1 Appendix D: Evidence Tables - Treatment of active TB (RQs O, R & X)

1.1 RQ O, R & X.

RQ O: In people with active TB receiving the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol), does surgery as an adjunct to an antituberculosis drug treatment regimen decrease morbidity and mortality compared to the standard recommended regimen alone?

RQ R: In people with active non-respiratory TB receiving the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol), does surgery as an adjunct to the antituberculosis drug treatment regimen decrease morbidity and mortality compared to the standard recommended regimen alone?

RQ X: In people with drug-resistant TB, does surgery as an adjunct to an antituberculosis drug treatment regimen decrease morbidity and mortality compared with an antituberculosis drug regimen alone?

Active *PULMONARY* tuberculosis

RANDOMISED CONTROLLED TRIALS

No randomised controlled trials identified

NON-RANDOMISED CONTROLLED TRIALS

No non-randomised controlled trials identified

OBSERVATIONAL STUDIES

1.1.1 Jaworski, 1972

Bibliographic reference	Jaworski J (1972) Comparison of late results of treatment in surgically treated patients with pulmonary tuberculosis and those who refused surgery. Part II. Period from 1960–1967. Polish Medical Journal 11(2): 333-9
Study type	Retrospective (survey of patients and antituberculosis dispensaries)
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* no – allocation based on qualification for surgery and subsequent agreement or refusal to undergo surgery by the patient *Blinding used?* unclear, though unlikely *Attempts made within the design or analysis to balance the groups for potential confounders?* no *Groups comparable at baseline?* unclear; both drug susceptible and drug resistant disease included – balance between the 2 groups is unclear *Groups received the same care apart from the intervention(s) studied?* unclear

	Groups followed up for an equal and appropriate length of time? unclear *Groups comparable for treatment completion and availability of outcome data?* yes *Study used precise definitions and reliable measures of outcome?* no – diagnostic criteria (for 'cure' and the number of patients to still have active tuberculosis) not provided *Population studied is the same as the population of interest?* some drug resistant cases were included *Intervention used is the same as the intervention of interest?* unclear which antituberculosis drugs were used, or if same regimens were used in the 2 groups *Have substitute outcomes been used instead of the patient-important outcomes of interest?* yes – number of patients to return to work was not pre-specified as an outcome of interest, but is a potentially useful indicator of a patient's ability to function after treatment
Number of patients	Eligible = 245 antituberculosis chemotherapy plus surgery = 193 antituberculosis chemotherapy alone = 52 Included = 232 antituberculosis chemotherapy plus surgery = 184 antituberculosis chemotherapy alone = 48
Patient characteristics	*Inclusion* Pulmonary tuberculosis

	'Qualified' for surgery *Baseline* Both drug susceptible and drug resistant disease – balance between the 2 groups is unclear
Intervention	*Antituberculosis chemotherapy plus surgery* Surgery: ranged from resection of 1 segment (59%), to resection of 2 or more segments (17.4%), lobectomy (15.2%), extended lobectomy (4.8%) and total pulmonectomy (3.2%) Antituberculosis chemotherapy: duration: prolonged antituberculosis treatment was applied – across the intervention and comparator groups, 41.8% of patients received antituberculosis drugs for up to 2 years, 24.5% received antituberculosis drugs for over 2 years, and 27.2% received antituberculosis drugs for up to 1.5 years combination of antituberculosis drugs: unclear – 'routine' drugs were administered in 57.1% of all patients, and combined with 'reserve' drugs in 1/3 cases
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: duration: prolonged antituberculosis treatment was applied – across the intervention and comparator groups, 41.8% of patients received antituberculosis drugs for up to 2 years, 24.5% received antituberculosis drugs for over 2 years, and 27.2% received antituberculosis drugs for up to 1.5 years combination of antituberculosis drugs: unclear – 'routine' drugs were administered in 57.1% of all patients, and combined with 'reserve' drugs in 1/3 cases
Length of follow up	Unclear
Location	Zakopane, Poland
Outcomes measures and effect size	**Mortality** Number of fatalities antituberculosis chemotherapy plus surgery = 6 of 184[1]

	antituberculosis chemotherapy alone = 3 of 48[1] OR[2] (95% CI) = 0.51 (0.12 to 2.10) i.e. not statistically significant
	Cure Number of patients to be classified as a 'cure' antituberculosis chemotherapy plus surgery = 175 of 184[1] antituberculosis chemotherapy alone = 35 of 48[1] **OR[2] (95% CI) = 7.22 (2.87 to 18.20)** **i.e. statistically significant**
	Treatment failure Number of patients who still had active tuberculosis antituberculosis chemotherapy plus surgery = 3 of 184[1] antituberculosis chemotherapy alone = 10 of 48[1] **OR[2] (95% CI) = 0.06 (0.02 to 0.24)** **i.e. statistically significant**
	Functionality – return to work Number of patients who were able to return to work antituberculosis chemotherapy plus surgery = 177 of 184[1] antituberculosis chemotherapy alone = 37 of 48[1] OR[2] (95% CI) = 7.52 (2.73 to 20.68) i.e. not statistically significant

	Post-operative complications note: data available for group receiving antituberculosis chemotherapy plus surgery only Pleural empyema with fistula = 6% Exacerbations = 4.4% Bleeding into the operated space requiring thoracotomy = 1.6% Jaundice = 3.3% Psychoses = 1.6% Early death resulting from fibrinolytic shock = 1.1% *By type of surgery* Fewest complications were found after segmentectomies (20%), and the most after pneumonectomies (56.3%) *By duration of disease* The influence of duration of disease was not negligible, with complications found in 15.5% of patients ill for 1 to 5 years, and in 50% ill over 5 years *By susceptibility status* Complications were most frequent in in patients resistant to 3 or more drugs (81.1%), occurring in 22.7% of those resistant to 2 drugs and in 9% of those resistant to 1 drug
Source of funding	No details provided
Comments	Questionnaires were sent to antituberculosis dispensaries and to patients Those patients whose questionnaires aroused doubts or were not filled out well enough were invited to the hospital for observation; this comprised 28.7% of all patients previously qualified for surgical treatment

[1] Percentages converted into number of events by reviewer

[2] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

Abbreviations: CI, confidence intervals; OR, odds ratio; RCT, randomised controlled trial

Evidence tables

Active *ENDOBRONCHIAL* tuberculosis

RANDOMISED CONTROLLED TRIALS

No randomised controlled trials identified

NON-RANDOMISED CONTROLLED TRIALS

No non-randomised controlled trials identified

OBSERVATIONAL STUDIES

1.1.2 Jin et al, 2013

Bibliographic reference	Jin F, Mu D, Xie Y et al (2013) Application of brochoscopic argon plasma coagulation in the treatment of tumorous endobronchial tuberculosis: historical controlled trial. Journal of Thoracic and Cardiovascular Surgery 145: 1650-3
Study type	'Historical controlled trial'; retrospective observational
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* no – allocation was based upon the time at which the patient was treated: before June 2007, routine antituberculosis chemotherapy alone was applied for tumorous endobronchial tuberculosis, and after June 2007 argon plasma coagulation was also used *Blinding used?* unclear, though unlikely *Attempts made within the design or analysis to balance the groups for potential confounders?* no *Groups comparable at baseline?* yes *Groups received the same care apart from the intervention(s) studied?*

	yes, although details provided are limited *Groups followed up for an equal and appropriate length of time?* yes *Groups comparable for treatment completion and availability of outcome data?* yes *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* yes, although there may have been some patients with resistance to one drug (only patients with disease resistant to a combination of rifampicin, isoniazid or ethambutol were excluded) *Intervention used is the same as the intervention of interest?* yes *Have substitute outcomes been used instead of the patient-important outcomes of interest?* recurrence is a substitute for relapse
Number of patients	Included = 115 antituberculosis chemotherapy plus APC = 41 antituberculosis chemotherapy alone = 74
Patient characteristics	*Inclusion* Tumorous endobronchial tuberculosis without bronchial stenosis Sputum smears positive for tubercle bacillus Sputum culture showed no multidrug resistance (defined as a combination of resistance to rifampicin, isoniazid or ethambutol)

Completed treatment and follow-up

Diagnostic criteria

Confirmed by microbiologic or histopathologic examination

All patients underwent bacteriologic studies of sputum and bronchoscopic aspirate, and pathologic studies of bronchoscopic biopsy specimens

Tumorous endobronchial tuberculosis defined according to the work of Chung and Lee[1,2]

Exclusion

Antituberculosis chemotherapy history on presentation

Other subtypes of endobronchial tuberculosis, or tumorous endobronchial tuberculosis that had already developed into bronchial stenosis

Baseline

	Antituberculosis chemotherapy plus APC (n = 41)	**Antituberculosis chemotherapy alone** (n = 74)
Sex		
male, n (%)	11 (26.8%)	26 (35.1%)
female, n (%)	30 (73.2%)	48 (64.9%)
Age (mean ± SD), years	30.2±10.4	33.1±11.3
Location of airway lesions		
trachea, n (%)	2 (4.9%)	5 (6.8%)
right main bronchus, n (%)	5 (12.2%)	12 (16.2%)
right upper lobar bronchus, n (%)	7 (17.1%)	8 (10.8%)

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<tr><td></td><td>
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<tr><td>right middle lobar bronchus, n (%)</td><td>5 (12.2%)</td><td>10 (13.5%)</td></tr>
<tr><td>right lower lobar bronchus, n (%)</td><td>3 (7.3%)</td><td>10 (13.5%)</td></tr>
<tr><td>left main bronchus, n (%)</td><td>19 (46.3%)</td><td>33 (44.6%)</td></tr>
<tr><td>left upper lobar bronchus, n (%)</td><td>8 (19.5%)</td><td>20 (27.0%)</td></tr>
<tr><td>left middle lobar bronchus, n (%)</td><td>2 (4.9%)</td><td>11 (14.9%)</td></tr>
<tr><td>left lower lobar bronchus, n (%)</td><td>6 (14.6%)</td><td>14 (18.9%)</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Antituberculosis chemotherapy plus APC
APC:
performed with an APC unit via an electronic bronchoscope; energy at 30 to 40 W and an argon flow at 0.3 to 2.0 l/min was applied through a 2.0 mm diameter, 150 cm long APC monopolar probe
the probe was inserted through the working channel of the bronchoscope; the APC was positioned 1 to 2 mm away from the mucosa, and 1- to 2-second pulses of ablation were repeated until the lesion was coagulated; the devitalised tissue was removed mechanically with grasping forceps
bronchoscopic APC was performed every 2 weeks until there were no tumorous endobronchial lesions observed
Antituberculosis chemotherapy: 2HRZE/4HR
details of dosing not provided</td></tr>
<tr><td>Comparison</td><td>Antituberculosis chemotherapy alone
Antituberculosis chemotherapy: 2HRZE/4HR
details of dosing not provided</td></tr>
<tr><td>Length of follow up</td><td>9 months after initiation of treatment</td></tr>
<tr><td>Location</td><td>Shaanxi Province, China</td></tr>
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Outcomes measures and effect size	**Changes in signs and symptoms – improvement in endobronchial lesions** Number of patients in whom lesions were improved (the number and/or volume of lesions reduced) or healed (lesions removed completely) after 16 weeks antituberculosis chemotherapy plus APC = 41 of 41 antituberculosis chemotherapy alone = 62 of 74 OR[3] (95% CI) = 16.60 (0.97 to 288.09) i.e. not statistically significant
	Changes in signs and symptoms – deterioration of endobronchial lesions Number of patients in whom lesions had deteriorated (the number and/or volume of lesions had increased) at 16 weeks antituberculosis chemotherapy plus APC = 0 of 41 antituberculosis chemotherapy alone = 3 of 74 OR[3] (95% CI) = 0.25 (0.01 to 4.88) i.e. not statistically significant
	Changes in signs and symptoms – recurrence of endobronchial lesions Number of patients in whom lesions and recurred after 9 months of follow-up antituberculosis chemotherapy plus APC = 0 of 41 antituberculosis chemotherapy alone = 0 of 74 OR[3] (95% CI) = 1.80 (0.04 to 92.15) i.e. not statistically significant
	Post-operative complications note: data available for group receiving antituberculosis chemotherapy plus APC only

	Laryngeal spasm = 1 (2.4%) Cough = 35 (85.4%) 5–10 ml bleeding = 5 (12.2%) Secondary pulmonary infection = 0 Esphagotrachea fistula = 0 Pneumothorax = 0 Trachea perforation = 0 Death = 0
Source of funding	No details provided
Comments	

[1] Chung HS & Lee JH (2000) Bronchoscopic assessment of the evolution of endobronchial tuberculosis. Chest 117: 385-92

[2] Tumorous endobronchial tuberculosis is characterized by an endobronchial mass whose surface is often covered with caseous material and nearly totally occluded the bronchial lumen

[3] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

Abbreviations: APC, argon plasma coagulation; CI, confidence intervals; E, ethambutol; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; SD, standard deviation; Z, pyrazinamide

Evidence tables

Active tuberculosis of the CHEST WALL

RANDOMISED CONTROLLED TRIALS

No randomised controlled trials identified

NON-RANDOMISED CONTROLLED TRIALS

No non-randomised controlled trials identified

OBSERVATIONAL STUDIES

1.1.3 Hsu et al, 1995

Bibliographic reference	Hsu H-S, Wang L-S, Wu Y-C et al (1995) Management of primary chest wall tuberculosis. Scandinavian Journal of Thoracic and Cardiovascular Surgery 29: 119-23
Study type	Retrospective case series
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* no *Blinding used?* no *Attempts made within the design or analysis to balance the groups for potential confounders?* no *Groups comparable at baseline?* no – significant variation in age, size and location of the chest wall mass, radiography, extent of bone and cartilage involvement, and histological status (see 'patient characteristics' below) *Groups received the same care apart from the intervention(s) studied?* no – received different combinations of antituberculosis drugs for treatment periods of different duration (see

	'intervention' and 'comparator' sections below) *Groups followed up for an equal and appropriate length of time?* unclear *Groups comparable for treatment completion and availability of outcome data?* yes *Study used precise definitions and reliable measures of outcome?* no – definition of 'good outcome' was not provided *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* antituberculosis regimens did not use all of or just the 4 standard recommended drugs intervention and comparator arms varied by more than the presence or absence of surgery *Have substitute outcomes been used instead of the patient-important outcomes of interest?* yes – 'good outcome' is a substitute for cure and/or treatment success, and perhaps the changes in signs and symptoms of disease
Number of patients	Included = 7 antituberculosis chemotherapy plus surgery = 6 antituberculosis chemotherapy alone = 1
Patient characteristics	*Inclusion* Primary chest wall tuberculosis *Diagnostic criteria* Finding of tubercle bacilli (acid-fast stain) in the needle aspirate or the debrided specimen, or histologic evidence of

tuberculoma (Langhan's giant cells and caseous necrosis)

Exclusion

Active pulmonary tuberculosis or tuberculous empyema with pleurocutaneous fistula

Baseline

	AntiTB drugs plus surgery (n = 7)						**AntiTB drugs alone** (n = 1)
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	
Age	62	47	61	54	56	57	25
Sex	male	female	male	male	male	male	female
Clinical features of the chest wall masses							
Consistency	firm	soft	firm	firm	firm	firm	firm
Local tenderness	–	–	+	–	+	–	–
Erythema	–	–	+	–	+	–	–
Size, cm	10 x 8	7 x 1	4 x 4	4 x 4	3 x 5	3 x 3	3 x 5
Duration, months	1	3	1	2	1	1	1
Location	right, lower chest wall	left, upper parasternal	left, lower chest wall	right, lower chest wall	left, lower chest wall	left, lower chest wall	left, lower parasternal
Radiologic, bacteriologic and histopathologic findings							
Radiography	old pulmonary TB	normal	normal	old pulmonary TB	old pulmonary TB	left pleural thickening	normal
Bone/cartilage involvement	none	sternum	sternum, cartilages	none	none	none	rib destruction

		V and VI					
	Aspirate AFB microscopy	positive	negative	no test	no test	no test	negative	positive
	Aspirate *M. tuberculosis* culture	negative	negative	negative	negative	negative	negative	negative
	Debridement specimen AFB microscopy	positive	positive	positive	positive	negative	negative	positive
	Debridement specimen histology	Langhans' cells, caseous necrosis	Langhans' cells, caseous necrosis	Langhans' cells, caseous necrosis	Langhans' cells, caseous necrosis	granuloma, epitheloid cells	Langhans' cells, caseous necrosis	no operation

Intervention

Antituberculosis chemotherapy plus surgery

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Number of operations	2	1	5	1	2	2
Antituberculosis regimen	12HRZE	11HRE	10HRE	9HZ	9HSE	19HRE

Surgery:

ranged from simple incision and drainage to extensive debridement of regional soft tissues and underlying ribs or cartilages

Dosing:

isoniazid: 300 mg/day

rifampicin: 600 mg/day

ethambutol: 800 mg/day

	pyrazinamide: 1500 mg/day streptomycin: not specified
Comparison	*Antituberculosis chemotherapy alone* 12HRE Dosing: isoniazid: 300 mg/day rifampicin: 600 mg/day ethambutol: 800 mg/day
Length of follow up	Unclear
Location	Taipei, Taiwan
Outcomes measures and effect size	**Response to treatment – 'good' outcome** Clear definition not provided, although appears to encompass reduction or disappearance of the mass, as well as a lack of recurrence Number of patients to have a good outcome antituberculosis chemotherapy plus surgery = 6 of 6 antituberculosis chemotherapy alone = 1 of 1 OR (95% CI) = 4.33 (0.06 to 320.42) i.e. not statistically significant
	Response to treatment *Antituberculosis chemotherapy plus surgery* (n = 6) Case 1: definite diagnosis established by needle aspiration; secondary staphylococcal infection appeared 1 month after initiation of antituberculosis chemotherapy and necessitated surgical debridement and drainage; the wound took

	4 weeks to heal, but after 12 months of chemotherapy the outcome was good Case 2 and 4: did not have a definite diagnosis; single operation performed; wounds healed within 2 months Case 3: did not have a definite diagnosis; required 5 surgical debridements within 2 years because of recurrent lesions and involvement of the underlying ribs Case 5: did not have a definite diagnosis; required 2 surgical debridements; wounds healed within 2 months Case 6: did not have a definite diagnosis; second operation performed 20 months after the first due to recurrence of the primary chest wall lesion; wounds healed within 1 month *Antituberculosis chemotherapy alone* (n = 1) Case 1: definite diagnosis established by needle aspiration; response of patient to antituberculosis chemotherapy alone was described as 'remarkable', with diminution of the chest-wall mass after 1 month and complete disappearance by 9 months; no recurrence during 2-year follow-up
Source of funding	No details provided
Comments	

[1] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

Abbreviations: acid-fast bacilli, AFB; antiTB, antituberculosis; CI, confidence intervals; E, ethambutol; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; TB, tuberculosis; Z, pyrazinamide

Evidence tables

Active *BONE AND JOINT* tuberculosis

RANDOMISED CONTROLLED TRIALS

No randomised controlled trials identified

NON-RANDOMISED CONTROLLED TRIALS

No non-randomised controlled trials identified

OBSERVATIONAL STUDIES

1.1.4 Chow & Yau, 1980

Bibliographic reference	Chow SP & Yau A (1980) Tuberculosis of the knee – a long term follow-up. International Orthopaedics 4: 87-92
Study type	Retrospective – review of clinical records and collection of additional data via interview
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* unclear *Blinding used?* unclear, though unlikely *Attempts made within the design or analysis to balance the groups for potential confounders?* no *Groups comparable at baseline?* no – 50% of the surgical group were treated before the age of 20, whereas 80% of those treated conservatively were treated before the age of 20 *Groups received the same care apart from the intervention(s) studied?* yes, although details provided are limited

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Groups followed up for an equal and appropriate length of time?

follow-up not equal – mean follow-up in the surgical group was 13 years, mean follow-up amongst those treated conservatively was 17 years

Groups comparable for treatment completion and availability of outcome data?

yes

Study used precise definitions and reliable measures of outcome?

yes

Population studied is the same as the population of interest?

yes, although details provided are limited

Intervention used is the same as the intervention of interest?

unclear – details of antituberculosis regimen not provided

Have substitute outcomes been used instead of the patient-important outcomes of interest?

yes – ‘recurrence’ is a substitute for ‘relapse’
</td></tr>
<tr><td>Number of patients</td><td>
Included = 30

antituberculosis chemotherapy plus surgery = 15

conservative management = 15
</td></tr>
<tr><td>Patient characteristics</td><td>
Inclusion

Tuberculosis of the knee

Baseline
<table>
<tr><th></th><th>Antituberculosis chemotherapy plus surgery</th><th>Conservative management

(n = 15)</th></tr>
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<tr><td></td><td>(n = 15)</td><td></td></tr>
<tr><td>Patients <20 years old at treatment initiation</td><td>50%</td><td>80%</td></tr>
<tr><td>Diagnosis</td><td></td><td></td></tr>
<tr><td>confirmed histologically</td><td>100.0%</td><td>60.0%</td></tr>
<tr><td>active tuberculosis elsewhere in the body</td><td>?</td><td>40.0%</td></tr>
<tr><td>discharging sinuses</td><td>?</td><td>26.7%</td></tr>
<tr><td>typical x-ray signs of erosion</td><td>?</td><td>13.3%</td></tr>
</table>
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<tr><td>Intervention</td><td>Antituberculosis chemotherapy plus surgery
Surgery:
13 underwent synovectomy and debridement followed by immobilisation in a plaster cast for 1 to 2 months before wearing a leather brace for up to 1 year; the brace was frequently removed and mobilisation of the knee encouraged
2 underwent synovectomy and debridement but because of the extent of joint destruction immobilisation was maintained until joint fusion occurred
Antituberculosis chemotherapy: regimen unclear</td></tr>
<tr><td>Comparison</td><td>Conservative management
Antituberculosis chemotherapy: regimen unclear
12 patients received plaster bracing
2 patients underwent simple bed rest
1 patient received skeletal traction</td></tr>
<tr><td>Length of follow up</td><td>mean = 15 years
antituberculosis chemotherapy plus surgery = 13 years</td></tr>
</table>

	conservative management = 17 years
Location	Hong Kong
Outcomes measures and effect size	**Changes in signs and symptoms – bony fusion** Number of patients to experience bony fusion/ankylosis antituberculosis chemotherapy plus surgery = 4 of 15 conservative management = 0 of 15 OR[1] (95% CI) = 12.13 (0.59 to 248.50) i.e. not statistically significant
	Changes in signs and symptoms – deformity The type of treatment did not influence the incidence of deformity
	Recurrence Number of patients to experience recurrence antituberculosis chemotherapy plus surgery = 0 of 15 conservative management = 0 of 15 OR[1] (95% CI) = 1.00 (0.02 to 53.66) i.e. not statistically significant
Source of funding	No details provided
Comments	

[1] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

Abbreviations: CI, confidence intervals; OR, odds ratio; RCT, randomised controlled trial

1.1.5 Kim et al, 1999

Bibliographic reference	Kim NH, Lee HM, Yoo JD et al (1999) Sacroiliac joint tuberculosis. Classification and treatment. Clinical Orthopaedics and Related Research 358: 215-22
Study type	Case series
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* unclear, but it appears not – all those that underwent surgery had more advanced disease *Blinding used?* unclear, though unlikely *Attempts made within the design or analysis to balance the groups for potential confounders?* no *Groups comparable at baseline?* severity of disease is greater in the surgery group antituberculosis chemotherapy alone group were all female, surgery group was a mix of males and females *Groups received the same care apart from the intervention(s) studied?* yes, although details provided were limited *Groups followed up for an equal and appropriate length of time?* no, mean follow-up was longer in those that received antituberculosis chemotherapy alone *Groups comparable for treatment completion and availability of outcome data?* yes *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?*

	yes, although details provided were limited *Intervention used is the same as the intervention of interest?* antituberculosis regimens do not use all of or just the 4 standard recommended drugs – lacked pyrazinamide and contained streptomycin *Have substitute outcomes been used instead of the patient-important outcomes of interest?* no
Number of patients	Included = 16 antituberculosis chemotherapy plus surgery = 12 antituberculosis chemotherapy alone = 4
Patient characteristics	*Inclusion* Tuberculosis of the sacroiliac joint Minimum of 2 years follow-up *Diagnostic criteria* Diagnosis was made by clinical symptoms and physical signs, laboratory data, cultures positive for tuberculosis bacilli, radiographic findings, and histologic findings *Baseline* Age (mean ± SD), years antituberculosis chemotherapy plus surgery = 32.8±16.2 antituberculosis chemotherapy alone = 28.8±13.6 Duration of symptoms (mean ± SD), months antituberculosis chemotherapy plus surgery = 7.3±3.3 antituberculosis chemotherapy alone = 9.8±17.5

		Gender/ age, years	Severity of disease[1]	Duration of symptoms, months	Involved side	Other affected site	Abscess formation	Draining sinus	Acid-fast bacilli
Antituberculosis chemotherapy plus surgery (n = 12)	Case 1	F/20	III	9	left	–	–	–	–
	Case 2	M/39	III	12	right	lung	–	–	+
	Case 3	F/26	IV	12	right	lung	gluteal	–	+
	Case 4	F/25	III	6	right	lung	–	–	+
	Case 5	M/11	IV	8	left	T7	gluteal	–	–
	Case 6	F/65	IV	1.5	right	L5	gluteal	–	–
	Case 7	F/35	III	7	left	lung	–	–	+
	Case 8	F/20	III	8	left	lung	gluteal	+	–
	Case 9	F/46	IV	2	right	–	gluteal	–	–
	Case 10	F/17	III	9	right	–	–	–	–
	Case 11	F/54	IV	8	left	–	inguinal	–	–
	Case 12	M/36	IV	5	right	L5	inguinal	–	–
[illegible] chemotherapy alone (n =	Case 13	F/14	I	36	bilateral	–	gluteal	+	–
	Case 14	F/46	IV	2	left	L4	–	–	–

	Case 15	F/23	II	0.5	left	–	–	–	–
	Case 16	F/32	I	0.5	right	–	–	–	–

Intervention	*Antituberculosis chemotherapy plus surgery* Surgery: curettage was done if there was abscess formation or mild cystic change of the sacroiliac joint margin if there were cystic changes and marked destruction of the joint, and instability was seen during the operation, curettage and arthrodesis of the sacroiliac joint were done all operations were performed using the posterior approach after surgery, 11 of the patients were immobilised with the application of a hip spica cast, and the 12th patient was immobilised with a brace; immobilisation ranged from 10 to 20 weeks Antituberculosis chemotherapy: 3HRSE/15HRE isoniazid: 5 mg/kg of bodyweight/day rifampicin: 10 mg/kg of bodyweight/day streptomycin: 15 mg/kg of bodyweight/day ethambutol: 15 mg/kg of bodyweight/day
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: 3HRSE/15HRE isoniazid: 5 mg/kg of bodyweight/day rifampicin: 10 mg/kg of bodyweight/day streptomycin: 15 mg/kg of bodyweight/day

	ethambutol: 15 mg/kg of bodyweight/day
Length of follow up	Follow-up (mean ± SD), months antituberculosis chemotherapy plus surgery = 28.3±6.0 antituberculosis chemotherapy alone = 32.4±5.8
Location	Seoul, Korea
Outcomes measures and effect size	**Changes in signs and symptoms – fusion** Number of patients to experience fusion of the sacroiliac joint, as assessed using plain radiographs and confirmed using CT or MRI scans antituberculosis chemotherapy plus surgery = 6 of 12 antituberculosis chemotherapy alone = 0 of 4 OR[3] (95% CI) = 9.00 (0.40 to 203.31) i.e. not statistically significant) Time (mean±SD, months) to fusion of the sacroiliac joint antituberculosis chemotherapy plus surgery[2] = 20.8±3.5 antituberculosis chemotherapy alone[2] = –
	Changes in signs and symptoms – healing criteria for healing: no pain or tenderness over the lesion site, no pain or discomfort during walking, a return to normal value of the erythrocyte sedimentation rate, disappearance of the abscess, clearance of sclerosis of the joint margin, and fusion of the sacroiliac joint Number of patients to heal antituberculosis chemotherapy plus surgery = 6 of 12 antituberculosis chemotherapy alone = 4 of 4

	OR[3] (95% CI) = 0.11 (0.00 to 2.51) i.e. not statistically significant) Time (mean±SD, months) to healing antituberculosis chemotherapy plus surgery[2] = 24.5±2.0 antituberculosis chemotherapy alone[2] = 23.5±1.0 MD[4] (95% CI) = 1.0 (-0.9 to 2.9) i.e. not statistically significant)
Source of funding	No details provided
Comments	

[1] Severity of disease:

type I: widening of the joint space and blurring on the margin of the sacroiliac joint

type II: erosion of the sacroiliac joint

type III: severe destruction of the sacroiliac joint with cyst formation of the ilium and sacrum and marginal sclerosis

type IV: lesion of the sacroiliac joint with abscess formation or other affected vertebra

