anastasatu 1993	Unable to retrieve full text
Sunakorn 1980	Case series
Single arm studies	
Chandra 1976	Unclear duration of treatment and no primary outcome measure reported
Chotmongkol 1991	Unable to retrieve full text
Crevel 2012	Duplicated study (data referring to Ruslami 2013)
Dutt 1986	Retrospective cohort study
Ellard 1993	Retrospective study
Elliott 1995	Pulmonary TB and extra-pulmonary TB patients, no disaggregated data for TBM patients
Escobar 1975	Intervention: ATT regimen does not include rifampicin and unclear duration of treatment
Ghosh 1971	Intervention: ATT regimen does not include rifampicin
Girgis 1991	Intervention: ATT regimen longer than nine months and does not include rifampicin
Girgis 1976	Intervention: ATT regimen longer than nine months and does not include rifampicin
Kalita 2014	Unclear duration of treatment. No primary outcome measure reported.
Kalita 2001	Unclear duration of treatment. No primary outcome measure reported.
Karak 1998	Duplicated study (data referring to Schoeman 1997)
Kumarvelu 1994	No primary outcome measure reported
Lardizabal 1998	Unable to retrieve full text
Malhotra 2009	Unclear duration of treatment and no primary outcome measure reported

Misra 2010	Intervention: ATT regimen longer than nine months
O'Toole 1969	Intervention: ATT regimen does not include rifampicin
Phuapradit 1987	Unable to retrieve full text
Rahajoe 1979	Intervention: ATT regimen longer than nine months
Ramachandran 1986	Intervention: ATT regimen longer than nine months
Ruslami 2013	No primary outcome measure reported
Schoeman 2011	No primary outcome measure reported
Schoeman 1997	No primary outcome measure reported
Shah 2014	Intervention: ATT regimen longer than nine months
te Brake 2015	No primary outcome measure reported
Thwaites 2004	No primary outcome measure reported
Thwaites 2011	No primary outcome measure reported
Torok 2008	No primary outcome measure reported
Torok & Bich Yen 2011	No primary outcome measure reported
Torok & Duc Bang 2011	No primary outcome reported
Other	
Chau 2000	Review article
Girgis 1978	Intervention: ATT regimen longer than nine months
Jubelt 2006	Duplicated study (data referring to Thwaites 2004)
Karande 2005	Duration of ATT not mentioned, no primary outcome measure reported
Marras 2005	Letter to the editor
Thwaites 2007	Duplicated study (data referring to Thwaites 2004)
Xu 1998	Unable to retrieve full text

References to Excluded Studies

Aspin, J. O. (1958). Steroid-treated tuberculous pleural effusions. *British Journal of Tuberculosis and Diseases of the Chest , 52*(1), 81-3.

Balasubramanian, R. N. (1997). Randomised controlled clinical trial of short course chemotherapy in abdominal tuberculosis: a five-year report. *International Journal of Tuberculosis and Lung Disease, 1*(1), 44-51.

Biadglegne, F. T. (2013, Dec 9). Tuberculous lymphadenitis in Northern Ethiopia: in a public health and microbiological perspectives. . *PLoS One, 8*(12), e81918. doi: 10.1371/journal.pone.0081918.

Bilaceroglu, S. P. (1999). Prednisolone: a beneficial and safe adjunct to antituberculosis treatment?A randomized controlled trial. *International Journal of Tuberculosis and Lung Disease, 3*(1), 47-54.

Blaich, A. F. (2014, Feb). Performance of the Xpert MTB/RIF assay on nonrespiratory specimens and accuracy of this assay for detection of rifampin resistance in a low-prevalence setting. *Journal of Clinical Microbiology, 52*(2), 706.

Cherednikova, G. (1973). Immediate and late results of treatment with corticosteroid hormones of children with tuberculosis [Blizhaishie i otdalennye rezul'taty lecheniia kortikosteroidnymi gormonami detei, bol'nykh tuberkulezom]. *Problemy Tuberkuleza, 51*(12), 46-9.

Christopher, D. J. (2013). Performance of Xpert MTB/RIF on pleural tissue for the diagnosis of pleural tuberculosis. *European Respiratory Journal , 42*(5), 1427-9.

Cisneros, J. M. (1996). Corticosteroids in tuberculosis. *Annals of Pharmacotherapy, 30*(11), 1298-303.

Coleman, M. F. (2015). Markers to differentiate between Kaposi's sarcoma and tuberculous pleural effusions in HIV-positive patients. *International Journal of Tuberculosis and Lung Disease, 19*(2), 144-50.