[2] Individual patient data pooled by reviewer

[3] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

[4] Mean difference and 95% confidence intervals not provided by authors; calculated by reviewer

Abbreviations: CI, confidence intervals; CT, computer tomography; F, female; M, male; MD, mean difference; MRI, magnetic resonance imaging; OR, odds ratio; RCT, randomised controlled trial; SD, standard deviation

Evidence tables

Active *SPINAL* tuberculosis

RANDOMISED CONTROLLED TRIALS

1.1.6 ICMR/MRC, 1994a/4b/9a/9b

Study type	RCT
Study quality	*Appropriate method of randomisation used?* unclear *Allocation concealment used?* unclear *Blinding used?* unclear *Groups comparable at baseline?* yes *Groups received the same care apart from the intervention(s) studied?* yes *Groups followed up for an equal and appropriate length of time?* yes *Groups comparable for treatment completion and availability of outcome data?* yes *Study used precise definitions and reliable measures of outcome?* yes

	Population studied is the same as the population of interest? yes *Intervention used is the same as the intervention of interest?* antituberculosis regimens do not use all of the 4 standard recommended drugs intervention and comparator differ by more than the presence of absence of surgery – some patients in the chemotherapy alone group received antituberculosis drugs for a longer period (duration of treatment = 6 or 9 months) than in the surgery group (duration of treatment = 6 months for all patients) *Have substitute outcomes been used instead of the patient-important outcomes of interest?* 'response to treatment' outcomes are substitute outcomes for cure / treatment success / treatment failure and changes in the signs and symptoms of disease *Analysis followed the intent-to-treat principle?* yes
Number of patients	Randomised = 304 antituberculosis chemotherapy (6 months) plus surgery = 100 antituberculosis chemotherapy alone = 204 6HR = 101 9HR = 103
Patient characteristics	*Inclusion* Patients with clinically and radiologically active tuberculosis of the spine involving any vertebral body from the first thoracic to the first sacral, inclusive *Exclusion* Paralysis of the lower limbs severe enough to prevent them from walking across a room Serious extraspinal disease (tuberculous or non-tuberculous)

	A history of previous specific chemotherapy for 12 months or more Those who had already had major surgery for the spinal disease Broadly similar with respect to sex, radiographic activity, vertebral body loss and number of vertebrae involved
Intervention	*Antituberculosis chemotherapy plus surgery* Surgery: radical Hong Kong surgery within 1 month of antituberculosis chemotherapy initiation; surgery consisted of radical anterior excision of the tuberculous focus and repair of the resultant gap with autologous bone grafts Antituberculosis chemotherapy: $6HR_7$ isoniazid: 5 to 7 mg/kg of bodyweight/day rifampicin: 10 to 15 mg/kg of bodyweight/day For all in-patients and for outpatients aged less than 5 years, every dose of drugs was administered under the direct supervision of a staff member Out-patients aged 5 years or more attended the clinic twice-weekly and at each attendance, the dose for that day was administered under direct supervision, and the medicament (2 or 3 doses) supplied for self-administration (or administration by the parent) for the days until the next visit
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: $6HR_7$ or $9HR_7$ isoniazid: 5 to 7 mg/kg of bodyweight/day rifampicin: 10 to 15 mg/kg of bodyweight/day For all in-patients and for outpatients aged less than 5 years, every dose of drugs was administered under the direct supervision of a staff member Out-patients aged 5 years or more attended the clinic twice-weekly and at each attendance, the dose for that day was administered under direct supervision, and the medicament (2 or 3 doses) supplied for self-administration (or administration by the parent) for the days until the next visit
Location	Madras, India

Bibliographic reference	Parthasarathy R, Sriram K, Santha T et al (1999) Short-course chemotherapy for tuberculosis of the spine. A comparison between ambulant treatment and radical surgery – ten-year report. Journal of Bone & Joint Surgery (British) 81-B:464-71
Number of patients	Randomised = 304 antituberculosis chemotherapy plus surgery = 100 antituberculosis chemotherapy alone = 204 6HR = 101 9HR = 103 Data available = 235 antituberculosis chemotherapy plus surgery = 78 antituberculosis chemotherapy alone = 157 6HR = 78 9HR = 79 Data available for kyphosis (only measured in patients with thoracic or thoracolumbar lesions) = antituberculosis chemotherapy plus surgery = 28 antituberculosis chemotherapy alone = 79 6HR = 41 9HR = 38
Length of follow up	10 years
Outcomes measures and effect size	**Mortality - spinal tuberculosis-associated deaths** Number of deaths associated with spinal tuberculosis antituberculosis chemotherapy (6 months) plus surgery = 4 of 100

	antituberculosis chemotherapy alone = 0 of 204 **OR[1] (95% CI) = 19.07 (1.02 to 357.83)** **i.e. statistically significant**
	Changes in signs and symptoms – bony fusion Number of patients to experience complete bony fusion within 10-year follow-up antituberculosis chemotherapy (6 months) plus surgery = 64 of 100 antituberculosis chemotherapy alone = 127 of 204 6HR = 61 of 101 9HR = 66 of 103 *Antituberculosis chemotherapy plus surgery* vs *antituberculosis chemotherapy alone (any duration)* OR[1] (95% CI) = 1.08 (0.66 to 1.77) i.e. not statistically significant *Antituberculosis chemotherapy (6 months) plus surgery* vs *antituberculosis chemotherapy alone (6 months)* OR[1] (95% CI) = 1.17 (0.66 to 2.06) i.e. not statistically significant Number of patients to experience partial bony fusion within 10-year follow-up antituberculosis chemotherapy (6 months) plus surgery = 5 of 100 antituberculosis chemotherapy alone = 21 of 204 6HR = 11 of 101 9HR = 10 of 103 *Antituberculosis chemotherapy plus surgery* vs *antituberculosis chemotherapy alone (any duration)*

	OR[1] (95% CI) = 0.46 (0.17 to 1.25) i.e. not statistically significant *Antituberculosis chemotherapy (6 months) plus surgery* vs *antituberculosis chemotherapy alone (6 months)* OR[1] (95% CI) = 0.43 (0.14 to 1.29) i.e. not statistically significant Number of patients to experience no bony fusion within 10-year follow-up antituberculosis chemotherapy (6 months) plus surgery = 2 of 100 antituberculosis chemotherapy alone = 5 of 204 6HR = 3 of 101 9HR = 2 of 103 *Antituberculosis chemotherapy plus surgery* vs *antituberculosis chemotherapy alone (any duration)* OR[1] (95% CI) = 0.81 (0.15 to 4.26) i.e. not statistically significant *Antituberculosis chemotherapy (6 months) plus surgery* vs *antituberculosis chemotherapy alone (6 months)* OR[1] (95% CI) = 0.67 (0.11 to 4.08) i.e. not statistically significant Number of patients to experience spontaneous bony fusion within 10-year follow-up antituberculosis chemotherapy (6 months) plus surgery = 1 of 100 antituberculosis chemotherapy alone = 7 of 204 *Antituberculosis chemotherapy plus surgery* vs *antituberculosis chemotherapy alone (any duration)* OR[1] (95% CI) = 0.28 (0.03 to 2.34)

	i.e. not statistically significant
	Changes in signs and symptoms – kyphosis Mean angle of kyphosis at 10-year follow-up amongst patients with thoracic or thoracolumbar lesions antituberculosis chemotherapy (6 months) plus surgery (n = 28) = 41° antituberculosis chemotherapy alone (n = 79) = 44° 6HR (n = 41) = 47° 9HR (n = 38) = 41° *Antituberculosis chemotherapy plus surgery* vs *antituberculosis chemotherapy alone (any duration)* MD^2 = -3° *Antituberculosis chemotherapy (6 months) plus surgery* vs *antituberculosis chemotherapy alone (6 months)* MD^2 = -6° Mean increase in angle of kyphosis from baseline to 10-year follow-up amongst patients with thoracic or thoracolumbar lesions antituberculosis chemotherapy (6 months) plus surgery (n = 28) = 15° antituberculosis chemotherapy alone (n = 79) = 15° 6HR (n = 41) = 17° 9HR (n = 38) = 13° *Antituberculosis chemotherapy plus surgery* vs *antituberculosis chemotherapy alone (any duration)* MD^2 = 0° *Antituberculosis chemotherapy (6 months) plus surgery* vs *antituberculosis chemotherapy alone (6 months)* MD^2 = -2°

	Response to treatment – favourable status Defined as no sinus or clinically evident abscess, no myelopathy and no modification of the allocated regimen, as well as no limitation of physical activity due to the spinal lesion and radiologically quiescent disease Number of patients to achieve a favourable status during 10-year follow-up antituberculosis chemotherapy (6 months) plus surgery = 70 of 100 antituberculosis chemotherapy alone = 151 of 204 6HR = 73 of 101 9HR = 78 of 103 *Antituberculosis chemotherapy plus surgery* vs *antituberculosis chemotherapy alone (any duration)* OR[1] (95% CI) = 0.82 (0.48 to 1.39) i.e. not statistically significant *Antituberculosis chemotherapy (6 months) plus surgery* vs *antituberculosis chemotherapy alone (6 months)* OR[1] (95% CI) = 0.90 (0.49 to 1.65) i.e. not statistically significant
	Response to treatment – need for additional intervention Number of patients to require additional chemotherapy or surgery during 10-year follow-up antituberculosis chemotherapy (6 months) plus surgery = 5 of 100 antituberculosis chemotherapy alone = 6 of 204 6HR = 5 of 101 9HR = 1 of 103 *Antituberculosis chemotherapy plus surgery* vs *antituberculosis chemotherapy alone (any duration)*

	OR[1] (95% CI) = 1.74 (0.52 to 5.83) i.e. not statistically significant *Antituberculosis chemotherapy (6 months) plus surgery* vs *antituberculosis chemotherapy alone (6 months)* OR[1] (95% CI) = 1.01 (0.28 to 3.60) i.e. not statistically significant
Bibliographic reference	Darbyshire J (1999) Five-year assessment of controlled trials of short-course chemotherapy regimens of 6, 9 or 18 months' duration for spinal tuberculosis in patients ambulatory from the start or undergoing radical surgery. Fourteenth report of the Medical Research Council Working Party on Tuberculosis of the Spine. International Orthopaedics (SICOT) 23:73-81
Number of patients	Randomised = 304 antituberculosis chemotherapy plus surgery = 100 antituberculosis chemotherapy alone = 204 6HR = 101 9HR = 103 Data available for bony fusion = 241 antituberculosis chemotherapy plus surgery = 77 antituberculosis chemotherapy alone = 164 6HR = 79 9HR = 85 Data available for vertebral loss = 232 antituberculosis chemotherapy plus surgery = 75 antituberculosis chemotherapy alone = 157

<table>
<tr><td></td><td>6HR = 75
9HR = 82
Data available for kyphosis = 130
antituberculosis chemotherapy plus surgery = 34
antituberculosis chemotherapy alone = 96
6HR = 45
9HR = 51
Data available for myelopathy = unclear</td></tr>
<tr><td>Length of follow up</td><td>5 years</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Changes in signs and symptoms – bony fusion
Number of patients to experience complete bony fusion
<table>
<tr><th rowspan="2">Months after treatment initiation</th><th rowspan="2">Antituberculosis chemotherapy (6 months) plus surgery
(n = 77)</th><th colspan="3">Antituberculosis chemotherapy alone
(n = 164)</th></tr>
<tr><th>6HR (n = 79)</th><th>9HR (n = 85)</th><th>total (n = 164)</th></tr>
<tr><td>6</td><td>8</td><td>12</td><td>13</td><td>25</td></tr>
<tr><td>12</td><td>26</td><td>26</td><td>25</td><td>51</td></tr>
<tr><td>24</td><td>42</td><td>41</td><td>43</td><td>84</td></tr>
<tr><td>36</td><td>50</td><td>52</td><td>49</td><td>101</td></tr>
<tr><td>42</td><td>52</td><td>53</td><td>53</td><td>106</td></tr>
<tr><td>48</td><td>53</td><td>55</td><td>56</td><td>111</td></tr>
<tr><td>54</td><td>56</td><td>55</td><td>61</td><td>116</td></tr>
</table></td></tr>
</table>

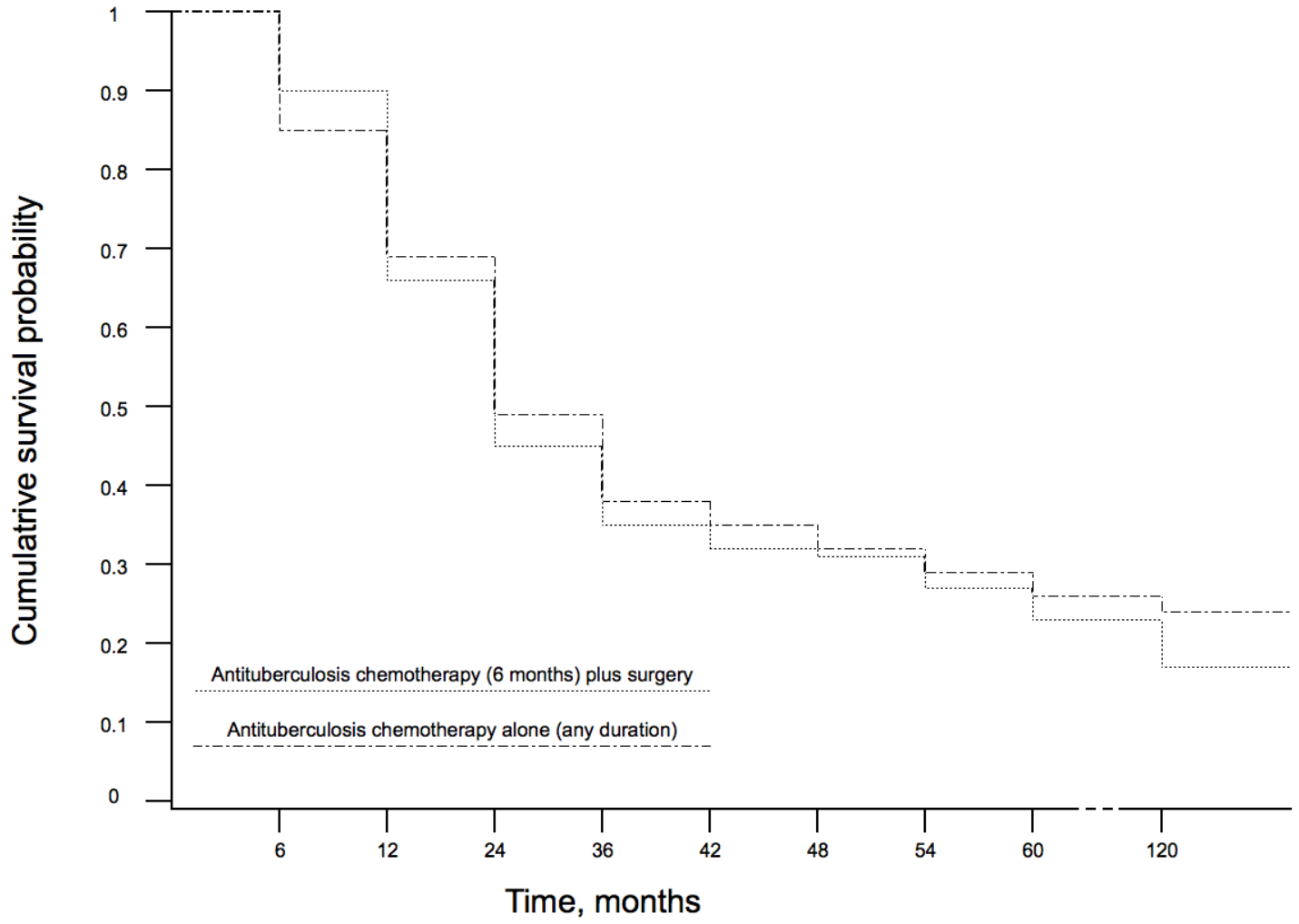
60	59	59	63	122
120[3]	64 (n = 71)	61 (n = 75)	64 (n = 75)	125 (n = 150)

Months after treatment initiation	***Antituberculosis chemotherapy (6 months) plus surgery*** (n = 77)			***Antituberculosis chemotherapy alone (any duration)*** (n = 164)		
	number at risk	number of new events	cumulative survival probability[4]	number at risk	number of new events	cumulative survival probability[4]
0	77	0	1	164	0	1
6	69	8	0.90	139	25	0.85
12	51	18	0.66	113	26	0.69
24	35	16	0.45	80	33	0.49
36	27	8	0.35	63	17	0.38
42	25	2	0.32	58	5	0.35
48	24	1	0.31	53	5	0.32
54	21	3	0.27	48	5	0.29
60	18	3	0.23	42	6	0.26
120[3]	13	5	0.17	39	3	0.24

Median 'survival' time[5], months

antituberculosis chemotherapy plus surgery = 24

antituberculosis chemotherapy alone (any duration) = 24



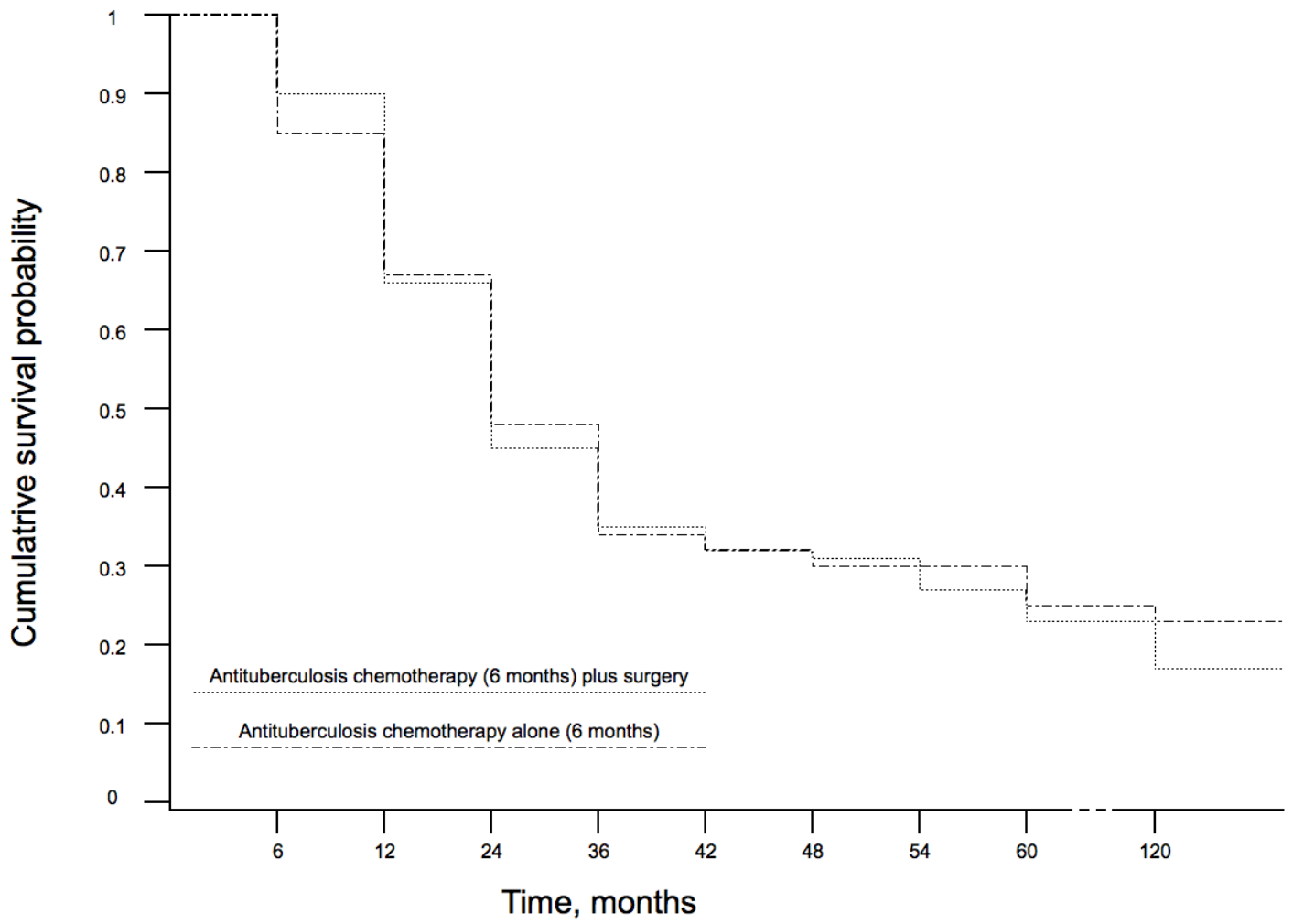
Months after treatment	*Antituberculosis chemotherapy (6 months) plus surgery* (n = 77)	*Antituberculosis chemotherapy alone (6 months)* (n = 79)

initiation	number at risk	number of new events	cumulative survival probability[4]	number at risk	number of new events	cumulative survival probability[4]
0	77	0	1	79	0	1
6	69	8	0.90	67	12	0.85
12	51	18	0.66	53	14	0.67
24	35	16	0.45	38	15	0.48
36	27	8	0.35	27	11	0.34
42	25	2	0.32	26	1	0.32
48	24	1	0.31	24	2	0.30
54	21	3	0.27	24	0	0.30
60	18	3	0.23	20	4	0.25
120[3]	13	5	0.17	18	2	0.23

Median 'survival' time[5], months

antituberculosis chemotherapy plus surgery = 24

antituberculosis chemotherapy alone (6 months) = 24



Changes in signs and symptoms – vertebral loss

Number of patients to experience an improvement of 0.25 vertebrae or more in their vertebral loss

antituberculosis chemotherapy (6 months) plus surgery = 5 of 100

	antituberculosis chemotherapy alone = 0 of 204 *Antituberculosis chemotherapy plus surgery* vs *antituberculosis chemotherapy alone (any duration)* **OR[1] (95% CI) = 23.56 (1.29 to 430.36)** **i.e. statistically significant** Number of patients to experience a deterioration of 0.25 vertebrae or more in their vertebral loss antituberculosis chemotherapy (6 months) plus surgery = 24 of 100 antituberculosis chemotherapy alone = 66 of 204 6HR = 37 of 101 9HR = 29 of 103 *Antituberculosis chemotherapy plus surgery* vs *antituberculosis chemotherapy alone (any duration)* OR[1] (95% CI) = 0.66 (0.38 to 1.14) i.e. not statistically significant *Antituberculosis chemotherapy (6 months) plus surgery* vs *antituberculosis chemotherapy alone (6 months)* OR[1] (95% CI) = 0.55 (0.30 to 1.01) i.e. not statistically significant
	Changes in signs and symptoms – kyphosis Number of patients to experience an improvement of 11° or more in their angle of kyphosis antituberculosis chemotherapy (6 months) plus surgery = 1 of 100 antituberculosis chemotherapy alone = 2 of 204 6HR = 0 of 101 9HR = 2 of 103

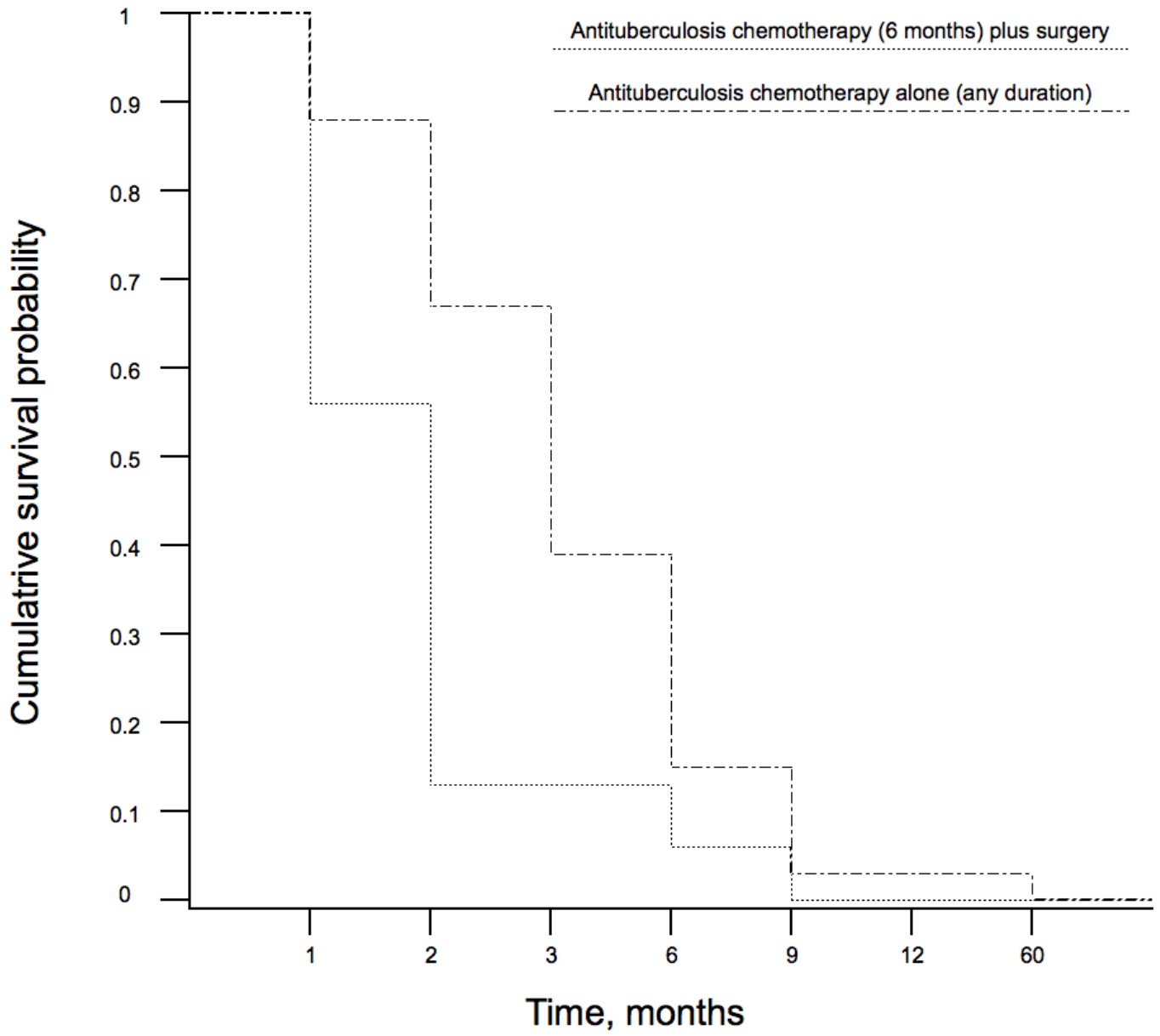
	Antituberculosis chemotherapy plus surgery vs *antituberculosis chemotherapy alone (any duration)* OR[1] (95% CI) = 1.02 (0.09 to 11.39) i.e. not statistically significant *Antituberculosis chemotherapy (6 months) plus surgery* vs *antituberculosis chemotherapy alone (6 months)* OR[1] (95% CI) = 3.06 (0.12 to 76.03) i.e. not statistically significant Number of patients to experience a deterioration of 11° or more in their angle of kyphosis antituberculosis chemotherapy (6 months) plus surgery = 13 of 100 antituberculosis chemotherapy alone = 40 of 204 6HR = 17 of 101 9HR = 23 of 103 *Antituberculosis chemotherapy plus surgery* vs *antituberculosis chemotherapy alone (any duration)* OR[1] (95% CI) = 0.61 (0.31 to 1.21) i.e. not statistically significant *Antituberculosis chemotherapy (6 months) plus surgery* vs *antituberculosis chemotherapy alone (6 months)* OR[1] (95% CI) = 0.74 (0.34 to 1.61) i.e. not statistically significant
	Changes in signs and symptoms – myelopathy Number of patients to experience residual myelopathy during 3-year follow-up antituberculosis chemotherapy (6 months) plus surgery = 2 of 100 antituberculosis chemotherapy alone = 0 of 204

<table>
<tr><td></td><td>Antituberculosis chemotherapy plus surgery vs antituberculosis chemotherapy alone (any duration)
OR[1] (95% CI) = 10.38 (0.49 to 218.30)
i.e. not statistically significant</td></tr>
<tr><td>Bibliographic reference</td><td>Balasubramanian R, Sivasubramanian S, Parthasarathy R et al (1994) Prevalence, incidence and resolution of abscesses and sinuses in patients with tuberculosis of spine: 5-year results of patients treated with short-course chemotherapy with or without surgery in Madras. Indian Journal of Tuberculosis 41: 151-60</td></tr>
<tr><td>Number of patients</td><td>Randomised = 304
antituberculosis chemotherapy plus surgery = 100
antituberculosis chemotherapy alone = 204
6HR = 101
9HR = 103
Data available = 253
antituberculosis chemotherapy plus surgery = 84
antituberculosis chemotherapy alone = 169
6HR = 81
9HR = 88</td></tr>
<tr><td>Length of follow up</td><td>5 years</td></tr>
<tr><td>Outcomes measure and effect size</td><td>Changes in signs and symptoms – sinuses and/or abscesses present on admission
Number of patients in whom the sinuses and/or clinically evident abscesses present on admission resolved
<table>
<tr><td rowspan="2">Months after treatment initiation</td><td rowspan="2">Antituberculosis chemotherapy (6 months) plus surgery
(n = 84; sinuses and/or</td><td colspan="3">Antituberculosis chemotherapy alone
(n = 169)</td></tr>
<tr><td>6HR (n = 81; sinuses</td><td>9HR (n = 88; sinuses</td><td>total (n = 169; sinuses</td></tr>
</table></td></tr>
</table>

	clinically evident abscesses present on admission = 16)	and/or clinically evident abscesses present on admission = 20)	and/or clinically evident abscesses present on admission = 13)	and/or clinically evident abscesses present on admission = 33)
0	0	0	0	0
1	7	3	1	4
2	14	7	4	11
3	14	13	7	20
6	15	17	11	28
9	16	20	12	32
12	16	20	12	32
60	16	20	13	33

Months after treatment initiation	***Antituberculosis chemotherapy (6 months) plus surgery*** (n = 84)			***Antituberculosis chemotherapy alone (any duration)*** (n = 169)		
	number at risk	number of new events	cumulative survival probability[4]	number at risk	number of new events	cumulative survival probability[4]
0	16	0	1	33	0	1
1	9	7	0.56	29	4	0.88
2	2	7	0.13	22	7	0.67
3	2	0	0.13	13	9	0.39
6	1	1	0.06	5	8	0.15

	9	0	1	0	1	4	0.03
	12	0	0	0	1	0	0.03
	60	0	0	0	0	1	0
	Median ‘survival’ time[5], months antituberculosis chemotherapy plus surgery = 2 antituberculosis chemotherapy alone (any duration) = 3						



Months after	***Antituberculosis chemotherapy (6 months) plus surgery*** (n = 84)	***Antituberculosis chemotherapy alone (6 months)*** (n = 81)

	Changes in signs and symptoms – new sinuses and/or abscesses Number of patients in whom the sinuses and/or clinically evident abscesses developed during 5-year follow-up antituberculosis chemotherapy plus surgery = 21 of 100 antituberculosis chemotherapy alone = 60 of 204 6HR = 32 of 101 9HR = 28 of 103 OR[1] (95% CI) = 0.64 (0.36 to 1.13) i.e. not statistically significant
Bibliographic reference	Reetha AM, Sivasubramanian S, Parthasarthy R et al (1994) Five-year findings of a comparison of ambulatory short course chemotherapy with radical surgery plus chemotherapy for tuberculosis of the spine in Madras. Indian Journal of Orthopaedics 28(1): 7-13
Number of patients	Randomised = 304 antituberculosis chemotherapy plus surgery = 100 antituberculosis chemotherapy alone = 204 6HR = 101 9HR = 103 Data available = 250 antituberculosis chemotherapy plus surgery = 82 antituberculosis chemotherapy alone = 168 6HR = 82 9HR = 86
Length of follow up	5 years

Outcomes measure and effect size	**Changes in signs and symptoms – vertebral loss** Mean increase in vertebral loss from baseline to 5 years antituberculosis chemotherapy plus surgery (n = 75) = 0.18 antituberculosis chemotherapy alone (n = 157) = 0.29 6HR (n = 75) = 0.34 9HR (n = 82) = 0.24 *Antituberculosis chemotherapy plus surgery* vs *antituberculosis chemotherapy alone (any duration)* MD[2] = -0.11 i.e. not statistically significant *Antituberculosis chemotherapy (6 months) plus surgery* vs *antituberculosis chemotherapy alone (6 months)* MD[2] = -0.16 i.e. not statistically significant
	Changes in signs and symptoms – reactivation of spinal lesions Number of patients in whom spinal lesions reactivated during follow-up antituberculosis chemotherapy plus surgery = 0 of 100 antituberculosis chemotherapy alone = 0 of 204 OR[1] (95% CI) = 2.03 (0.04 to 103.30) i.e. not statistically significant
Source of funding	No details provided
Comments	

[1] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

[2] Mean difference not provided by authors; calculated by reviewer

[3] Data for 10-year follow-up obtained from Parthasarathy et al (1999)

[4] Cumulative survival not provided by authors; calculated by reviewer

[5] Kaplan-Meier plot generated by reviewer; median survival time read off plot at a cumulative survival probability of 0.5

Abbreviations: CI, confidence intervals; H, isoniazid; MD, mean difference; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial

NON-RANDOMISED CONTROLLED TRIALS

1.1.7 Rajeswari et al, 1997

Bibliographic reference	Rajeswari R, Balasubramanian R, Venkatesan P (1997) Short-course chemotherapy in the treatment of Pott's paraplegia: report on five year follow-up. International Journal of Tuberculosis and Lung Disease 1(2): 152-8
Study type	Partially randomised controlled trial
Study quality	*Appropriate method of randomisation used?* no – only 23 of the 33 patients included underwent randomisation: the first 10 patients all received antituberculosis chemotherapy plus surgery (modified Hong Kong technique); all subsequent patients were randomly allocated, although the method was unclear *Allocation concealment used?* unclear *Blinding used?* unclear *Groups comparable at baseline?* unclear, although all 3 patients who had sinuses at baseline were in the surgery group *Groups received the same care apart from the intervention(s) studied?*

	yes *Groups followed up for an equal and appropriate length of time?* yes *Groups comparable for treatment completion and availability of outcome data?* yes *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* 3 cases of drug resistance (1 to streptomycin, 1 to isoniazid and 1 to isoniazid and rifampicin) *Intervention used is the same as the intervention of interest?* antituberculosis regimens do not use all of or just the 4 standard recommended drugs *Have substitute outcomes been used instead of the patient-important outcomes of interest?* 'hospital stay' and 'time to become ambulant' are substitute outcomes
Number of patients	Initial allocation = 33 antituberculosis chemotherapy plus surgery = 20 antituberculosis chemotherapy alone = 13 Data available = 29 antituberculosis chemotherapy plus surgery = 21 radical Hong Kong surgery within 10 days of antituberculosis chemotherapy initiation = 13 costotransversectomy surgery within 10 days of antituberculosis chemotherapy initiation = 5 radical Hong Kong surgery after treatment failure[1] following 2 months of antituberculosis chemotherapy alone = 3

	antituberculosis chemotherapy alone = 8
Patient characteristics	*Inclusion* Pott's paraplegia, defined as impairment of spinal cord function (severe enough to prevent waking unaided across a room) due to spinal tuberculosis Patients with spastic paraplegia due to clinically and radiographically active spinal tuberculosis involving vertebral bodies at levels D4 to L1 *Exclusion* Flaccid paraplegia or paraplegia with late onset *Baseline* Age: <10 years = 5 11–20 years = 8 21–30 years = 4 >30 years = 16 Sinuses = 3 (all in the surgical group) Site of spinal lesion: upper-dorsal = 39% mid-dorsal = 36% lower-dorsal = 24% History of difficulty walking: <1 month = 16 >1 month = 11

	Total loss of muscle power = 16 Sensory blunting = 21 Difficulty in micturition requiring catheterization = 12 Drug resistance = 3 (1 to streptomycin, 1 to isoniazid and 1 to isoniazid and rifampicin)
Intervention	*Antituberculosis chemotherapy plus surgery* Surgery: radical Hong Kong surgery (modified technique) within 10 days of antituberculosis chemotherapy initiation; or costotransversectomy surgery within 10 days of antituberculosis chemotherapy initiation; or radical Hong Kong surgery (modified technique) after treatment failure[1] following 2 months of antituberculosis chemotherapy alone (see 'comparator' below) Antituberculosis chemotherapy: $2HRSE_7/7HR_2$ isoniazid: 6 to 10 mg/kg of bodyweight/day rifampicin: 10 to 12 mg/kg of bodyweight/day streptomycin: 15 to 30 mg/kg of bodyweight/day ethambutol: 20 to 25 mg/kg of bodyweight/day All patients hospitalised for 3 to 4 months until they recovered from paraplegia During hospitalisation, patients were nursed on ordinary firm beds As a routine, passive exercise of lower and upper limbs were performed and skin care was given in addition Whenever there was bladder involvement and retention of urine, indwelling Folley's catheters were used until recovery of bladder tone justified their removal Drugs given under the supervision of the clinic staff whilst hospitalised; after discharge, patients collected drugs every 15 days as outpatients for self-administration

<table>
<tr><td>Comparison</td><td>
Antituberculosis chemotherapy alone
Antituberculosis chemotherapy: $2HRSE_7/7HR_2$
isoniazid: 6 to 10 mg/kg of bodyweight/day
rifampicin: 10 to 12 mg/kg of bodyweight/day
streptomycin: 15 to 30 mg/kg of bodyweight/day
ethambutol: 20 to 25 mg/kg of bodyweight/day
All patients hospitalised for 3 to 4 months until they recovered from paraplegia
Patients were nursed on hard boards, and plaster shell or any other method of immobilisation were used as indicated
Ambulation was permitted as soon as the patient was able to walk without pain; a plaster jacket or posterior spinal support was provided if considered necessary
As a routine, passive exercise of lower and upper limbs were performed and skin care was given in addition
Whenever there was bladder involvement and retention of urine, indwelling Folley’s catheters were used until recovery of bladder tone justified their removal
Drugs given under the supervision of the clinic staff whilst hospitalised; after discharge, patients collected drugs every 15 days as outpatients for self-administration
</td></tr>
<tr><td>Length of follow up</td><td>27 were followed up for 5 years, 1 for 15 months and 1 for 12 months</td></tr>
<tr><td>Location</td><td>Madras, India</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
Changes in signs and symptoms – complete motor recovery
Number of patients to achieve complete motor recovery
<table>
<tr><th rowspan="2">Months after treatment initiation</th><th colspan="3">Antituberculosis chemotherapy plus surgery
(n = 21)</th><th rowspan="2">Antituberculosis chemotherapy alone
(n = 8)</th></tr>
<tr><th>radical Hong Kong surgery</th><th>costotransversectomy surgery within 10 days</th><th>radical Hong Kong surgery</th></tr>
</table>
</td></tr>
</table>

	within 10 days		following treatment failure	
1	4	0	-	1
2	7	2	-	3
3	9	5	0	4
4	10	5	1	6
5	11	5	1	8
6	12	5	1	8
≥7	13	5	3	8
Total	13	5	3	8

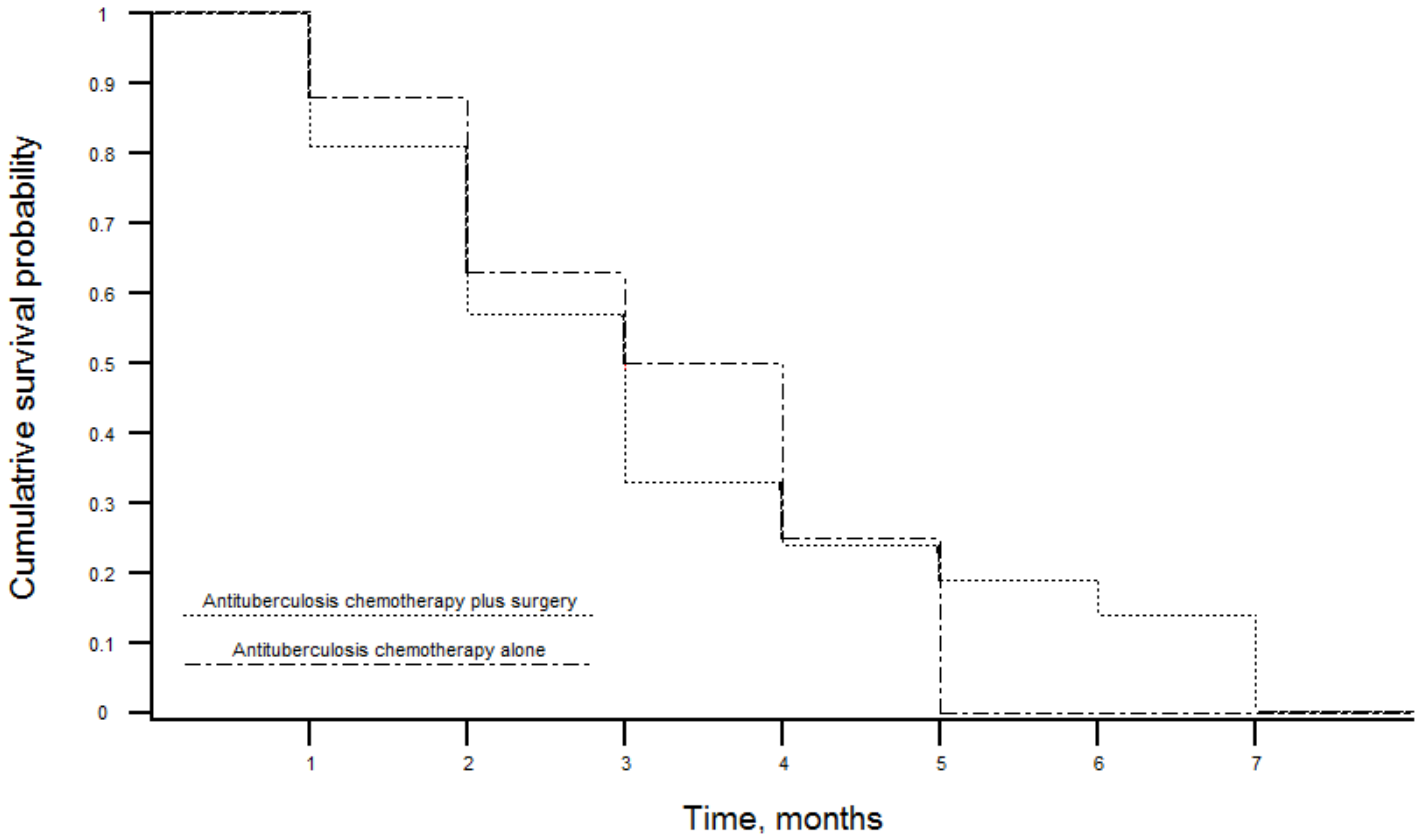
Months after treatment initiation	***Antituberculosis chemotherapy plus surgery*** (n = 21)			***Antituberculosis chemotherapy alone*** (n = 8)		
	number at risk	number of new events	cumulative survival probability[2]	number at risk	number of new events	cumulative survival probability[2]
0	21	0	1	8	0	1
1	21	4	0.81	8	1	0.88
2	17	5	0.57	7	2	0.63
3	12	5	0.33	5	1	0.5
4	7	2	0.24	4	2	0.25
5	5	1	0.19	2	2	0
6	4	1	0.14	0	0	0

≥7	3	3	0	0	0	0

Median 'survival' time[3], months

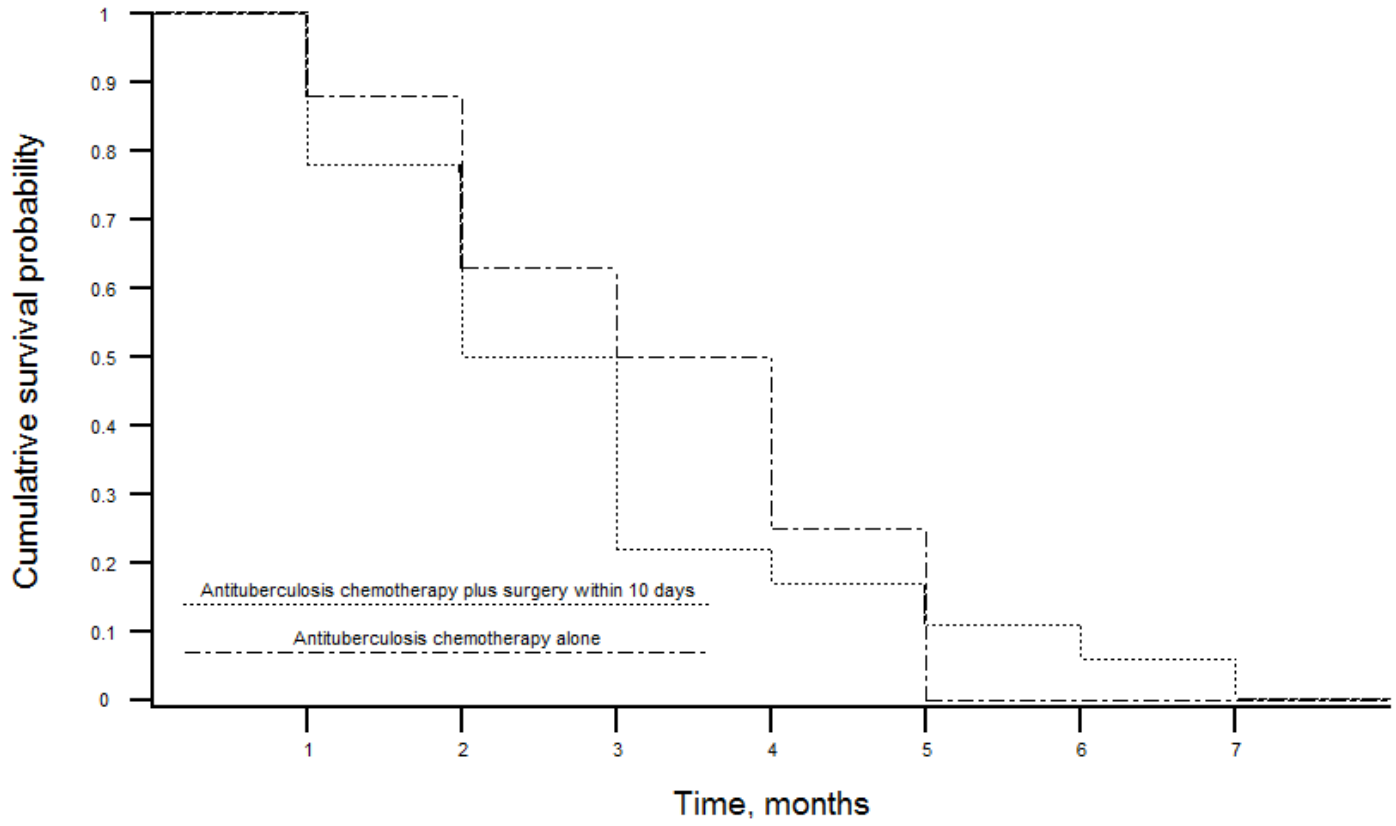
antituberculosis chemotherapy plus surgery = 3

antituberculosis chemotherapy alone = 3



Months after	***Antituberculosis chemotherapy plus surgery within 10 days***	***Antituberculosis chemotherapy alone***

	treatment initiation	(n = 18)			(n = 8)	
		number at risk	number of new events	cumulative survival probability[2]	number at risk	number of new events	cumulative survival probability[2]
	0	18	0	1	8	0	1
	1	18	4	0.78	8	1	0.88
	2	14	5	0.50	7	2	0.63
	3	9	5	0.22	5	1	0.5
	4	4	1	0.17	4	2	0.25
	5	3	1	0.11	2	2	0
	6	2	1	0.06	0	0	0
	≥7	1	1	0	0	0	0
	Median survival time, months antituberculosis chemotherapy plus surgery within 10 days = 2 antituberculosis chemotherapy alone = 3						



Changes in signs and symptoms – myelopathy

Number of patients to experience myelopathy during long-term follow-up

antituberculosis chemotherapy plus surgery = 0 of 21

antituberculosis chemotherapy alone = 0 of 8

OR[4] (95% CI) = 0.40 (0.01 to 21.58)

i.e. not statistically significant

	Changes in signs and symptoms – sinuses Number of patients to develop a sinus during long-term follow-up antituberculosis chemotherapy plus surgery = 0 of 21 antituberculosis chemotherapy alone = 0 of 8 OR[4] (95% CI) = 0.40 (0.01 to 21.58) i.e. not statistically significant
	Changes in signs and symptoms – abscesses Number of patients to develop an abscess during long-term follow-up antituberculosis chemotherapy plus surgery = 0 of 21 antituberculosis chemotherapy alone = 0 of 8 OR[4] (95% CI) = 0.40 (0.01 to 21.58) i.e. not statistically significant
	Changes in signs and symptoms – limitation of physical activity Interval (mean (range)) to becoming ambulant, days antituberculosis chemotherapy plus surgery (n = 21) = 192 (62–322) radical Hong Kong surgery within 10 days of antituberculosis chemotherapy initiation (n = 13) = 185 (62–322) costotransversectomy surgery within 10 days of antituberculosis chemotherapy initiation (n = 5) = 154 (94–234) radical Hong Kong surgery after treatment failure[1] (n = 3) = 284 (277–296) antituberculosis chemotherapy alone (n = 8) = 132 (68–212) *Any surgery* MD[5] = 60

	Surgery within 10 days antituberculosis chemotherapy plus surgery within 10 days (n = 18) = 176 (62–322) MD[5] = 44 *Surgery after treatment failure* MD[5] = 152 Number of patients to experience limitation to their physical activity due to a spinal lesion during long-term follow-up antituberculosis chemotherapy plus surgery = 0 of 21 antituberculosis chemotherapy alone = 0 of 8 OR[4] (95% CI) = 0.40 (0.01 to 21.58) i.e. not statistically significant
	Relapse Number of patients to experience relapse during long-term follow-up antituberculosis chemotherapy plus surgery = 0 of 21 antituberculosis chemotherapy alone = 0 of 8 OR[4] (95% CI) = 0.40 (0.01 to 21.58) i.e. not statistically significant
	Hospitalisation Duration of hospital stay (mean (range)), days antituberculosis chemotherapy plus surgery (n = 21) = 114 (38–367) radical Hong Kong surgery within 10 days of antituberculosis chemotherapy initiation (n = 13) = 91 (38–122) costotransversectomy surgery within 10 days of antituberculosis chemotherapy initiation (n = 5) = 95 (43–165)

	radical Hong Kong surgery after treatment failure[1] (n = 3) = 244 (151–367) antituberculosis chemotherapy alone (n = 8) = 89 (47–153) *Any surgery* MD[5] = 55 *Surgery within 10 days* antituberculosis chemotherapy plus surgery within 10 days (n = 18) = 92 (38–165) MD[5] = 3
Source of funding	No details provided
Comments	

[1] Treatment failure defined as: no neurological improvement at 2 months; clinical deterioration as characterised by bladder involvement, change of muscle tone to flaccidity, bedsore development or deterioration in motor power

[2] Cumulative survival not provided by authors; calculated by reviewer

[3] Kaplan-Meier plot generated by reviewer; median survival time read off plot at a cumulative survival probability of 0.5

[4] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

[5] Mean difference not provided by authors; calculated by reviewer

Abbreviations: CI, confidence intervals; E, ethambutol; H, isoniazid; MD, mean difference; OR, odds ratio; R, rifampicin; S, streptomycin

OBSERVATIONAL STUDIES

1.1.8 Arthornthurasook, 1983

Bibliographic reference	Arthornthurasook A (1983) Tuberculosis of the Spine in Southern Thailand. Journal of the Medical Association of Thailand 66(2): 106-21
Study type	Observational – unclear if prospective or retrospective

Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* unclear *Blinding used?* unclear, though unlikely *Attempts made within the design or analysis to balance the groups for potential confounders?* unclear *Groups comparable at baseline?* unclear *Groups received the same care apart from the intervention(s) studied?* unclear *Groups followed up for an equal and appropriate length of time?* follow-up ranged from 1.5 to 3 years in the antituberculosis chemotherapy alone group, and from 1 month to 3 years in the group that also underwent surgery *Groups comparable for treatment completion and availability of outcome data?* unclear *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* antituberculosis regimen unclear

	Have substitute outcomes been used instead of the patient-important outcomes of interest? yes – 'response to treatment' is a substitute for cure / treatment success and changes in the signs and symptoms of the disease
Number of patients	Included = 25 antituberculosis chemotherapy plus surgery = 20 antituberculosis chemotherapy alone = 5
Patient characteristics	*Inclusion* Spinal tuberculosis *Diagnostic criteria* Unclear *Baseline* Unclear
Intervention	*Antituberculosis chemotherapy plus surgery* Surgery: debridement and fusion Antituberculosis chemotherapy: 'long-term chemotherapy'
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: 'long-term chemotherapy'
Length of follow up	Follow-up antituberculosis chemotherapy plus surgery = 1 month to 3 years antituberculosis chemotherapy alone = 1.5 to 3 years
Location	Thailand

Outcomes measures and effect size	**Response to treatment – favourable** Number of patients to achieve favourable results, defined as significant relief of pain, general good health, able to work, free from sinus, normal central nervous system with radiological progression to disease-free antituberculosis chemotherapy plus surgery = 19 of 20 antituberculosis chemotherapy alone = 5 of 5 OR[1] (95% CI) = 1.18 (0.04 to 33.27) i.e. not statistically significant
Source of funding	No details provided
Comments	
[1] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer Abbreviations: CI, confidence intervals; OR, odds ratio; RCT, randomised controlled trial	

1.1.9 Eisen et al, 2012

Bibliographic reference	Eisen S, Honywood L, Shingadia D et al (2012) Spinal tuberculosis in children. Archives of Disease in Childhood 97: 724-9
Study type	Retrospective case series
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* no – decision to use surgery was based on clinical features (cord compression with neurological manifestations or spinal instability) *Blinding used?* unclear, though unlikely *Attempts made within the design or analysis to balance the groups for potential confounders?* no

	Groups comparable at baseline? yes, although some baseline characteristics are not reported by group *Groups received the same care apart from the intervention(s) studied?* unclear *Groups followed up for an equal and appropriate length of time?* length of follow-up appropriate, though it is unclear if it was equal in the 2 groups *Groups comparable for treatment completion and availability of outcome data?* yes *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* yes – reviewer excluded drug resistant cases *Intervention used is the same as the intervention of interest?* antituberculosis regimens do not use all of or just the 4 standard recommended drugs; a number of patients received second-line antituberculosis drugs some patients in the surgery group received antituberculosis chemotherapy for more than 12 months, whereas all patients in the antituberculosis chemotherapy alone group received antituberculosis chemotherapy for 12 months *Have substitute outcomes been used instead of the patient-important outcomes of interest?* no
Number of patients	Reported = 21 Included[1] = 12 antituberculosis chemotherapy plus surgery = 5

antituberculosis chemotherapy alone = 7

Patient characteristics

Inclusion

Spinal tuberculosis

Diagnostic criteria

Microbiological confirmation from vertebral tissue or paravertebral abscess, or combined clinical, radiological and/or histological findings

Exclusion

Reviewer excluded cases for which outcome data were not available, or cases which were drug resistant

Baseline

	Antituberculosis chemotherapy plus surgery (n = 5)	**Antituberculosis chemotherapy alone** (n = 7)
HIV-positive (note: not all patients were tested), n (%)	0 (0%)	0 (0%)
Presenting features		
back pain, n (%)	3 (60%)	7 (100%)
night sweats, n (%)	4 (80%)	4 (57%)
fever, n (%)	2 (40%)	3 (43%)
weight loss, n (%)	3 (60%)	3 (43%)
cough, n (%)	3 (60%)	3 (43%)
anorexia, n (%)	4 (80%)	1 (14%)
limp, n (%)	2 (40%)	3 (43%)

	weakness or reduced power, n (%)	3 (60%)	1 (14%)
	lymphadenopathy, n (%)	1 (20%)	2 (29%)
	deformity, n (%)	2 (40%)	2 (29%)
	sensory change, n (%)	2 (40%)	2 (29%)
	abdominal pain, n (%)	1 (20%)	1 (14%)
	hyperreflexia, n (%)	0 (0%)	0 (0%)
	discharging sinus, n (%)	0 (0%)	0 (0%)

Characteristics not broken down by group (n = 21 – i.e. includes cases excluded by reviewer):

age (median (range), years) = 9.7 (3.4–15.9) – i.e. all children

visited a country where tuberculosis is endemic within the year preceding diagnosis = 10

previous diagnosis of tuberculosis disease = 4

history of recent active disease in a relative = 11

symptom duration (median (range), weeks) = 6 (2–16)

Intervention

Antituberculosis chemotherapy plus surgery

Surgery:

debridement and decompression to resolve cord compression in patients with neurological manifestations; or

instrumented spinal stabilisation in patients with instability

Antituberculosis chemotherapy:

all received rifampicin, isoniazid and pyrazinamide

some received 1 or more of the following: ethambutol, streptomycin and moxifloxacin

duration of antituberculosis chemotherapy = 12 or 18 months

<table>
<tr><td></td><td>Corticosteroids given to patients with radiologically demonstrated cord compression or raised intracranial pressure (with coexistant tuberculous meningitis confirmed on lumbar puncture)