Damany, S. S. (1968). Treatment of pleural effusion with and without triamcinolone in addition to usual antituberculosis chemotherapy. *Journal of the Indian Medical Association, 51*(8), 391-3.

Dhasmana, D. R. (2014, Mar). Performance of Xpert MTB/RIF in the diagnosis of tuberculous mediastinal lymphadenopathy by endobronchial ultrasound. *Annals of the Americal Thoracic Society, 11*(3), 392-6.

Donald, P. S. (2004). Tuberculous meningitis. *New England Journal of Medicine, 351*(17), 1719-20.

Escobar, J. A. (1975). Mortality from tuberculous meningitis reduced by steroid therapy. *Pediatrics, 56*(6), 1050-5.

Filler, J. P. (1963). Physiologic studies of the sequelae of tuberculous pleural effusion in children treated with antimicrobial drugs and prednisone. *American Review of Respiratory Disease, 88*, 181-8.

Fleishman, S. C. (1960). Antituberculous therapy combined with adrenal steroids in the treatment of pleural effusions: a controlled therapeutic trial. *Lancet, 23*(1), 199-201.

Frieman, I. G. (1970). Evaluation of intrathecal therapy with streptomycin and hydrocortisone in tuberculous meningitis. *Journal of Pediatrics , 76*(6), 895-901.

Girgis, N. F. (1983). The use of dexamethasone in preventing ocular complications in tuberculous meningitis. *Transactions of the Royal Society of Tropical Medicine and Hygiene , 77*(5), 658-9.

Grewal, K. D. (1969). A comparative study of therapeutic regimens with and without corticosteroids in the treatment of tuberculous pleural effusion. *Journal of the Indian Medical Association, 52*(11), 514-6.

Hockaday, J. S. (1966). Corticosteroids as an adjuvant to the chemotherapy of tuberculous meningitis. *Tubercle, 47*(1), 75-91.

Iram, S. Z. (2015, Jan-Feb). Rapid diagnosis of tuberculosis using Xpert MTB/RIF assay - Report from a developing country. *Pakistan Journal of Medical Sciences, 31*(1), 105-10.

Kalita, J. M. (2001). Effect of methyl prednisolone on sensory motor functions in tuberculous meningitis. *Neurology India, 49*(3), 267-71.

Kapur, S. (1969). Evaluation of treatment of tuberculous meningitis since the use of steroids as an adjuvant. *Indian Pediatrics, 6*(3), 166-71.

Karak, B. G. (1998). Corticosteroids in tuberculous meningitis. *Indian Pediatrics, 35*(2), 193-4.

Khomenko, I. C. (1990). Effectiveness of antitubercular chemotherapy combined with corticosteroids and immunomodulators [Effektivnost' protivotuberkuleznoi khimioterapii v sochetanii s kortikosteroidami i immunomoduliatorami]. *Problemy Tuberkuleza, 1*, 24-8.

Kim, Y. W. (2015). Accuracy of the Xpert(R) MTB/RIF assay for the diagnosis of extra-pulmonary tuberculosis in South Korea. *International Journal of Tuberculosis and Lung Disease, 19*(1), 81-6.

Kwak, N. S. (2015). Accuracy of the Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis in South Korea. *International Journal of Tuberculosis and Lung Disease, 19*(1), 81-6.

Lepper, M. S. (1963). The present status of the treatment of tuberculosis of the central nervous system. *Annals of the New York Academy of Sciences, 106*, 106-23.

Manresa, F. G. (1997). Using corticosteroids to treat tuberculous pleurisy. *Chest, 112*(1), 291-2.

Mansour, A. A.-R. (2006). Adjunct therapy with corticosteroids or paracentesis for treatment of tuberculous pleural effusion. *Eastern Mediterreanean Health Journal, 12*(5), 504-8.

Marras, T. (2005). Dexamethasone for tuberculous meningitis. *New England Journal of Medicine, 352*(6), 628-30.

Mathur, K. M. (1965). Treatment of tuberculosis pleural effusion with local instillation of hydrocortisone. *Diseases of the Chest, 47*, 303-9.

Mathur, K. P. (1960). Intrapleural hydrocortisone in tuberculous pleural effusion. *Tubercle, 41*, 358-62.

Mayanja-Kizza, H. J.-L.-C. (2005). Immunoadjuvant prednisolone therapy for HIV-associated tuberculosis: a phase 2 clinical trial in Uganda. *Journal of Infectious Diseases, 191*(6), 856-65.

Menon, N. (1964). Steroid therapy in tuberculous effusion. *Tubercle , 45*, 17-20.

Ozkutuk, N. S. (2014). Evaluation of the Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary tuberculosis in an intermediate-prevalence setting. *Mikrobiyol Bul, 48*(2), 223-32.

Pacheco, C. V.-O. (1973). Clinical study of a new synthetic steroid in the treatment of pleural tuberculosis [Estudio clinico de un nuevo esteroide de sintesis en el tratamiento de la pleuresia tuberculosa]. *Gaceta Medica de Mexico, 106*(3), 249-55.

Paley, S. M. (1959). Prednisolone in the treatment of tuberculous pleural effusions. *American Review of Tuberculosis, 79*, 307-14.

Patel, V. B. (2013). Diagnostic accuracy of quantitative PCR (Xpert MTB/RIF) for tuberculous meningitis in a high burden setting: a prospective study. *PLoS Medicine, 10*(10), e1001536.

Porsio, A. B. (1966). Controlled clinical trials of the use of a new anabolic agent in a Sanatorium. *La Clinica Terapeutica, 37*(6), 502-18.

Quagliarello, V. (2004). Adjunctive steroids for tuberculous meningitis - more evidence, more questions. *New England Journal of Medicine, 351*(17), 1792-4.

Rajasingham, R. R. (2015). Epidemiology of meningitis in an HIV-infected Ugandan cohort. *American Journal of Tropical Medicine and Hygiene, 92*(2), 274-9.

Razack, R. L. (2014). Diagnostic yield of fine needle aspiration biopsy in HIV-infected adults with suspected mycobacterial lymphadenitis. *South African Medical Journal, 104*(1), 27-8.

Salvador, F. L.-A.-M. (2015). Epidemiology and diagnosis of tuberculous lymphadenitis in a tuberculosis low-burden country. *Medicine (Baltimore), 94*(4), e509.

Scott, L. E. (2014). Diagnostic accuracy of Xpert MTB/RIF for extrapulmonary tuberculosis specimens: establishing a laboratory testing algorithm for South Africa. *Journal of Clinical Microbiology, 52*(6), 1818-23.

Seligman, S. (2005). Dexamethasone for tuberculous meningitis. *New England Journal of Medicine, 352*(6), 628-30.

Shah, I. M. (2014). High dose versus low dose steroids in children with tuberculous meningitis. *Journal of Clinical Neuroscience, 21*(5), 761-4.

Sharma, S. K. (2014). Evaluation of Xpert MTB/RIF assay performance in diagnosing extrapulmonary tuberculosis among adults in a tertiary care centre in India. *European Respiratory Journal, 44*(4), 1090-3.

Singh, D. Y. (1965). Role of intrapleural corticosteroids in tuberculous pleural effusion: a clinicotherapeutic trial of 50 cases. *Journal of the Indian Medical Association, 45*(6), 306-9.

Starostenko, E. N. (1989). Indications for the use of prednisolone in tuberculosis. *Problemy Tuberkuleza, 1*, 44-7.

Tani, P. P. (1964). Cortisone therapy for exudative tuberculous pleurisy in the light of a follow-up study. *Acta Tuberculosea Scandinavica, 44*, 303-9.

Tanzj, P. A. (1965). On therapeutic use of corticosteroids in pleuro-pulmonary tuberculosis. *Archivio di Tisiologia e delle Malattie dell'Apparato Respiratorio, 20*(5), 331-57.

Vagenakis, A. K. (2005). Dexamethasone for tuberculous meningitis. *New England Journal of Medicine , 352*(6), 628-30.

Volijavec, B. C. (1960). The influence of corticosteroid hormones in the treatment of tuberculous meningitis in Negroes. *American Review of Respiratory Disease, 81*(4), 539-45.

Weiss, W. F. (1965). The changing incidence of and prognosis of tuberculous meningitis. *American Journal of the Medical Sciences, 250*, 46-59.

Wiysonge, C. N. (2008). Contemporary use of adjunctive corticosteroids in tuberculous pericarditis. *International Journal of Cardiology, 124*, 388-90.

Wosz-Höckert, O. (1963). Modern treatment and late prognosis of tuberculous meningitis. *Acta Paediatrica, 52*(Suppl 141), 93-102.

Zmak, L. J. (2013). Evaluation of Xpert MTB/RIF assay for rapid molecular diagnosis of tuberculosis in a two-year period in Croatia. *International Journal of Mycobacteriology, 2*(3), 179-182.