Treatment was not directly observed</td></tr>
<tr><td>Comparison</td><td>Antituberculosis chemotherapy alone

Antituberculosis chemotherapy:

all received rifampicin and pyrazinamide

some received 1 or more of the following: isoniazid, ethambutol, streptomycin, ciprofloxacin and clarithromycin

duration of antituberculosis chemotherapy = 12 months

Corticosteroids given to patients with radiologically demonstrated cord compression or raised intracranial pressure (with coexistant tuberculous meningitis confirmed on lumbar puncture)

Treatment was not directly observed</td></tr>
<tr><td>Length of follow up</td><td>median 24 months</td></tr>
<tr><td>Location</td><td>London, UK</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Summary
<table>
<tr><th>Group</th><th>Patient</th><th>Combination of antituberculosis drugs</th><th>Duration of antituberculosis chemotherapy</th><th>Use of corticosteroids</th><th>Outcome</th></tr>
<tr><td rowspan="5">Antituberculosis chemotherapy plus surgery</td><td>1</td><td>HRZ</td><td>12</td><td>–</td><td>resolved</td></tr>
<tr><td>2</td><td>HRZS</td><td>12</td><td>yes</td><td>resolved</td></tr>
<tr><td>3</td><td>HRZE + moxifloxacin</td><td>18</td><td>yes</td><td>resolved</td></tr>
<tr><td>4</td><td>HRZE</td><td>18</td><td>yes</td><td>2 relapses, then resolved</td></tr>
<tr><td>5</td><td>HRZE</td><td>12</td><td>yes</td><td>resolved</td></tr>
</table></td></tr>
</table>

Antituberculosis chemotherapy alone	**1**	HRZS	12	–	resolved
	2	HRZE	12	yes	resolved
	3	HRZE	12	yes	resolved
	4	HRZE	12	–	resolved
	5	RZE	12	–	residual deformity and pain
	6	HRZSE + clarithromycin + ciprofloxacin	12	yes	relapse
	7	HRZE	12	–	resolved

Mortality

Number of deaths

antituberculosis chemotherapy plus surgery = 0 of 5

antituberculosis chemotherapy alone = 0 of 7

OR[2] (95% CI) = 1.36 (0.02 to 79.97)

i.e. not statistically significant

Response to treatment – disease resolution

Number of patients in whom the disease fully resolved

antituberculosis chemotherapy plus surgery = 5 of 5

antituberculosis chemotherapy alone = 5 of 7

OR[2] (95% CI) = 5.00 (0.19 to 130.03)

	i.e. not statistically significant
	Changes in signs and symptoms – residual deformity Number of patients to experience residual deformity antituberculosis chemotherapy plus surgery = 0 of 5 antituberculosis chemotherapy alone = 1 of 7 OR[2] (95% CI) = 0.39 (0.01 to 11.76) i.e. not statistically significant
	Relapse Number of patients to experience relapse antituberculosis chemotherapy plus surgery = 1 of 5 antituberculosis chemotherapy alone = 1 of 7 OR[2] (95% CI) = 1.50 (0.07 to 31.58) i.e. not statistically significant
	Post-operative complications None
Source of funding	No details provided
Comments	Cases for which outcome data was missing were not extracted, nor was data for the drug resistant cases

[1] Reviewer excluded cases for which outcome data was not provided and cases that were drug resistant

[2] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

Abbreviations: CI, confidence intervals; E, ethambutol; H, isoniazid; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; S, streptomycin; Z, pyrazinamide

1.1.10 Kumar et al, 2007

Bibliographic reference	Kumar S, Jain AK, Dhammi IK et al (2007) Treatment of intraspinal tuberculoma. Clinical Orthopaedics and Related Research 460: 62-6
Study type	Retrospective case series
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* no – decision to operate was based upon presence of extradural granuloma (19 patients), although 1 of the 3 patients without extradural granuloma, all of whom had intramedullary lesions, also underwent surgery – the indication for surgery in this patient is not reported *Blinding used?* unclear, though unlikely *Attempts made within the design or analysis to balance the groups for potential confounders?* no *Groups* comparable *at baseline?* unclear *Groups received the same care apart from the intervention(s) studied?* yes, although details are limited *Groups followed up for an equal and appropriate length of time?* length of follow-up appropriate, though it is unclear if it was equal in the 2 groups *Groups comparable for treatment completion and availability of outcome data?* yes *Study used precise definitions and reliable measures of outcome?* definition of neural recovery unclear *Population studied is the same as the population of interest?*

	yes *Intervention used is the same as the intervention of interest?* antituberculosis regimen unclear *Have substitute outcomes been used instead of the patient-important outcomes of interest?* no
Number of patients	Included = 22 antituberculosis chemotherapy plus surgery = 20 antituberculosis chemotherapy alone = 2
Patient characteristics	*Inclusion* Intraspinal tuberculoma Compressive myelopathy and neural deficits *Diagnostic criteria* Based on clinical, radiographic and operative findings *Baseline* Age (mean (range), years) = 29.6 (17–70) Sex (M:F) = 16:6 History of paraplegia or paraparesis = 22 acute onset (complete paraplegia within 12 hours of appearance of the first sign of neural deficit) = 3 gradual onset (over 3 months) = 19 Previous antituberculosis treatment = 3 for tuberculous pleurisy = 1

	for tubercular cervical lymphadenitis = 1 for tubercular abdominal lymphadenitis = 1 History of constitutional symptoms suggestive of tuberculosis = 0 Spinal tenderness = 4 Bone involvement = 3
Intervention	*Antituberculosis chemotherapy plus surgery* Surgery: laminectomy and decompression Antituberculosis chemotherapy: regimen unclear, although duration of treatment was at least 1 year
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: regimen unclear, although duration of treatment was at least 1 year
Length of follow up	Follow-up (mean (range), years) = 2.6 (2–5)
Location	Delhi, India
Outcomes measures and effect size	**Summary** *Antituberculosis chemotherapy plus surgery* 13 showed neural recovery within 2 years; they regained an ASIA motor score[1] of 100 but continued to have exaggerated deep tendon reflexes distal to the lesion for up to 2 years 1 patient achieved an ASIA motor score of 78, but did not experience complete neural recovery even after 2 years; the patient was, however, able to walk with support 6 patients had no neural recovery; 1 patient, the patient with intramedullary involvement, died within 2 months of surgery *Antituberculosis chemotherapy alone* Both patients started to show neural recovery within 3 months of treatment initiation; complete neural recovery was noted at 6 months

	Changes in signs and symptoms – neural recovery Number of patients to experience complete neural recovery antituberculosis chemotherapy plus surgery = 13 of 20 antituberculosis chemotherapy alone = 2 of 2 OR[2] (95% CI) = 0.36 (0.02 to 8.53) i.e. not statistically significant
Source of funding	No details provided
Comments	

[1] The ASIA impairment scale is an international standard for the neurological classification of spinal cord injury, based upon sensory and motor function

[2] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

Abbreviations: CI, confidence intervals; F, female; M, male; OR, odds ratio; RCT, randomised controlled trial

1.1.11 Moon et al, 2007

Bibliographic reference	Moon M-S, Moon J-L, Kim S-S et al (2007) Treatment of tuberculosis of the cervical spine. Operative versus nonoperative. Clinical Orthopaedics and Related Research 460: 67-77
Study type	Retrospective observational
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* no – decision to operate was based upon clinical signs and symptoms *Blinding used?* unclear, though unlikely *Attempts made within the design or analysis to balance the groups for potential confounders?*

	unclear *Groups comparable at baseline?* unclear *Groups received the same care apart from the intervention(s) studied?* unclear *Groups followed up for an equal and appropriate length of time?* length of follow-up appropriate, although it is unclear if it was equal in the 2 groups *Groups comparable for treatment completion and availability of outcome data?* yes *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* antituberculosis regimens do not use all of the 4 standard recommended drugs some surgeries were undertaken for diagnostic rather than therapeutic purposes *Have substitute outcomes been used instead of the patient-important outcomes of interest?* no
Number of patients	Included = 54 antituberculosis chemotherapy plus surgery = 31 children = 5

	adults = 26 antituberculosis chemotherapy alone = 23 children = 10 adults = 13
Patient characteristics	*Inclusion* Tuberculosis of the cervical spine *Baseline* Age: 39 adults, age range = 20–64 15 children, age range = 2–14 Stage of disease: early without or with minimal kyphosis = 32 (5 children, 27 adults) moderately advanced (destruction of 1/3 to ½ of the vertebral body and disc) with mild kyphosis = 22 (10 children, 12 adults) Angle of kyphosis (mean (range)): antituberculosis chemotherapy plus surgery = 13° (6–24°) children = 14° (6–16°) adults = 13° (9–24°) antituberculosis chemotherapy alone = 10° (6–14°) children = 12° (7–14°) adults = 9° (6–11°)

	Quadriparesis = 14 (4 children, 10 adults) Frankel's neurologic grade in quadriplegic patients: grade A = 0 grade B = 2 (2 adults) grade C = 4 (2 children, 2 adults) grade D = 8 (2 children, 6 adults) Coexisting early lung tuberculosis = 6
Intervention	*Antituberculosis chemotherapy plus surgery* Surgery: aims: anterior decompression alone stabilisation alone deformity correction and stabilisation immediate decompression surgery was recommended when there was a marked neurologic deficit with respiratory obstruction due to a large abscess and a sudden onset of complete paralysis the relative indications for decompression surgery were: a marked neurological deficit with visible kyphosis or a retropulsed bone or disc in the neural canal a worsening neurological deficit despite adequate chemotherapy over 4 weeks the possibility in some patients that prolonged bed rest might lead to other medical problems a persistence of pain or spasticity caused by a demonstrable mechanical block for patients without paralysis, there were no definite indications for immediate surgery, and all surgeries were elective – the objectives were:

	to excise diseased focus to provide stability for the alleviation of pain related to spinal instability to prevent the progression of kyphosis or to correct the deformity and stabilise the diseased segment to obtain adequate material for histological study and culture (note: objective is diagnostic rather than therapeutic) Antituberculosis chemotherapy: adults: 12HRE children: 12HRZ Strict supervision of chemotherapy High-calorie diets All patients were maintained with bed rest with head halter traction for 1 to 2 weeks followed by stabilisation with either a Minerva cast or a cervical or halo brace for 10 to 14 weeks For neural involvement without deformities, regardless of severity, bed rest of 4 to 6 weeks was prescribed
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: adults: 12HRE children: 12HRZ Strict supervision of chemotherapy High-calorie diets All patients were maintained with bed rest with head halter traction for 1 to 2 weeks followed by stabilisation with either a Minerva cast or a cervical or halo brace for 10 to 14 weeks For neural involvement without deformities, regardless of severity, bed rest of 4 to 6 weeks was prescribed
Length of follow up	At least 24 months

Location	Seoul, Korea
Outcomes measures and effect size	**Changes in signs and symptoms – angle of kyphosis** Mean (range) angle of kyphosis at end of follow-up antituberculosis chemotherapy plus surgery (n = 31) = 5° (0–21°) children (n = 5) = 18° (13–21°) adults (n = 26) = 2° (0–4°) antituberculosis chemotherapy alone (n = 23) = 15° (9–21°) children (n = 10) = 17° (14–21°) adults (n = 13) = 13° (9–16°) *All ages* MD[1] = -10° *Children only* MD[1] = 1° *Adults only* MD[1] = -11° note: baseline kyphosis was not comparable across the 2 groups – higher in the surgical group Change in mean angle of kyphosis from baseline to the end of follow-up[2] antituberculosis chemotherapy plus surgery (n = 31) = -8° children (n = 5) = 4° adults (n = 26) = -11° antituberculosis chemotherapy alone (n = 23) = 5°

	children (n = 10) = 5° adults (n = 13) = 4° *All ages* MD[1] = -13° *Children only* MD[1] = -1° *Adults only* MD[1] = -15°
	Changes in signs and symptoms – fusion Number of patients to experience intracorporeal fusion antituberculosis chemotherapy plus surgery = 26 of 31 children = 0 of 5 adults = 26 of 26 antituberculosis chemotherapy alone = 15 of 23 children = 2 of 10 adults = 13 of 13 *All ages* OR[3] (95% CI) = 2.77 (0.77 to 10.03) i.e. not statistically significant *Children only* OR[3] (95% CI) = 0.31 (0.01 to 7.74)

	i.e. not statistically significant *Adults only* OR[3] (95% CI) = 1.96 (0.04 to 104.47) i.e. not statistically significant
Source of funding	No details provided
Comments	

[1] Mean difference not provided by authors; calculated by reviewer

[2] Increase in mean not provided by authors; calculated by reviewer

[3] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

Abbreviations: CI, confidence intervals; E, ethambutol; H, isoniazid; MD, mean difference; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; Z, pyrazinamide

1.1.12 Pun et al, 1990

Bibliographic reference	Pun WK, Chow SP, Luk KDK et al (1990) Tuberculosis of the lumbosacral junction. Long-term follow-up of 26 cases. Journal of Bone and Joint Surgery (British) 72-B: 675-8
Study type	Retrospective case series
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* unclear *Blinding used?* unclear, though unlikely *Attempts made within the design or analysis to balance the groups for potential confounders?* unclear

	Groups comparable at baseline? unclear *Groups received the same care apart from the intervention(s) studied?* unclear *Groups followed up for an equal and appropriate length of time?* follow-up was an appropriate length, though it is unclear if it is comparable in the 2 groups *Groups comparable for treatment completion and availability of outcome data?* yes *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* antituberculosis regimen(s) unclear *Have substitute outcomes been used instead of the patient-important outcomes of interest?* no
Number of patients	Included = 26 antituberculosis chemotherapy plus surgery = 18 antituberculosis chemotherapy alone = 8
Patient characteristics	*Inclusion* Tuberculosis of the lumbosacral spine

	Diagnostic criteria Unclear *Baseline* Sex (M:F) = 12:14 Age (mean (range), years) = 17.3 (1.5–38) Discharging sinus or abscess = 14 Low back pain = 12 Kyphosis = 11
Intervention	*Antituberculosis chemotherapy plus surgery* Surgery: anterior debridement and fusion with strut grafts (n = 7); or posterior spinal fusion (n = 4); or anterior and posterior spinal fusion (n = 1); or anterior debridement alone without bone grafting (n = 6) Antituberculosis chemotherapy: 'full course'
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: 'full course'
Length of follow up	Follow-up (mean (range), years) = 20.2 (6–34.5) 24 patients were followed up for more than 10 years
Location	Hong Kong
Outcomes	**Changes in signs and symptoms – fusion**

measures and effect size	Number of patients to experience radiographic fusion antituberculosis chemotherapy plus surgery = 18 of 18 antituberculosis chemotherapy alone = 8 of 8 OR[1] (95% CI) = 2.18 (0.04 to 119.22) i.e. not statistically significant
	Changes in signs and symptoms – kyphosis Number of patients to have kyphosis antituberculosis chemotherapy plus surgery = 6 of 18 antituberculosis chemotherapy alone = 8 of 8 **OR[1] (95% CI) = 0.03 (0.00 to 0.62)** **i.e. statistically significant** Mean angle of kyphosis antituberculosis chemotherapy plus surgery (n = 6) = 29.3° antituberculosis chemotherapy alone (n = 8) = 60.4° MD[2] = -31.1° i.e. not statistically significant
	Post-operative complications No significant postoperative complications
Source of funding	No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of the article
Comments	

[1] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

[2] Mean difference not provided by authors; calculated by reviewer

Abbreviations: CI, confidence intervals; F, female; M, male; MD, mean difference; OR, odds ratio; RCT, randomised controlled trial

1.1.13 Rajasekaran et al, 1987

Bibliographic reference	Rajasekaran S, Orth D & Shnmugasundaram TK (1987) Prediction of the angle of gibbus deformity in tuberculosis of the spine. Journal of Bone and Joint Surgery (American) 69-A(4): 503-9
Study type	Retrospective observational
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* unclear *Blinding used?* unclear, though unlikely *Attempts made within the design or analysis to balance the groups for potential confounders?* unclear *Groups comparable at baseline?* no – only data for age is available by group, and this shows that the antituberculosis chemotherapy alone has significantly more patients <16 years of age than the surgery group *Groups received the same care apart from the intervention(s) studied?* unclear *Groups followed up for an equal and appropriate length of time?* follow-up was an appropriate length, though it is unclear if it is comparable in the 2 groups *Groups comparable for treatment completion and availability of outcome data?*

	yes *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* antituberculosis regimens do not use all of the 4 standard recommended drugs intervention and comparator differ by more than the presence of absence of surgery – some patients in the chemotherapy alone group received antituberculosis drugs for a longer period (duration of treatment = 6 or 9 months) than in the surgery group (duration of treatment = 6 months for all patients) *Have substitute outcomes been used instead of the patient-important outcomes of interest?* no
Number of patients	Included = 90 antituberculosis chemotherapy (6 months) plus surgery = 30 antituberculosis chemotherapy alone = 60 6HR = 29 9HR = 31
Patient characteristics	*Inclusion* Tuberculosis of the spine *Diagnostic criteria* Unclear *Baseline*

<table>
<tr><td></td><td>
<table>
<tr><td></td><td>Antituberculosis chemotherapy (6 months) plus surgery
(n = 30)</td><td colspan="2">Antituberculosis chemotherapy alone
(n = 60)</td></tr>
<tr><td></td><td></td><td>6HR (n = 29)</td><td>9HR (n = 31)</td></tr>
<tr><td>Age, years</td><td></td><td></td><td></td></tr>
<tr><td>≤10, n (%)</td><td>6 (20.0%)</td><td>11 (37.9%)</td><td>9 (29.0%)</td></tr>
<tr><td>11–15, n (%)</td><td>1 (3.3%)</td><td>6 (20.7%)</td><td>4 (12.9%)</td></tr>
<tr><td>16–20, n (%)</td><td>3 (10.0%)</td><td>2 (6.9%)</td><td>2 (6.5%)</td></tr>
<tr><td>21–30, n (%)</td><td>7 (23.3%)</td><td>4 (13.8%)</td><td>10 (32.3%)</td></tr>
<tr><td>31–40, n (%)</td><td>8 (26.7%)</td><td>2 (6.9%)</td><td>5 (16.1%)</td></tr>
<tr><td>>41, n (%)</td><td>5 (16.7%)</td><td>4 (13.8%)</td><td>1 (3.2%)</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Antituberculosis chemotherapy plus surgery
Radical surgery
Antituberculosis chemotherapy: 6HR</td></tr>
<tr><td>Comparison</td><td>Antituberculosis chemotherapy alone
Antituberculosis chemotherapy: 6HR or 9HR</td></tr>
<tr><td>Length of follow up</td><td>At least 72 months</td></tr>
<tr><td>Location</td><td>Madras, India</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Change is signs and symptoms – angle of kyphosis
Number of patients to experience an improvement (decrease) in their angle of kyphosis
antituberculosis chemotherapy (6 months) plus surgery = 4 of 30</td></tr>
</table>

	antituberculosis chemotherapy alone = 7 of 60 OR[1] (95% CI) = 1.16 (0.31 to 4.34) i.e. not statistically significant Number of patients to experience moderate or severe deterioration (an increase of more than 11°) in their angle of kyphosis antituberculosis chemotherapy (6 months) plus surgery = 14 of 30 antituberculosis chemotherapy alone = 34 of 60 OR[1] (95% CI) = 0.67 (0.28 to 1.61) i.e. not statistically significant
	Change is signs and symptoms – angle of kyphosis (<16 years of age) Number of patients below the age of 16 to experience an improvement (decrease) in their angle of kyphosis antituberculosis chemotherapy (6 months) plus surgery = 4 of 7 antituberculosis chemotherapy alone = 6 of 30 OR[1] (95% CI) = 5.33 (0.93 to 30.51) i.e. not statistically significant Number of patients below the age of 16 to experience moderate or severe deterioration (an increase of more than 11°) in their angle of kyphosis antituberculosis chemotherapy (6 months) plus surgery = 3 of 7 antituberculosis chemotherapy alone = 17 of 30 OR[1] (95% CI) = 0.57 (0.11 to 3.02) i.e. not statistically significant
	Change is signs and symptoms – angle of kyphosis (≥16 years of age)

	Number of patients aged 16 years or above to experience an improvement (decrease) in their angle of kyphosis antituberculosis chemotherapy (6 months) plus surgery = 0 of 23 antituberculosis chemotherapy alone = 1 of 30 OR[1] (95% CI) = 0.42 (0.02 to 10.75) i.e. not statistically significant Number of patients aged 16 years or above to experience moderate or severe deterioration (an increase of more than 11°) in their angle of kyphosis antituberculosis chemotherapy (6 months) plus surgery = 11 of 23 antituberculosis chemotherapy alone = 17 of 30 OR[1] (95% CI) = 0.70 (0.24 to 2.09) i.e. not statistically significant
Source of funding	No funds were received in support of this study
Comments	Appears to be a subpopulation of the Madras RCT
[1] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer Abbreviations: CI, confidence intervals; OR, odds ratio; RCT, randomised controlled trial	

1.1.14 Rezai et al, 1995

Bibliographic reference	Rezai AR, Lee M, Cooper PR (1995) Modern management of spinal tuberculosis. Neurosurgery 36(1): 87-97
Study type	Retrospective case series
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* the majority of 'non-operative' patients did not meet the clinical criteria for surgical management, which were based on potentially confounding factors (clinical signs and symptoms, responsiveness to antituberculosis chemotherapy, non-

	adherence) *Blinding used?* unclear, though unlikely *Attempts made within the design or analysis to balance the groups for potential confounders?* unclear *Groups comparable at baseline?* the majority of 'non-operative' patients did not meet the clinical criteria for surgical management, which were based on potentially confounding factors (clinical signs and symptoms, responsiveness to antituberculosis chemotherapy, non-adherence), whereas all patients in the 'operative' group met these criteria the 'operative' group generally had disease of a higher grade of severity the 'operative' group consisted of both males and females, whereas the 'non-operative' group was all-male *Groups received the same care apart from the intervention(s) studied?* yes, although bracing was undertaken for a longer period in those who did not undergo surgery *Groups followed up for an equal and appropriate length of time?* follow-up is an appropriate length (at least 1 year), although it is unclear if it is equal in the 2 groups *Groups comparable for treatment completion and availability of outcome data?* 2 patients died in the surgery group and therefore did not complete treatment or follow-up; no loss to follow-up occurred in the 'non-operative' group *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* 2 patients had drug-resistant strains of tuberculosis *Intervention used is the same as the intervention of interest?*

<table>
<tr><td></td><td>yes, although duration of antituberculosis chemotherapy is not reported

2 patients in the ‘non-operative’ group underwent aspiration – although this is an invasive technique, the authors do not consider it a surgical technique

Have substitute outcomes been used instead of the patient-important outcomes of interest?

no</td></tr>
<tr><td>Number of patients</td><td>Included = 20

‘operative’ = 11

‘non-operative’ = 9 (includes 2 patients that underwent abscess aspiration)</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion

Tuberculosis of the spine

Diagnostic criteria

Unclear

Baseline
<table>
<tr><th>Group</th><th>Patient</th><th>Age/sex</th><th>Neurological grade</th><th>Surgical indications</th><th>Smear</th><th>Culture</th></tr>
<tr><td rowspan="4">‘operative’ (n = 11)</td><td>1</td><td>53/F</td><td>IV</td><td>neurological deficit; deformity</td><td>–ve</td><td>+ve</td></tr>
<tr><td>2</td><td>81/F</td><td>IV</td><td>acute neurological deficit</td><td>–ve</td><td>+ve</td></tr>
<tr><td>3</td><td>64/F</td><td>I</td><td>neurological deficit</td><td></td><td>+ve</td></tr>
<tr><td>4</td><td>34/F</td><td>I</td><td>medication non-adherence; neurological deficit; worsening deformity; intractable pain</td><td>+ve</td><td>+ve</td></tr>
</table></td></tr>
</table>

		5	32/F	I	unresponsive to antituberculosis chemotherapy	–ve	+ve
		6	76/F	IV	neurological deficit; deformity	+ve	+ve
		7	51/M	IV	neurological deficit; deformity	–ve	+ve
		8	45/M	III	acute neurological deficit; deformity	+ve	–ve
		9	50/M	IV	neurological deficit; deformity	–ve	+ve
		10	45/M	0	?	–ve	+ve
		11	30/M	0	unresponsive to antituberculosis chemotherapy; persistent pain; abscess enlargement	+ve	–ve
		mean or ratio	51 5M:6F	–	–	–	–
	'non-operative' (n = 9)	1	?	III	–	–ve	–ve
		2	?	0	–	–ve	+ve
		3	?	0	–	–ve	+ve
		4	?	0	–	–ve	–ve
		5	?	0	–	+ve	+ve
		6	?	0	–	+ve	+ve

	7	?	0	–	–ve	+ve
	8	?	0	–	+ve	+ve
	9	?	0	–	–ve	+ve
	mean or ratio	47 9M:0F	–	–	–	–

Intervention	*Antituberculosis chemotherapy plus surgery* Surgery: 1 or more of the following, depending on the extent of vertebral destruction and site of dural compression: laminectomy debridement abscess drainage vertebrectomy transpedicular decompression retroperitoneal approach posterior instrumentation graft Antituberculosis chemotherapy: HRZE isoniazid: 300 mg/day rifampicin: 600 mg/day pyrazinamide: 25 mg/kg of bodyweight/day ethambutol: 15 mg/kg of bodyweight/day

<table>
<tr><td></td><td>Bracing: 6 to 12 months</td></tr>
<tr><td>Comparison</td><td>Antituberculosis chemotherapy alone
Antituberculosis chemotherapy: HRZE
isoniazid: 300 mg/day
rifampicin: 600 mg/day
pyrazinamide: 25 mg/kg of bodyweight/day
ethambutol: 15 mg/kg of bodyweight/day
Bracing: 12 to 18 months</td></tr>
<tr><td>Length of follow up</td><td>At least 1 year amongst those who survived</td></tr>
<tr><td>Location</td><td>New York, US</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Mortality
Number of deaths
antituberculosis chemotherapy plus surgery = 2 of 11
antituberculosis chemotherapy alone = 0 of 9
OR[1] (95% CI) = 5.00 (0.21 to 118.66)
i.e. not statistically significant</td></tr>
<tr><td></td><td>Changes in signs and symptoms – neurological changes
<table>
<tr><th>Group</th><th>Patient</th><th>Neurological grade on admission</th><th>Neurological grade at follow-up</th><th>Change</th></tr>
<tr><td rowspan="2">‘operative’ (n = 11)</td><td>1</td><td>IV</td><td>I</td><td>improvement</td></tr>
<tr><td>2</td><td>IV</td><td>II</td><td>improvement</td></tr>
</table></td></tr>
</table>

		3	I	0	improvement
		4	I	0	improvement
		5	I	0	improvement
		6	IV	II	improvement
		7	IV	0	improvement
		8	III	I	improvement
		9	IV	died before assessment	–
		10	0	0	remains neurologically intact
		11	0	0	remains neurologically intact
	'non-operative' (n = 9)	1	III	I	improvement
		2	0	0	remains neurologically intact
		3	0	0	remains neurologically intact
		4	0	0	remains neurologically intact
		5	0	0	remains neurologically intact
		6	0	0	remains neurologically intact
		7	0	0	remains neurologically intact
		8	0	0	remains neurologically intact
		9	0	0	remains neurologically intact
	Number of patients to improve or remain neurologically intact antituberculosis chemotherapy plus surgery = 10 of 11 antituberculosis chemotherapy alone = 9 of 9				

	OR[1] (95% CI) = 0.37 (0.01 to 10.18) i.e. not statistically significant
	Changes in signs and symptoms – kyphosis Change in mean angle of kyphosis from baseline to follow-up antituberculosis chemotherapy plus surgery = -7° antituberculosis chemotherapy alone = 4° MD[2] = -11°
	Changes in signs and symptoms – pain Number of patients with persistent pain antituberculosis chemotherapy plus surgery = 0 of 11 antituberculosis chemotherapy alone = 2 of 9 OR[1] (95% CI) = 0.13 (0.01 to 3.11) i.e. not statistically significant
Source of funding	No details provided
Comments	

[1] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

[2] Mean difference not provided by authors; calculated by reviewer

Abbreviations: CI, confidence intervals; E, ethambutol; F, female; H, isoniazid; M, male; MD, mean difference; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; Z, pyrazinamide

1.1.15 Richardson et al, 1976

Bibliographic	Richardson JD, Campbell DL, Grover FL et al (1976) Transthoracic approach for Pott's disease. Annals of Thoracic

reference	Surgery 21: 552-6
Study type	Observational – unclear if prospective or retrospective
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* no – not all patients in the antituberculosis chemotherapy alone group met the criteria for surgery *Blinding used?* unclear, though unlikely *Attempts made within the design or analysis to balance the groups for potential confounders?* no *Groups comparable at baseline?* unclear *Groups received the same care apart from the intervention(s) studied?* unclear *Groups followed up for an equal and appropriate length of time?* unclear *Groups comparable for treatment completion and availability of outcome data?* yes *Study used precise definitions and reliable measures of outcome?* neurological ‘improvement’ was not defined *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?*

	antituberculosis regimen(s) not reported *Have substitute outcomes been used instead of the patient-important outcomes of interest?* response to treatment
Number of patients	Included = 28 antituberculosis chemotherapy plus surgery = 22 antituberculosis chemotherapy alone = 6
Patient characteristics	*Inclusion* Spinal tuberculosis *Diagnostic criteria* Unclear *Baseline* Sex (M:F) = 16:12 Age: mean (range), years = 25 (3–68) <12 years = 9 Common signs and symptoms: back pain = 27 gibbous spinal deformity = 19 neurological symptoms involving the lower extremities = 13 paraplegia = 9 subcutaneous soft tissue mass = 4

	draining sinus = 1 fever = 8 leukocytosis = 13 granuloma = 8 Active pulmonary tuberculosis = 3
Intervention	*Antituberculosis chemotherapy plus surgery* Surgery: thoracotomy – evacuation of tuberculous abscesses, debridement of necrotic bone, and fusion of the anterior spine using a bone graft Antituberculosis chemotherapy: usually 3 drugs – no further details of the regimen(s) provided antituberculosis chemotherapy was started 4 to 6 weeks before surgery where possible; however, neurological emergencies in several patients precluded the use of antituberculosis drugs prior to surgery, although there were no discernible differences in the operative results Post-operative care: all the children and several of the adults were placed in a bivalved jacket cast; patients were left in the cast for 6 to 12 weeks or were kept supine in bed for 12 to 16 weeks chest tubes were usually removed in 3 to 5 days
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: usually 3 drugs – no further details of the regimen(s) provided Patients were left in the cast for 6 to 12 weeks or were kept supine in bed for 12 to 16 weeks
Length of follow up	Unclear
Location	San Antonio, Texas, US
Outcomes	**Mortality**

measures and effect size	Number of deaths antituberculosis chemotherapy plus surgery = 1 of 22 antituberculosis chemotherapy alone = 1 of 6 OR[1] (95% CI) = 0.24 (0.01 to 4.50) i.e. not statistically significant Number of TB-related deaths antituberculosis chemotherapy plus surgery = 0 of 22 antituberculosis chemotherapy alone = 1 of 6 OR[1] (95% CI) = 0.08 (0.00 to 2.28) i.e. not statistically significant Number of treatment-related deaths antituberculosis chemotherapy plus surgery = 1 of 22 antituberculosis chemotherapy alone = 0 of 6 OR[1] (95% CI) = 0.91 (0.03 to 25.06) i.e. not statistically significant
	Changes in signs and symptoms – spinal fusion Number of patients with spinal fusion antituberculosis chemotherapy plus surgery = 22 of 22 antituberculosis chemotherapy alone = 3 of 6 **OR[1] (95% CI) = 45.00 (1.89 to 1071.38)** **i.e. statistically significant**

	Changes in signs and symptoms – neurological improvement Number of patients with neurological improvement antituberculosis chemotherapy plus surgery = 21 of 22 antituberculosis chemotherapy alone = 3 of 6 **OR[1] (95% CI) = 21.00 (1.61 to 273.35)** **i.e. statistically significant**
	Response to treatment – hospitalisation Mean stay in hospital (months) antituberculosis chemotherapy plus surgery (n = 22) = 2.4 antituberculosis chemotherapy alone (n = 6) = 26.4 MD[2] = -24.0 i.e. not statistically significant
	Post-operative complications Blood loss: excessive bleeding = 1 mean blood loss: adults = 380 ml children = 80 ml need for transfusion = 5 Operative mortality = 1 Intraoperative neurological complications = 0

	Wound infection = 1 Draining sinus tracts after chest tube removal = 2
Source of funding	No details provided
Comments	

[1] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

[2] Mean difference not provided by authors; calculated by reviewer

Abbreviations: CI, confidence intervals; F, female; M, male; MD, mean difference; OR, odds ratio; RCT, randomised controlled trial

1.1.16 Zaoui et al, 2012

Bibliographic reference	Zaoui A, Kanoun S, Boughamoura H et al (2012) Patients with complicated Pott's disease: management in a rehabilitation department and functional prognosis. Annals of Physical and Rehabilitation Medicine 55: 190-200
Study type	Retrospective case series
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* no – allocation to surgery was based upon the presence of compressive abscess with neurological complications *Blinding used?* unclear, though unlikely *Attempts made within the design or analysis to balance the groups for potential confounders?* no *Groups comparable at baseline?* more patients that underwent surgery had complete neurological impairment *Groups received the same care apart from the intervention(s) studied?* yes

	Groups followed up for an equal and appropriate length of time? unclear *Groups comparable for treatment completion and availability of outcome data?* yes *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* antituberculosis regimen(s) unclear *Have substitute outcomes been used instead of the patient-important outcomes of interest?* response to treatment
Number of patients	Included = 9 antituberculosis chemotherapy plus surgery = 5 antituberculosis chemotherapy alone = 4
Patient characteristics	*Inclusion* Tuberculosis of the spine (Pott's disease) Neurological deficit *Diagnostic criteria* Based on anatomopathological examination and positive Koch bacillus cultures *Baseline*

Group	Patient	Age (years)	Sex	Functional status (MFI score[1])	Neurological status (ASIA score[2])	Walking ability	Micturition mode
Antituberculosis chemotherapy plus surgery	1	47	F	70	A	paraplegia	intermittent sounding
	2	49	M	72	A	paraplegia	intermittent sounding
	3	72	F	72	C	paraparesis	intermittent sounding
	4	67	M	68	A	paraplegia	intermittent sounding
	5	35	F	74	C	paraparesis	peniflow
	summary (mean/ratio)	54	2M:3F	71	2A:2C	3 paraplegia: 2 paraparesis	4 intermittent sounding : 1 peniflow
Antituberculosis chemotherapy alone	1	31	F	86	B	paraparesis	intermittent sounding
	2	60	M	82	C	paraparesis	intermittent sounding
	3	54	M	72	C	paraparesis	peniflow
	4	63	M	60	A	paraplegia	intermittent sounding
	summary (mean/ratio)	52	3M:1F	62	1A:1B:2C	1 paraplegia: 3 paraparesis	3 intermittent sounding : 1 peniflow

Intervention	*Antituberculosis chemotherapy plus surgery* Surgery: decompression by laminectomy with or without arthrodesis Antituberculosis chemotherapy: 4 drugs for 2 months, followed by 2 drugs for at least 10 months isoniazid: 5 to 10 mg/kg of bodyweight/day rifampicin: 10 mg/kg of bodyweight/day pyrazinamide: 20 to 40 mg/kg of bodyweight/day ethambutol: 15 to 25 mg/kg of bodyweight/day Rehabilitation programme: confinement to bed with adapted supports, position changes, nursing and early verticalisation on an inclined plane according to the patient's tolerance; these measures were associated with a preventive anticoagulant treatment global articulary work through passive, helped active or active mobilisations, and alternated positions athletisation of the upper limbs associated with breathing exercises postures of inhibition of spasticity management of the vesicosphincter disorders with vesicle drainage adapted to the vesicle profile in late phase, exercises for respiratory capacity increase were started rehabilitation of walking ability was set up according to muscular recovery when bone consolidation became complete, exercises aiming to increase cardiovascular endurance was performed following discharge, an outpatient rehabilitation programme was started and complemented by exercises at home
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy:

<table>
<tr><td></td><td>4 drugs for 2 months, followed by 2 drugs for at least 10 months
isoniazid: 5 to 10 mg/kg of bodyweight/day
rifampicin: 10 mg/kg of bodyweight/day
pyrazinamide: 20 to 40 mg/kg of bodyweight/day
ethambutol: 15 to 25 mg/kg of bodyweight/day
Rehabilitation programme:
confinement to bed with adapted supports, position changes, nursing and early verticalisation on an inclined plane according to the patient’s tolerance; these measures were associated with a preventive anticoagulant treatment
global articulary work through passive, helped active or active mobilisations, and alternated positions
athletisation of the upper limbs associated with breathing exercises
postures of inhibition of spasticity
management of the vesicosphincter disorders with vesicle drainage adapted to the vesicle profile
in late phase, exercises for respiratory capacity increase were started
rehabilitation of walking ability was set up according to muscular recovery
when bone consolidation became complete, exercises aiming to increase cardiovascular endurance was performed
following discharge, an outpatient rehabilitation programme was started and complemented by exercises at home</td></tr>
<tr><td>Length of follow up</td><td>Unclear</td></tr>
<tr><td>Location</td><td>Sousse, Tunisia</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Change in signs and symptoms – neurological status
<table>
<tr><td></td><td colspan="5">Antituberculosis chemotherapy plus surgery</td><td colspan="4">Antituberculosis chemotherapy alone</td></tr>
<tr><td></td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>1</td><td>2</td><td>3</td><td>4</td></tr>
</table></td></tr>
</table>

ASIA score[2] on admission	A	A	C	A	C	B	C	C	A
ASIA score[2] on discharge	A	A	D	A	C	D	D	D	A
Effect	no change	no change	improved	no change	no change	improved	improved	improved	no change

Number of patients with improved neurological status

antituberculosis chemotherapy plus surgery = 1 of 5

antituberculosis chemotherapy alone = 3 of 4

OR[5] (95% CI) = 0.08 (0.00 to 1.95)

i.e. not statistically significant

Change in signs and symptoms – walking ability

	Antituberculosis chemotherapy plus surgery					**Antituberculosis chemotherapy alone**			
	1	2	3	4	5	1	2	3	4
Walking ability on admission	paraplegia	paraplegia	paraparesis	paraplegia	paraparesis	paraparesis	paraparesis	paraparesis	paraplegia
Walking ability on discharge	wheel chair	wheel chair	walking	walking with frame	walking with frame	walking	walking	walking with frame	wheel chair

Number of patients able to walk on discharge

antituberculosis chemotherapy plus surgery = 3 of 5

antituberculosis chemotherapy alone = 3 of 4

OR[5] (95% CI) = 0.50 (0.03 to 8.95)

i.e. not statistically significant

Change in signs and symptoms – functional independence

	Antituberculosis chemotherapy plus surgery					**Antituberculosis chemotherapy alone**			
	1	2	3	4	5	1	2	3	4
MFI[1] on admission	70	72	72	68	74	86	82	72	60
MFI[1] on disharge	73	78	108	94	92	112	104	94	70
Change	3	6	36	26	18	26	22	22	10
Self-care (of 56 points) on admission	20	21	20	18	23	25	21	20	12
Self-care (of 56 points) on discharge	22	23	46	34	32	50	42	33	19
Change	2	2	26	16	9	25	21	13	7
Mobility / transfer (of 21 points) on admission	9	10	10	9	10	18	18	11	8
Mobility / transfer (of 21	10	12	17	15	15	17	17	16	10

points) on discharge									
Change	1	2	7	6	5	-1	-1	5	2
Locomotion (of 14 points) on admission	6	6	7	6	6	7	7	6	5
Locomotion (of 14 points) on discharge	6	8	10	10	10	10	10	10	6
Change	0	2	3	4	4	3	3	4	1

Mean(±SD)[3] change in MFI

antituberculosis chemotherapy plus surgery (n = 5) = 17.8±13.8

antituberculosis chemotherapy alone (n = 4) = 20.0±6.9

MD[4] (95% CI) = -2.20 (-16.06 to 11.66)

i.e. not statistically significant

Mean(±SD)[3] change in self-care score

antituberculosis chemotherapy plus surgery (n = 5) = 11.0±10.2

antituberculosis chemotherapy alone (n = 4) = 16.5±8.1

MD[4] (95% CI) = -5.5 (-17.46 to 6.46)

i.e. not statistically significant

Mean(±SD)[3] change in mobility and transfer score

antituberculosis chemotherapy plus surgery (n = 5) = 4.3±2.6

antituberculosis chemotherapy alone (n = 4) = 1.3±2.9

MD[4] (95% CI) = 3.00 (-0.64 to 6.64)

i.e. not statistically significant

Mean(±SD)[3] change in locomotion score

antituberculosis chemotherapy plus surgery (n = 5) = 2.6±1.7

antituberculosis chemotherapy alone (n = 4) = 2.8±1.3

MD[4] (95% CI) = -0.20 (-2.16 to 1.76)

i.e. not statistically significant

Response to treatment - hospitalisation

	Antituberculosis chemotherapy plus surgery					**Antituberculosis chemotherapy alone**			
	1	2	3	4	5	1	2	3	4
Duration of hospitalisation, days	35	63	70	45	32	42	34	50	54

Mean(±SD)[3] duration of hospitalisation, days

antituberculosis chemotherapy plus surgery (n = 5) = 49.0±16.9

antituberculosis chemotherapy alone (n = 4) = 45.0±8.9

MD[4] (95% CI) = 4.00 (-13.19 to 21.19)

i.e. not statistically significant

Source of funding: No details provided

Comments:

[1] MFI scores: assessment includes self-care, mobility and transfer, and locomotion

[2] ASIA scores:

A = complete neurological impairment – no sensory or motor function is preserved in the sacral segments S4-S5

B = sensory function incomplete – sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5, and no motor function is preserved more than three levels below the motor level on either side of the body.

C = motor function incomplete – motor function is preserved below the neurological level, and more than half of key muscle functions below the single neurological level of injury have a muscle grade less than 3 (grades 0-2)

D = motor function incomplete – motor function is preserved below the neurological level, and at least half (half or more) of key muscle functions below the neurological level of injury have a muscle grade > 3

E = normal – sensation and motor function are graded as normal in all segments, and the patient had prior deficits

[3] Mean and standard deviation not provided by authors; calculated by reviewer

[4] Mean difference and 95% confidence intervals not provided by authors; calculated by reviewer

[5] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

Abbreviations: ASIA, American Spinal Injury Association; CI, confidence intervals; F, female; M, male; MFI, measure of functional independence; OR, odds ratio; RCT, randomised controlled trial; SD, standard deviation

Evidence tables

Active CENTRAL NERVOUS SYSTEM tuberculosis

RANDOMISED CONTROLLED TRIALS

No randomised controlled trials identified

NON-RANDOMISED CONTROLLED TRIALS

No non-randomised controlled trials identified

OBSERVATIONAL STUDIES

1.1.17 Kalita et al, 2007

Bibliographic reference	Kalita J, Misra UK & Ranjan P (2007) Predictors of long-term neurological sequelae of tuberculous meningitis: a multivariate analysis. European Journal of Neurology 14: 33-7
Study type	Prospective observational
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* no – allocation to receive shunt was based on clinical status (see 'intervention' below) *Blinding used?* unclear, though unlikely *Attempts made within the design or analysis to balance the groups for potential confounders?* no *Groups comparable at baseline?* no – those that received shunt were selected due to the presence of hydrocephalus and raised intracranial pressure *Groups received the same care apart from the intervention(s) studied?* unclear *Groups followed up for an equal and appropriate length of time?*

	yes *Groups comparable for treatment completion and availability of outcome data?* yes *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* yes *Have substitute outcomes been used instead of the patient-important outcomes of interest?* no
Number of patients	Included = 65 antituberculosis chemotherapy plus shunt = 12 antituberculosis chemotherapy alone = 43
Patient characteristics	*Inclusion* Tuberculous meningitis based on clinical, CT scan and CSF criteria 1 year of follow-up *Diagnostic criteria* Essential criteria: presence of meningitic symptoms, comprising fever, headache and vomiting for 2 weeks or more exclusion of malarial, septic, fungal and carcinomatous meningitides

	Supportive criteria: CSF cells 0.2 x 10^9/l or more with predominant lymphocytes, protein more than 2 g/l, sterile bacterial and fungal culture CT scan evidence of exudates, infarctions, hydrocephalus and tuberculoma in various combinations evidence of extra-CNS tuberculosis response to antituberculosis chemotherapy Presence of essential and 3 or 4 supportive criteria was considered suggestive of tuberculous meningitis Positive PCR for *M. tuberculosis*, IgM ELISA or acid-fast bacilli in CSF smear or culture was considered definitive evidence of tuberculous meningitis *Exclusions* Associated HIV infection *Baseline* Age (mean (range)), years = 33.2 (13–80) Sex (M:F) = 38:27 Duration of illness (mean (range)), months = 6 (0.5–16) Definitive evidence acid-fast bacilli in CSF smear or culture = 4 positive PCR = 13 positive in IgM ELISA = 33 BCG vaccination = 24 of 65 Presence of extra-CNS tuberculosis = 17 of 65 pulmonary = 14 (6 miliary)

	spinal = 2 lymphadenopathy = 1 Multi-drug resistant tuberculosis = 0 of 65 Severity of disease[1] stage I = 14 stage II = 15 stage III = 36 Glasgow Coma Score mean (range) = 11.6 (4–15) deeply comatose (score <6) = 6 moderately comatose (score 6–12) = 20 mild alteration of sensorium = 10 Seizures = 21 of 65 Opthalmoplegia = 13 of 65 Focal motor deficit = 26 of 65 Cerebellar ataxia = 3 of 65
Intervention	*Antituberculosis chemotherapy plus shunt* Ventriculoperitoneal shunt – criteria: raised intracranial pressures and features of herniation caused by obstructive hydrocephalus; or communicating hydrocephalus with features of raised intracranial pressure – repeated CSF drainage by lumbar puncture was tried before subjecting the patient to shunt surgery

	Antituberculosis chemotherapy: $8HRZE_7/4HRE_7/6HE_7$ isoniazid: 5 mg/kg of bodyweight/day rifampicin: 10 mg/kg of bodyweight/day pyrazinamide: 25 mg/kg of bodyweight/day ethambutol: 15 mg/kg of bodyweight/day Corticosteroids: prednisolone (0.5 to 1 mg/kg of bodyweight/day) for a period of 1 month followed by a rapid taper in the next month prescribed to the patients with encephalopathy, raised intracranial pressure and impending visual failure
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: $8HRZE_7/4HRE_7/6HE_7$ isoniazid: 5 mg/kg of bodyweight/day rifampicin: 10 mg/kg of bodyweight/day pyrazinamide: 25 mg/kg of bodyweight/day ethambutol: 15 mg/kg of bodyweight/day Corticosteroids: prednisolone (0.5 to 1 mg/kg of bodyweight/day) for a period of 1 month followed by a rapid taper in the next month prescribed to the patients with encephalopathy, raised intracranial pressure and impending visual failure
Length of follow up	1 year
Location	Lucknow, India
Outcomes measures and effect size	**Changes in signs and symptoms – neurological sequelae** Number of patients to experience neurological sequelae, including neurological deficit, cognitive impairment[2], optic

	atrophy and/or motor deficit antituberculosis chemotherapy plus shunt = 9 of 12[3] antituberculosis chemotherapy alone = 17 of 53 **OR[4] (95% CI) = 6.35 (1.52 to 26.50)** **i.e. statistically significant**
Source of funding	No details provided
Comments	

[1] Severity of disease:

stage I: meningitis only

stage II: meningitis with focal neurological signs

stage III: meningitis with altered sensorium

[2] Cognitive impairment evaluated with the Mini Mental State Examination; patients were considered to be cognitively impaired if the score was <29 for 9 years of schooling, <26 for 5 to 8 years of schooling or <22 if 0 to 4 years of schooling

[3] p = 0.01

[4] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

Abbreviations: CI, confidence intervals; CSF, cerebrospinal fluid; CT, computerised tomography; E, ethambutol; F, female; H, isoniazid; IgM ELISA, immunoglobulin M enzyme-linked immunoabsorbent assay; M, male; OR, odds ratio; PCR, polymerase chain reaction; R, rifampicin; RCT, randomised controlled trial; Z, pyrazinamide

1.1.18 Lee, 2000

Bibliographic reference	Lee LV (2000) Neurotuberculosis among Filipino children: an 11 years experience at the Philippine Children's Medical Center. Brain & Development 22: 469-74
Study type	Retrospective observational
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?*

	approach to allocation unclear *Blinding used?* unclear, though unlikely *Attempts made within the design or analysis to balance the groups for potential confounders?* no *Groups comparable at baseline?* unclear *Groups received the same care apart from the intervention(s) studied?* unclear *Groups followed up for an equal and appropriate length of time?* unclear *Groups comparable for treatment completion and availability of outcome data?* no data for stage I – it appears that this is because no one with stage I disease underwent shunting (stage I patients by definition did not have hydrocephalus[1]); data about the incidence of 'poor outcome' in stage I would have all been within the antituberculosis alone group, and therefore it is only this group for which outcome data is not available *Study used precise definitions and reliable measures of outcome?* no – 'poor outcome' defined only as the incident of severe neurologic deficit or death *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* antituberculosis regimens do not use all of or just the 4 standard recommended drugs *Have substitute outcomes been used instead of the patient-important outcomes of interest?*

	yes – 'poor outcome' a composite, and therefore substitute, outcome of changes in the signs and symptoms of disease (severe neurologic deficit) and mortality
Number of patients	Included (stages I, II and III[1]) = 405 antituberculosis chemotherapy plus shunt = 147 antituberculosis chemotherapy alone = 258 Data available (only stages II and III; shunt did not appear to be a treatment option for stage I) = 387 antituberculosis chemotherapy plus shunt = 147 antituberculosis chemotherapy alone = 240
Patient characteristics	*Inclusion* Tuberculous meningitis Children *Diagnostic criteria* Highly probable diagnosis of tuberculous meningitis: clinical course compatible with subacute or chronic meningitis CSF compatible with subacute or chronic meningitis any 1 or more of the following: PCR of CSF positive for tuberculosis; ELISA of CSF positive for tuberculosis; neuroimaging results such as cranial ultrasound, CT scan or MRI compatible with tuberculous meningitis Definitive diagnosis: histopathology of autopsy sample positive culture of *M. tuberculosis* *Baseline* Age:

	mean (range), years = 3.81 (0.25–13) <24 months = 47% <5 years = 77% Sex (M:F) = 1.3:1 Presenting symptoms: fever = 88% vomiting = 57% cough and nasal catarrh = 31% poor feeding or sucking = 29% headaches = 28% lethargy = 17% neck rigidity = 11% Clinical findings: depressed sensorium (usually stupor) = 42% behavioral changes = 16% motor weakness = 14% abnormal gait = 7% facial asymmetry = 4% CSF profile: <60 cells/mm^3 = 50% 60–500 cells/mm^3 = 45%

	500–1000 cells/mm^3 = 4% >1000 cells/mm^3 = 1% protein <45 mg = 13% protein >100 mg = 65% glucose <50% of blood glucose = 80%
Intervention	*Antituberculosis chemotherapy plus shunt* Ventriculoperitoneal shunt – patients with hydrocephalus only (stages II and III) Antituberculosis chemotherapy: HRZ isoniazid: 10 to 20 mg/kg of bodyweight/day rifampicin: 20 mg/kg of bodyweight/day pyrazinamide: 30 mg/kg of bodyweight/day duration and dosing frequency unclear Patients also received decompressants and steroids
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: HRZ isoniazid: 10 to 20 mg/kg of bodyweight/day rifampicin: 20 mg/kg of bodyweight/day pyrazinamide: 30 mg/kg of bodyweight/day duration and dosing frequency unclear Patients also received decompressants and steroids
Length of follow up	Unclear

Location	Quezon City, Philippines
Outcomes measures and effect size	**Response to treatment – 'poor outcome'** Number of patients (stage II or III) to have a 'poor outcome' (severe neurologic deficit or death) antituberculosis chemotherapy plus shunt = 85 of 147 antituberculosis chemotherapy alone = 108 of 240 **OR[2] (95% CI) = 1.68 (1.11 to 2.54)** **i.e. statistically significant** Number of patients with stage II disease to have a 'poor outcome' (severe neurologic deficit or death) antituberculosis chemotherapy plus shunt = 17 of 54 antituberculosis chemotherapy alone = 23 of 102 OR[2] (95% CI) = 1.58 (0.75 to 3.30) i.e. not statistically significant Number of patients with stage III disease to have a 'poor outcome' (severe neurologic deficit or death) antituberculosis chemotherapy plus shunt = 68 of 93 antituberculosis chemotherapy alone = 85 of 138 OR[2] (95% CI) = 1.70 (0.97 to 3.01) i.e. not statistically significant
Source of funding	No details provided
Comments	

[1] Severity of disease:

stage I: patients conscious and rational with meningism but no focal neurological signs or signs of hydrocephalus

stage II: patients confused or with focal neurological signs such as squint or hemiparesis

stage III: patients mentally inaccessible due to depth of stupor or delirium, or have complete hemiplegia or paraplegia

[2] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

Abbreviations: CI, confidence intervals; CSF, cerebrospinal fluid; CT, computerised tomography; ELISA, enzyme-linked immunoabsorbent assay; F, female; M, male; OR, odds ratio; PCR, polymerase chain reaction; RCT, randomised controlled trial

1.1.19 Misra et al, 1996

Bibliographic reference	Misra UK, Kalita J, Srivastava M et al (1996) Prognosis of tuberculous meningitis: a multivariate analysis. 137: 57-61
Study type	Prospective observational
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* no – allocation to receive shunt was based on clinical status (see 'intervention' below) *Blinding used?* unclear, though unlikely *Attempts made within the design or analysis to balance the groups for potential confounders?* yes, although this only benefits the p-value and z-statistic (odds ratio was calculated by the reviewer) *Groups comparable at baseline?* no – those that received shunt were selected due to the presence of obstructive hydrocephalus *Groups received the same care apart from the intervention(s) studied?* unclear *Groups followed up for an equal and appropriate length of time?* follow-up for an equal time, although only 3 months

	Groups comparable for treatment completion and availability of outcome data? yes *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* duration of antituberculosis chemotherapy unclear, and children received streptomycin instead of ethambutol *Have substitute outcomes been used instead of the patient-important outcomes of interest?* 'poor outcome' is a substitute for changes in signs and symptoms
N/lumber of patients	Included = 49 antituberculosis chemotherapy plus shunt = 14 antituberculosis chemotherapy alone = 35
Patient characteristics	*Inclusion* Tuberculous meningitis Only those with obstructive hydrocephalus received shunt surgery; it is unclear if any patients in the antituberculosis chemotherapy alone group also had obstructive hydrocephalus *Diagnostic criteria* Clinical criteria = fever, headache and neck stiffness for more than 2 weeks Supporting evidence: CSF cells 0.02 x 10^9 or more with lymphocytes predominating

	CSF protein >1 g/l sterile bacterial and fungal culture presence of hydrocephalus and exudates on CT scan evidence of tuberculosis outside of the central nervous system response to antituberculosis chemotherapy positive therapeutic response at 3 months Highly probable tuberculosis = clinical criteria and 3 supporting criteria Probable tuberculosis = clinical criteria and 2 supporting criteria Possible tuberculosis = clinical criteria and 1 supporting criteria *Exclusion* Those that did not fulfill the diagnostic criteria Those not followed for 3 months *Baseline* Age (mean (range)), years = 26.6 (4–63) Sex (M:F) = 28:21 Duration of illness (mean (range)), months = 2.4 (0.5–7) Severity of disease[1] stage I = 11 stage II = 17 stage III = 21 Seizures = 23 of 49

	Extracranial tuberculosis = 15 of 49 Cranial nerve palsy = 35 of 49 opthalmoplegia = 21 facial weakness = 7 nasal speech and regurgitation = 4 visual impairment = 13 hearing deficit = 1 Abnormal cranial CT scan = 39 of 49 hydrocephalus = 24 basal exudates = 22 infarction = 13 tuberculoma = 11
Intervention	*Antituberculosis chemotherapy plus shunt* Shunt – criteria = obstructive hydrocephalus Antituberculosis chemotherapy: HRZE preferred in adults (>12 years of age) or HRZS (preferred in children) isoniazid: 300 mg/day rifampicin: 450 mg/day pyrazinamide: 1500 mg/day ethambutol: 800 mg/day streptomycin: dosage unclear doses in children were adjusted according to bodyweight

	duration unclear
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: HRZE preferred in adults (>12 years of age) or HRZS (preferred in children) isoniazid: 300 mg/day rifampicin: 450 mg/day pyrazinamide: 1500 mg/day ethambutol: 800 mg/day streptomycin: dosage unclear doses in children were adjusted according to bodyweight duration unclear
Length of follow up	3 months
Location	Lucknow, India
Outcomes measures and effect size	**Response to treatment – 'poor outcome'** Number of patients to have a 'poor outcome', as defined by death or a Barthel Index score[2] of <12 antituberculosis chemotherapy plus shunt = 9 of 14 antituberculosis chemotherapy alone = 11 of 35 **p < 0.05** **Z = 2.17** **OR[3] (95% CI) = 3.93 (1.06 to 14.49)** **i.e. statistically significant**
	Post-operative complications

	note: data only available for group that underwent shunt surgery (n = 14) Shunt surgery complications = 6 of 14[4] obstruction = 2 infection = 2 slit ventricles = 2 subdural haematoma = 1 intracerebral haematoma = 1
Source of funding	No details provided
Comments	

[1] Severity of disease:

stage I: meningitis only

stage II: meningitis with neurological signs

stage III: meningitis with neurological signs and altered sensorium

[2] The Barthel Index measures a patient's mobility and their performance in the 'activities of daily living' (presence or absence of faecal or urinary incontinence, and help needed with grooming, toilet use, feeding, transfers (e.g. from chair to bed), walking, dressing, climbing stairs and bathing); each performance item is rated on this scale with a given number of points assigned to each level or ranking – a higher number is associated with a greater likelihood of being able to live at home with a degree of independence following discharge from hospital

[3] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

[4] More than 1 complication occurred in some patients

Abbreviations: CI, confidence intervals; CSF, cerebrospinal fluid; CT, computerized tomography; OR, odds ratio; RCT, randomised controlled trial

1.1.20 Peacock & Deeny, 1984

Bibliographic reference	Peacock WJ & Deeny JE (1984) Improving the outcome of tuberculous meningitis in childhood. South African Medical Journal 66: 597-8
Study type	Retrospective case-control
Study quality	*Study addresses an appropriate and clearly focused question?* not reported – question is not explicitly detailed *Cases and controls are taken from comparable populations?* poorly addressed and/or reported – matched for age and stage of disease, but no further details given *Same exclusion criteria are used for both cases and controls?* not reported *Participation rate:* not reported *Participants and non-participants compared to establish their similarities or differences?* not reported *Cases and controls clearly differentiated?* adequately addressed *Groups followed up for an equal and appropriate length of time?* follow-up was appropriate (at least 1 year), but it is unclear if it was equal in the 2 groups *Measures taken to prevent knowledge of primary exposure from influencing case ascertainment?* not reported *Exposure status measured in a standard, valid and reliable way?* adequately addressed

	Main potential confounders identified and taken into account in the design and analysis? poorly addressed and/or reported *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* antituberculosis regimen unclear *Have substitute outcomes been used instead of the patient-important outcomes of interest?* no
Number of patients	Included = 56 antituberculosis chemotherapy plus shunt = 28 antituberculosis chemotherapy alone = 28
Patient characteristics	*Inclusion* Tuberculous meningitis with hydrocephalus Children (age threshold unclear) *Diagnostic criteria* Unclear *Baseline* Unclear
Intervention	*Antituberculosis chemotherapy plus shunt*

	Ventriculoperitoneal or lumboperitoneal shunt Antituberculosis chemotherapy: unclear – all patients received 'appropriate antituberculosis therapy'
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: unclear – all patients received 'appropriate antituberculosis therapy'
Length of follow up	At least 1 year
Location	Cape Town, South Africa
Outcomes measures and effect size	**Mortality** Number of deaths antituberculosis chemotherapy plus shunt = 3 of 28 antituberculosis chemotherapy alone = 11 of 28 **OR[1] (95% CI) = 0.19 (0.04 to 0.77)** **i.e. statistically significant**
	Changes in signs and symptoms – disability Number of patients to experience disability antituberculosis chemotherapy plus shunt = 16 of 28 antituberculosis chemotherapy alone = 18 of 28 OR[1] (95% CI) = 0.74 (0.25 to 2.17) i.e. not statistically significant Number of patients to experience major disability, such as severe mental retardation or mild mental retardation with physical abnormalities such as hemiparesis or athetoid movements antituberculosis chemotherapy plus shunt = 8 of 28

	antituberculosis chemotherapy alone = 10 of 28 OR[1] (95% CI) = 0.72 (0.23 to 2.22) i.e. not statistically significant Number of patients to be considered 'well', or had a minor physical abnormality which did not interfere with his or her lifestyle antituberculosis chemotherapy plus shunt = 9 of 28 antituberculosis chemotherapy alone = 2 of 28 **OR[1] (95% CI) = 6.16 (1.19 to 31.82)** **i.e. statistically significant**
Source of funding	No details provided
Comments	

[1] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

Abbreviations: CI, confidence intervals; OR, odds ratio; RCT, randomised controlled trial

Evidence tables

Active *GENITOURINARY* tuberculosis

RANDOMISED CONTROLLED TRIALS

No randomised controlled trials identified

NON-RANDOMISED CONTROLLED TRIALS

No non-randomised controlled trials identified

OBSERVATIONAL STUDIES

1.1.21 Shin et al, 2002

Bibliographic reference	Shin KY, Park HJ, Lee JJ et al (2002) Role of early endourologic management of tuberculous ureteral strictures. Journal of Endourology 16(10): 755-8
Study type	Prospective observational
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* allocation to surgical intervention or antituberculosis chemotherapy alone appears to have been based on timing of treatment – all those that received antituberculosis chemotherapy alone were treated before September 1985 *Blinding used?* unclear, though unlikely *Attempts made within the design or analysis to balance the groups for potential confounders?* no *Groups comparable at baseline?* unclear *Groups received the same care apart from the intervention(s) studied?* yes, although details provided are limited

	Groups followed up for an equal and appropriate length of time? unclear if equal, though median follow-up for the 2 groups as a while (34 months) was appropriate *Groups comparable for treatment completion and availability of outcome data?* yes *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* antituberculosis regimens do not use all of or just the 4 standard recommended drugs *Have substitute outcomes been used instead of the patient-important outcomes of interest?* yes – 'need for additional intervention', a measure of response to treatment, is a substitute for treatment failure
Number of patients	Included = 77 patients, with 84 renal units antituberculosis chemotherapy plus surgery = 47 renal units antituberculosis chemotherapy alone = 37 renal units
Patient characteristics	*Inclusion* Renal tuberculosis Tuberculous ureteral strictures *Diagnostic criteria* Renal tuberculosis: urine cultures positive for acid-fast bacilli or cultures for pathogenic mycobacteria; and

<table>
<tr><td></td><td>
histopathologic evidence for tuberculosis
Tuberculous ureteral strictures:
excretory urography or retrograde or antegrade pyelography
Exclusion
Those with almost totally destroyed kidneys on initial ultrasonography
Nonappearance of kidney on initial excretory urography
Baseline
<table>
<tr><td>Age (mean (range)), years</td><td>38 (18–68)</td></tr>
<tr><td>Sex, M:F</td><td>48:29</td></tr>
<tr><td>Site of stricture
lower ureter, n
middle ureter, n
multiple, n</td><td>
45
25
14</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>
Antituberculosis chemotherapy plus surgery
Surgery:
6F or 7F double-pigtail ureteral stent placed cytoscopically (n = 28 renal units); or
percutaneous nephrostomy (n = 19 renal units)
Antituberculosis chemotherapy: HRE
9 to 22 months
dosing unclear
</td></tr>
</table>

Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: HRE 9 to 22 months dosing unclear
Length of follow up	Median (maximum), months = 34 (62)
Location	Seoul, Korea
Outcomes measures and effect size	**Response to treatment – need for additional intervention** Number of patients in whom reconstructive surgery or nephrectomy[1] was required antituberculosis chemotherapy plus surgery = 39 of 47 renal units antituberculosis chemotherapy alone = 30 of 37 renal units OR[2] (95% CI) = 1.14 (0.37 to 3.49) i.e. not statistically significant Number of patients in whom reconstructive surgery was required antituberculosis chemotherapy plus surgery = 23 of 47 renal units antituberculosis chemotherapy alone = 3 of 37 renal units **OR[2] (95% CI) = 10.86 (2.93 to 40.32)** **i.e. statistically significant** Number of patients in whom nephrectomy was required antituberculosis chemotherapy plus surgery = 16 of 47 renal units antituberculosis chemotherapy alone = 27 of 37 renal units **OR[2] (95% CI) = 0.19 (0.07 to 0.49)**

	i.e. statistically significant
Source of funding	Details not provided
Comments	

[1] Nephrectomy was performed in cases of totally or almost totally destroyed kidney, intractable pain, or failure of chemotherapy; criteria for reconstructive surgery is not reported; those who did not receive reconstructive surgery or nephrectomy had undergone spontaneous resolution

[2] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

Abbreviations: CI, confidence intervals; E, ethambutol; F, female; H, isoniazid; M, male; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial

1.1.22 Wong et al, 1984

Bibliographic reference	Wong SH, Lau WY, Poon GP et al (1984) The treatment of urinary tuberculosis. Journal of Urology 131: 297-301
Study type	Observational – unclear if prospective or retrospective
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* unclear – authors do not explain approach to allocation *Blinding used?* unclear, though unlikely *Attempts made within the design or analysis to balance the groups for potential confounders?* no *Groups comparable at baseline?* yes, although only details of age and sex were provided *Groups received the same care apart from the intervention(s) studied?*

	yes, although details provided were limited *Groups followed up for an equal and appropriate length of time?* follow-up had a wide range within each group, though the ranges appeared to be comparable across the groups *Groups comparable for treatment completion and availability of outcome data?* yes *Study used precise definitions and reliable measures of outcome?* definition for 'default' not provided, and only a loose definition provided for 'treatment failure' *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* intervention varies by more than the presence or absence of surgery – duration of antituberculosis chemotherapy is longer amongst those patients that received surgery *Have substitute outcomes been used instead of the patient-important outcomes of interest?* no
Number of patients	Included = 92 antituberculosis chemotherapy plus surgery = 74 plus ablative surgery = 45; plus reconstructive surgery = 29 antituberculosis chemotherapy alone = 18
Patient characteristics	*Inclusion* Confirmed diagnosis of tuberculosis of the urinary tract *Diagnostic criteria*

<table>
<tr><td></td><td>
Positive culture for M. tuberculosis from early morning urine, or fluid or pus from the surgical or resected surgical specimen, or negative culture for M. tuberculosis but with strong radiological evidence of tuberculosis of the urinary tract

Unequivocal histological evidence of tuberculosis from the resected specimen

Exclusion

No confirmed evidence of tuberculosis postoperatively

Baseline
<table>
<tr><td></td><td colspan="2">Antituberculosis chemotherapy plus surgery (n = 74)</td><td rowspan="2">Antituberculosis chemotherapy alone

(n = 18)</td></tr>
<tr><td></td><td>Antituberculosis chemotherapy plus ablative surgery

(n = 45)</td><td>Antituberculosis chemotherapy plus reconstructive surgery

(n = 29)</td></tr>
<tr><td>Age (range), years</td><td>21–64</td><td>21–79</td><td>19–59</td></tr>
<tr><td>Sex, M:F</td><td>32:13</td><td>20:9</td><td>11:7</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>
Antituberculosis chemotherapy plus surgery

Surgery:

ablative surgery: total (n = 41) or partial (n = 4) nephrectomy

reconstructive surgery: with intestinal segment (n = 19), plastic reconstruction with local tissue (n = 6), combination procedure (n = 3) or ileal conduit (n = 1)

Antituberculosis chemotherapy: HRZE

ablative surgery regimen: daily regimen of 1 to 2 months preoperatively and 2 months postoperatively, followed by a thrice-weekly intermittent regimen for a further 4 months
</td></tr>
</table>

	reconstructive surgery: daily regimen of 1 to 2 months preoperatively and 2 months postoperatively, followed by a thrice-weekly intermittent regimen for a further 7 months isoniazid: daily dose of 300 mg, and intermittent dose of 15 mg/kg of bodyweight rifampicin: daily dose of 450 to 600 mg, and intermittent dose of 600 mg pyrazinamide: daily dose of 1500 to 2000 mg, and intermittent dose of 2000 to 2500 mg ethambutol: 25 mg/kg of bodyweight
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: HRZE 2 months daily, followed by 4 months thrice-weekly isoniazid: daily dose of 300 mg, and intermittent dose of 15 mg/kg of bodyweight rifampicin: daily dose of 450 to 600 mg, and intermittent dose of 600 mg pyrazinamide: daily dose of 1500 to 2000 mg, and intermittent dose of 2000 to 2500 mg ethambutol: 25 mg/kg of bodyweight
Length of follow up	Follow-up (range), months antituberculosis chemotherapy plus ablative surgery = 9–58 antituberculosis chemotherapy plus reconstructive surgery = 16–47 antituberculosis chemotherapy alone = 14–60
Location	Hong Kong
Outcomes measures and effect size	**Treatment failure** Number of patients to experience bacteriological failure antituberculosis chemotherapy plus ablative surgery = 0 of 45

	antituberculosis chemotherapy plus reconstructive surgery = 0 of 29 antituberculosis chemotherapy alone = 0 of 18 *antituberculosis chemotherapy plus any surgery* vs *antituberculosis chemotherapy alone* OR[1] (95% CI) = 0.40 (0.01 to 20.42) i.e. not statistically significant *antituberculosis chemotherapy plus ablative surgery* vs *antituberculosis chemotherapy alone* OR[1] (95% CI) = 0.21 (0.00 to 11.19) i.e. not statistically significant *antituberculosis chemotherapy plus reconstructive surgery* vs *antituberculosis chemotherapy alone* OR[1] (95% CI) = 0.32 (0.01 to 17.37) i.e. not statistically significant
	Adverse events – drug toxicity leading to drug withdrawal Number of patients to experience drug toxicity leading to withdrawal of drug (without change to duration of treatment) antituberculosis chemotherapy plus ablative surgery = 5 of 45 antituberculosis chemotherapy plus reconstructive surgery = 4 of 29 antituberculosis chemotherapy alone = 2 of 18 *antituberculosis chemotherapy plus any surgery* vs *antituberculosis chemotherapy alone* OR[1] (95% CI) = 1.11 (0.22 to 5.64) i.e. not statistically significant *antituberculosis chemotherapy plus ablative surgery* vs *antituberculosis chemotherapy alone* OR[1] (95% CI) = 1.00 (0.10 to 9.75)

	i.e. not statistically significant *antituberculosis chemotherapy plus reconstructive surgery* vs *antituberculosis chemotherapy alone* OR[1] (95% CI) = 1.28 (0.12 to 13.17) i.e. not statistically significant
	Post-operative complications note: data available only for surgery groups (n = 72) Chest infection = 5 (6.8%) Wound infection = 2 (2.7%) Pneumothorax requiring chest drainage = 2 (2.7%) Haemorrhage from anastomosis = 1 (1.4%) Burst abdomen = 1 (1.4%) Intestinal obstruction owing to adhesion (late complication) = 1 (1.4%)
	Adherence – treatment default Number of patients to default treatment antituberculosis chemotherapy plus ablative surgery = 0 of 45 antituberculosis chemotherapy plus reconstructive surgery = 1 of 29 antituberculosis chemotherapy alone = 1 of 18 *antituberculosis chemotherapy plus any surgery* vs *antituberculosis chemotherapy alone* OR[1] (95% CI) = 0.38 (0.02 to 6.34) i.e. not statistically significant
Source of funding	Details not provided

Comments	
[1] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer Abbreviations: CI, confidence intervals; E, ethambutol; F, female; H, isoniazid; M, male; OR, odds ratio; R, rifampicin; RCT, randomised controlled trial; Z, pyrazinamide	

Active *DRUG RESISTANT* tuberculosis

RANDOMISED CONTROLLED TRIALS

No randomised controlled trials identified

NON-RANDOMISED CONTROLLED TRIALS

No non-randomised controlled trials identified

OBSERVATIONAL STUDIES

1.1.23 Cameron & Harrison, 1997

Bibliographic reference	Cameron RJ & Harrison AC (1997) Multidrug resistant tuberculosis in Auckland 1988-95. New Zealand Medical Journal 110(1041): 119-21
Study type	Case series
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* unclear, though unlikely *Blinding used?* unclear, though unlikely *Attempts made within the design or analysis to balance the groups for potential confounders?* no *Groups comparable at baseline?* the mean age in the surgery group was significantly older than in the group that received antituberculosis chemotherapy alone (41 *vs* 27 years) *Groups received the same care apart from the intervention(s) studied?* yes, although the details provided are limited

<table>
<tr><td></td><td>
Groups followed up for an equal and appropriate length of time?
unclear
Groups comparable for treatment completion and availability of outcome data?
yes
Study used precise definitions and reliable measures of outcome?
yes
Population studied is the same as the population of interest?
2 patients, both in the surgery group, had comorbidities that might effect the choice or management of treatment
Intervention used is the same as the intervention of interest?
the interventions used varied by more than the presence or absence of surgery – the regimens of antituberculosis chemotherapy contained, on average, more drugs in the surgery group (3.7 vs 2)
Have substitute outcomes been used instead of the patient-important outcomes of interest?
no
</td></tr>
<tr><td>Number of patients</td><td>
Included = 8
antituberculosis chemotherapy plus surgery = 3
antituberculosis chemotherapy alone = 5
</td></tr>
<tr><td>Patient characteristics</td><td>
Inclusion
Smear- or culture-positive tuberculosis
Specimens screened for resistance to isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin
Baseline
<table>
<tr><th></th><th>Resistance</th><th>Age (years)/sex</th><th>Risk factors for drug</th><th>Time from TB</th><th>Sputum status</th><th>Site of disease</th></tr>
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					resistance	**diagnosis to MDR-TB treatment** (days)		
	Antituberculosis chemotherapy plus surgery (n = 3)	Case 1	HRZ	26/F	chronic renal failure; nephrotic syndrome	5	positive	lung and urinary tract
		Case 2	HRZ	39/F	–	20	positive	lung
		Case 3	HRZS+rifa	58/M	non-insulin dependent diabetes mellitus	25	positive	lung
		mean or ratio	3.7 drugs	age = 41 M:F = 1:2	–	16.7	3 positive : 0 negative	–
	Antituberculosis chemotherapy alone (n = 5)	Case 1	HR	23/M	–	17	positive	lung
		Case 2	HR	24/M	–	0	negative	lung and cervical lymph nodes
		Case 3	HR	29/M	HIV	69	positive	lung and pleura
		Case 4	HR	31/M	inadequately treated TB	0	positive	lung
		Case 5	HR	28/F	inadequately treated TB	0	positive	lung
		mean or ratio	2 drugs	age = 27 M:F = 4:1	–	17.2	4 positive : 1 negative	–

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<tr><td></td><td></td></tr>
<tr><td>Intervention</td><td>Antituberculosis chemotherapy plus surgery
<table>
<tr><th></th><th>Case 1</th><th>Case 2</th><th>Case 3</th></tr>
<tr><td>Drugs</td><td>HRZE+cap+cip</td><td>HRE+cip+clo
Z started but stopped after 3 weeks when resistance known
eth and cap were stopped due to side effects</td><td>HRE+eth+ami+cap+cip
Z started but stopped after 3 weeks when resistance known</td></tr>
<tr><td>Surgery</td><td>left thoracoplasty</td><td>left upper lobectomy</td><td>left upper lobectomy</td></tr>
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<tr><td>Comparison</td><td>Antituberculosis chemotherapy alone
<table>
<tr><th></th><th>Case 1</th><th>Case 2</th><th>Case 3</th><th>Case 4</th><th>Case 5</th></tr>
<tr><td>Drugs</td><td>HRZE</td><td>ZSE+eth+cip</td><td>HRZE+cap+cip</td><td>HRZE+eth+cap+cip</td><td>HRZE+eth+cip
cap was stopped due to side effects</td></tr>
</table></td></tr>
<tr><td>Length of follow up</td><td>Unclear – length of follow-up not reported for all patients</td></tr>
<tr><td>Location</td><td>Auckland, New Zealand</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Mortality
Number of deaths
antituberculosis chemotherapy plus surgery = 1 of 3
antituberculosis chemotherapy alone = 1 of 5</td></tr>
</table>

	OR[1] (95% CI) = 22.00 (0.08 to 51.60) i.e. not statistically significant
	Clinical response Number of patients to achieve a clinical response, defined as the disappearance of signs and symptoms associated with active tuberculosis, regression of chest radiograph shadowing, and 2 consecutive culture-negative sputum specimens collected 2 weeks apart antituberculosis chemotherapy plus surgery = 2 of 3 antituberculosis chemotherapy alone = 4 of 5 OR[1] (95% CI) = 0.50 (0.02 to 12.90) i.e. not statistically significant
	Adherence Number of patients to complete the intended course of therapy antituberculosis chemotherapy plus surgery = 1 of 3 antituberculosis chemotherapy alone = 2 of 5 OR[1] (95% CI) = 0.75 (0.04 to 14.97) i.e. not statistically significant
Source of funding	Financial assistance provided by the Asser Trust and the Auckland Tuberculosis and Chest Diseases Association
Comments	

[1] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

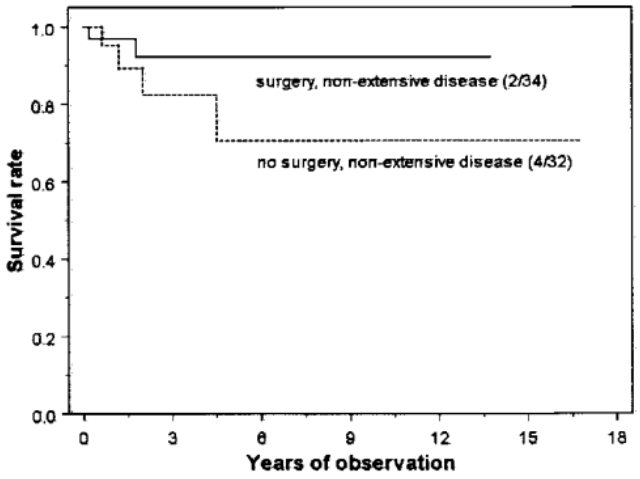
Abbreviations: ami, amikacin; cap, capreomycin; CI, confidence intervals; cip, ciprofloxacin; clo, clofazamine; eth, ethionamide; F, female; H, isoniazid; M, male; MDR-TB, multidrug resistant tuberculosis; OR, odds ratio; R, rifampicin; rif, rifabutin; S, streptomycin; TB, tuberculosis; Z, pyrazinamide

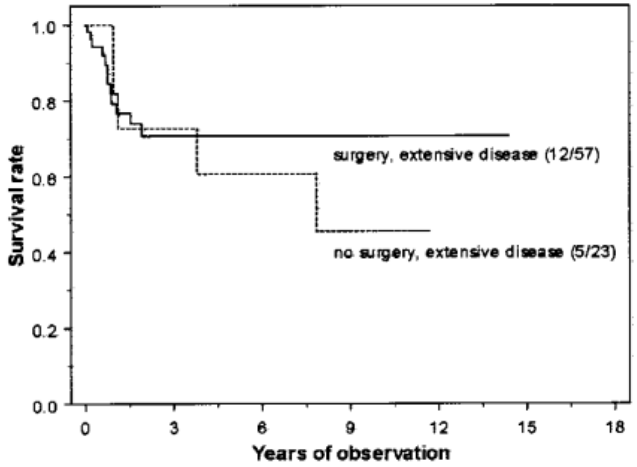
1.1.24 Chan et al, 2004

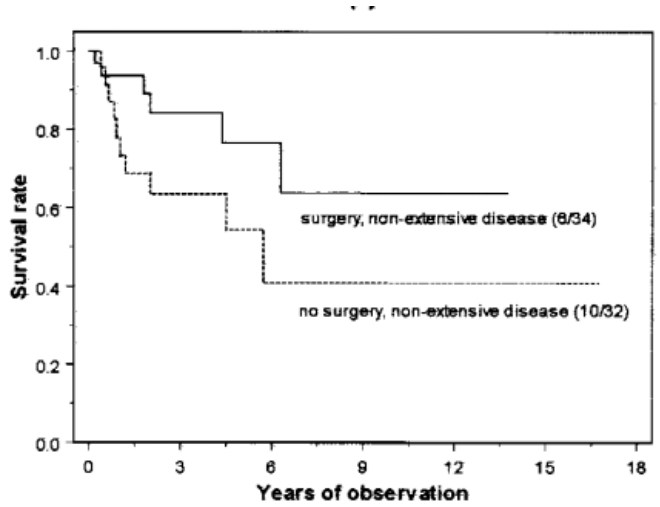
Bibliographic reference	Chan ED, Laurel V, Strand MJ (2004) Treatment and outcome analysis of 205 patients with multidrug-resistant tuberculosis. American Journal of Respiratory and Critical Care Medicine 169: 1103-9
Study type	Retrospective cohort
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* allocation to surgery was broadly based on potential confounding factors (a high likelihood of medical failure based on extensive drug resistance, localized cavitary disease within a lobe or total destruction of one lung, and predictably adequate postoperative lung function), although the authors also state that because of the retrospective nature of the study, there were no rigid criteria for selection or exclusion for surgery *Blinding used?* unclear, though unlikely *Attempts made within the design or analysis to balance the groups for potential confounders?* a stepwise selection procedure was used to create a multiple predictor model for the incidence of favourable response; it is unclear if the survival analyses attempted to balance the groups for potential confounders *Groups comparable at baseline?* unclear *Groups received the same care apart from the intervention(s) studied?* unclear *Groups followed up for an equal and appropriate length of time?* follow-up appropriate, although unclear if it was balanced between the groups *Groups comparable for treatment completion and availability of outcome data?* unclear *Study used precise definitions and reliable measures of outcome?*

	yes *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* it is unclear if the 2 interventions varied by more than the presence or absence of surgery; in particular, there is insufficient detail around the precise regimens of antituberculosis chemotherapy used in each group *Have substitute outcomes been used instead of the patient-important outcomes of interest?* 'favourable response' is a substitute outcome
Number of patients	Included = 205 antituberculosis chemotherapy plus surgery = 130 antituberculosis chemotherapy alone = 75 'Adequate' microbiological data available = 162 antituberculosis chemotherapy plus surgery = 108 antituberculosis chemotherapy alone = 54
Patient characteristics	*Inclusion* MDR-TB, defined as *M. tuberculosis* strains that are resistant to at least rifampicin and isoniazid *Baseline* Age (median (range), years) = 39.9 (2–85) Sex, males = 57.6% Duration of recorded disease before treatment (median, years) = 4.2 Number of drugs previously received for 3 or more months (median) = 5

	Number of drugs to which the strains were resistant (median) = 6
Intervention	*Antituberculosis chemotherapy plus surgery* Surgery: surgical resection of cavitary lobes or destroyed lungs was aggressively considered for patients who, from prior experience, were deemed likely to fail medical treatment based on their resistance patterns and/or extent of disease due to the retrospective nature of the study, there were no rigid criteria for selection or exclusion for surgery; the medical and surgical staff clinically evaluated each patient individually with the following general criteria for an acceptable surgical candidate: (1) a high likelihood of medical failure based on extensive drug resistance, (2) localized cavitary disease within a lobe or total destruction of one lung, and (3) predictably adequate postoperative lung function Antituberculosis chemotherapy: *in vitro* susceptibility testing was used to guide therapy of MDR-TB patients, preferentially choosing drugs that had not been used previously in instances of highly resistant organisms, drugs to which the organisms were at least partially susceptible or that had been given previously for only a short time were used injectable agents such as amikacin, kanamycin, or capreomycin were recommended for 3 to 6 months after the initial date of culture conversion; 96% received an aminoglycoside or capreomycin, and 80% received a fluoroquinolone oral drugs were continued for 15 to 18 months after the last positive sputum culture a median of 6 drugs (range: 3–10) was given to each patient Directly observed therapy was enforced during hospitalization and was encouraged after discharge Rigorous efforts were made to continue therapy in spite of adverse drug reactions unless they were deemed potentially life threatening or intolerable
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: *in vitro* susceptibility testing was used to guide therapy of MDR-TB patients, preferentially choosing drugs that had not been used previously

	in instances of highly resistant organisms, drugs to which the organisms were at least partially susceptible or that had been given previously for only a short time were used injectable agents such as amikacin, kanamycin, or capreomycin were recommended for 3 to 6 months after the initial date of culture conversion; 96% received an aminoglycoside or capreomycin, and 80% received a fluoroquinolone oral drugs were continued for 15 to 18 months after the last positive sputum culture a median of 6 drugs (range: 3–10) was given to each patient Directly observed therapy was enforced during hospitalization and was encouraged after discharge Rigorous efforts were made to continue therapy in spite of adverse drug reactions unless they were deemed potentially life threatening or intolerable
Length of follow up	Unclear, though survival analysis is available for at least 12 years
Location	Denver, US
Outcomes measures and effect size	**Mortality – TB-related and/or surgical** Survival time[1] from TB-related and/or surgical deaths amongst patients with non-extensive[2] disease 

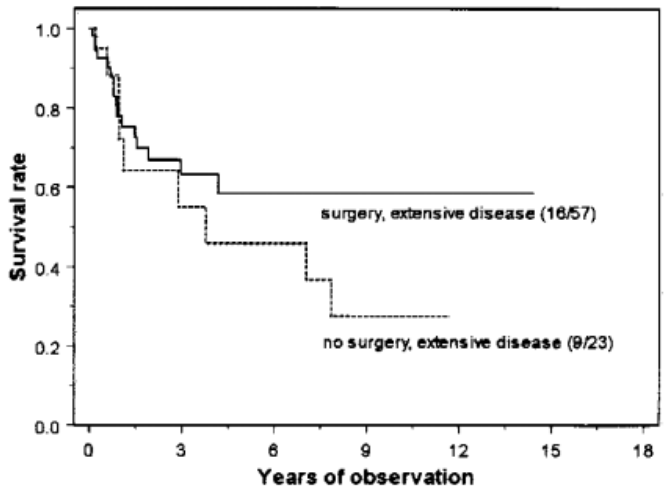
	p = 0.23 i.e. not statistically significant Survival time[1] from TB-related and/or surgical deaths amongst patients with extensive[2] disease  p = 0.84 i.e. not statistically significant
	Mortality – all-cause Survival time[1] from death of any cause amongst patients with non-extensive[2] disease



p = 0.08

i.e. not statistically significant

Survival time[1] from death of any cause amongst patients with extensive[2] disease



p = 0.36

i.e. not statistically significant

Treatment failure

Number of patients to experience microbiological failure, defined as patients who failed to achieve three consecutive negative sputum cultures over at least a 3-month period

antituberculosis chemotherapy plus surgery = 9 of 108

antituberculosis chemotherapy alone = 16 of 54

OR[3] (95% CI) = 0.22 (0.09 to 0.53)

i.e. statistically significant

Response to treatment - favourable

Number of patients to experience an initial favourable response, defined as patients with at least three consecutive negative sputum cultures over a period of at least 3 months while on treatment

	antituberculosis chemotherapy plus surgery = 99 of 108 antituberculosis chemotherapy alone = 38 of 54 *Model with intercept plus individual predictor*[4] **OR (95% CI) = 4.63 (1.89 to 11.37)** **p = 0.0008** **i.e. statistically significant** *Final model after step-wise selection*[4] **OR (95% CI) = 4.23 (1.28 to 13.93)** **p = 0.02** **i.e. statistically significant**
Source of funding	No details provided
Comments	

[1] Survival time was defined as the time from the hospital admission date to the date of the most recent information (or date of death); for subjects without follow-up information after discharge from hospital, the most recent date of information used was their discharge date; survival times for subjects without known TB death were right censored

[2] 'Extensive disease' was determined radiographically and deemed present when combined cavity diameters totalled 15 cm or more or moderately dense infiltrates involved 75% or more of lung fields or both were present

[3] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

[4] Several explanatory variables were analysed for their association with initial favourable response using logistic regression:

first, explanatory variables were fit in separate regression models

next, a stepwise selection procedure was used to create a multiple predictor model, including those variables that were first tested individually, plus all two-way interaction terms involving surgery and/or fluoroquinolone therapy

goodness-of-fit criteria were also evaluated to assess model adequacy.

Abbreviations: CI, confidence intervals; MDR-TB, multidrug resistant tuberculosis; OR, odds ratio; TB, tuberculosis

1.1.25 Geiga et al, 2012

Bibliographic reference	Geiga M, Kalandadaze I, Kempker RR et al (2012) Adjunctive surgery improves treatment outcomes among patients with multidrug-resistant and extensively drug-resistant tuberculosis. International Journal of Infectious Diseases 16: e391-6
Study type	Prospective cohort
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* decision to perform surgical resection was made by the Georgian National TB Program's Drug Resistance Committee; in addition, sufficient pulmonary function to tolerate resection and a localised lesion amenable to resection were required *Blinding used?* unclear, though unlikely *Attempts made within the design or analysis to balance the groups for potential confounders?* a binary multivariable logistic regression model was used to evaluate the independent association of potential risk factors with poor outcome; model building and selection was based on the purposeful selection of covariates based on epidemiological findings and biological plausibility *Groups comparable at baseline?* unclear *Groups received the same care apart from the intervention(s) studied?* unclear *Groups followed up for an equal and appropriate length of time?* unclear *Groups comparable for treatment completion and availability of outcome data?*

	unclear *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* some patients had comorbidities that may affect the choice or management of treatment (e.g. 9% had diabetes mellitus) *Intervention used is the same as the intervention of interest?* it is unclear if the 2 interventions varied by more than the presence or absence of surgery; in particular, there is insufficient detail around the precise regimens of antituberculosis chemotherapy used in each group *Have substitute outcomes been used instead of the patient-important outcomes of interest?* 'poor outcome' is a substitute outcome
Number of patients	Included = 380 antituberculosis chemotherapy plus surgery = 37 antituberculosis chemotherapy alone = 343
Patient characteristics	*Inclusion* All patients in Georgia aged ≥16 years with laboratory confirmed pulmonary MDR- or XDR-TB initiating treatment between March and December 2008 through the Georgian National TB Program *Baseline* Age (mean (range), years) = 38 (16–81) Sex, female = 29% Prior history of TB treatment = 88% Newly diagnosed TB cases = 12%

	BMI ≤18.5 kg/m^2 = 24% HIV infection = 1% Diabetes mellitus = 9%
Intervention	*Antituberculosis chemotherapy plus surgery* Surgery: surgical resection decision to undertake surgery was made by the Georgian National TB Program's Drug Resistance Committee; in addition, sufficient pulmonary function to tolerate resection and a localised lesion amenable to resection were required Antituberculosis chemotherapy: treatment regimens were individualized based on the results of drug susceptibility testing and guided by WHO recommendations regimens regimens were designed to include at least 4 drugs to which the patient's M. tuberculosis isolate was susceptible all treatment regimens included a fluoroquinolone (moxifloxacin or levofloxacin) and also an injectable agent (i.e. kanamycin or capreomycin) for at least 6 months treatment was continued for at least 18 months after achieving a negative sputum culture All patients received treatment through directly observed therapy Most patients received initial care as an inpatient before transitioning to outpatient treatment
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: treatment regimens were individualized based on the results of drug susceptibility testing and guided by WHO recommendations regimens regimens were designed to include at least 4 drugs to which the patient's M. tuberculosis isolate was susceptible all treatment regimens included a fluoroquinolone (moxifloxacin or levofloxacin) and also an injectable agent (i.e.

	kanamycin or capreomycin) for at least 6 months treatment was continued for at least 18 months after achieving a negative sputum culture All patients received treatment through directly observed therapy Most patients received initial care as an inpatient before transitioning to outpatient treatment
Length of follow up	Unclear
Location	Georgia
Outcomes measures and effect size	**Response to treatment – poor outcome** Number of patients to experience a poor outcome, defined as treatment failure, death during treatment or default antituberculosis chemotherapy plus surgery = 8 of 37 antituberculosis chemotherapy alone = 171 of 343 *Univariable analysis* **OR (95% CI) = 0.28 (0.12 to 0.62)** **p = 0.002** **i.e. statistically significant** *Multivariable analysis*[1] **OR (95% CI) = 0.27 (0.11 to 0.64)** **p = 0.003** **i.e. statistically significant**
Source of funding	Supported in part by a grant from the US National Institutes of Health (NIH) Fogarty International Center
Comments	

[1] A binary multivariable logistic regression model was used to evaluate the independent association of potential risk factors with poor outcome; model building and selection was based on the purposeful selection of covariates based on epidemiological findings and biological plausibility

Abbreviations: BMI, body mass index; CI, confidence intervals; MDR-TB multidrug resistant tuberculosis; OR, odds ratio; TB, tuberculosis; XDR-TB, extremely drug resistant tuberculosis

1.1.26 Jeon et al, 2009

Bibliographic reference	Jeon DS, Kim DH, Kang HS et al (2009) Survival and predictors of outcomes in non-HIV-infected patients with extensively drug-resistant tuberculosis. International Journal of Tuberculosis and Lung Disease 13(5): 594-600
Study type	Retrospective cohort
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* allocation to surgery was based on specific criteria (surgical resection was considered for patients with localised cavitary lesions and anticipated adequate postoperative lung function, and for selected patients with bilateral lesions if medical treatment had failed or was expected to fail) *Blinding used?* unclear, though unlikely *Attempts made within the design or analysis to balance the groups for potential confounders?* to identify the risk factors associated with poor outcome, the authors compared variables between poor outcome and favourable outcome through univariate analysis; binary logistic regression analysis with the backward elimination method was performed for variables with $p < 0.2$ in the univariate analysis, which included the use of surgery, and the Hosmer-Lemeshow test was used for testing the goodness-of-fit of the models *Groups comparable at baseline?* unclear *Groups received the same care apart from the intervention(s) studied?* unclear *Groups followed up for an equal and appropriate length of time?* unclear *Groups comparable for treatment completion and availability of outcome data?*

	unclear *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* some patients had comorbidities that may affect the choice or management of treatment (15% had diabetes mellitus) *Intervention used is the same as the intervention of interest?* it is unclear if the 2 interventions varied by more than the presence or absence of surgery; in particular, there is insufficient detail around the precise regimens of antituberculosis chemotherapy used in each group *Have substitute outcomes been used instead of the patient-important outcomes of interest?* 'poor outcome' is a substitute outcome
Number of patients	Included = 176 antituberculosis chemotherapy plus surgery = 16 antituberculosis chemotherapy alone = 160 Data available = 142 antituberculosis chemotherapy plus surgery = 12 antituberculosis chemotherapy alone = 130
Patient characteristics	*Inclusion* XDR-TB HIV-negative *Drug susceptibility testing* Performed using the absolute concentration method; the critical concentration of resistance for each drug was as follows:

	isoniazid 0.2 µg/ml rifampicin 40 µg/ml ethambutol 2 µg/ml streptomycin 10 µg/ml kanamycin 40 µg/ml paraaminosalicylate 1 ug/ml prothionamide 40 ug/ml cycloserine 30 µg/ml ofloxacin 2 µg/ml Pyrazinamide resistance was determined by the pyrazinamidase test *Baseline* Number of drugs strains resistant to (mean (range)) = 6.9 (5–8) Resistant to all 10 drugs tested = 10% Newly diagnosed TB = 4% Previously treated with first-line drugs only = 27% Previously treated with second-line drugs = 69% Surgical resection before the diagnosis of XDR-TB = 11%
Intervention	*Antituberculosis chemotherapy plus surgery* Surgery: surgical resection performed a mean of 7.8 months (median = 8; range = 0–19) after the diagnosis of XDR-TB

	Antituberculosis chemotherapy: each regimen included a mean of 5.3 drugs (median = 5; range 3–8), of which a mean of 1.9 drugs (median = 2, range = 0–5) were active according to drug susceptibility testing mean of 1.4 regimen changes (median = 1; range =1–5) after their XDR-TB diagnosis
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: each regimen included a mean of 5.3 drugs (median = 5; range 3–8), of which a mean of 1.9 drugs (median = 2, range = 0–5) were active according to drug susceptibility testing mean of 1.4 regimen changes (median = 1; range =1–5) after their XDR-TB diagnosis
Length of follow up	Unclear
Location	Masan, South Korea
Outcomes measures and effect size	**Response to treatment – poor outcome** Number of patients to experience a poor outcome, defined as treatment failure, death during treatment or default antituberculosis chemotherapy plus surgery = 4 of 13 antituberculosis chemotherapy alone = 110 of 129 *Univariate analysis* **OR (95% CI) = 0.08 (0.02 to 0.28)** **i.e. statistically significant** *Multivariate analysis* **OR (95% CI) = 0.18 (0.04 to 0.78)** **i.e. statistically significant**
Source of funding	No details provided

Comments	
[1] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer Abbreviations: CI, confidence intervals; OR, odds ratio; TB, tuberculosis; XDR-TB, extremely drug resistant tuberculosis	

1.1.27 Karagöz et al, 2009

Bibliographic reference	Karagöz T, Yazicioglu Moçin Ö, Pazarli P et al (2009) The treatment results of patients with multidrug resistant tuberculosis and factors affecting treatment outcome. Tüberküloz ve Toraks Dergisi 57(4): 383-92
Study type	Prospective observational
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* allocation to surgery was based on specific criteria (drug resistance with high probability of failure or relapse, sufficiently localized disease with adequate cardiopulmonary reserve and the availability of drugs with adequate efficacy to cause rapid healing of the bronchial stump) *Blinding used?* unclear, though unlikely *Attempts made within the design or analysis to balance the groups for potential confounders?* no for treatment failure, default and mortality; unclear for cure *Groups comparable at baseline?* unclear *Groups received the same care apart from the intervention(s) studied?* unclear *Groups followed up for an equal and appropriate length of time?* unclear *Groups comparable for treatment completion and availability of outcome data?*

	yes *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* some patients had comorbidities that may affect the choice or management of treatment (12% had diabetes mellitus and 21.8% had COPD) no females *Intervention used is the same as the intervention of interest?* it is unclear if the 2 interventions varied by more than the presence or absence of surgery – in particular, there is insufficient detail around the precise regimens of antituberculosis chemotherapy used in each group *Have substitute outcomes been used instead of the patient-important outcomes of interest?* no
Number of patients	Included = 142 antituberculosis chemotherapy plus surgery = 35 antituberculosis chemotherapy alone = 107
Patient characteristics	*Inclusion* A combination of sputum smear microscopy using Ziehl-Neelsen technique and LöwensteinJensen culture medium was used for diagnosis Amongst new cases of tuberculosis receiving drugs under direct observation at hospital, previously treated with first-line drugs (isoniasid, rifampin, pyrazinamide, ethambutol or streptomycin during the initial phase, and with isoniazid and rifampin during the continuation phase), a positive smear in the fifth month after initiation of treatment was considered to indicate treatment failure due to MDR-TB and further treatment was individualized for these patients after resistance against at least isoniazid and rifampin was presented with drug susceptibility tests New cases of tuberculosis, receiving drugs without direct observation, were treated as above. If positive smear was

	detected at fifth month of treatment, they were also accepted as failure; nevertheless as their compliance was unknown, they were retreated with eight months regimen (2HRZES + 1HRZE + 5HRE). Smear positivity at eight months of retreatment was considered as failure, and these cases were treated as MDR-TB patients with the promoting drug susceptibility test results. For patients with history of previous infections (relapse or defaulter), they were considered as MDR-TB after eight months regimens containing isoniazid and rifampin were failed An isolate was considered resistant if there was > 1% growth of *M. tuberculosis* complex in the presence of 1 µg/mL for isoniazid, 40 µg/mL for rifampin, 2 µg/mL for ethambutol and >10% growth in the presence of 8 µg/mL for streptomycin *Baseline* All male Age (mean±SD (range), years) = 39±11 (16–65) At least 1 concomitant disease = 40.8% diabetes mellitus = 12% COPD = 21.8% Duration of disease before hospitalisation with MDR-TB (mean±SD (range), years) = 7.9±7.3 (1–35) Number of drugs used in previous regimens (mean±SD (range)) = 5.7±1.7 (3–12) Number of patients in whom second-line drugs had previously been used = 43% Number of first-line drugs to which resistance was shown (mean±SD (range)) = 4±1 (2–5)
Intervention	*Antituberculosis chemotherapy plus surgery* Surgery: surgical resection considered after at least 2 months of therapy in patients who met the following criteria: drug resistance with high probability of failure or relapse, sufficiently localized disease with adequate cardiopulmonary reserve and the availability of drugs with adequate efficacy to cause rapid healing of the bronchial stump

	Antituberculosis chemotherapy: no details given
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: no details given
Length of follow up	Unclear
Location	Istanbul, Turkey
Outcomes measures and effect size	**Mortality** Number of deaths antituberculosis chemotherapy plus surgery = 2 of 35 antituberculosis chemotherapy alone = 12 of 107 OR[1] (95% CI) = 0.48 (0.10 to 2.26) i.e. not statistically significant
	Cure Number of patients to be considered a cure, defined as negative smear and culture throughout treatment for at least 18 months (or 24 months, in the absence of first line drugs) and if only one positive culture was reported during that time and there was no concomitant evidence of deterioration, a patient may still be considered cured, provided that this positive culture was followed by a minimum of three consecutive negative cultures antituberculosis chemotherapy plus surgery = 31 of 35 antituberculosis chemotherapy alone = 71 of 107 **OR[1] (95% CI) = 3.93 (1.29 to 11.99)** **i.e. statistically significant** *Logistic regression – treatment without adjuvant therapy[2]* **OR (95% CI) = 0.30 (0.09 to 0.96)**

	i.e. statistically significant
	Treatment failure Number of patients to be considered a treatment failure, defined as persistence of positive smear and culture despite treatment for 18-24 months antituberculosis chemotherapy plus surgery = 1 of 35 antituberculosis chemotherapy alone = 9 of 107 OR[1] (95% CI) = 0.32 (0.04 to 2.62) i.e. not statistically significant
	Adherence - default Number of patients to be considered a defaulter, defined as failure to complete treatment for any reason antituberculosis chemotherapy plus surgery = 1 of 35 antituberculosis chemotherapy alone = 15 of 107 OR[1] (95% CI) = 0.18 (0.02 to 1.42) i.e. not statistically significant
	Post-operative complications Bronchial fistula and empyema = 2.8% Acute respiratory failure leading to death = 5.7%
Source of funding	No details provided
Comments	

[1] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

[2] note: authors calculated OR in the reverse

Abbreviations: CI, confidence intervals; COPD, chronic obstructive pulmonary disease; E, ethambutol; H, isoniazid; MDR-TB; OR, odds ratio; R, rifampicin; S, streptomycin; SD, standard deviation; Z, pyrazinamide

1.1.28 Keshajvee et al, 2008

Bibliographic reference	Keshajvee S, Gelmanova IY, Farmer PE et al (2008) Treatment of extensively drug-resistant tuberculosis in Tomsk, Russia: a retrospective cohort study. Lancet 372: 1403-9
Study type	Retrospective cohort
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* unclear *Blinding used?* unclear, though unlikely *Attempts made within the design or analysis to balance the groups for potential confounders?* no *Groups comparable at baseline?* unclear *Groups received the same care apart from the intervention(s) studied?* yes, though details provided were limited *Groups followed up for an equal and appropriate length of time?* unclear *Groups comparable for treatment completion and availability of outcome data?* unclear *Study used precise definitions and reliable measures of outcome?*

	'favourable outcome' is defined as treatment completion or cure, but the definitions for treatment completion and cure are not provided *Population studied is the same as the population of interest?* yes *Intervention used is the same as the intervention of interest?* it is unclear if the 2 interventions varied by more than the presence or absence of surgery – in particular, there is insufficient detail around the precise regimens of antituberculosis chemotherapy used in each group *Have substitute outcomes been used instead of the patient-important outcomes of interest?* 'favourable outcome' is a composite of outcomes of interest
Number of patients	Included = 636 antituberculosis chemotherapy plus surgery = 56 antituberculosis chemotherapy alone = 580 Data available = 608[1]
Patient characteristics	*Inclusion* Patients treated for MDR- and XDR-TB in Tomsk, Russia Baseline MDR-TB was defined as resistance to isoniazid and rifampin in any DST before starting MDR-TB treatment *Diagnostic criteria* Patients were diagnosed with tuberculosis with radiographic, bacteriological, and clinical criteria DST was done on all culture-positive isolates DST was performed according to the absolute concentration method on Löwenstein–Jensen media at the following concentrations: 1 µg/mL isoniazid, 40 µg/mL rifampin, 5 µg/mL ethambutol, 10 µg/mL streptomycin, and 30 µg/mL kanamycin DST quality assurance was conducted according to the proportion method on 7H10 agar plates for all drugs, except

	pyrazinamide, for which BACTEC was used, at the following concentrations: 0·2, 1, and 5 μg/mL isoniazid, 1 μg/mL rifampin, 100 μg/mL pyrazin amide, 5 μg/mL ethambutol, 2 and 10 μg/mL strepto mycin, 5 μg/mL kanamycin, 10 μg/mL capreomycin, 5 μg/mL ethionamide, 30 μg/mL cycloserine, 1 μg/mL para-aminosalicylic acid, 6 μg/mL amikacin, 1 μg/mL levofloxacin, 2 μg/mL ofloxacin, and 2 μg/mL ciprofloxacin *Baseline* Sex, female = 16.8% Age (mean, years) = 35.8 Number of previous treatments against tuberculosis (median (interquartile range)): XDR-TB = 3.0 (2.0–4.0) MDR-TB = 2.0 (1.0–3.0) New patients (no previous treatment for tuberculosis) = 0.5% Previous surgery for tuberculosis = 1.8% Previous default = 0.5% Low body mass index = 42.4% HIV-positive = 0.8% Baseline respiratory insufficiency = 52.0% Fibrotic or cavitatory lesions of chest x-ray = 16.8% Alcoholism = 42.9% Illegal drug use = 18.9%
Intervention	*Antituberculosis chemotherapy plus surgery* Physicians designed individual therapies against MDR-TB with a standard algorithm that accounted for DST results and history of previous treatments against tuberculosis Surgery: no details given

	Antituberculosis chemotherapy: when possible, treatment contained at least five drugs to which the patient's isolate was susceptible if discrepant resistance data were encountered, physicians often included the drug in question, but did not regard it as one of the five effective drugs if five effective drugs were not available, physicians considered including drugs to which resistance was known, especially if patients had scarce or no previous exposure to them patients with DST results showing resistance to fluoroquinolones were also treated with ofloxacin or levofloxacin, whereas those with DST results showing resistance to kanamycin with or without capreomycin were treated with capreomycin individualised regimens relied heavily on second-line drugs treatment generally lasted at least 18 months after culture conversion All drugs were given under direct observation Adverse reactions were managed aggressively, avoiding dis continuation of drugs whenever possible Patients were routinely admitted for the duration of parenteral therapy (intensive phase), generally 6–9 months, and were then discharged to complete treatment as outpatients, unless they had a condition needing inpatient care (for example, diabetes, alcoholism, homelessness, or psychiatric disorder) Nutritional support was provided to all prisoners, inpatients, and adherent ambulatory patients All patients who failed treatment received medical care for palliation of symptoms
Comparison	*Antituberculosis chemotherapy alone* Physicians designed individual therapies against MDR-TB with a standard algorithm that accounted for DST results and history of previous treatments against tuberculosis Antituberculosis chemotherapy: When possible, treatment contained at least five drugs to which the patient's isolate was susceptible If discrepant resistance data were encountered, physicians often included the drug in question, but did not regard it as

	one of the five effective drugs If five effective drugs were not available, physicians considered including drugs to which resistance was known, especially if patients had scarce or no previous exposure to them Patients with DST results showing resistance to fluoroquinolones were also treated with ofloxacin or levofloxacin, whereas those with DST results showing resistance to kanamycin with or without capreomycin were treated with capreomycin Individualised regimens relied heavily on second-line drugs Treatment generally lasted at least 18 months after culture conversion All drugs were given under direct observation Adverse reactions were managed aggressively, avoiding dis continuation of drugs whenever possible Patients were routinely admitted for the duration of parenteral therapy (intensive phase), generally 6–9 months, and were then discharged to complete treatment as outpatients, unless they had a condition needing inpatient care (for example, diabetes, alcoholism, homelessness, or psychiatric disorder) Nutritional support was provided to all prisoners, inpatients, and adherent ambulatory patients All patients who failed treatment received medical care for palliation of symptoms
Length of follow up	Unclear
Location	Siberia, Russia
Outcomes measures and effect size	**Response to treatment – favourable outcome** Number of patients to experience a favourable outcome, defined as treatment completion or cure OR (95% CI) = 1.24 (0.69 to 2.26) i.e. not statistically significant
Source of funding	The funding sources had no role in study design, data collection, data analysis, data interpretation, or writing of the report
Comments	

[1] Data only provided for this with confirmed baseline MDR-TB; those with presumed MDR-TB, based on treatment or contact history, were excluded from the analysis by the authors

Abbreviations: CI, confidence intervals; DST, drug susceptibility testing; MDR-TB, multidrug resistant tuberculosis; OR, odds ratio; XDR-TB, extremely drug resistant tuberculosis

1.1.29 Kim et al, 2007

Bibliographic reference	Kim H-R, Hwang SS, Kim HJ et al (2007) Impact of extensive drug resistance on treatment outcomes in non-HIV-infected patients with multidrug-resistant tuberculosis. Clinical Infectious Diseases 45: 1290-5
Study type	Retrospective cohort
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* no – the criteria for surgery was MDR-TB refractory to at least 6 months of medical treatment with a primary localized lesion *Blinding used?* unclear, though unlikely *Attempts made within the design or analysis to balance the groups for potential confounders?* no *Groups comparable at baseline?* no – surgery was performed more frequently in patients with XDR-TB (p<0.001) *Groups received the same care apart from the intervention(s) studied?* unclear *Groups followed up for an equal and appropriate length of time?* unclear *Groups comparable for treatment completion and availability of outcome data?*

	unclear *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* no – 34.1% of patients had a comorbidity that might affect the choice or management of antituberculosis treatment *Intervention used is the same as the intervention of interest?* it is unclear if the 2 interventions varied by more than the presence or absence of surgery – in particular, there is insufficient detail around the precise regimens of antituberculosis chemotherapy used in each group *Have substitute outcomes been used instead of the patient-important outcomes of interest?* no
Number of patients	Included = 211 antituberculosis chemotherapy plus surgery = 63 antituberculosis chemotherapy alone = 148 Data available = 197 antituberculosis chemotherapy plus surgery = 60 antituberculosis chemotherapy alone = 137
Patient characteristics	*Inclusion* Patients who had received the diagnosis of and treatment as having MDR-TB at Seoul National University Hospital between January 1996 and December 2005 MDR-TB was defined as TB caused by bacilli showing resistance to at least isoniazid and rifampicin XDR-TB was defined as TB caused by bacilli showing resistance to isoniazid and rifampicin and also showing resistance to any fluoroquinolone and to any of the following 3 injectable antituberculosis drugs: capreomycin, kanamycin, and amikacin

	No HIV infection *Baseline* Age (median (range), years) = 37 (13–91) Sex, male = 58.8% Body mass index (mean±SD) = 19.9±3.4 Comorbidities: any = 34.1% diabetes = 14.2% cardiovascular disease = 9.0% chronic liver disease = 6.2% chronic renal disease = 0.9% chronic obstructive pulmonary disease = 3.3% malignancy = 3.3% other = 10.9% Family history of tuberculosis = 30.4% Radiographic finding: cavity = 75.8% bilateral cavities = 33.2% Combined extrapulmonary tuberculosis = 13.7%
Intervention	*Antituberculosis chemotherapy plus surgery* Treatment for these patients was individualized by each physician on the basis of drug-susceptibility testing

	Surgery: surgical resection general indication = MDR-TB refractory to at least 6 months of medical treatment with a primary localized lesion Antituberculosis chemotherapy: used any first-line agents to which TB shows susceptibility used injectable anti-TB drugs and quinolones if susceptible added second-line bacteriostatic agents as needed to make up the 5-drug regimen number of drugs used (mean (range)) = 6 (3–12) treated for 2 years after culture conversion
Comparison	*Antituberculosis chemotherapy alone* Treatment for these patients was individualized by each physician on the basis of drug-susceptibility testing Antituberculosis chemotherapy: used any first-line agents to which TB shows susceptibility used injectable anti-TB drugs and quinolones if susceptible added second-line bacteriostatic agents as needed to make up the 5-drug regimen number of drugs used (mean (range)) = 6 (3–12) treated for 2 years after culture conversion (median (range), months = 26 (1–136))
Length of follow up	Unclear
Location	Seoul, Korea

Outcomes measures and effect size	**Response to treatment – poor outcome** Number of patients to experience treatment failure, defined as failure[1], relapse[2] or death antituberculosis chemotherapy plus surgery = 17 of 60 antituberculosis chemotherapy alone = 48 of 137 OR[3] (95% CI) = 0.73 (0.38 to 1.42) i.e. not statistically significant
Source of funding	Financial support was provided from the Ministry of Health and Welfare, Republic of Korea
Comments	May be some overlap in population with Kim et al (2008) and Kwon et al (2008)

[1] 'Failure' was defined as ≥2 of 5 positive culture results recorded during the final 12 months or any 1 of the final 3 cultures being positive

[2] 'Relapse' was defined as a cured patient or a patient who completed therapy who resumed treatment 16 months after completion of the first treatment because of the emergence of MDR-tuberculous bacilli

[3] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

Abbreviations: CI, confidence intervals; MDR-TB, multidrug resistant tuberculosis; OR, odds ratio; SD, standard deviation; XDR-TB, extremely drug resistant tuberculosis

1.1.30 Kim et al, 2008

Bibliographic reference	Kim DH, Kim HJ Park S-K et al (2008) Treatment outcomes and long-term survival in patients with extensively drug-resistant tuberculosis. American Journal of Respiratory and Critical Care Medicine 178: 1075-82
Study type	Retrospective cohort
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* unclear *Blinding used?* unclear, though unlikely

	=Attempts made within the design or analysis to balance the groups for potential confounders? yes – in multivariate analysis *Groups comparable at baseline?* unclear *Groups received the same care apart from the intervention(s) studied?* yes, though details were limited *Groups followed up for an equal and appropriate length of time?* follow-up was for an appropriate period, though unclear if it was comparable in the 2 groups *Groups comparable for treatment completion and availability of outcome data?* unclear *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* no – 22.6% of patients had a comorbidity that might affect the choice or management of antituberculosis treatment *Intervention used is the same as the intervention of interest?* it is unclear if the 2 interventions varied by more than the presence or absence of surgery – in particular, there is insufficient detail around the precise regimens of antituberculosis chemotherapy used in each group *Have substitute outcomes been used instead of the patient-important outcomes of interest?* no
Number of patients	Included = 1407 antituberculosis chemotherapy plus surgery = 60

	antituberculosis chemotherapy alone = 1347
Patient characteristics	*Inclusion* Patients newly diagnosed with, or retreated for, culture-proven XDR-TB from January 2000 to December 2002 in all Korean National Tuberculosis Association chest clinics, and 8 randomly selected university hospitals near Seoul XDR-TB was defined as MDR-TB with bacillary resistance to both (1) ofloxacin and (2) one of the second-line injectable drugs (kanamycin, capreomycin, or enviomycin) *Baseline* Age (mean±SD (range), years) = 42.9±14.9 (13–89) Sex, males = 73.8% Body mass index (mean±SD (range), years) = 19.2±3.2 (12.0–32.0) Previous history of antituberculosis treatment: no history of treatment = 28.3% history of antituberculosis treatment with first-line drugs only = 58.2% history of antituberculosis treatment with second-line drugs = 13.5% number of drugs previously used (median (range)) = 4 (0–16) Underlying diseases: diabetes mellitus = 17.0% chronic liver disease = 1.8% malignancy = 0.9% other = 2.8% HIV seropositive = 1.5% Extrapulmonary tuberculosis = 3.8%

	Positive acid-fast bacilli smear at treatment initiation = 68.1% Radiologic severity: minimal = 7.6% moderately advanced = 59.5% far advanced = 32.9% Cavitatory disease = 42.6% Bilateral disease = 73.9%
Intervention	*Antituberculosis chemotherapy plus surgery* All patients were treated by individualized regimens on the basis of DST results and history of previous TB drug use Surgery: surgical resection Antituberculosis chemotherapy: the duration of adequate treatment was defined as 18 months or more and 12 months or more after culture conversion number of drugs used (median (range)) = 5 (2–9) Directly observed therapy was performed only on patients admitted in national TB hospitals
Comparison	*Antituberculosis chemotherapy alone* All patients were treated by individualized regimens on the basis of DST results and history of previous TB drug use Antituberculosis chemotherapy: the duration of adequate treatment was defined as 18 months or more and 12 months or more after culture conversion number of drugs used (median (range)) = 5 (2–9) Directly observed therapy was performed only on patients admitted in national TB hospitals

Length of follow up	All study patients were monitored for 3 to 7 years after treatment began
Location	Korea
Outcomes measures and effect size	**Mortality – all-cause (patients aged ≤40 years)** Number of deaths of any cause among patients aged 40 years or younger *Univariate analysis* OR (95% CI) = 0.53 (0.17 to 1.67) p = 0.275 i.e. not statistically significant
	Mortality – TB-related (patients aged ≤40 years) Number of TB-related deaths among patients aged 40 years or younger *Univariate analysis* OR (95% CI) = 0.67 (0.21 to 2.14) p = 0.502 i.e. not statistically significant
	Response to treatment – favourable outcome Number of patients to experience treatment success, defined as the sum of cure[1], treatment completion[2], and short-term treatment completion[3] antituberculosis chemotherapy plus surgery = 41 of 60 antituberculosis chemotherapy alone = 596 of 1347 *Univariate analysis* **OR (95% CI) = 2.72 (1.56 to 4.73)**

	p<0.001 **i.e. statistically significant** *Multivariate analysis* **OR (95% CI) = 3.87 (1.69 to 8.88)** **p = 0.001** **i.e. statistically significant**
Source of funding	No details provided
Comments	May be some overlap in population with Kim et al (2007) and Kwon et al (2008)

[1] 'Cure' was defined as a patient who has completed treatment for appropriate treatment duration and has at least 5 consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment

[2] 'Treatment completion' was defined as a patient who has completed treatment for appropriate treatment duration, but does not meet the definition for cure because fewer than 5 consecutive negative cultures were obtained in the final 12 months of treatment

[3] 'Short-term treatment completion' was defined as patients who met all of the following criteria: (1) inadequate treatment duration but duration of more than 6 months, (2) more than 3 consecutive negative cultures before treatment completion, and (3) treatment completion by a doctor based on favourable treatment response

Abbreviations: CI, confidence intervals; DST, drug-susceptibility testing; OR, odds ratio; SD, standard deviation; XDR-TB, extremely drug resistant tuberculosis

1.1.31 Kwon et al, 2008

Bibliographic reference	Kwon YS, Kim YH, Suh GY et al (2008) Treatment outcomes for HIV-uninfected patients with multidrug-resistant and extensively drug-resistant tuberculosis. Clinical Infectious Diseases 47: 496-502
Study type	Retrospective cohort
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* no – the criteria for surgery was MDR-TB refractory to at least 6 months of medical treatment with a primary localized

	lesion *Blinding used?* unclear, though unlikely *Attempts made within the design or analysis to balance the groups for potential confounders?* yes – in the multiple logistic regression *Groups comparable at baseline?* unclear *Groups received the same care apart from the intervention(s) studied?* yes, although details provided are limited *Groups followed up for an equal and appropriate length of time?* unclear *Groups comparable for treatment completion and availability of outcome data?* unclear *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* no – some patients had a comorbidity that might affect the choice or management of antituberculosis treatment (15% diabetes mellitus, 5% chronic liver disease, 3% malignancy) *Intervention used is the same as the intervention of interest?* it is unclear if the 2 interventions varied by more than the presence or absence of surgery – in particular, there is insufficient detail around the precise regimens of antituberculosis chemotherapy used in each group *Have substitute outcomes been used instead of the patient-important outcomes of interest?*

	'favourable outcome' is a composite of outcomes of interest
Number of patients	Included = 155 antituberculosis chemotherapy plus surgery = 35 antituberculosis chemotherapy alone = 120
Patient characteristics	*Inclusion* Patients with MDR TB who were referred to and given treatment with second-line drugs for at least 3 months from January 1995 through December 2004 at a tertiary care hospital in Seoul, Korea MDR-TB was defined by a culture positive for *M. tuberculosis* with in vitro resistance to both isoniazid and rifampin The drug susceptibility of the *M. tuberculosis* isolates was determined with use of the absolute concentration method with Löwenstein-Jensen medium; the drugs and their critical concentrations for resistance were as follows: isoniazid, 0.2 mg/mL; rifampin, 40 mg/mL; ethambutol, 2 mg/mL; streptomycin, 10 mg/mL, kanamycin, 40 mg/mL; capreomycin, 40 mg/mL; ofloxacin, 2 mg/mL; prothionamide, 40 mg/mL; cycloserine, 30 mg/mL; and para-aminosalicylic acid, 1 mg/mL Pyrazinamide susceptibility was determined with use of the pyrazinamidase test No HIV infection *Baseline* Sex, males = 53% Age (median (interquartile range), years) = 40 (27–54) Body mass index (median (interquartile range)) = 20.0 (18.0–22.2) Comorbid conditions: diabetes mellitus = 15% chronic liver disease = 5% malignancy = 3%

	History of antituberculosis chemotherapy: none = 12% first-line drugs only = 52% second-line drugs only = 36% Number of drugs to which isolates were resistant (median (interquartile range)) = 5 (3–6) Extensively drug resistant tuberculosis = 17% Positive sputum smear result = 85% Cavity (or cavities) on radiograph = 71% Bilateral disease = 69%
Intervention	*Antituberculosis chemotherapy plus surgery* Individualised treatment regimens based on drug susceptibility Surgery: surgical resection although the decision to perform surgical resection was made by the attending physicians, the general indication was MDR-TB refractory to or deemed likely to be unresponsive to medical treatment on the basis of resistance patterns all candidates for surgery were required to have sufficient pulmonary function to tolerate resection and a localized lesion with a high bacterial burden, such as a cavity (or cavities) for those patients with bilateral lesions, the area with the greatest bacterial burden was resected, and the remaining lesion (i.e. in the ipsilateral or contralateral lung) was managed with medical therapy performed after a median duration of medical treatment of 6 months (interquartile range = 1–14 months) pneumonectomies were performed for 14 patients, lobectomies or bilobectomies were performed for 20 patients, and a segmentectomy was performed for 1 patient Antituberculosis chemotherapy:

	all individualised treatment regimens were based on a combination of the first- and second-line drugs to which the strains displayed susceptibility daily doses when available, the regimens included at least 3 effective drugs on the basis of the DST results; for cases in which 3 effective drugs could not be supplied or in cases involving extensive disease, drugs with unproven activity (amoxicillin-clavulanate, clarithromycin, and rifabutin) were included in the regimen as a rule, treatment was given for 18–24 months, including at least 12 months after culture conversion (defined as ≥2 consecutive negative results of cultures performed at least 4 weeks apart) the treatment regimen included 1 injectable agent for 73% of patients and 1 fluoroquinolone 95% of patients number of drugs used for ≥3 months (median (range)) = 6 (5–7) duration of antituberculosis chemotherapy (median (range), months) = 24 (18–30) In general, treatment was provided on an outpatient basis, although 45 patients were hospitalized for a short time at the start of second-line therapy; duration of hospitalization (median (interquartile range), days) = 7 (5–15) Treatment was directly observed during the hospitalization period, and the drugs were self-administered with the support of trained nurses during outpatient therapy
Comparison	*Antituberculosis chemotherapy alone* Individualised treatment regimens based on drug susceptibility Antituberculosis chemotherapy: all individualised treatment regimens were based on a combination of the first- and second-line drugs to which the strains displayed susceptibility daily doses when available, the regimens included at least 3 effective drugs on the basis of the DST results; for cases in which 3 effective drugs could not be supplied or in cases involving extensive disease, drugs with unproven activity (amoxicillin-clavulanate, clarithromycin, and rifabutin) were included in the regimen as a rule, treatment was given for 18–24 months, including at least 12 months after culture conversion (defined as ≥2

	consecutive negative results of cultures performed at least 4 weeks apart) the treatment regimen included 1 injectable agent for 73% of patients and 1 fluoroquinolone 95% of patients number of drugs used for ≥3 months (median (range)) = 6 (5–7) duration of antituberculosis chemotherapy (median (range), months) = 24 (18–30) In general, treatment was provided on an outpatient basis, although 45 patients were hospitalized for a short time at the start of second-line therapy; duration of hospitalization (median (interquartile range), days) = 7 (5–15) Treatment was directly observed during the hospitalization period, and the drugs were self-administered with the support of trained nurses during outpatient therapy
Length of follow up	Unclear
Location	Seoul, Korea
Outcomes measures and effect size	**Mortality** Number of deaths antituberculosis chemotherapy plus surgery = 1 of 35 antituberculosis chemotherapy alone = 9 of 120 OR[1] (95% CI) = 0.39 (0.05 to 3.21) i.e. not statistically significant
	Cure Number of patients to achieve a cure, defined as a patient who has completed treatment and consistently had negative culture results (with at least 5 negative results) during the final 12 months of treatment antituberculosis chemotherapy plus surgery = 26 of 35 antituberculosis chemotherapy alone = 60 of 120 **OR[1] (95% CI) = 2.89 (1.25 to 6.68)** **i.e. statistically significant**

	Treatment failure Number of patients to experience treatment failure, s defined as ≥2 positive culture results recorded during the final 12 months or a positive result of any 1 of the final 3 cultures antituberculosis chemotherapy plus surgery = 3 of 35 antituberculosis chemotherapy alone = 19 of 120 OR[1] (95% CI) = 0.50 (0.14 to 1.79) i.e. not statistically significant
	Response to treatment – favourable outcome Number of patients to achieve a favourable outcome, defined as cure or treatment completion[2] antituberculosis chemotherapy plus surgery = 31 of 35 antituberculosis chemotherapy alone = 71 of 120 *Univariate regression*[3] **p = 0.001** **i.e. statistically significant** *Multivariate regression*[3] **OR (95% CI) = 11.35 (3.02 to 42.74)** **p<0.001** **i.e. statistically significant**
Source of funding	Korea Science and Engineering Foundation grant funded by the Korean government
Comments	May be some overlap in population with Kim et al (2007 and 2008)

[1] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

[2] Patients who completed treatment but who did not meet the definition for cure or who experienced treatment failure were considered to have completed treatment

[3] To evaluate the predictors for a favourable outcome, the authors compared selected clinical variables between the favourable outcome and the unfavourable outcome groups, using univariate comparison and subsequent multiple logistic regression; in regression, stepwise and backward selection procedures were used to select variables to be maintained in the final model

Abbreviations: CI, confidence intervals; DST, drug susceptibility; MDR-TB, multidrug resistant tuberculosis OR, odds ratio

1.1.32 Leimane et al, 2005

Bibliographic reference	Lemaine V, Riekstina V, Holtz TH et al (2005) Clinical outcome of individualised treatment of multidrug-resistant tuberculosis in Latvia: a retrospective cohort study. Lancet 365: 318-26
Study type	Retrospective cohort
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* unclear *Blinding used?* unclear, though unlikely *Attempts made within the design or analysis to balance the groups for potential confounders?* no *Groups comparable at baseline?* unclear *Groups received the same care apart from the intervention(s) studied?* yes, although details were limited *Groups followed up for an equal and appropriate length of time?* unclear

	Groups comparable for treatment completion and availability of outcome data? unclear *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* no – some patients had a comorbidity that might affect the choice or management of antituberculosis treatment *Intervention used is the same as the intervention of interest?* it is unclear if the 2 interventions varied by more than the presence or absence of surgery – in particular, there is insufficient detail around the precise regimens of antituberculosis chemotherapy used in each group *Have substitute outcomes been used instead of the patient-important outcomes of interest?* no
Number of patients	Included = 204 antituberculosis chemotherapy plus surgery = 19 antituberculosis chemotherapy alone = 185
Patient characteristics	*Inclusion* All patients, both newly diagnosed and previously treated, with laboratory-confirmed MDR-TB who began treatment in Latvia between Jan 1 and Dec 31, 2000 An isolate of *M. tuberculosis* was regarded as MDR-TB if it showed *in vitro* resistance to at least isoniazid and rifampicin All drug-susceptibility tests were done with the absolute concentration method on: streptomycin (4·0 μg/mL), isoniazid (0·2 μg/mL and 2·0 μg/mL), rifampicin (40·0 μg/mL), ethambutol (2·0 μg/mL), kanamycin (30·0 μg/mL), paraaminosalicylic acid (0·5 μg/mL), cycloserine (30·0 μg/mL), thioacetazone (2·0 μg/mL), protionamide (30·0 μg/mL), and capreomycin (20·0 μg/mL) *Exclusion*

	Prisoners because the DOTS-Plus programme in the prison sector was not fully functional until 2001 *Baseline* Sex, males = 75% Existing comorbidities: number of comorbidities (median (range)) = 1 (0–4) any comorbidities = 61% no comorbidity = 34% unknown = 5% Bodyweight >10% below ideal: men = 28% women = 18% HIV status: positive = 1% negative = 96% unknown = 3% Previous antituberculosis treatment: never treated = 27% previously treated for tuberculosis = 58% previously treated for MDR-TB = 15% Site of MDR-TB: pulmonary = 96%

	pulmonary and extrapulmonary = 4% Radiological findings at onset: unilateral cavitary = 47% bilateral cavitary = 26% non-cavitary = 20% unknown = 7% Smear-positive = 44% Culture-positive = 82% Number of drugs to which isolates resistant (median (range)) = 4 (2–7)
Intervention	*Antituberculosis chemotherapy plus surgery* Individualised treatment regimens based on drug susceptibility Surgery: 5 had resection procedures, 6 had lobectomies or combined segmental resection, and 8 had pulmonectomies Antituberculosis chemotherapy: treatment with second-line antituberculosis drugs was started as soon as MDR-TB was identified because of a delay of 3–8 weeks to receive drug susceptibility test results for second-line drugs, treatment was started with an empirical individualised regimen, taking into account any previous receipt of antituberculosis drugs; this initial regimen consisted of between four and eight drugs (including one injectable) regimens were modified according to results of drug susceptibility tests for second-line drugs, and included at least five drugs to which the patient's tuberculosis isolate was susceptible the typical treatment regimen contained at least four oral drugs that were used for the full course of treatment; whenever possible, an injectable drug was included in the initial daily treatment regimen until the monthly *M. tuberculosis* culture converted to negative; after culture conversion the injectable medication was continued five times per week for an additional 2–3 months, and then three times per week thereafter, on the basis of the clinical status of

	the patient number of drugs used for ≥3 months: 3 = 3% 4 = 8% 5 = 33% 6 = 36% 7 = 19% 8 = 3% treatment continued for 12–18 months after *M. tuberculosis* culture conversion, dependent on severity of lung disease, history of treatment for tuberculosis, and general response to treatment; duration of antituberculosis chemotherapy (median (range), days) = 538 (31–1126) All treatment was provided under direct observation For all patients, initial treatment for MDR-TB was provided on an inpatient basis at 1 of 4 specialised hospitals after each case was discussed by a panel of specialist physicians; patients remained in one of the four reference centres until culture conversion and radiological improvement was achieved and they could tolerate their drug regimen; after discharge they were followed-up with ambulatory care; nurses managed ambulatory treatment and surveillance for adverse events, providing directly observed therapy five to six times per week Patients received nutritional support and transport reimbursement to visit the clinic for this treatment
Comparison	*Antituberculosis chemotherapy alone* Individualised treatment regimens based on drug susceptibility Antituberculosis chemotherapy: treatment with second-line antituberculosis drugs was started as soon as MDR-TB was identified because of a delay of 3–8 weeks to receive drug susceptibility test results for second-line drugs, treatment was started with an empirical individualised regimen, taking into account any previous receipt of antituberculosis drugs; this initial regimen consisted of between four and eight drugs (including one injectable)

	regimens were modified according to results of drug susceptibility tests for second-line drugs, and included at least five drugs to which the patient's tuberculosis isolate was susceptible the typical treatment regimen contained at least four oral drugs that were used for the full course of treatment; whenever possible, an injectable drug was included in the initial daily treatment regimen until the monthly *M. tuberculosis* culture converted to negative; after culture conversion the injectable medication was continued five times per week for an additional 2–3 months, and then three times per week thereafter, on the basis of the clinical status of the patient number of drugs used for ≥3 months: 3 = 3% 4 = 8% 5 = 33% 6 = 36% 7 = 19% 8 = 3% treatment continued for 12–18 months after *M. tuberculosis* culture conversion, dependent on severity of lung disease, history of treatment for tuberculosis, and general response to treatment; duration of antituberculosis chemotherapy (median (range), days) = 538 (31–1126) All treatment was provided under direct observation For all patients, initial treatment for MDR-TB was provided on an inpatient basis at 1 of 4 specialised hospitals after each case was discussed by a panel of specialist physicians; patients remained in one of the four reference centres until culture conversion and radiological improvement was achieved and they could tolerate their drug regimen; after discharge they were followed-up with ambulatory care; nurses managed ambulatory treatment and surveillance for adverse events, providing directly observed therapy five to six times per week Patients received nutritional support and transport reimbursement to visit the clinic for this treatment
Length of follow up	Unclear
Location	Latvia

Outcomes measures and effect size	**Mortality – all-cause** Number of deaths antituberculosis chemotherapy plus surgery = 1 of 19 antituberculosis chemotherapy alone = 13 of 185 OR[1] (95% CI) = 0.74 (0.09 to 5.95) i.e. not statistically significant
	Cure Number of patients to achieve a cure, defined as patients who completed treatment and were *M. tuberculosis* culture negative for the last 12 months of treatment antituberculosis chemotherapy plus surgery = 14 of 19 antituberculosis chemotherapy alone = 113 of 185 OR[1] (95% CI) = 1.78 (0.62 to 5.17) i.e. not statistically significant
	Treatment failure Number of patients to experience treatment failure, defined as patients with more than 1 positive *M. tuberculosis* culture during the past 12 months of treatment, those with 1 of their last 3 *M. tuberculosis* cultures positive, or those remaining persistently M tuberculosis culture positive with treatment being stopped by their physician antituberculosis chemotherapy plus surgery = 1 of 19 antituberculosis chemotherapy alone = 28 of 185 OR[1] (95% CI) = 0.31 (0.04 to 2.43) i.e. not statistically significant
	Adherence - default

	Number of patients to default on treatment, defined as patients who interrupted treatment for 2 or more consecutive months antituberculosis chemotherapy plus surgery = 1 of 19 antituberculosis chemotherapy alone = 25 of 185 OR[1] (95% CI) = 0.36 (0.05 to 2.78) i.e. not statistically significant
Source of funding	Funding for this project was provided by USAID; USAID had no role in study design, data collection, data analysis, data interpretation, or writing of the report
Comments	

[1] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

Abbreviations: CI, confidence intervals; MDR-TB, multidrug resistant tuberculosis; OR, odds ratio

1.1.33 Törün et al, 2007

Bibliographic reference	Törün T, Tahaoglu K, Özmen I et al (2007) The role of surgery and fluoroquinolones in the treatment of multidrug-resistant tuberculosis. International Journal of Tuberculosis and Lung Disease 11(9): 979-85
Study type	Retrospective cohort
Study quality	*Method of allocation to treatment groups unrelated to potential confounding factors?* allocation to surgery was based on specific criteria (resistance to a high number of drugs and therefore a high possibility of relapse or treatment failure; continued localised cavitary disease; destroyed lung, and only if they had relatively robust cardiopulmonary functions) *Blinding used?* unclear, though unlikely *Attempts made within the design or analysis to balance the groups for potential confounders?* yes – in multivariate analysis

	Groups comparable at baseline? unclear *Groups received the same care apart from the intervention(s) studied?* yes, although details provided were limited *Groups followed up for an equal and appropriate length of time?* follow-up appears to have been for an appropriate duration, though overall durations for each group are unclear *Groups comparable for treatment completion and availability of outcome data?* unclear *Study used precise definitions and reliable measures of outcome?* yes *Population studied is the same as the population of interest?* no – 18.7 % of patients had a comorbidity that might affect the choice or management of antituberculosis treatment *Intervention used is the same as the intervention of interest?* it is unclear if the 2 interventions varied by more than the presence or absence of surgery – in particular, there is insufficient detail around the precise regimens of antituberculosis chemotherapy used in each group *Have substitute outcomes been used instead of the patient-important outcomes of interest?* 'poor outcome' is a composite of outcomes of interest
Number of patients	Included = 252 antituberculosis chemotherapy plus surgery = 66 antituberculosis chemotherapy alone = 186
Patient characteristics	*Inclusion*

	MDR-TB The drug susceptibility of the *M. tuberculosis* isolates was determined with use of the following concentrations and controls: isoniazid, 0.5 and 1 µg/mL; rifampicin, 20 and 40 µg/mL; ethambutol, 2 µg/mL; streptomycin, 5 and 10 µg/mL; resistance was indicated by the growth of more than 1% of the colonies on drug-containing medium, as compared with that on drug-free medium *Baseline* Sex, females = 19.0% Age (mean±SD (range), years) = 37.9±12.5 (14–68) New infection = 23.8% Chronic infection = 76.2% Duration of disease (mean±SD (range), months) = 75.6±86.4 (0–416) Number of drugs previously used for ≥1 month (mean±SD (range)) = 5.3±1.7 (0–13) Number of drugs to which patients were resistant (mean±SD (range)) = 4.1±1.3 (2–9) Extent of disease: extensive = 37.7% limited = 62.3% ≥1 cavity = 91.7% Comorbidities: any = 18.7% diabetes = 13.5% ischaemic heart disease = 0.8% chronic obstructive pulmonary disease = 1.6%

	epilepsy = 0.4% hypertension = 1.6% amyloidosis = 0.8% psoriasis = 0.4%
Intervention	*Antituberculosis chemotherapy plus surgery* Surgery: surgical resection all cases were evaluated for resectional surgery after 2 months of treatment using the following criteria: resistance to a high number of drugs and therefore a high possibility of relapse or treatment failure; continued localised cavitary disease; destroyed lung, and only if they had relatively robust cardiopulmonary functions surgical resection was performed after 12 to 16 months of treatment (mean±SD = 4.9±2.4) pneumonectomy was performed in 40 cases, lobectomy or bilobectomy in 25 cases and a bilateral upper lobectomy in 1 case Antituberculosis chemotherapy: drugs were selected according to DST results and the patients' previous treatment histories when available, the regimens included at least 3 first- and/or second-line active drugs[1]; drugs with uncertain activity[2] were also added to regimens; in cases where 3 active drugs could not be supplied, drugs with unproven activity (clofazimine, clarithromycin and amoxicillin-clavulanate) and rifabutin were included in the regimen treatment was routinely planned to continue for 18 to 24 months after culture conversion; rigorous efforts were made to continue treatment with all drugs unless life-threatening side effects developed number of drugs used (mean±SD (range)) = 5.4±0.7 (3–9); number of active drugs[1] used (mean±SD (range)) = 4.5±1.0 (1–8) 97.6% of patients received 1 aminoglycoside or capreomycin; 85.3% of patients received 1 fluoroquinolone All cases were hospitalised at least during the parenteral treatment period

	Treatment was directly observed during the hospitalization period and drugs were self-administered after discharge
Comparison	*Antituberculosis chemotherapy alone* Antituberculosis chemotherapy: drugs were selected according to DST results and the patients' previous treatment histories when available, the regimens included at least 3 first- and/or second-line active drugs[1]; drugs with uncertain activity[2] were also added to regimens; in cases where 3 active drugs could not be supplied, drugs with unproven activity (clofazimine, clarithromycin and amoxicillin-clavulanate) and rifabutin were included in the regimen treatment was routinely planned to continue for 18 to 24 months after culture conversion; rigorous efforts were made to continue treatment with all drugs unless life-threatening side effects developed number of drugs used (mean±SD (range)) = 5.4±0.7 (3–9); number of active drugs[1] used (mean±SD (range)) = 4.5±1.0 (1–8) 97.6% of patients received 1 aminoglycoside or capreomycin; 85.3% of patients received 1 fluoroquinolone All cases were hospitalised at least during the parenteral treatment period Treatment was directly observed during the hospitalization period and drugs were self-administered after discharge
Length of follow up	Unclear
Location	Istanbul, Turkey
Outcomes measures and effect size	**Mortality** Number of deaths antituberculosis chemotherapy plus surgery = 5 of 66 antituberculosis chemotherapy alone = 13 of 186 OR[3] (95% CI) = 1.09 (0.37 to 3.19) i.e. not statistically significant
	Cure

	Number of patients to achieve a cure, defined as completion of treatment and at least 5 consecutive negative cultures from samples collected at least 30 days apart in the final 12 months antituberculosis chemotherapy plus surgery = 55 of 66 antituberculosis chemotherapy alone = 138 of 186 *Univariate regression* OR (95% CI) = 1.7 (0.8 to 3.5) p = 0.08 i.e. not statistically significant *Multivariate regression* OR (95% CI) = 1.5 (0.64 to 3.46) p = 0.35 i.e. not statistically significant
	Treatment failure Number of patients to experience treatment failure, defined as 2 or more positive cultures amongst final 5 samples collected in the final 12 months of therapy, or if any 1 of the final 3 cultures were positive antituberculosis chemotherapy plus surgery = 2 of 66 antituberculosis chemotherapy alone = 14 of 186 OR[3] (95% CI) = 0.38 (0.08 to 1.74) i.e. not statistically significant
	Adherence – incomplete treatment Number of patients to experience incomplete treatment, defined as treatment interrupted for 2 or more consecutive months for any reason

	antituberculosis chemotherapy plus surgery = 4 of 66 antituberculosis chemotherapy alone = 21 of 186 OR[3] (95% CI) = 0.51 (0.17 to 1.54) i.e. not statistically significant
	Response to treatment – long-term poor outcome Number of patients to experience a long-term poor outcome, defined as death, treatment failure or incomplete treatment antituberculosis chemotherapy plus surgery = 11 of 66 antituberculosis chemotherapy alone = 48 of 186 OR[3] (95% CI) = 0.58 (0.28 to 1.19) i.e. not statistically significant
Source of funding	No details provided
Comments	

[1] Active drugs were defined as:

previously unused drugs or those used for less than a month that had been found to be susceptible *in vitro*

all previously unused second-line drugs, because the probability of primary resistance is low as a result of limited use of these drugs in Turkey

[2] Drugs with uncertain activity were defined as drugs for which no resistance determined on DST but which had been used for more than 1 month

[3] Odds ratio and 95% confidence intervals not provided by authors; calculated by reviewer

Abbreviations: CI, confidence intervals; DST, drug susceptibility; MDR-TB, multidrug resistant tuberculosis; OR, odds ratio; SD, standard deviation